Received: 8 April 2019 | Accepted: 10 April 2019

DOI: 10.1002/ccd.28308

ORIGINAL STUDIES

WILEY

Impact of intravascular ultrasound-guided drug-eluting stent implantation on patients with chronic kidney disease: Results from ULTIMATE trial

Junjie Zhang MD, PhD[1] | Xiaofei Gao MD[1] | Zhen Ge MD[1] | Leng Han MD[2] | Shu Lu MD[3] | Xuesong Qian MD[4] | Qihua Li MD[5] | Qinghua Lu MD[6] | Chonghao Chen MD[7] | Shao-Liang Chen MD, PhD[1] | ULTIMATE Investigators

[1]Department of Cardiology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

[2]Department of Cardiology, Changshu No. 1 People's Hospital, Changshu, China

[3]Department of Cardiology, The First People's Hospital of Taicang, Taicang, China

[4]Department of Cardiology, The First People's Hospital of Zhangjiagang, Zhangjiagang, China

[5]Department of Cardiology, Changzhou Traditional Chinese Medicine Hospital, Changzhou, China

[6]Department of Cardiology, The Second Hospital of Shandong University, Jinan, China

[7]Department of Cardiology, Wuxi Third People's Hospital, Wuxi, China

Correspondence
Shao-Liang Chen, Department of Cardiology, Nanjing First Hospital, Nanjing Medical University, No. 68 Changle Road, 210006 Nanjing, China.
Email: chmengx@126.com

Funding information
Nanjing Health and Family Planning Commission, Grant/Award Number: YKK16124; Nanjing Health Youth Talent Training Project, Grant/Award Number: QRX17017; Nanjing Municipal Commission of Science & Technology, Grant/Award Number: 201715026; National Natural Science Foundation of China, Grant/Award Numbers: 81270191, 91439118, 91639303; Six Talent Peaks Project in Jiangsu Province, Grant/Award Number: 2014-WSN-058

Abstract

Objectives: This study aimed to investigate the impacts of intravascular ultrasound (IVUS)-guided drug-eluting stent (DES) implantation on patients with chronic kidney disease (CKD) based on the ULTIMATE trial.

Background: IVUS-guided DES implantation improves clinical outcomes in complex lesions. However, routine IVUS guidance in patients with CKD remains controversial.

Methods: CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL min^{-1} 1.73 m^{-2}. The primary end point was target vessel failure (TVF) at 12 months, including cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularization.

Results: eGFR was available in 1,443 patients, of whom 723 were in the IVUS guidance group, and 720 were in the angiography guidance group. Finally, CKD was present in 349 (24.2%) patients. At 12 months, TVF in the CKD group was 7.2%, which was significantly higher than 3.2% in the non-CKD group (p = .001). Moreover, there were 25 TVFs in the CKD patients, with 7 (3.9%) TVFs in the IVUS group and 18 (10.7%) TVFs in the angiography group (hazard ratio [HR]: 0.35; 95% confidence interval [CI]: 0.15–0.84; p = .01), whereas 35 TVFs occurred in patients without CKD, with 14 (2.6%) TVFs in the IVUS group and 21 (3.8%) TVFs in the angiography group (HR: 0.67; 95% CI: 0.34–1.32; p = .25; p for interaction = .24).

Abbreviations: CG, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IVUS, intravascular ultrasound; MDRD, Modification of Diet in Renal Disease; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; TVF, target vessel failure; TVMI, target vessel myocardial infarction; TVR, target vessel revascularization; eGFR, an estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; DES, drug-eluting stent; CIN, Contrast-induced nephropathy; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; HF, heart failure; LVEF, left ventricular ejection fraction.

Junjie Zhang and Xiaofei Gao contributed equally to this study.

Conclusions: This study demonstrated that CKD patients undergoing DES implantations were associated with a higher risk of TVF at 12 months. More importantly, the risk of TVF in the CKD patients could be significantly decreased through IVUS guidance.

Clinical Trial: NCT02215915.

KEYWORDS

angiography, chronic kidney disease, drug-eluting stent, intravascular ultrasound, target vessel failure

1 | INTRODUCTION

Chronic kidney disease (CKD) is a common disease, and the primary mortality cause of CKD is due to cardiovascular events.[1] CKD patients present more frequently with long, atherosclerotic lesions, multivessel disease, and coronary calcification, which results in more complex and extensive lesions, compared with patients without CKD.[2,3] The use of coronary revascularization treatment for these complex lesions in CKD patients is associated with increasing rates of mortality and other cardiovascular adverse events.[4–6]

Intravascular ultrasound (IVUS), with a high spatial resolution, may provide more accurate lesion morphology information and may optimize stent implantation. Several randomized trials and observational studies have established the clinical benefits of IVUS-guided drug-eluting stent (DES) implantation for patients with long lesions,[7,8] chronic total occlusions,[9,10] left main disease,[11,12] and complex bifurcation lesions.[13,14] Notably, the latest ULTIMATE trial[15] added new evidence of the benefits of IVUS guidance in all-comer coronary lesions. However, it still remains controversial that routine IVUS guidance could be beneficial to patients with CKD, due to the longer procedural times and higher contrast media volumes that are caused by IVUS guidance, as well as the potential risks of acute renal failure and atheroembolism. Therefore, the present study, which was a prespecified subgroup analysis of the ULTIMATE trial, was designed to explore the impacts of IVUS-guided second-generation DES implantations on patients with CKD.

2 | METHODS

2.1 | Study population

The methods and principal results of the ULTIMATE trial have been previously reported.[15] Briefly, the ULTIMATE trial was a prospective, multicenter, randomized study, in which 1,448 all-comer patients were randomized to undergo either IVUS-guided or angiography-guided second-generation DES implantations in eight Chinese centers from August 2014 to May 2017. The inclusion criteria were patients who had silent ischemia, stable or unstable angina, or myocardial infarctions (MIs, including both ST-elevation and non-ST-elevation MIs) >24 hr from the onset of chest pain to admission, as well as de novo coronary lesions that were eligible for DES implantation. The trial was approved by the institutional review board at each participating center, and all the participating patients signed informed consents.

2.2 | Study end points and definitions

The primary end point was target vessel failure (TVF) at 12 months after the indexed procedure, which was defined as the composite of cardiac death, target vessel myocardial infarction (TVMI), and clinically driven target vessel revascularization (TVR). The major secondary end points included all-cause death, MI, clinically driven target lesion revascularization (TLR), stroke, and each individual component of the primary end point. The safety end point was stent thrombosis (ST). The definitions of these end points have been previously described.[15]

The present study was a prespecified subgroup analysis of the ULTIMATE trial for the evaluation of the impacts of IVUS-guided DES implantations on patients with CKD. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL min^{-1} 1.73 m^{-2} for at least 3 months, according to the Cockcroft–Gault (CG) formula.[16] Moreover, eGFR was also calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[17] and the Modification of

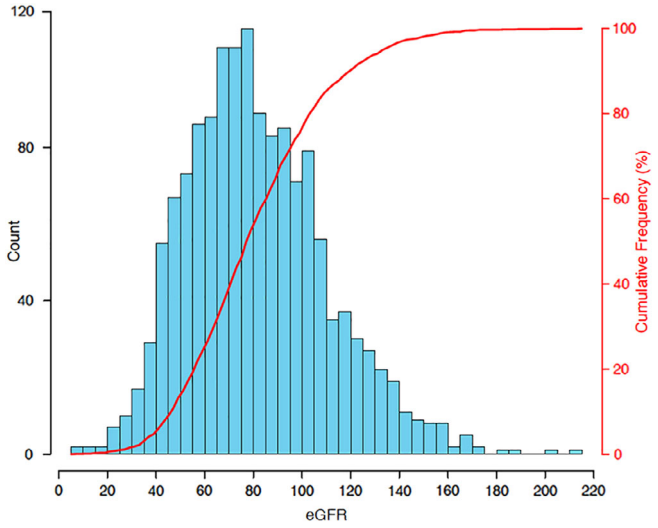

FIGURE 1 Distribution of the estimated glomerular filtration rate in the ULTIMATE trial using the CG formula [Color figure can be viewed at wileyonlinelibrary.com]

Diet in Renal Disease (MDRD) study equation.[18] Contrast-induced nephropathy (CIN) was defined as an increase in serum creatinine by more than 25%, or 44.1 μmol/L, within 3 days after the procedure.

2.3 | Statistical analysis

All the principal analyses were performed based on the intention-to-treat principle from the patient level. The distribution of continuous variables was assessed via the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± *SD* for normally distributed data and were compared by using Student's *t* tests, or the data were expressed as medians for non-normally distributed data and compared by using Mann–Whitney *U* tests. Categorical variables were expressed as frequencies or percentages and were compared by using Chi-square statistics or Fisher's exact tests. Survival curves, with time-to-event data that were generated by the Kaplan–Meier method, were compared by using the log-rank test. Differences in clinical end points between IVUS guidance and angiography guidance in patients who were stratified by CKD were compared by using the Cox proportional hazard model, with reports of hazard ratios (HRs) and 95% confidence intervals (CIs). A Cox regression with interaction testing was used to assess whether the IVUS guidance effect was consistent between patients with or without CKD. A multivariable Cox proportional hazards forward stepwise regression was also performed to determine the independent predictors of the primary end point, with a purposeful selection of covariates. The variables showing possible statistical significance ($p < .10$) in the univariable model were entered into the Cox multivariable model. The primary analyses were performed based on the CG formula-defined CKD, and CKD-EPI and MDRD equations were also used to explore a sensitivity analysis. A two-side *p* value <.05 was

TABLE 1 Baseline clinical characteristics

	CKD (*n* = 349)	Non-CKD (*n* = 1,094)	*p* value
Age, year	74.5 ± 7.1	62.7 ± 9.7	<.001
Male	213 (61.0)	847 (77.4)	<.001
Hypertension	276 (79.1)	754 (68.9)	<.001
Hyperlipidemia	202 (57.9)	587 (53.7)	.17
Diabetes mellitus	100 (28.7)	342 (31.3)	.36
Insulin treated	35 (10.0)	91 (8.3)	.32
Current smoker	79 (22.6)	399 (36.5)	<.001
Clinical presentation			
Silent ischemia	42 (12.0)	78 (7.1)	.004
Stable angina	36 (10.3)	155 (14.2)	.06
Unstable angina	232 (66.5)	721 (65.9)	.85
Acute myocardial infarction	39 (11.2)	140 (12.8)	.42
Prior stroke	67 (19.2)	103 (9.4)	<.001
Prior MI	40 (11.5)	112 (10.2)	.52
Prior PCI	66 (18.9)	203 (18.6)	.88
Prior CABG	5 (1.4)	13 (1.2)	.78
Symptomatic HF	84 (24.1)	129 (11.8)	<.001
LVEF (%)	59.3 ± 9.8	61.0 ± 8.2	.01
LVEF < 40	22 (7.9)	28 (3.3)	.001
Laboratory measures			
White blood cell count ($\times 10^9$/L)	6.6 ± 2.1	6.5 ± 1.8	.32
Red blood cell count ($\times 10^9$/L)	4.1 ± 0.6	4.5 ± 0.5	<.001
Hemoglobin (g/L)	124.6 ± 16.0	136.7 ± 14.5	<.001
Platelet count ($\times 10^9$/L)	190.1 ± 75.8	188.4 ± 55.5	.69
Serum creatinine (mg/dL)	1.2 ± 0.9	0.8 ± 0.2	<.001
eGFR (ml/min/1.73 m^2)	47.1 ± 10.0	92.3 ± 24.0	<.001
eGFR < 30	23 (6.6)	0	<.001
eGFR < 45	124 (35.5)	0	<.001

Note: Values are mean ± *SD* or *n* (%).

Abbreviations: CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 2 Angiographic and procedural characteristics

	CKD	Non-CKD	*p* value
Patient level	349	1,094	
Radial access	322 (92.3)	1,060 (96.9)	<.001
IVUS guidance	180 (51.6)	543 (49.6)	.53
Optimal PCI	82 (45.6)	301 (55.4)	.02
Multivessel disease	221 (63.3)	572 (52.3)	<.001
Complete revascularization	235 (67.3)	836 (76.4)	.001
Procedural time (min)	53.8 ± 26.9	52.2 ± 28.0	.35
Contrast volume (mL)	164.3 ± 57.1	170.6 ± 62.6	.11
CIN	27 (7.7)	72 (6.6)	.46
Lesion level	486	1,487	
IVUS guidance	251 (51.6)	710 (47.7)	.14
Optimal PCI	126 (50.2)	451 (63.5)	<.001
Chronic total occlusion	44 (9.1)	132 (8.9)	.91
Bifurcation lesion	137 (28.2)	356 (23.9)	.06
Two-stent technique	54 (11.1)	127 (8.5)	.09
Moderate to severe calcification	155 (31.9)	333 (22.4)	<.001
AHA/ACC lesion type B2/C	333 (68.5)	987 (66.4)	.38
Stent number	1.94 ± 0.81	1.73 ± 0.78	<.001
Mean stent diameter (mm)	3.02 ± 0.42	3.08 ± 0.44	.01
Mean stent length (mm)	50.78 ± 24.62	47.27 ± 23.51	.01
Maximum balloon diameter (mm)	3.57 ± 0.56	3.63 ± 0.56	.04
Maximum postdilation pressure (atm)	19.34 ± 3.72	19.36 ± 3.72	.94
Angiographic success	476 (97.9)	1,456 (97.9)	.97

Note: Values are mean ± SD or *n* (%).
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; DES, drug-eluting stent; IVUS, intravascular ultrasound; PCI: percutaneous coronary intervention.

considered to be statistically significant. All of the analyses were performed with the use of the statistical program SPSS 24.0 (SPSS Institute Inc, Chicago, IL).

3 | RESULTS

3.1 | Baseline clinical characteristics

The baseline serum creatinine levels were available in 1,443 of 1,448 randomized patients (99.7%), with 723 in the IVUS guidance group and 720 in the angiography guidance group, of whom CKD was present in 349 (24.2%), 185 (12.8%), and 151 (10.5%) patients, based on the CG formula, CKD-EPI, and MDRD equations, respectively. The distribution of baseline eGFR with the CG formula (mean eGFR: 81.41 ± 28.92 mL min^{-1} 1.73 m^{-2}) is shown in Figure 1, and the distribution of baseline eGFR with the CKD-EPI equation (mean eGFR: 86.77 ± 22.09 mL min^{-1} 1.73 m^{-2}) is listed in Figure S1.

The baseline clinical characteristics between the CKD group and the non-CKD group using the CG formula are listed in Table 1. CKD patients were older and more frequently presented with a history of stroke, hypertension, silent ischemia, symptomatic heart failure (HF), and lower left ventricular ejection fraction (LVEF). CKD patients were also more likely to have reduced red blood cell counts and hemoglobin levels than non-CKD patients. Moreover, 124 (35.5%) patients and 23 (6.6%) patients presented with eGFR values <45 and 30 mL min^{-1} 1.73 m^{-2} in the CKD group, respectively. Similar baseline clinical characteristics in the CKD patients who were calculated using the CKD-EPI equation are shown in Table S1.

3.2 | Angiographic and procedural characteristics

As shown in Table 2, the percentages of IVUS guidance were comparable between the CKD and non-CKD groups (51.6% vs. 49.6%, $p = .53$), but the rate of optimal PCI was significantly reduced in the CKD group, compared to the non-CKD group (45.6% vs. 55.4%, respectively, $p = .02$), partly due to the higher percentages of multivessel disease, bifurcation lesions, and moderate-to-severe calcification in the CKD patients. More complex lesions in the CKD patients also resulted in lower rates of radial access and complete revascularization, as well as more stent numbers and longer stent lengths. Moreover, the procedural time and contrast volume in the IVUS guidance group were significantly higher than those in the angiography guidance group, but the serum creatinine changes and the risk of CIN were similar between two groups, both in patients with and without CKD (Table 4). The angiographic and procedural characteristics between the CKD group and the non-CKD group using the CKD-EPI equation are listed in Table S2.

3.3 | Clinical outcomes of CKD versus non-CKD

A 12-month clinical follow-up was available in 1,439 patients (99.7%, with four patients having been lost to the follow-ups, with two patients lost in each group). CKD patients had a significantly higher risk of 30-day TVF, compared with the non-CKD patients (2.6% vs. 1.0%, respectively, $p = .03$; Table 3), which was primarily driven by an increasing trend of TVMI in CKD patients, compared to non-CKD patients (2.0% vs. 0.8%, respectively, $p = .07$). The incidence of procedural MI was also elevated in CKD patients, compared with non-CKD patients (2.0% vs. 0.6%, respectively, $p = .02$). Cardiac death, all-cause death, clinically driven TVR, and ST events were comparable between the two groups.

At 12 months, the TVF in the CKD group was 7.2%, which was significantly higher than 3.2% in the non-CKD group (HR: 2.30; 95% CI: 1.38–3.84; $p = .001$; Table 3 and Figure 2) and was primarily driven by an increased risk of cardiac death in CKD patients, compared to non-CKD patients (2.9% vs. 0.5%, respectively, $p < .001$). In particular, CKD patients were also associated with more than a five-fold higher risk of all-cause death, compared with patients without

TABLE 3 Clinical outcomes in patients with or without chronic kidney disease

	CKD (*n* = 349)	Non-CKD (*n* = 1,094)	HRs (95% CI)	*p* value
At 30-day follow-up				
TVF	9 (2.6)	11 (1.0)	2.58 (1.07–6.23)	.03
Cardiac death	2 (0.6)	2 (0.2)	3.14 (0.44–22.27)	.23
TVMI	7 (2.0)	9 (0.8)	2.45 (0.91–6.57)	.07
Clinically driven TVR	0	2 (0.2)	–	.42
Procedural MI	7 (2.0)	7 (0.6)	3.14 (1.10–8.96)	.02
Spontaneous MI	0	2 (0.2)	–	.42
Clinically driven TLR	0	2 (0.2)	–	.42
CABG	0	0	–	NS
TLF	9 (2.6)	11 (1.0)	2.58 (1.07–6.23)	.03
All-cause death	2 (0.6)	4 (0.4)	1.57 (0.29–8.57)	.60
Definite or probable ST	2 (0.6)	4 (0.4)	1.57 (0.29–8.55)	.60
Stroke	1 (0.3)	2 (0.2)	1.57 (0.14–17.31)	.71
At 1-year follow-up				
TVF	25 (7.2)	35 (3.2)	2.30 (1.38–3.84)	.001
Cardiac death	10 (2.9)	5 (0.5)	6.36 (2.17–18.59)	<.001
TVMI	7 (2.0)	11 (1.0)	2.01 (0.78–5.18)	.14
Clinically driven TVR	10 (2.9)	22 (2.0)	1.46 (0.69–3.09)	.32
Spontaneous MI	0	5 (0.5)	–	.21
Clinically driven TLR	9 (2.6)	19 (1.7)	1.53 (0.69–3.37)	.29
CABG	1 (0.3)	1 (0.1)	3.21 (0.20–51.33)	.38
TLF	24 (6.9)	33 (3.0)	2.34 (1.38–3.95)	.001
All-cause death	17 (4.9)	10 (0.9)	5.41 (2.48–11.82)	<.001
Definite or probable ST	2 (0.6)	4 (0.4)	1.57 (0.29–8.55)	.60
Stroke	5 (1.4)	4 (0.4)	3.99 (1.07–14.85)	.03

Note: Data are number of events (Kaplan–Meier estimated event rate), compared by the log-rank test. HRs with 95% CIs were generated with Cox regression models.

Abbreviations: CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CIs, confidence intervals; HRs, hazard ratios; IVUS, intravascular ultrasound; MI, myocardial infarction; ST, stent thrombosis; TLF, target lesion failure; TVF, target vessel failure; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

CKD (4.9% vs. 0.9%, respectively; HR: 5.41; 95% CI: 2.48–11.82; $p < .001$). However, there were no significant differences in spontaneous MI, clinically driven TVR, clinically driven TLR, and ST events between the two groups. Moreover, 1.4% of CKD patients had a risk of 12-month stroke, which was approximately three times higher than the 0.4% risk in patients without CKD ($p = .06$). A sensitivity analysis provided similar results, based on the CKD-EPI (Table S3 and Figure S2) and MDRD equations (Figure S3a).

3.4 | Clinical outcomes of IVUS versus angiography guidance in patients with and without CKD

The 30-day rate of TVF in the IVUS guidance group was 0.6%, which was lower than the 4.7% rate in the angiography guidance group, in CKD patients ($p = .01$; Table 4); this effect was primarily driven by a reduced TVMI risk in the IVUS guidance group, compared to the angiography guidance group (0.6% vs. 3.6%, respectively, borderline $p = .05$). Cardiac death, TVR, TLR, and ST events were similar between the two groups in the CKD patients. All the primary and secondary end points were comparable in patients without CKD.

By 12 months after the index procedures, there were 25 TVFs in the CKD patients, with 7 (3.9%) TVFs in the IVUS group, and 18 (10.7%) TVFs in the angiography group (HR: 0.35, 95% CI: 0.15–0.84; $p = .01$), whereas 35 TVFs occurred in patients without CKD, with 14 (2.6%) TVFs in the IVUS group and 21 (3.8%) TVFs in the angiography group (HR: 0.67; 95% CI: 0.34–1.32; $p = .25$; p for interaction = .24; Table 4 and Figure 3). The reduced risk of TVF in the IVUS group for CKD patients (compared to non-CKD patients) was primarily driven by the lower risk of TVMI (0.6% vs. 3.6%, respectively, $p = .05$) and TVR (1.1% vs. 4.7%, respectively, $p = .04$). The rate of TVF was 11.4% in the CKD patients through angiography guidance using the CKD-EPI equation, which was decreased to 4.1% by IVUS guidance (borderline $p = .06$), which was similar to the rates of 2.7% and 4.6% in the patients without CKD (Table S4 and Figure S4). A sensitivity analysis provided a similar decreasing trend of TVF through IVUS guidance for CKD patients, based on the MDRD equation (Figure S3b).

TABLE 4 Procedural characteristics and clinical outcomes for IVUS versus angiography-guided PCI in patients with or without CKD

	CKD (*n* = 349)				Non-CKD (*n* = 1,094)				
	IVUS (*n* = 180)	Angiography (*n* = 169)	HRs (95% CI)	*p* value	IVUS (*n* = 543)	Angiography (*n* = 551)	HRs (95% CI)	*p* value	*p* for interaction
Procedural time (min)	62.2 ± 27.4	45.0 ± 23.4	–	<.001	59.2 ± 26.8	45.3 ± 27.4	–	<.001	.33
Contrast volume (mL)	175.3 ± 61.7	151.7 ± 48.6	–	<.001	178.6 ± 66.2	162.0 ± 57.5	–	<.001	.37
Serum creatinine changes (μmol/L)	0.8 ± 42.6	−1.1 ± 28.5	–	.62	1.8 ± 10.8	0.7 ± 12.3	–	.13	.73
CIN	15 (8.3)	12 (7.1)	–	.67	42 (7.7)	30 (5.4)	–	.13	.67
At 30-day follow-up									
Target vessel failure	1 (0.6)	8 (4.7)	0.12 [0.02, 0.93]	.01	5 (0.9)	6 (1.1)	0.85 [0.26, 2.77]	.78	.10
Cardiac death	0	2 (1.2)	–	.14	1 (0.2)	1 (0.2)	1.01 [0.06, 16.18]	.99	.99
Target vessel MI	1 (0.6)	6 (3.6)	0.16 [0.02, 1.30]	.05	4 (0.7)	5 (0.9)	0.81 [0.22, 3.02]	.76	.19
Clinically driven TVR	0	0	–	NS	0	2 (0.4)	–	.16	.82
Spontaneous MI	0	0	–	NS	0	2 (0.4)	–	.16	.82
Procedural MI	1 (0.6)	6 (3.6)	0.16 [0.02, 1.30]	.05	4 (0.7)	3 (0.5)	1.35 [0.30, 6.05]	.69	.10
Clinically driven TLR	0	0	–	NS	0	2 (0.4)	–	.16	.82
CABG	0	0	–	NS	0	0	–	NS	NS
TLF	1 (0.6)	8 (4.7)	0.12 [0.02, 0.93]	.01	5 (0.9)	6 (1.1)	0.85 [0.26, 2.77]	.78	.10
All-cause death	0	2 (1.2)	–	.14	1 (0.2)	3 (0.5)	0.34 [0.04, 3.25]	.32	.99
Definite or probable ST	0	2 (1.2)	–	.14	1 (0.2)	3 (0.5)	0.34 [0.04, 3.24]	.32	.99
Stroke	0	1 (0.6)	–	.30	1 (0.2)	1 (0.2)	1.01 [0.06, 16.19]	.99	.99
At 1-year follow-up									
TVF	7 (3.9)	18 (10.7)	0.35 [0.15, 0.84]	.01	14 (2.6)	21 (3.8)	0.67 [0.34, 1.32]	.25	.24
Cardiac death	4 (2.2)	6 (3.6)	0.62 [0.17, 2.19]	.91	1 (0.2)	4 (0.7)	0.25 [0.03, 2.26]	.51	.49
TVMI	1 (0.6)	6 (3.6)	0.16 [0.02, 1.30]	.05	6 (1.1)	5 (0.9)	1.22 [0.37, 3.99]	.75	.10
Clinically driven TVR	2 (1.1)	8 (4.7)	0.22 [0.05, 1.05]	.04	9 (1.7)	13 (2.4)	0.70 [0.30, 1.63]	.40	.21
Spontaneous MI	0	0	–	NS	3 (0.6)	2 (0.4)	1.51 [0.25, 9.06]	.65	.99
Clinically driven TLR	2 (1.1)	7 (4.1)	0.26 [0.05, 1.23]	.07	7 (1.3)	12 (2.2)	0.59 [0.23, 1.49]	.26	.38
CABG	0	1 (0.6)	–	.29	0	1 (0.2)	–	.32	.99
TLF	7 (3.9)	17 (10.1)	0.37 [0.15, 0.89]	.02	13 (2.4)	20 (3.6)	0.66 [0.33, 1.32]	.23	.32
All-cause death	7 (3.9)	10 (5.9)	0.65 [0.25, 1.70]	.37	3 (0.6)	7 (1.3)	0.43 [0.11, 1.68]	.21	.64
Definite or probable ST	0	2 (1.2)	–	.14	1 (0.2)	3 (0.5)	0.34 [0.04, 3.24]	.32	.99
Stroke	2 (1.1)	3 (1.8)	0.61 [0.10, 3.65]	.58	3 (0.6)	1 (0.2)	3.04 [0.32, 29.17]	.31	.28

Note: Values of procedural characteristics are mean ± *SD*, compared by Students' *t* test. Values of clinical outcomes are number of events (Kaplan–Meier estimated event rate), compared by the log-rank test. HRs with 95% CIs were generated with Cox regression models.

Abbreviations: CABG, coronary artery bypass grafting; CIN, contrast-induced nephropathy; CIs, confidence intervals; CKD, chronic kidney disease; HRs, hazard ratios; IVUS, intravascular ultrasound; MI, myocardial infarction; ST, stent thrombosis; TLF, target lesion failure; TVF, target vessel failure; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

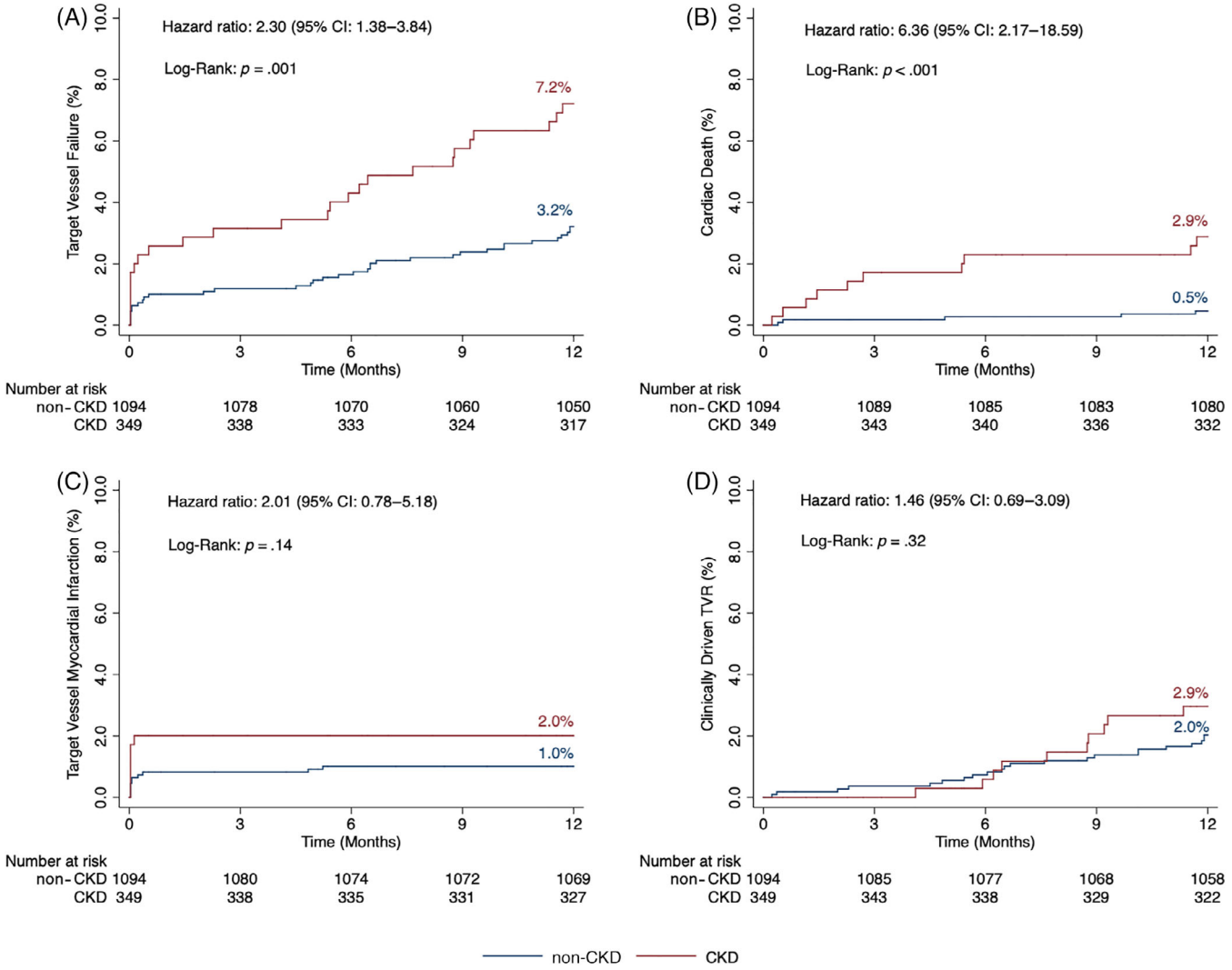

FIGURE 2 The Kaplan–Meier failure analysis in patients with or without CKD: (A) target vessel failure; (B) cardiac death; (C) target vessel myocardial infarction; (D) clinically driven TVR. CKD, chronic kidney disease; TVR, target vessel revascularization [Color figure can be viewed at wileyonlinelibrary.com]

The multivariable Cox regression showed that age > 75 years old (adjusted HR: 1.83; 95% CI: 1.07–3.14; p = .03), CKD (adjusted HR: 2.66; 95% CI: 1.19–5.95; p = .02), stent length (per 10 mm) (adjusted HR: 1.11; 95% CI: 1.01–1.23; p = .03), and IVUS guidance (adjusted HR: 0.48; 95% CI: 0.28–0.82; p = .01) were all independent predictors of 12-month TVF in all-comer patients undergoing second generation DES (Table S5).

4 | DISCUSSION

For the first time, the present prespecified subgroup analysis from the ULTIMATE trial reports impact of IVUS-guided DES implantation on patients with CKD. We found that CKD patients were associated with higher risks of cardiac death, all-cause death, procedural MI, and stroke during 12 months of follow-up. We also found that the rate of TVF in CKD patients could be significantly decreased through the use of IVUS guidance, which was primarily driven by the lower risk of TVMI and TVR, compared to the use of angiography guidance. Furthermore, on the basis of the multivariable Cox regression, old age, CKD, and long stent length were risk factors for 12-month TVF, which could be reduced by 52% when using IVUS guidance in all-comer patients.

CKD patients are frequently encountered in our daily clinical practice, and these patients always present unique challenges, such as complex coronary lesions, higher levels of comorbidity (hypertension, diabetes, and HF), and drug usage restriction, which lead to relatively unfavorable, long-term clinical outcomes. These complex lesions, including severe coronary calcification, long lesion length, and multivessel disease, may partly explain why the periprocedural MI levels were significantly elevated in the CKD patients in our study, which is similar to data from previous studies.[2,3] Notably, we reported that the rates of clinically driven TVR and TLR in CKD patients were similar to those in patients without CKD, which is inconsistent with the fact that more inflammation, more severe calcification, and greater atherosclerosis levels occur in CKD patients. Specifically, patients with CKD

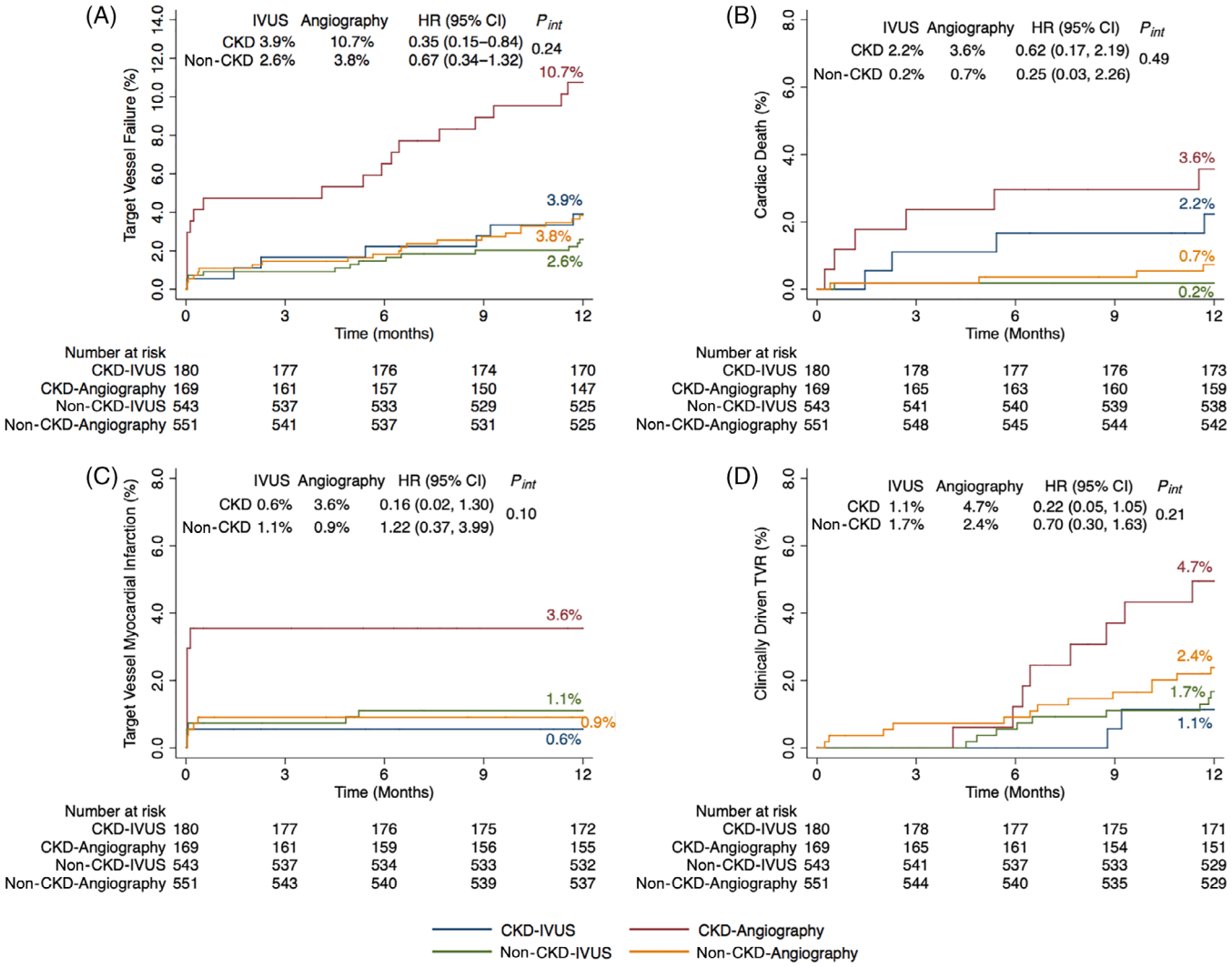

FIGURE 3 The Kaplan–Meier failure analysis for IVUS guidance versus angiography guidance in patients with or without CKD: (A) target vessel failure; (B) cardiac death; (C) target vessel myocardial infarction; (D) clinically driven TVR. IVUS, intravascular ultrasound; CKD, chronic kidney disease; TVR, target vessel revascularization [Color figure can be viewed at wileyonlinelibrary.com]

were less likely to receive repeat revascularization procedures in real-world clinical practice, which may be due to worse clinical conditions, the administration of challenging procedures, high CIN risks, and poor prognoses in CKD patients. This trend has been confirmed by previous studies,[19,20] which have reported that CKD patients were more likely to receive conservative management, instead of extensive invasive strategies. However, we should note that large-scale registries[19,20] have shown that revascularization strategies in CKD patients were associated with a significantly reduced long-term mortality, compared with conservative approaches; these results need to be verified by an ongoing ISCHEMIA-CKD trial (NCT01985360).

The use of IVUS with a high resolution could provide detailed anatomical information, could guide optimal stent selection and could optimize stent implantation. Our ULTIMATE trial[15] has established that IVUS-guided second-generation DES implantation (specifically, an IVUS-defined optimal procedure) significantly improves clinical outcomes in all-comer patients, compared with the outcomes of angiography guidance, rather than solely in those with complex lesions.[7–10] The benefit of IVUS-guided DES implantation may be attributed to the larger stent/balloon sizes and a more frequent post-dilation from IVUS guidance, which could then result in a larger, postprocedural, minimal lumen diameter, which could subsequently reduce adverse events. Currently, several small-sized studies[21–23] have focused on the feasibility and safety of IVUS-guided zero or minimal contrast coronary intervention in reducing CIN risks in CKD patients, which are inconsistent with our data. In our study protocol, in order to achieve optimal IVUS guidance criteria, multiple IVUS check and additional post-dilation or stent were performed accordingly, which leaded to a higher contrast volume in the IVUS guidance group, but the risk of CIN was not increased. Furthermore, IVUS guidance could reduce the risks of TVMI and TVR compared to the use of angiography guidance in patients with CKD.

The benefit of IVUS-guided DES implantation in CKD patients using the CG formula was not achieved when CKD was defined by the CKD-EPI and MDRD equations, although the difference in TVF between IVUS guidance and angiography guidance in CKD patients was marked (no statistical significance). Three methods of calculating

eGFR were used to assess and verify the impact of CKD on IVUS guidance in patients undergoing DES implantations. The CG formula[16] was developed in 1973 by using data from 249 men with a creatinine clearance of approximately 30–130 mL/m^2, without adjustments for body surface area, which was proportional to kidney size and kidney function. The CKD-EPI equation[17] was developed in 2009 to estimate kidney function from age, sex, race, and serum creatinine factors. The CKD-EPI equation is as accurate as the MDRD equation[18] in subgroups with eGFRs <60 mL min^{-1} 1.73 m^{-2} and is substantially more accurate in subgroups with eGFRs >60 mL min^{-1} 1.73 m^{-2}.[24] Therefore, the CKD-EPI equation was recommended by the Kidney Disease: Improving Global Outcomes guidelines.[24] However, the CG formula is still important and has become the standard for drug dosing[25] because pharmacokinetic studies over the last several years have used this formula to determine levels of kidney function for dosage adjustments in drug labels. Regardless, eGFRs <60 mL/min/1.73 m^2 using the CG formula reflect high-risk patients with poor kidney function, although it is less accurate than the CKD-EPI equation. Furthermore, the superiority of IVUS guidance over angiography guidance was validated in CKD patients by the significant difference in using the CG formula, as well as by the marked trends of using the CKD-EPI and MDRD equations.

4.1 | Limitations

There were several limitations in the present study. First, our study was not a randomized trial, and potential biases may have existed, although we used a prespecified subgroup analysis from a multicenter randomized trial. Second, the regimen of hydration with the use of isotonic saline for CKD patients was at the physician's discretion in the ULTIMATE trial, which may affect the results of CIN risk in CKD patients; however, this phenomenon could represent real-world data in China. Third, the secondary end point of the ULTIMATE trial did not include the incidence of bleeding; thus, we could not compare the bleeding risks between the CKD and non-CKD groups. However, it is well known that CKD patients are associated with higher risks of minor and major bleeding, compared to patients without CKD.

5 | CONCLUSIONS

The present prespecified subgroup analysis from the ULTIMATE trial demonstrated that CKD patients undergoing DES implantation were associated with a higher risk of TVF during 12 months of follow-up. More importantly, the risk of TVF in CKD patients could be significantly decreased through IVUS guidance, compared to angiography guidance.

ACKNOWLEDGMENTS

The authors acknowledge Dr Zhimin Du (First Hospital of Zhongshan University, Guangzhou, China) as the director of the independent committee. We thank Ms. Ling Lin and Ms. Hai-Mei Xu (clinical trial coordinator) for their contributions to the completion of this study. The authors also appreciate Ms. Lingling Liu, Ms. Wen Teng, Ms. Yingying Zhao, Ms. Tian Xu, and Ms. Xiaoyu Huang for remote monitoring and data collection throughout the study. The authors also appreciate the support throughout the entire study period by the Key Cardiovascular Laboratory, Cooperative Innovational Center of Nanjing Medical University.

CONFLICT OF INTERESTS

The authors certify that (a) the paper is not under consideration elsewhere, (b) no portion of the paper has been previously published, (c) all of the authors have read and approved the manuscript, and (d) none of the authors have any relevant disclosures.

REFERENCES

1. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296-1305.
2. Baber U, Stone GW, Weisz G, et al. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. JACC Cardiovasc Imaging. 2012;5:S53-S61.
3. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: pathogenesis and prognostic implications. J Am Coll Cardiol. 2014;63:1703-1714.
4. Giustino G, Mehran R, Serruys PW, et al. Left Main revascularization with PCI or CABG in patients with chronic kidney disease: EXCEL trial. J Am Coll Cardiol. 2018;72:754-765.
5. Baber U, Farkouh ME, Arbel Y, et al. Comparative efficacy of coronary artery bypass surgery vs. percutaneous coronary intervention in patients with diabetes and multivessel coronary artery disease with or without chronic kidney disease. Eur Heart J. 2016;37:3440-3447.
6. Milojevic M, Head SJ, Mack MJ, et al. The impact of chronic kidney disease on outcomes following percutaneous coronary intervention versus coronary artery bypass grafting in patients with complex coronary artery disease: five-year follow-up of the SYNTAX trial. EuroIntervention. 2018;14:102-111.
7. Hong SJ, Kim BK, Shin DH, et al. Effect of intravascular ultrasound-guided vs angiography-guided Everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. JAMA. 2015;314:2155-2163.
8. Kim JS, Kang TS, Mintz GS, et al. Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. JACC Cardiovasc Interv. 2013;6:369-376.
9. Kim BK, Shin DH, Hong MK, et al. Clinical impact of intravascular ultrasound-guided chronic Total occlusion intervention with Zotarolimus-eluting versus Biolimus-eluting stent implantation: randomized study. Circ Cardiovasc Interv. 2015;8:e002592.
10. Tian NL, Gami SK, Ye F, et al. Angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions: two-year results from a randomised AIR-CTO study. EuroIntervention. 2015;10:1409-1417.
11. Gao XF, Kan J, Zhang YJ, et al. Comparison of one-year clinical outcomes between intravascular ultrasound-guided versus angiography-guided implantation of drug-eluting stents for left main lesions: a single-center analysis of a 1,016-patient cohort. Patient Prefer Adherence. 2014;8:1299-1309.
12. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv. 2009;2:167-177.

13. Chen L, Xu T, Xue XJ, et al. Intravascular ultrasound-guided drug-eluting stent implantation is associated with improved clinical outcomes in patients with unstable angina and complex coronary artery true bifurcation lesions. Int J Cardiovasc Imaging. 2018;34:1685-1696.
14. Chen SL, Ye F, Zhang JJ, et al. Intravascular ultrasound-guided systematic two-stent techniques for coronary bifurcation lesions and reduced late stent thrombosis. Catheter Cardiovasc Interv. 2013;81:456-463.
15. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound-guided versus angiography-guided implantation of drug-eluting stent in all-comers: the ULTIMATE trial. J Am Coll Cardiol. 2018;72:3126-3137.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med. 1999;130:461-470.
19. Shavadia JS, Southern DA, James MT, Welsh RC, Bainey KR. Kidney function modifies the selection of treatment strategies and long-term survival in stable ischaemic heart disease: insights from the Alberta provincial project for outcomes assessment in coronary heart disease (APPROACH) registry. Eur Heart J Qual Care Clin Outcomes. 2018;4:274-282.
20. Smilowitz NR, Gupta N, Guo Y, Mauricio R, Bangalore S. Management and outcomes of acute myocardial infarction in patients with chronic kidney disease. Int J Cardiol. 2017;227:1-7.
21. Ali ZA, Karimi Galougahi K, Nazif T, et al. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. Eur Heart J. 2016;37:3090-3095.
22. Sakai K, Ikari Y, Nanasato M, et al. Impact of intravascular ultrasound-guided minimum-contrast coronary intervention on 1-year clinical outcomes in patients with stage 4 or 5 advanced chronic kidney disease. Cardiovasc Interv Ther. 2018. https://doi.org/10.1007/s12928-018-0552-7. [Epub ahead of print]
23. Mariani J Jr, Guedes C, Soares P, et al. Intravascular ultrasound guidance to minimize the use of iodine contrast in percutaneous coronary intervention: the MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasTy) randomized controlled trial. JACC Cardiovasc Interv. 2014;7:1287-1293.
24. Stevens PE, Levin A. Kidney disease: improving global outcomes chronic kidney disease guideline development work Group M. evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158:825-830.
25. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis. 2009;54:33-42.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhang J, Gao X, Ge Z, et al. Impact of intravascular ultrasound-guided drug-eluting stent implantation on patients with chronic kidney disease: Results from ULTIMATE trial. *Catheter Cardiovasc Interv*. 2019;1–10. https://doi.org/10.1002/ccd.28308