One-year clinical outcomes in patients with renal insufficiency after contemporary PCI: data from a multicenter registry

Scholz, Sean S. et al. "One-year clinical outcomes in patients with renal insufficiency after contemporary PCI: data from a multicenter registry." Clinical Research in Cardiology 109, 7 (December 2019): 845–856 © 2019 Springer Nature

http://dx.doi.org/10.1007/s00392-019-01575-y

Publisher
Springer Science and Business Media LLC

Version
Final published version

Citable link
https://hdl.handle.net/1721.1/126861

Terms of Use
Creative Commons Attribution

Detailed Terms
https://creativecommons.org/licenses/by/4.0/
One-year clinical outcomes in patients with renal insufficiency after contemporary PCI: data from a multicenter registry

Sean S. Scholz1, Lucas Lauder1, Sebastian Ewen1, Saarraaken Kulenthiran1, Nikolaus Marx2, Orazbek Sakhov3, Floris Kauer4, Adam Witkowski5, Marco Vaglimigli6, William Wijns7, Bruno Scheller1, Michael Böhm1, Felix Mahfoud1,8

Received: 7 September 2019 / Accepted: 15 November 2019 / Published online: 2 December 2019
© The Author(s) 2019, corrected publication 2020

Abstract
Background Chronic kidney disease (CKD) is highly prevalent in patients with coronary artery disease (CAD).
Objective The outcome following revascularization using contemporary technologies (new-generation abluminal sirolimus-eluting stents with thin struts) in patients with CKD (i.e., glomerular filtration rate of < 60 mL/min/1.73m2) and in patients with hemodialysis (HD) is unknown.
Methods e-Ultimaster is a prospective, single-arm, multi-center registry with clinical follow-up at 3 months and 1 year.
Results A total of 19,475 patients were enrolled, including 1466 patients with CKD, with 167 undergoing HD. Patients with CKD had a higher prevalence of overall comorbidities, multiple/small vessel disease (≤ 2.75 mm), bifurcation lesions, and more often left main artery treatments (all \( p < 0.0001 \)) when compared with patients with normal renal function (reference). CKD patients had a higher risk of target lesion failure (unadjusted OR, 2.51 [95% CI 2.04–3.08]), target vessel failure (OR, 2.44 [95% CI 2.01–2.96]), patient-oriented composite end point (OR, 2.19 [95% CI 1.87–2.56]), and major adverse cardiovascular events (OR, 2.34 [95% CI 1.93–2.83, \( p \) for all < 0.0001]) as reference. The rates of target lesion revascularization (OR, 1.17 [95% CI 0.79–1.73], \( p = 0.44 \)) were not different. Bleeding complications were more frequently observed in CKD than in the reference (all \( p < 0.0001 \)).
Conclusion In this worldwide registry, CKD patients presented with more comorbidities and more complex lesions when compared with the reference population. They experienced higher rate of adverse events at 1-year follow-up.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-019-01575-y) contains supplementary material, which is available to authorized users.

Sean S. Scholz
sean.scholz@uks.eu

1 Klinik für Innere Medizin III, Kardiologie, Angiologie Und Internistische Intensivmedizin, Saarland University Hospital, Saarland University, Kirrberger Str. 1, Geb. 41, IMED, 66421 Homburg/Saar, Germany
2 Medizinische Klinik I, Klinik für Kardiologie, Angiologie Und Internistische Intensivmedizin, RWTH Aachen University, Aachen, Germany
3 Department of Interventional Cardiology, City Heart Center, Almaty, Kazakhstan
4 Department of Cardiology, Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands
5 Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland
6 Universitätsklinik für Kardiologie, Universitätsspital Bern, Bern, Schweiz
7 The Lambe Institute for Translational Medicine, National University of Ireland and Saolta University Healthcare Group, Galway, Ireland
8 Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA
Introduction

Chronic kidney disease (CKD) is highly prevalent, affecting more than 1.5 million patients in Europe and the USA and represents one of the most frequent comorbidities in patients with coronary artery disease (CAD) [1–4]. There is a linear relationship between cardiovascular mortality and impaired glomerular filtration rate (GFR) [5–8]. Severe and diffuse CAD is prevalent in patients with CKD [5–10]. In those patients, revascularization options include coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) [11–13]. Adverse event rates following PCI and CABG were significantly higher in CKD patients when compared to patients with normal renal function [5–8, 14–16]. Moreover, these patients differ from the general population concerning symptoms of acute cardiac events, poor access sites, complex vascular lesions, and a higher rate of complications [8, 13–18]. However, patients with CKD are under-represented in clinical studies on revascularization, and, thus, knowledge on performance of PCI using newest-generation drug-eluting stents (DES) is limited [9, 13]. We aimed at evaluating the outcomes following revascularization using contemporary technologies (abluminal sirolimus-eluting stents with thin struts) in patients with CKD (defined as an estimated glomerular filtration rate of < 60 mL/min/1.73 m²) including a subgroup of patients undergoing hemodialysis (HD) in the prospective, single-arm, multi-center, international e-Ultimaster registry. CKD patients were compared with patients with normal kidney function (no CKD) undergoing sirolimus-eluting stent implantation.

Methods

We analyzed the results of e-Ultimaster (NCT 02188355), a prospective, single-arm, multi-center, international registry with clinical follow-up at 3 months and 1 year (Fig. 1). This study sought to validate the safety and efficacy of an abluminal, sirolimus-coated stent with thin struts (Ultimaster DES) in unselected patients representing everyday practice. Secondary objectives were to evaluate the utilization of DES and the detection of rare events in a representative high-risk patient population such as patients with CKD (eGFR < 60 mL/min/1.73 m²). The predefined objective was to enroll a representative population of patients (≥ 400) with impaired renal function. Additionally, we aimed to identify predictors of major adverse events, to assess access site utilization, vascular complications, procedural particularities, the duration of dual antiplatelet therapy (DAPT), and overall performance of the newest-generation DES (Ultimaster) across different patient and lesion subsets. The primary outcome measure was target lesion failure (TLF) defined as a composite of cardiac death, target vessel-related myocardial infarction (MI), and clinically driven target lesion revascularization (TLR) at 1 year. Patient-oriented composite end
point (POCE) was defined as any cause of mortality, any MI or any coronary revascularization. Target vessel failure rate (TVF) was defined as cardiac death, target vessel-related MI, and target vessel revascularization. Additionally, major adverse cardiac events (MACE: cardiac death, any MI, clinically driven TVR, and emergent CABG) were documented. Stent thrombosis was documented and defined according to the Academic Research Consortium definitions. An independent clinical event committee reviewed and adjudicated all end point-related serious adverse events. Inclusion criteria were age ≥ 18 years, eligibility for PCI using DES, reference vessel diameter matches, available Ultimaster DES sizes, and written informed consent. The registry was conducted in accordance with the Declaration of Helsinki and country-specific regulatory requirements. All patients signed informed consent form, reviewed and approved by the institutional review board/ethics committee of each participating center. Patients with CKD were automatically allocated to this sub-study (Fig. 1). The data were collected using Electronic CRF (e-Capture). Patients were enrolled between October 2014 and June 2018 and follow-up is currently still ongoing. The current analysis includes all patients enrolled between October 2014 and November 2016, who had a 1-year follow-up visit completed or had died by the date of census (30 November 2016).

Statistical analyses

Patients’ demographics, comorbidities, medical history, target lesion characteristics, and procedural characteristics are summarized with mean, standard deviation for continuous variables, and with frequencies and percentages for discrete variables (Table 1, 2, 3, 4, supplement Table 1). All variables were tested for normal distribution with the Kolmogorov–Smirnov test. For non-normally distributed variables, the Wilcoxon-signed rank test was used. Fisher’s exact test or Chi-squared tests were used for categorical variables, as appropriate. Furthermore, medians with interquartile ranges (IQR) were reported where applicable. When appropriate, the multivariate logistic regression was used for dichotomous variables to adjust for the known risk and potential confounding factors identified with stepwise regression (multivariable p values thresholds to enter and stay in the model were 0.25 and 0.10, respectively), odds ratios and 95% confidence intervals. Variables considered for entry in the stepwise model include: age, gender, body mass index, smoking, diabetes, hypertension, hypercholesterolemia, renal failure, hemodialysis, family history of heart disease, history of MI, previous PCI, previous CABG, acute coronary syndrome, STEMI, multivessel disease, number of lesions identified, number of lesions treated, target vessel treated (right coronary artery, left main, left ascending coronary artery, circumflex artery, graft), type B2 and C lesions (according to classification of American College of Cardiology/American Heart Association/ [ACC/AHA]), bifurcation, moderate to severe calcification, chronic total occlusion, in-stent restenosis, ostial lesions, long lesions (≥ 25 mm), small vessels (≤ 2.75 mm), radial access, number of study stents implanted, total length of implanted study stents. Additionally, we included Kaplan–Meier estimates, Kaplan–Meier estimates adjusted for confounding using estimated propensity scores (“overlap weights” method), and hazard ratios for comparison of survival curves using a log-rank test where appropriate [19]. Patients were matched for lesion type C,
number of lesions treated, number of study stents implanted, bifurcation, acute coronary syndrome, lesion type B2, previous percutaneous coronary intervention, ST elevated MI pre-procedure, number of lesions detected, use of intravascular ultrasound (IVUS)/coronary optical frequency domain imaging (OFDI), current smoker, diabetes mellitus, and age using the Xie, Liu method to control for possible confounding from these prognostic factors [19].

Results

Patient characteristics

A total of 19,475 patients were eligible for inclusion (Fig. 1). Of these, 1,466 had CKD including 167 patients undergoing HD. Patients with CKD were older (CKD: 72.5 IQR: 64–79 vs. no-CKD: 64.0 IQR: 56–72, p < 0.0001), had a lower left ventricular ejection fraction (CKD: 55.0 IQR: 43–60 vs. no-CKD: 56.0 IQR: 49–62, p < 0.0001), and presented with more comorbidities including diabetes (CKD: 48.9% vs. no-CKD: 26.5%, p < 0.0001), hypertension (CKD: 83.9% vs. no-CKD: 62.2%, p < 0.0001), and hypercholesterolemia (CKD: 66.7% vs. no-CKD: 55.9%, p < 0.0001) compared with patients with normal kidney function (Table 1). Patients without CKD consisted of more than twice as many current smokers (CKD: 11.6% vs. no-CKD: 24.3%, p < 0.0001) and included a higher percentage with positive family history of heart disease (CKD: 48.9% vs. no-CKD: 26.5%, p < 0.0001). Of note, patients without CKD had a significantly lower number of previous CABG (CKD: 10.5% vs. no-CKD: 5.6%, p < 0.0001), PCI (CKD: 34.0% vs. no-CKD: 24.9%, p < 0.0001), and myocardial infarction (CKD: 30.4% vs. no-CKD: 21.5%, p < 0.0001). In addition, CKD patients had lower rates of acute coronary syndrome (CKD: 50.5% vs. no-CKD: 56.2%, p < 0.0001) and higher rates of silent ischemia at baseline (CKD: 12.7% vs. no-CKD: 8.6%, p < 0.0001).

Procedural details

Patients with CKD had a higher average number of vessels diseased, lesions in total, and small vessel disease (≤2.75 mm; all p ≤ 0.0001), as summarized in Table 2. The lesions were more commonly located within 3 mm from the ostium (CKD: 8.3% vs. no-CKD: 5.7%, p < 0.0001), involved left main artery treatment (CKD: 6.6% vs. no-CKD: 2.9%, p < 0.0001), and more commonly affected bifurcations (CKD: 16.8% vs. no-CKD: 12.9%, p < 0.0001). In-stent restenosis of DES were significantly more often observed among patients with CKD (CKD: 4.5% vs. no-CKD: 3.0%, p = 0.002) with no difference in in-stent restenosis of bare-metal stents (BMS; CKD: 1.9% vs. no-CKD: 1.8%, p = 0.84). Additionally, the total length of successfully implanted stents

Table 1 Baseline patient characteristics

| Baseline characteristics | CKD N=1466 | No CKD N=18,009 | p value |
|--------------------------|-----------|----------------|---------|
| Age, years (IQR)         | 72.5 (64.0 to 79.0) | 64.0 (56.0 to 72.0) | <0.0001 |
| Male, % (n)              | 72.2 (1058/1466) | 76.9 (13,849/18,009) | <0.0001 |
| Body mass index, kg/m² (IQR) | 27.2 (24.3 to 30.5) | 27.2 (24.6 to 30.2) | 0.82   |
| Left ventricular ejection fraction, % (IQR) | 55.0 (43.0 to 60.0) | 56.0 (49.0 to 62.0) | <0.0001 |
| Diabetes, % (n)          | 48.9 (715/1466) | 26.5 (4770/18,008) | <0.0001 |
| Hypertension, % (n)      | 83.9 (1206/1438) | 62.2 (10,706/17,205) | <0.0001 |
| Hypercholesterolemia, % (n) | 66.7 (949/1423) | 55.9 (9609/17,185) | <0.0001 |
| Current smoker, % (n)    | 11.6 (156/1347) | 24.3 (4055/16,716) | <0.0001 |
| Family history of heart disease, % (n) | 17.8 (193/1083) | 28.1 (3559/12,691) | <0.0001 |
| Previous CABG, % (n)     | 10.5 (151/1440) | 5.6 (969/17,365) | <0.0001 |
| Previous PCI, % (n)      | 34.0 (491/1444) | 24.9 (4344/17,456) | <0.0001 |
| Previous MI, % (n)       | 30.4 (436/1433) | 21.5 (3749/17,461) | <0.0001 |
| Age, years (IQR)         | 72.5 (64.0 to 79.0) | 64.0 (56.0 to 72.0) | <0.0001 |
| Male, % (n)              | 72.2 (1058/1466) | 76.9 (13,849/18,009) | <0.0001 |
| Body mass index, kg/m² (IQR) | 27.2 (24.3 to 30.5) | 27.2 (24.6 to 30.2) | 0.82   |
| Left ventricular ejection fraction, % (IQR) | 55.0 (43.0 to 60.0) | 56.0 (49.0 to 62.0) | <0.0001 |
| Diabetes, % (n)          | 48.9 (715/1466) | 26.5 (4770/18,008) | <0.0001 |
| Hypertension, % (n)      | 83.9 (1206/1438) | 62.2 (10,706/17,205) | <0.0001 |
| Hypercholesterolemia, % (n) | 66.7 (949/1423) | 55.9 (9609/17,185) | <0.0001 |
| Current smoker, % (n)    | 11.6 (156/1347) | 24.3 (4055/16,716) | <0.0001 |
| Family history of heart disease, % (n) | 17.8 (193/1083) | 28.1 (3559/12,691) | <0.0001 |
| Previous CABG, % (n)     | 10.5 (151/1440) | 5.6 (969/17,365) | <0.0001 |
| Previous PCI, % (n)      | 34.0 (491/1444) | 24.9 (4344/17,456) | <0.0001 |
| Previous MI, % (n)       | 30.4 (436/1433) | 21.5 (3749/17,461) | <0.0001 |

Values are presented as mean ± standard deviation (SD), or %, or median with interquartile ranges (IQR 1–3).

PCI percutaneous coronary intervention, CABG coronary artery bypass graft, MI myocardial infarction, CKD chronic kidney disease, (N)STEMI (non-)ST elevated myocardial infarction, N number of patients
was slightly higher in CKD (per lesion; CKD: 27.0 ± 16 mm vs. no-CKD 25.8 ± 14, p = 0.002). Further, procedures in CKD patients were more complex when compared with the reference population (less frequent direct stenting; CKD: 30.4% vs. no-CKD: 38.6%, p < 0.0001; balloon dilatation only; CKD: 1.6% vs. no-CKD: 2.3%, p = 0.03; thrombus aspiration; CKD: 3.3% vs. no-CKD: 5.0%, p = 0.0002). Support devices (such as balloon pre-dilatation, post-dilatation, cutting balloon, atherectomy, microcatheters) and peri-interventional imaging (IVUS/OFDI) were more commonly used in patients with CKD (Table 2). Although, radial access was used in the majority of cases in both groups (CKD: 74.2% vs. no-CKD: 82.8%, p < 0.0001), it was significantly less utilized in patients with CKD. In contrast, femoral (CKD: 25.2% vs. no-CKD: 18.5%, p < 0.0001) and brachial access (CKD: 1.8% vs. no-CKD: 0.34%, p < 0.0001) were more frequently used in CKD.

### Safety and efficacy

Safety and efficacy data were available for 19,475 patients at baseline and 12-month follow-up. Reported complications related to access site (CKD: 2.2% vs. no-CKD: 1.1%, p = 0.001), minor bleeding (CKD: 3.1% vs. no-CKD: 1.6%, p = 0.0002), and major bleeding (CKD: 1.4% vs. no-CKD: 0.5%, p = 0.0003) occurred more commonly among patients with CKD (Table 3). However, CKD patients had a significantly higher percentage of patients treated with oral
anticoagulation at baseline (CKD: 11.1% vs. no-CKD: 4.0%, \(p < 0.001\)). The primary outcome measure TLF (composite of cardiac death, target-vessel-related MI, and clinically driven TLR) occurred more often in the CKD group (unadjusted OR, 2.51 [95% CI 2.04–3.08] \(p < 0.0001\); Fig. 2a). Adjusted Kaplan–Meier estimates on TLF indicate significantly more events in CKD patients as depicted in Fig. 3. Furthermore, patients with CKD were at higher risk for TVF (OR, 2.44 [95% CI 2.01–2.96]; \(p < 0.0001\)), POCE (OR, 2.19 [95% CI 1.87–2.56] \(p < 0.0001\)), and MACE (OR, 2.34 [95% CI 1.93–2.83] \(p < 0.0001\)). In contrast, the risk for TLR (OR, 1.17 [95% CI 0.79–1.73] \(p = 0.44\)) did not differ significantly between patients with and without CKD (Fig. 2a). Unadjusted Kaplan–Meier estimates on cumulative incidence of TLF, clinically driven TLR, TVF, and POCE are provided in supplement Fig. 1. The 1-year risk of TLF was significantly increased by age, body mass index, diabetes, smoking status, previous PCI, ACS, number of lesions, target vessel location, bifurcation involvement, type C lesions, number of stents implanted, CKD, and hemodialysis. One-year adjusted odds ratios for MACE, POCE, TLF, and TLR are presented in Fig. 4.

**Subgroup of HD patients**

Patients with CKD on HD (11.4% of all patients with CKD) were younger \((p < 0.0001)\), had a lower body mass index \((p < 0.0001)\), a higher prevalence of diabetes \((p < 0.0001)\), and less frequently a family history of heart diseases \((p = 0.05)\) compared with patients with CKD not requiring HD (Table 4). In CKD patients on HD, left main arteries were more frequently treated (HD: 12.0% vs. CKD: 5.9%, \(p = 0.007\)). Although multiple vessels were not more commonly diseased (HD: 58.7% vs. CKD: 57.7%, \(p = 0.80\)), they were more likely to be treated in HD patients (HD: 24.6% vs. CKD: 16.4%, \(p = 0.01\)). Debubking strategies were commonly utilized in HD patients, such as balloon pre-dilatation, atherectomy, microcatheters, and intravascular ultrasound. The preferred

Table 3 End points, complications, and follow-up (1 year)

| Endpoints                      | CKD \(N = 1466\) | No CKD \(N = 18,009\) | \(p\) value |
|-------------------------------|------------------|------------------------|-------------|
| Any death, % \((n)\)         | 8.3 (121/1466)   | 1.8 (327/18,009)       | <0.0001     |
| Cardiac death, % \((n)\)     | 5.1 (74/1466)    | 1.1 (203/18,009)       | <0.0001     |
| Any MI, % \((n)\)            | 1.6 (23/1466)    | 1.1 (195/18,009)       | 0.07        |
| Target vessel MI, % \((n)\)  | 1.4 (20/1466)    | 0.9 (155/18,009)       | 0.06        |
| Clinically driven TLR, % \((n)\) | 1.8 (27/1466)   | 1.6 (283/18,009)       | 0.45        |
| Clinically driven TVR, % \((n)\) | 3.0 (44/1466)   | 2.2 (387/18,009)       | 0.04        |
| Composite end points         | \|                  |                        |             |
| TLF, % \((n)\)              | 7.5 (109/1466)   | 3.0 (534/18,009)       | <0.0001     |
| TVF, % \((n)\)              | 8.4 (123/1466)   | 3.4 (619/18,009)       | <0.0001     |
| POCE, % \((n)\)             | 12.6 (185/1466)  | 5.8 (1039/18,009)      | <0.0001     |
| MACE, % \((n)\)             | 8.5 (124/1466)   | 3.6 (654/18,009)       | <0.0001     |
| Stent thrombosis             | \|                  |                        |             |
| Definite ST, % \((n)\)      | 0.3 (5/1466)     | 0.4 (76/18,009)        | 0.83        |
| Probable ST, % \((n)\)      | 0.4 (6/1466)     | 0.2 (41/18,009)        | 0.16        |
| Definite and probable ST, % \((n)\) | 0.8 (11/1466) | 0.6 (115/18,099)       | 0.61        |
| Complications (reported)     | \|                  |                        |             |
| Any bleeding, % \((n)\)     | 4.2 (61/1466)    | 2.1 (384/18,009)       | <0.0001     |
| Major bleeding, % \((n)\)   | 1.4 (20/1466)    | 0.5 (97/18,009)        | 0.0003      |
| Minor bleeding, % \((n)\)   | 2.9 (43/1466)    | 1.6 (289/18,009)       | 0.0002      |
| Complication related to access site, % \((n)\) | 2.2 (32/1466) | 1.1 (203/18,009)       | 0.001       |
| Follow-up                    | \|                  |                        |             |
| Days from procedure to discharge | 3.2±4.1    | 2.4±2.9               | <0.0001     |
| DAPT 3-month follow-up, % \((n)\) | 89.5 (1282/1433) | 94.8 (16,823/17,748) | <0.0001     |
| DAPT 12-month follow-up, % \((n)\) | 60.9 (843/1384) | 67.0 (11,898/17,747) | <0.0001     |

**CKD** chronic kidney disease, **DAPT** dual antiplatelet therapy, **MACE** major adverse cardiac events (cardiac death, any MI, clinically driven TVR and emergent coronary artery bypass graft), **MI** myocardial infarction, **POCE** patient-oriented composite end point (all death, any MI, any coronary revascularization), **ST** stent thrombosis, **TLF** target lesion failure (cardiac death, target vessel MI, clinically driven TLR), **TLR** target lesion revascularization, **TVF** target vessel failure (cardiac death, target vessel MI, clinically driven TVR), **TVR** target vessel revascularization, \(N\) number of patients.
Table 4 Summary results of patients on HD

| Summary results                                      | HD  
|------------------------------------------------------|----------------------------------|----------------------|-----------------------|
|                                                      | \(N = 167\)                      | CKD (no HD) \(N = 1299\) | \(p\) value          |
| Age, years (IQR)                                     | 68.0 (61.0 to 75.0)             | 73.0 (65.0 to 79.0)    | <0.0001              |
| Male, % (\(n\))                                     | 67.1 (112/167)                  | 72.8 (946/1299)        | 0.12                 |
| Body mass index, kg/m² (IQR)                         | 26.0 (22.4 to 28.8)             | 27.4 (24.6 to 30.7)    | <0.0001              |
| Diabetes, % (\(n\))                                 | 63.5 (106/167)                  | 46.9 (609/1299)        | <0.0001              |
| Hypertension, % (\(n\))                             | 86.4 (140/162)                  | 83.5 (1066/1276)       | 0.43                 |
| Hypercholesterolemia, % (\(n\))                     | 67.1 (108/161)                  | 66.6 (841/1262)        | 0.99                 |
| Current smoker, % (\(n\))                           | 8.1 (12/167)                    | 12.0 (144/1198)        | 0.18                 |
| Family history of heart disease, % (\(n\))          | 11.5 (15/131)                   | 18.7 (178/952)         | 0.05                 |
| Left ejection fraction, % (IQR)                      | 53.0 (45.0 to 63.0)             | 55.0 (42.0 to 60.0)    | 0.46                 |
| Previous CABG, % (\(n\))                            | 7.3 (12/164)                    | 10.9 (139/1276)        | 0.18                 |
| Previous PCI, % (\(n\))                             | 33.3 (55/165)                   | 34.1 (436/1279)        | 0.93                 |
| Previous MI, % (\(n\))                              | 29.3 (48/164)                   | 30.6 (388/1269)        | 0.79                 |
| Peri-procedural differences                          |                                  |                      |                      |
| Left main treated, % (\(n\))                        | 12.0 (20/167)                   | 5.9 (77/1298)          | 0.007                |
| Small vessels (≤2.75 mm), % (\(n\))                 | 52.1 (87/166)                   | 48.8 (631/1294)        | 0.46                 |
| Multiple vessels diseased, % (\(n\))                | 58.7 (98/167)                   | 57.5 (747/1299)        | 0.80                 |
| Multiple vessels treated, % (\(n\))                 | 24.6 (41/167)                   | 16.4 (213/1298)        | 0.01                 |
| Number of vessels diseased, \(n\)                   | 1.80 ± 0.8                      | 1.83 ± 0.8             | 0.63                 |
| Femoral access site, % (\(n\))                      | 53.9 (90/167)                   | 21.5 (279/1299)        | <0.0001              |
| Radial access site, % (\(n\))                       | 40.1 (67/167)                   | 78.6 (1021/1299)       | <0.0001              |
| Brachial access site, % (\(n\))                     | 6.6 (11/167)                    | 1.2 (16/1299)          | <0.0001              |
| End points at 1-year                                 |                                  |                      |                      |
| Any death, % (\(n\))                                | 16.2 (27/167)                   | 7.3 (94/1299)          | 0.0005               |
| Cardiac death, % (\(n\))                            | 7.8 (13/167)                    | 4.8 (61/1299)          | 0.13                 |
| Non-cardiac death, % (\(n\))                        | 8.4 (14/167)                    | 2.5 (33/1299)          | 0.0004               |
| Target vessel MI, % (\(n\))                         | 0.6 (1/167)                     | 1.5 (22/1299)          | 0.72                 |
| Clinically driven TLR, % (\(n\))                    | 3.6 (6/167)                     | 1.7 (21/1299)          | 0.12                 |
| Clinically driven TVR, % (\(n\))                    | 5.4 (9/167)                     | 2.7 (35/1299)          | 0.09                 |
| Composite endpoints                                  |                                  |                      |                      |
| TLF, % (\(n\))                                      | 11.4 (19/167)                   | 6.9 (90/1299)          | 0.06                 |
| TVF, % (\(n\))                                      | 12.6 (21/167)                   | 7.9 (102/1299)         | 0.05                 |
| POCE, % (\(n\))                                     | 21.0 (35/167)                   | 11.6 (150/1299)        | 0.001                |
| MACE, % (\(n\))                                     | 12.6 (21/167)                   | 7.9 (103/1299)         | 0.05                 |
| Stent thrombosis                                     |                                  |                      |                      |
| Definite ST, % (\(n\))                              | 0.6 (1/167)                     | 0.3 (4/1299)           | 0.45                 |
| Probable ST, % (\(n\))                              | 0.6 (1/167)                     | 0.4 (5/1299)           | 0.52                 |
| Possible ST, % (\(n\))                              | 3.0 (5/167)                     | 2.3 (30/1299)          | 0.59                 |
| Complications                                        |                                  |                      |                      |
| Major bleeding, % (\(n\))                           | 3.0 (5/167)                     | 1.2 (15/1299)          | 0.07                 |
| Minor bleeding, % (\(n\))                           | 2.4 (4/167)                     | 3.0 (39/1299)          | 0.81                 |
| Complication related to access site, % (\(n\))      | 0.6 (1/167)                     | 2.4 (31/1299)          | 0.17                 |
| Follow-up                                            |                                  |                      |                      |
| DAPT 3-month follow-up, % (\(n\))                   | 81.7 (134/164)                  | 90.5 (1148/1269)       | 0.002                |
| DAPT 1-year follow-up, % (\(n\))                    | 67.1 (100/149)                  | 60.2 (743/1235)        | 0.08                 |

Values are presented as mean ± standard deviation (SD), % or median with interquartile ranges (IQR 1–3). **CKD** chronic kidney disease, **DAPT** dual antiplatelet therapy, **HD** hemodialysis, **MACE** major adverse cardiac events (cardiac death, any MI, clinically driven TVR and emergent coronary artery bypass graft), **MI** myocardial infarction, **POCE** patient-oriented composite endpoint (all death, any MI, any coronary revascularization), **ST** stent thrombosis, **TLF** target lesion failure (cardiac death, target vessel MI, clinically driven TLR), **TLR** target lesion revascularization, **TVF** target vessel failure (cardiac death, target vessel MI, clinically driven TVR), **TVR** target vessel revascularization, **CABG** coronary artery bypass graft, **PCI** percutaneous coronary intervention, \(N\) number of patients.
access site in HD patients was femoral access, followed by radial or brachial, which is different compared with the CKD population (all; \( p < 0.0001 \); Table 4). Access site complications were comparable between the two groups. At 3 months, DAPT rates were significantly lower in patients with CKD on HD compared with non-HD patients with no significant difference at 1-year follow-up (Table 4). All-cause death occurred more commonly in patients with HD (HD: 16.2% vs. CKD: 7.3%, \( p = 0.0005 \)), with no significant difference in cardiac death (HD: 7.8% vs. CKD: 4.8%, \( p = 0.13 \)), but a difference in non-cardiac death (HD: 8.4% vs. CKD: 2.5%, \( p = 0.0004 \)), respectively. In comparison to the included CKD population, HD further increased the risk for the predefined end points TLF (unadjusted OR, 1.64 [95% CI 1.00–2.69]; \( p = 0.049 \)), TLR (OR, 2.22 [95% CI 0.90–5.51]; \( p = 0.08 \)), TVR (OR, 2.00 [95% CI 0.96–4.16]; \( p = 0.06 \)), MACE (OR, 1.59 [95% CI 0.99–2.54]; \( p = 0.05 \)), POCE (OR, 1.82 [95% CI 1.26–2.62]; \( p = 0.002 \)), and TVF (OR, 1.60 [95% CI 1.00–2.56]; \( p = 0.049 \)) (Fig. 2b).

**Discussion**

In this large, contemporary, international, real-world registry, patients with CKD undergoing new-generation DES implantation have a significantly higher risk of 1-year adverse events including TLF, defined as the composite of cardiac death, target vessel-related MI, clinically driven TLR, and more bleeding events. Patients with CKD had a
higher prevalence of comorbidities and complex coronary lesions frequently requiring debulking strategies. Compared with other risk factors, the presence of CKD, and in particular need for HD, was one of the most impactful parameters in increasing the risk of TLF, MACE, and POCE.

Chronic kidney disease is a worldwide growing health issue, affecting more than 1.5 million patients in Europe and the USA and is associated with worse outcome [1, 2]. Cardiovascular disease, specifically CAD, is the leading cause of morbidity and mortality in patients with CKD. The optimal revascularization strategy is being debated and includes CABG and PCI, preferably with the use of DES in CKD [11–13, 20, 21]. While CABG was shown to be superior to PCI in patients with multivessel CAD and end-stage renal disease regarding long-term survival, PCI was superior to CABG in short-term survival, stroke, and repeat revascularization [11]. However, data on the long-term performance of new-generation DES indicate no significant difference between PCI and CABG in patients with CKD [11–13, 22–24]. Previous studies on revascularization have shown that patients with CKD after PCI and CABG are at increased risk of death and adverse events, correlating with the severity of renal insufficiency [23–25]. Herein, the 1-year event rates for patients with CKD were significantly higher when compared with the reference population. In contrast, the 1-year event rate for patients with preserved renal function was comparable to that in other recently published studies evaluating the safety and performance of new-generation DES indicating good performance of the Ultimaster stent. The prospective COMBO Stent registry, for instance, included 3614 patients and documented TLF in 3.9%, cardiac death in 1.6%, and definite stent thrombosis in 0.5% (versus 3.3%, 1.4%, and 0.4% herein) [25–30]. Although complication rates were relatively low in general, patients with CKD had a higher risk of major and minor bleeding as well as access site-related complications leading to prolonged hospitalization and higher rates of end points at discharge (supplement Table 1), which is in line with

Fig. 4 One-year adjusted odds ratios for major adverse cardiovascular events (MACE: cardiac death, any MI, clinically driven TVR, and emergent coronary artery bypass graft, a patient-oriented composite end point (POCE: all death, any MI, any coronary revascularization, b target lesion failure (TLF: cardiac death, target vessel MI, clinically driven TLR, c and target lesion revascularization TLR, d yes versus no; CKD chronic kidney disease, HD hemodialysis, PCI percutaneous coronary intervention, No number, MI ST elevated myocardial infarction, CI confidence interval, ACS acute coronary syndrome, PP per patient, CABG coronary artery bypass graft

---

**Table 1**

| Variable | MACE | POCE | TLF | TLR |
|----------|------|------|-----|-----|
| Age      |      |      |     |     |
| Previous PCI |     |      |     |     |
| Current smokers |     |      |     |     |
| ACS      |      |      |     |     |
| Diabetes mellitus |     |      |     |     |
| Lesion type C |     |      |     |     |
| Previous MI |     |      |     |     |
| No of lesions pp |     |      |     |     |
| No of stents pp |     |      |     |     |
| Bifurcation |     |      |     |     |
| CKD      |      |      |     |     |
| HD       |      |      |     |     |

Adjusted odds ratio (95% CI)

---

**Table 2**

| Variable | TLF | TLR |
|----------|-----|-----|
| Previous CABG |     |     |
| Previous PCI |     |     |
| Current smoker |     |     |
| ACS      |      |     |
| Diabetes mellitus |     |     |
| Lesion type C |     |     |
| Total stent length |     |     |
| No of lesions pp |     |     |
| No of stents pp |     |     |
| Bifurcation |     |     |
| CKD      |      |     |
| HD       |      |     |

Adjusted odds ratio (95% CI)
previous publications [28–32]. Bleeding occurred in 2.3% of all included patients, with twofold higher rates of minor and major bleeding in CKD. In this context, the choice of access site is of special importance. Interestingly, the rates of radial access were lower in CKD when compared with no-CKD patients (74% vs. 83%, \( p < 0.0001 \)), implying that operators might have chosen different arterial accesses in CKD. One may speculate that this was due to an expectably higher complexity of PCI requiring debulking strategies, intravascular imaging, and maintaining radial arterial integrity to provide future dialysis vascular access. Of note, the use of radial access was associated with a 24% lower risk (OR 0.76, 95% CI 0.63–0.91, \( p = 0.003 \)) of TLF (Fig. 4) and should also be considered as a bleeding avoidance strategy in patients with CKD.

The deleterious effect of CKD on the vasculature is reflected by significant anatomical and procedural differences (Tables 2 and 4). Patients with CKD have increased prevalence of medial calcification, which may impair response to PCI and pose several challenges [20–22]. This is supported by our findings showing a higher number of affected vessels, small vessel disease (≤ 2.75 mm), instant restenosis (primarily in DES), and severely calcified lesions, which were more commonly located in the left main artery. As a result, lesions in CKD patients were frequently treated using peri-interventional imaging (IVUS, OFDI) and debulking strategies, such as balloon pre- and post-dilation, cutting balloon, atherectomy, and microcatheters. Although more lesions were identified in CKD patients, the number of treated lesions did not differ when compared with the reference population, which might be another indicator for the higher complexity in CKD patients leading to a higher rate of non-complete revascularization.

There is a linear relationship between cardiovascular mortality and decreasing GFR with the highest cardiovascular morbidity and mortality in patients on HD [5–8]. Patients with CKD on HD exhibit a high risk for cardiovascular events as well as an altered coagulation with both increased thrombotic and bleeding risks, which may be caused by denser clot structures [33]. Interestingly, HD patients were younger compared with CKD non-HD patients and, apart from a higher prevalence of diabetes (64%), did not have significantly more comorbidities. Patients with CKD on HD had higher rates of all-cause mortality (including non-cardiac death) and TLF at 1-year compared with patients with CKD not requiring HD (Table 4). Of note, data on the 3-month and 1-year follow-up indicate a lower percentage of patients on DAPT in patients with CKD when compared to the reference population. This might be associated with higher bleeding rates in CKD suspected by patients and physicians, which were subsequently documented in this registry, although with a higher rate of patients on oral anticoagulation in patients with CKD in this registry.

**Limitations**

It is recognized that registry-based studies have limitations. Follow-up procedures were not standardized and, thus, may have influenced the reporting of safety and adverse events. This may have led to underreporting of adverse events, which may have occurred, due to the discretion of the investigator. The characteristics of the patients included in this study were representative of patients with CKD in everyday practice. However, the results could be influenced by confounders in patient characteristics such as age and comorbidities. Furthermore, there may be biological heterogeneity, e.g., due to different disease severity regarding categorical variables, different glomerular filtration rates within the groups, and underlying causes of CKD within the groups. Also, adherence to medication is often dynamic, and rigorous assessment with toxicological screening and type of DAPT was not reported.

**Conclusion**

In this large cohort of all-comer patients undergoing new-generation DES implantation, CKD and in particular HD were associated with a higher risk of adverse events including TLF when compared with the reference population. Although higher rates of adverse events were observed, low stent thrombosis rates indicate good performance in this high-risk patient population. Additional research on this topic preferably in randomized controlled trials is required to validate these findings.

**Clinical perspectives**

CKD is a common comorbidity in everyday practice and patients with CAD. Moreover, these patients present with more comorbidities and complex lesions when compared with the reference population. Therefore, a high level of expertise is necessary to assure sufficient treatment. Randomized controlled trials are needed to validate these findings.

**Funding** e-Ultimaster is supported by Terumo Corporation, Tokyo, Japan. SSS has received speaker honoraria from Pfizer, MB, FM, and NM are supported by Deutsche Forschungsgemeinschaft (SFB TRR219). MB receives honoraria for lectures and scientific advice from Abbott, Astra-Zeneca, Boehringer-Ingelheim, Medtronic, Novartis, Servier, and Vifor. FM is supported by Deutsche Hochdruckliga (DHL) and Deutsche Gesellschaft für Kardiologie (DGK).
Compliance with ethical standards

Conflict of interest FM and SE have received scientific support and speaker honoraria from Medtronic and ReCor Medical. NM has received support for clinical trial leadership from Boehringer Ingelheim and Novo Nordisk and served as a consultant to Boehringer Ingelheim, Merck, Novo Nordisk, AstraZeneca, BMS, received grant support from Boehringer Ingelheim, and served as a speaker for Boehringer Ingelheim, Merck, Novo Nordisk, Lilly, BMS, and Astra Zeneca. NM declines all personal compensation from pharma or device companies. The remaining authors have no disclosures to report.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. United States Renal Data System (2015) URDS annual data report: Epidemiology of Kidney Disease in the United States. National Institute of Health, National Institute of Diabetes and Digestive Kidney Disease: 2015 https://www.usrds.org/2017/download/2017_Volume_2_ESRD_in_the_US.pdf
2. Kramer A, Stel V, Zoccali C et al (2009) An update on renal replacement therapy in Europe: ERA-EDTA Registry data from 1997 to 2006. Nephrol Dial Transplant 24:3557–3566. https://doi.org/10.1093/ndt/gfp519
3. Liyanage T, Ninomiya T, Jha V et al (2015) Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet 385:1975–1982. https://doi.org/10.1016/S0140-6736(14)61601-9
4. Jha V, Garcia-Garcia G, Iseki K et al (2013) Chronic kidney disease: global dimension and perspectives. Lancet 382:260–272. https://doi.org/10.1016/S0140-6736(13)60687-X
5. Astor BC, Hallan SI, Miller ER et al (2008) Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. Am J Epidemiol 167:1226–1234. https://doi.org/10.1093/aje/kwn033
6. Ou S-M, Chen Y-T, Hung S-C et al (2016) Association of estimated glomerular filtration rate with all-cause and cardiovascular mortality: the role of malnutrition–inflammation–cachexia syndrome: eGFR with mortality and the role of MCS. J Cachexia Sarcopenia Muscle 7:144–151. https://doi.org/10.1002/jcum.12053
7. Go AS, Chertow GM, Fan D et al (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296–1305. https://doi.org/10.1056/NEJMoa0401031
8. Grandjean-Thomsen NL, Marley P, Shadbolt B, Farshid A (2017) Impact of mild-to-moderate chronic kidney disease on one year outcomes after percutaneous coronary intervention. Nephron 137:23–28. https://doi.org/10.1159/0004738603
9. Edwards NC, Steeds RP, Ferro CJ, Townsend JN (2006) The treatment of coronary artery disease in patients with chronic kidney disease. QJM 99:723–736. https://doi.org/10.1093/qjmed/hcl101
10. Blacher J, Guerin AP, Pannier B et al (2001) Arterial calcification, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 38:938–942. https://doi.org/10.1161/1096358
11. Bangalore S, Guo Y, Samadashvili Z et al (2015) Revascularization in patients with multivessel coronary artery disease and chronic kidney disease. J Am Coll Cardiol 66:1209–1220. https://doi.org/10.1016/j.jacc.2015.06.1334
12. Zheng H, Xue S, Lian F et al (2013) Meta-analysis of clinical studies comparing coronary artery bypass grafting with percutaneous coronary intervention in patients with end-stage renal disease. Eur J Cardiothorac Surg 43:459–467. https://doi.org/10.1093/ejcts/ezs360
13. Shroff GR, Herzog CA (2016) Coronary revascularization in patients with CKD stage 5D: pragmatic considerations. J Am Soc Nephrol 27:3521–3529. https://doi.org/10.1681/ASN.2016030345
14. Smilowitz NR, Gupta N, Guo Y et al (2017) Management and outcomes of acute myocardial infarction in patients with chronic kidney disease. Int J Cardiol 227:1–7. https://doi.org/10.1016/j.ijcard.2016.11.026
15. Giustino G, Mehran R, Serruys PW et al (2018) Left main revascularization with PCI or CABG in patients with chronic kidney disease. J Am Coll Cardiol 72:754–765. https://doi.org/10.1016/j.jacc.2018.05.057
16. Miliojevic M, Head SJ, Mack MJ et al (2018) 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 14:102–111. https://doi.org/10.4244/EIJ-D-17-00620
17. Weiner DE, Tabatabai S, Tighiouart H et al (2006) Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. Am J Kidney Dis 48:392–401. https://doi.org/10.1053/j.ajkd.2006.05.021
18. Foley RN, Parfrey PS, Sarnak MJ (1998) Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 9:S16–23
19. Xie J, Liu C (2005) Adjusted Kaplan–Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med 24:3089–3110. https://doi.org/10.1002/sim.2174
20. Madhavan MV, Tarigopula M, Mintz GS et al (2014) Coronary artery calcification. J Am Coll Cardiol 63:1703–1714. https://doi.org/10.1016/j.jacc.2014.01.017
21. Alfonso F, Rivero F (2016) Coronary revascularization in diabetic patients with chronic kidney disease. Eur Heart J 37:3448–3451. https://doi.org/10.1093/eurheartj/ehw453
22. Bangalore S, Vlachos HA, Selzer F et al (2011) Percutaneous coronary intervention of moderate to severe calcified coronary lesions: Insights from the National Heart, Lung, and Blood Institute Dynamic Registry. Catheter Cardiovasc Interv 77:22–28. https://doi.org/10.1002/ccd.22613
23. Tsai TT, Messenger JC, Brennan JM et al (2011) Safety and efficacy of drug-eluting stents in older patients with chronic kidney disease. J Am Coll Cardiol 58:1859–1869. https://doi.org/10.1016/j.jacc.2011.06.056
24. Lee JM, Kang J, Lee E et al (2016) Chronic kidney disease in the second-generation drug-eluting stent era. J Am Coll Cardiol Intv 9:2097–2109. https://doi.org/10.1016/j.jcin.2016.06.051
25. Latif F, Kleiman NS, Cohen DJ et al (2009) In-hospital and 1-year outcomes among percutaneous coronary intervention patients with chronic kidney disease in the era of drug-eluting stents. JACC Cardiovasc Interv 2:37–45. https://doi.org/10.1016/j.jcin.2008.06.012
26. de Winter RJ, Chandrasekhar J, Kalkman DJ et al (2018) 1-year clinical outcomes of all-comer patients treated with the dual-therapy COMBO stent. JACC Cardiovasc Interv 11:1969–1978. https://doi.org/10.1016/j.jcin.2018.04.038
27. von Birgelen C, Sen H, Lam MK et al (2014) Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer
patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet 383:413–423. https://doi.org/10.1016/S0140-6736(13)62037-1

28. Shimizu A, Sonoda S, Muraoka Y et al (2019) Bleeding and ischemic events during dual antiplatelet therapy after second-generation drug-eluting stent implantation in hemodialysis patients. J Cardiol 73:470–478. https://doi.org/10.1016/j.jjcc.2018.12.009

29. Naidu SS, Krucoff MW, Rutledge DR et al (2012) Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after XIENCE V implantation. J Am Coll Cardiol Intv 5:626–635. https://doi.org/10.1016/j.jcin.2012.02.014

30. Lu R, Tang F, Zhang Y et al (2016) Comparison of drug-eluting and bare metal stents in patients with chronic kidney disease: an updated systematic review and meta-analysis. JAHA. https://doi.org/10.1161/JAHA.116.003990

31. Marx N, Noels H, Jankowski J et al (2018) Mechanisms of cardiovascular complications in chronic kidney disease: research focus of the Transregional Research Consortium SFB TRR219 of the University Hospital Aachen (RWTH) and the Saarland University. Clin Res Cardiol 107:120–126. https://doi.org/10.1007/s00392-018-1260-0

32. Kaya E, Cuneo A, Hochadel M et al (2011) Impact of chronic kidney disease on the prognosis of patients undergoing percutaneous coronary interventions using drug-eluting stents. Clin Res Cardiol 100:1103–1109. https://doi.org/10.1007/s00392-011-0347-7

33. Schuett K, Savvaidis A, Maxeiner S et al (2017) Clot structure: a potent mortality risk factor in patients on hemodialysis. J Am Soc Nephrol 28:1622–1630. https://doi.org/10.1681/ASN.2016030336