

Original Paper

Long-Term Percutaneous Coronary Intervention Outcomes of Patients with Chronic Kidney Disease in the Era of Second-Generation Drug-Eluting Stents

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Key Words

Percutaneous coronary intervention · Drug-eluting stents · Chronic kidney disease · Bleeding complications

Abstract

Background: The following registry (Katowice-Zabrze retrospective registry) aimed to assess the influence of a chronic kidney disease (CKD) on long-term clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) using either first-generation (DES-I) or second-generation (DES-II) drug-eluting stents. **Methods:** The study group consisted of 1,908 consecutive patients, of whom 331 (17.3%) had CKD. CKD was defined as an estimated glomerular filtration rate of <60 mL/min/m². We evaluated the major adverse cardiac and cerebral events (MACCE), i.e., the composite of death, myocardial infarction (MI), stroke, and target vessel revascularization at the 12-month follow-up. **Results:** CKD patients had a lower left ventricular ejection fraction and more often a history of MI and PCI. Coronary angiography revealed that multivessel coronary artery disease, intracoronary thrombus, and extensive calcifications were more frequent in patients with CKD. However, the SYNTAX score did not vary between patients with or without CKD. There was a higher rate of in-hospital bleedings requiring blood transfusion in patients with CKD. At the 1-year follow-up, MACCE (17.8 vs. 12.6%, HR = 1.46 [95% CI 1.05–2.03], $p = 0.009$) and death (8.4 vs. 2.3%, HR = 3.9 [95% CI 2.0–7.5], $p < 0.001$) were more often observed in CKD patients. Multivariable Cox analysis revealed that CKD was an independent risk predictor of death after PCI at the 1-year follow-up (HR = 2.1

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[95% CI 1.2–3.6], $p = 0.004$). In comparison to DES-I, the use of DES-II did not decrease the adverse effect of CKD on MACCE. **Conclusion:** CKD patients had an increased risk of in-hospital bleeding requiring blood transfusion and a higher risk of MACCE and death at the 12-month follow-up. The use of second-generation DES did not improve clinical outcomes in patients with CKD at the 12-month follow-up.

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Background

Chronic kidney disease (CKD) is relatively frequent in patients presenting with acute coronary syndrome (ACS) (30–40%) [1], and increases the risk of death, myocardial infarction (MI), stent thrombosis (ST) and bleeding complications of percutaneous coronary interventions (PCI) [2, 3]. Previous observation documented that the relation between the risk of adverse cardiovascular (CV) events and renal function was inverse. The HOPE study showed that a creatinine level >1.4 mg/dL or a glomerular filtration rate (GFR) <65 mL/min/m² was associated with worse clinical outcomes [4]. Hence, such patients require an adequate risk assessment and a multidisciplinary approach to avoid complications during and after PCI. Similar to patients without CKD, an early revascularization compared to medical therapy was associated with better survival in all CKD stages including dialysis patients [5, 6]. Further analysis also proved that drug-eluting stents (DES) had better outcomes, as compared to bare metal stents, in terms of MI and death and target vessel revascularization (TVR) [7, 8]. Introduction of second-generation DES (DES-II) brought benefit to patients without CKD, but there is still a debate whether DES-II improve clinical outcomes in CKD patients.

Because CKD patients usually do not meet inclusion criteria for large clinical trials, the current registry, consisting of a representative group of the general population, may broadly address the problem. Hence, the present report analyzed the impact of CKD on clinical outcomes in patients treated either with DES-I or DES-II.

Methods and Study Population

The Katowice-Zabrze retrospective registry included 1,916 consecutive patients treated with either first-generation (paclitaxel, sirolimus; 33.6%) or second-generation (everolimus, zotarolimus, biolimus A9, 66.4%) DES. Estimated GFR (eGFR) was assessed on admission and before PCI. CKD was defined as eGFR <60 mL/min/1.73 m² calculated using the Modification of Diet in Renal Disease method [9]. An eGFR <60 mL/min/1.73 m² is referred to as stage 2 CKD. For our analysis, 8 patients were excluded because eGFR has not been measured. Baseline characteristics, cardiac history, risk factors, medications, and angiographic and procedural data were obtained and recorded. Angiographic data were collected in all patients undergoing PCI and recorded in the CV information registry. The SYNTAX score was calculated in all patients except those after coronary artery bypass graft. The primary study endpoint was DES efficacy and safety in all patients. DES efficacy was measured as the presence of major adverse cardiac and cerebral events (MACCE). MACCE was defined as MI, TVR, death, or stroke at the 1-year follow-up. The safety of DES was defined as definite stent thrombosis (acute, subacute, late). TVR, definite stent thrombosis, acute, subacute, and late stent thrombosis were defined according to the definitions of endpoints for clinical trials [10]. Data regarding long-term clinical outcomes (mortality and MACCE) were obtained from the database of the National Health Fund Service (Ministry of Health).

Statistics

Statistical analysis was performed using MedCalc Software (v.12, Ostend, Belgium). Quantitative variables are presented as mean \pm standard deviation and median with interquartile range (Q1–Q3). Qualitative data are expressed as crude values and/or percentages. Between-group differences were assessed using the

Table 1. Patient characteristics, risk factors, and clinical presentation according to the presence of CKD

	CKD+ <i>n</i> = 331 (17.3%)	CKD– <i>n</i> = 1,577 (82.7%)	<i>p</i>
Demographic data			
Age, years	71 [64–76]	61 [56–69]	<0.001
Male	163 (49.2)	1,066 (67.5)	<0.001
Female	168 (50.7)	511 (32.4)	<0.001
BMI	29 [26–32]	28.4 [25–31]	0.043
Discharge diagnosis			
UA	246 (74.3)	1,247 (79.0)	0.066
NSTEMI	68 (20.5)	216 (13.6)	0.002
STEMI/LBBB	17 (5.1)	114 (7.2)	0.211
CAD history			
Previous MI	179 (54.0)	734 (46.5)	0.014
Previous PCI	203 (61.3)	858 (54.4)	0.024
Previous CABG	80 (24.1)	317 (20.1)	0.113
CAD risk factors			
Hypertension	305 (92.1)	1,331 (84.4)	<0.001
Dyslipidemia	212 (64.0)	1,046 (66.3)	0.464
Diabetes mellitus	167 (50.4)	548 (34.7)	<0.001
Smoking	43 (12.9)	418 (26.5)	<0.001
Concomitant disease			
Anemia	69 (20.8)	147 (9.3)	<0.001
Cancer	31 (9.3)	84 (5.3)	0.007
COPD	33 (9.9)	84 (5.3)	0.002
PAD	58 (17.5)	160 (10.1)	<0.001
Length of hospital stay, days	5 [4–8]	4 [3–6]	<0.001
Left ventricular function	50 [40–55]	55 [46–60]	<0.001
Laboratory			
GFR, mL/min/1.73 m ²	49 [40–55]	87 [75–96]	<0.001
Creatinine, mg/dL	1.2 [1.1–1.5]	0.8 [0.7–0.9]	<0.001
Hemoglobin on admission, g/dL	13 [12–14]	14 [13–15]	<0.001
Clinical status on admission			
HR, bpm	71 [60–80]	70 [60–77]	0.076
SBP, mm Hg	130 [120–145]	130 [120–150]	0.780
CCS			
II	87 (26.2)	508 (32.2)	0.040
III–IV	244 (73.7)	1,069 (67.7)	
KILLIP			
I–II	83 (97.6)	321 (97.2)	0.851
III–IV	2 (2.3)	9 (2.7)	
GRACE score >140 points	37 (77.0)	99 (51.5)	0.002

Values are median [ranges] or *n* (%). BMI, body mass index; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LBBB, left bundle branch block; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; HR, heart rate; SBP, systolic blood pressure. CKD was defined as estimated GFR <60 mL/min/1.73 m² calculated using the Modification of Diet in Renal Disease method.

Mann-Whitney U test for quantitative variables and the χ^2 test for qualitative variables. Data distribution was verified with the Smirnov-Kolmogorov test. Kaplan-Meier curves were used to present the unadjusted time-to-event data for investigated endpoints. Additionally, multivariable modeling was performed using the Cox proportional hazards method to assess the adjusted association between all endpoints and DES type. All tests were 2-tailed. *p* < 0.05 was considered significant.

Table 2. Drug therapy according to the presence of CKD

	CKD+ <i>n</i> = 331 (17.3%)	CKD– <i>n</i> = 1,577 (82.7%)	<i>p</i>
ASA	324 (98.4)	1,555 (98.7)	0.848
Clopidogrel	325 (98.7)	1,556 (98.8)	0.863
Glycoprotein IIb/IIIa inhibitors	11 (3.3)	84 (5.3)	0.166
β-Blockers	297 (90.2)	1,413 (89.7)	0.861
ACEI	238 (72.3)	1,271 (80.7)	<0.001
ARB	39 (11.8)	190 (12.0)	0.986
Statins	303 (92.0)	1,480 (94.0)	0.235
Ca blockers	122 (37.0)	399 (25.3)	<0.001
VKA	34 (10.2)	59 (3.7)	<0.001
Prasugrel	–	0.3	0.666

Figures are numbers, with percentages in parentheses. ASA, acetylsalicylic acid; VKA, vitamin K antagonists; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca blockers, calcium channel blockers.

Results

Demographics

During the 24 months between January 2009 and December 2010, 1,908 patients were admitted with the following diagnoses: unstable angina (*n* = 1,493, 78.2%), non-ST-segment elevation myocardial infarction (*n* = 284, 14.8%), and ST-segment elevation myocardial infarction (STEMI/left bundle branch block) (*n* = 131, 6.8%). There were 679 females (35.5%) and 1,229 males (64.5%). CKD was present in 331 (17.3%) patients (163 men [49.2%] and 168 women [50.7%], *p* < 0.001). According to the eGFR, the most common type of CKD was moderate CKD, i.e., between stages 3A and 3B (eGFR 30–59 mL/min/1.73 m²; *n* = 299 [90.3%]), followed by severe CKD, i.e., stage 4 (eGFR 15–29 mL/min/1.73 m²; *n* = 21 [6.3%]), and the least common type was end-stage CKD, i.e., stage 5 (eGFR <15 mL/min/1.73 m²; *n* = 11 [3.3%]). In the total population of ACS patients, the median eGFR value was 82 (IQR: 66.8–94.2 mL/min/1.73 m²) and the respective values for STEMI/left bundle branch block, non-ST-segment elevation myocardial infarction, and unstable angina were 87.7 (IQR: 74.1–101.0 mL/min/1.73 m²), 76.8 (IQR: 60.9–91.7 mL/min/1.73 m²), and 82.9 (IQR: 67.5–93.9 mL/min/1.73 m²).

Comorbidities and Chronic Medications

Patients with CKD presented a higher angina Canadian Cardiovascular Society class at baseline, were older, more often females, and had a higher prevalence of comorbidities (hypertension, diabetes, lung disease, peripheral artery disease, and anemia). Also, they more often had Global Registry of Acute Coronary Events (GRACE) risk scores over 140 points (72.0 vs. 51.5%, *p* = 0.002). They more frequently had a history of MI and PCI in comparison to patients without CKD. The patient's data are summarized in Table 1. There were no differences in peri- and postprocedural medical treatment regimens in both groups except that CKD patients less often received angiotensin-converting enzyme inhibitors, but more often vitamin K antagonists and calcium channel blockers (Table 2).

Left Ventricular Function

Left ventricular ejection fraction (LVEF) values were available in 98.7% of all patients. In the general population, the LVEF was normal in 70% patients, moderately reduced (31–50%) in

Table 3. Angiographic and procedural data according to the presence of CKD

	CKD+ n = 331 (17.3%)	CKD– n = 1,577 (82.7%)	p
SYNTAX score, points	16 [8–26]	14 [8–23]	0.314
DES-I	100 (30.2)	542 (34.3)	0.164
DES-II	231 (69.7)	1,035 (65.6)	
Number of vessels with significant stenosis			
1	99 (29.9)	611 (38.7)	0.003
2	119 (35.9)	559 (35.4)	0.911
3	113 (34.1)	407 (25.8)	0.002
Type of the culprit lesion (AHA/ACC)			
A	76 (22.9)	347 (22.0)	0.757
B	204 (61.6)	991 (63.2)	0.725
B/C	5 (1.5)	7 (0.4)	0.064
C	46 (13.8)	232 (14.7)	0.767
Target vessel			
Left main	27 (8.1)	98 (6.2)	0.239
Left anterior desc	142 (42.9)	829 (52.5)	0.001
Left circumflex	59 (17.8)	278 (18.1)	0.995
Right coronary artery	75 (22.6)	304 (19.2)	0.184
Arterial bypass graft	2 (0.6)	9 (0.5)	0.744
Saphenous vein graft	26 (7.8)	59 (3.7)	0.001
Extensive calcifications	23 (6.9)	63 (3.9)	<0.001
Stent thrombosis in culprit lesion	10 (3.0)	24 (1.6)	<0.001
Average stent diameter, mm	3 [2.5–3.5]	3 [2.7–3.5]	0.334
Total stent length, mm	23 [16–30]	22 [15–28]	0.248

Values are n (%) or median [ranges]. DES-I, first-generation drug-eluting stents; DES-II, second-generation drug-eluting stents.

24% and severely ($\leq 30\%$) reduced in 6% of patients. Patients with CKD had lower LVEF values as compared to patients with no CKD (50, IQR 40–55 vs. 55, IQR 46–60, $p < 0.001$) (Table 1).

Interventional Treatment and Reperfusion Strategy

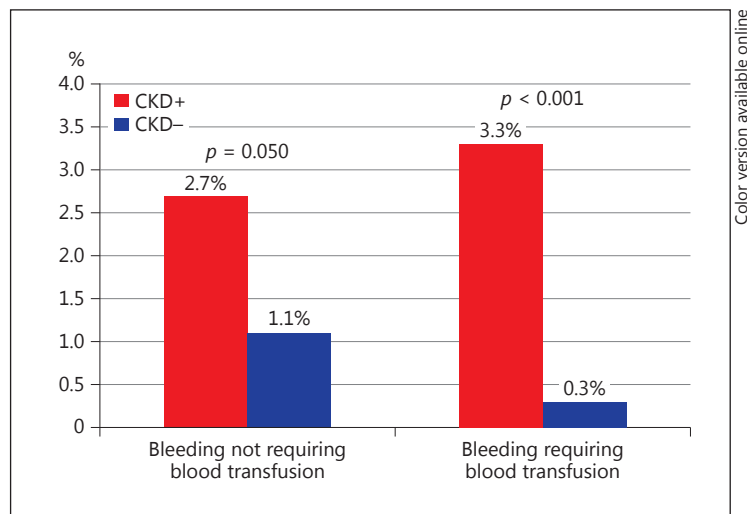
Although the SYNTAX score was comparable in patients with or without CKD, patients with CKD more often had multivessel disease, evidence of thrombus in culprit lesion, and extensive coronary calcifications. First- and second-generation DES were used with similar frequency in patients with and without CKD (Table 3).

In-Hospital and 30-Day Outcomes

There was a significantly higher rate of in-hospital bleedings requiring blood transfusion in patients with CKD (3.3 vs. 0.3%, $p < 0.001$) as compared to those with normal renal function (Fig. 1), especially in patients with CKD and reduced LVEF (CKD 1.7% vs. non-CKD 0.5%, $p < 0.001$). Patients with CKD more often had cardiogenic shock (2.4 vs. 0.6%, $p = 0.006$) and resuscitated cardiac arrest (3.0 vs. 0.8%, $p = 0.002$) during hospitalization. Also, the risk of respiratory insufficiency was higher in CKD (2.1 vs. 0.2, $p < 0.001$). Even so, we did not observe differences in rates of acute and subacute ST in patients with and without CKD (Table 4).

Twelve-Month Outcomes

The 12-month follow-up showed that there was a 46% higher risk of MACCE (17.8 vs. 12.6%, HR = 1.46 [95% CI 1.05–2.03], $p = 0.009$) and death (8.4 vs. 2.3%, HR = 3.9 [95% CI

Fig. 1. In-hospital follow-up: bleeding complications according to the presence of CKD.**Table 4.** In-hospital, 30-day and 1-year follow-up according to the presence of CKD

	CKD+ n = 331 (17.3%)	CKD- n = 1,577 (82.7%)	p
In-hospital adverse events			
Cardiogenic shock	8 (2.4)	10 (0.6)	0.006
Respiratory insufficiency	7 (2.1)	4 (0.2)	<0.001
Cardiac arrest	10 (3.0)	13 (0.8)	<0.001
Stent thrombosis			
Acute stent thrombosis	0 (0)	10 (0.6)	0.301
Subacute stent thrombosis	1 (0.3)	6 (0.3)	0.775
Late stent thrombosis	3 (0.9)	2 (0.1)	0.454

Figures are numbers, with percentages in parentheses.

2.0–7.5], $p < 0.001$) in CKD patients. We did not observe differences in rates of TVR, MI and stroke (Fig. 2, 3). The rate of late ST did not differ significantly between patients with and without CKD ($p = 0.454$) (Table 4). Multivariable Cox analysis revealed that CKD was an independent risk factor for death (HR = 2.1 [95% CI 1.2–3.6], $p = 0.004$) after PCI at the 1-year follow-up (Table 5). There was no difference in death and MACCE according to the type of DES (DES-I vs. DES-II) (Fig. 4, 5).

Discussion

The following report revealed that a high proportion (17.3%) of patients hospitalized with ACS and DES implantation suffered from CKD, and confirmed previous data that CKD is a strong risk factor of death at the 12-month follow-up [11, 12]. Furthermore, our study is the first to present that the introduction of DES-II did not bring benefit in CKD patients at the 12-month follow-up, which is a contrast to the non-CKD population [13].

Similarly to other studies, CKD patients in the presented registry carried a higher risk of adverse events, they were older [2, 11, 12, 14–16], were more often females [11, 14, 16], and

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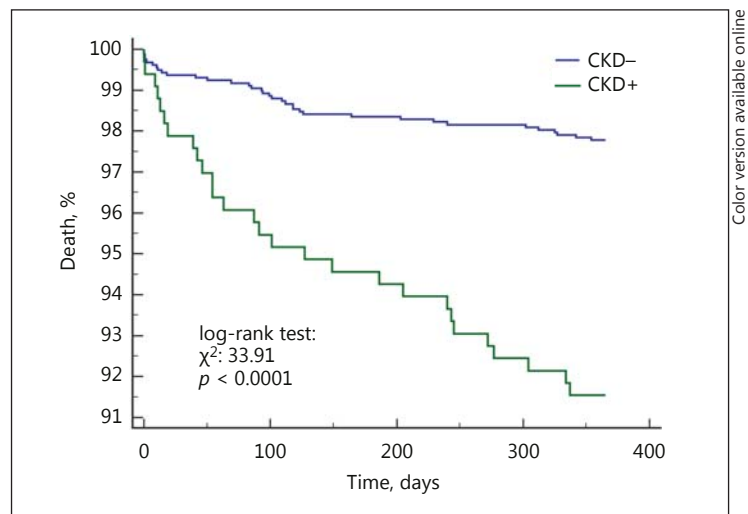


Fig. 2. Kaplan-Meier curves for all-cause mortality in patients with and without CKD.

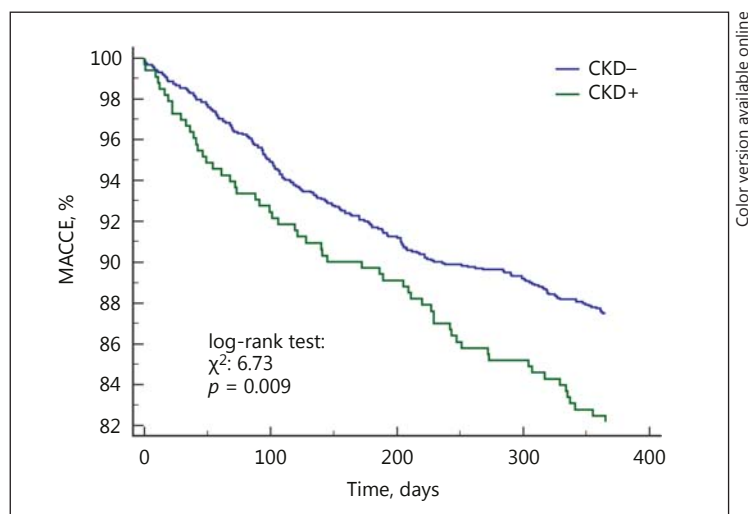


Fig. 3. Kaplan-Meier curves for MACCE in patients with and without CKD.

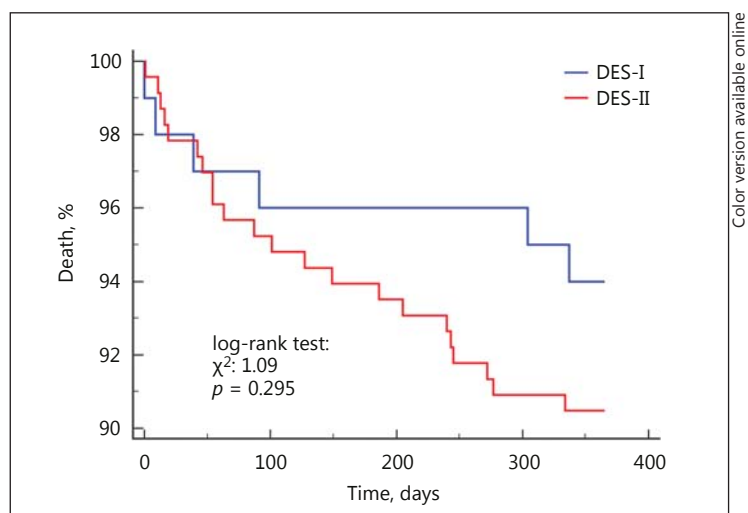


Fig. 4. Kaplan-Meier curves for all-cause mortality in patients with CKD treated with DES-I vs. DES-II.

Fig. 5. Kaplan-Meier curves for MACCE in patients with CKD treated with DES-I vs. DES-II.

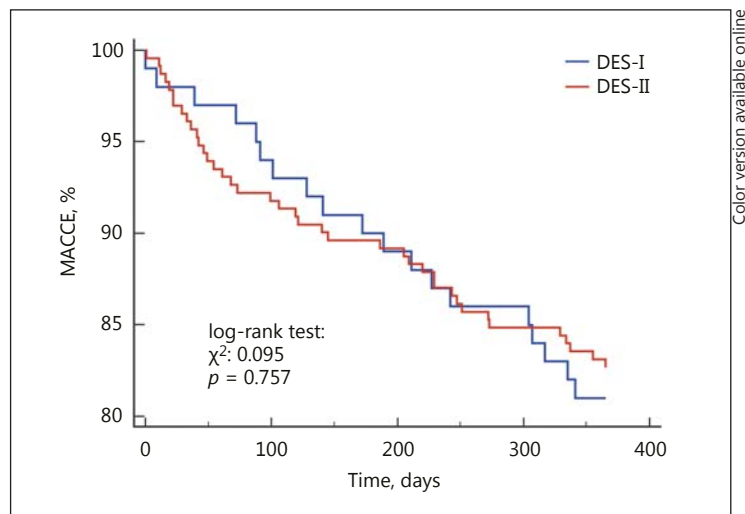


Table 5. Multivariable Cox analysis

	<i>p</i>	HR	95% CI
Chronic kidney disease	0.004	2.175	1.28–3.69
Anemia	0.334	1.342	0.73–2.49
Diabetes mellitus	0.088	1.554	0.93–2.57
PAD	0.007	2.213	1.24–3.93
LVEF <50%	<0.001	6.138	2.99–12.58
Age >65 years	0.004	2.3851	1.32–4.28
Previous MI	0.723	1.100	0.65–1.86

PAD, peripheral artery disease; LVEF, left ventricular function; MI, myocardial infarction.

had a higher percentage of comorbidities, such as hypertension [11, 14–16], diabetes [12, 15, 16], peripheral artery disease [11, 16], and more severe CV disease [14, 15].

In addition to that, these patients more often had a history of CV events, myocardial revascularization (PCI, coronary artery bypass graft) and had a higher GRACE risk score as compared to patients without CKD, which was also observed in other studies [15, 16]. Besides that, the current analysis revealed that only 48.9% patients with MI had normal LVEF, and moderate and severe LVEF dysfunction was significantly more frequent in patients with CKD.

It is well proven that patients with CKD have a worse prognosis compared with patients with normal renal function [11, 12]. As observed in other studies, the incidence of adverse CV events during hospitalization was higher in CKD patients [12, 17]. In the present study, patients with CKD more often had cardiogenic shock and cardiac arrest during hospitalization. In the 12-month follow-up, rates of MACCE were also significantly higher in patients with CKD.

Moreover, survival for patients with CKD was lower than for those without CKD. Several studies demonstrated the adverse effects of CKD. Barthelemy et al. [14] provided evidence that patients with CKD had an increased risk of CV death and MACCE at the 1-year follow-up, with a stepwise increase according to creatinine clearance. Manjunath et al. [18] reported

that the level of kidney function is an independent risk factor for CVD, de novo CVD, and all-cause mortality in elderly subjects. However, the creatinine clearance threshold value that predicts possible adverse CV events would be most helpful in deciding on optimal intervention to improve outcomes.

Santopinto et al. [2] reported that the value of creatinine clearance is an important independent predictor of major bleeding in ACS patients. In the current study, there was an increase in bleedings requiring blood transfusion in patients with CKD. The association of CKD with the incidence of major bleeding was also related to a higher risk in a subpopulation of patients with a reduction in LVEF. In patients with reduced LVEF, the risk of bleeding requiring blood transfusion was higher when CKD was present. Data from the other studies showed a strong association between CKD and increased risk of bleeding in patients with ACS managed invasively [19, 20]. Bleeding rates are more than 3-fold higher in patients with non-ST-segment elevation ACS with CKD compared with patients without CKD [17]. According to the VALIANT Trial baseline, renal insufficiency is one of the independent predictors of gastrointestinal bleeding in patients with STEMI. Moreover, a 10 mL/min/1.73m² decrement in eGFR was associated with 18% increase in the hazard of gastrointestinal bleeding [20]. In the study by Mathis and Gugger [19], the major influences on bleeding risk appeared to be creatinine clearance <30 mL/min/m², whereas other markers of renal function, including serum creatinine value and serum creatinine at a cutoff level of 1.5 mg/dL did not predict bleeding events. All of that together suggests a need for an individualized approach with adequate antiplatelet treatment in patients with CKD to decrease thrombotic events without increasing bleeding [21, 22].

Analysis of available angiographic data demonstrated that the population of patients with and without CKD differed in terms of the complexity of coronary atherosclerotic lesions. Patients with CKD more often had a multivessel disease and PCI of saphenous vein graft as compared to patients with a normal eGFR, which is in keeping with previous observations [11, 14, 16, 23]. In addition to that, CKD patients more often had ST at culprit lesion in our group, which confirmed results of Miao et al. [24]. Data from other studies showed that PCI with DES-II in a real-world population is associated with lower risk of clinically meaningful restenosis, ST, and a lower risk of death compared with DES-I [25, 26]. There is limited data comparing DES-I with DES-II in CKD. Our results suggest that the use of new-generation DES (everolimus-, zotarolimus-, and biolimus-eluting stents) in CKD patients does not attenuate the high risk of MACCE and death at the 1-year follow-up. This finding echoes Chan et al. [27] who compared DES-I and DES-II in CKD, but in a 2-year follow-up. As in our study, they did not observe any significant difference in terms of safety and efficacy between the 2 generations of DES. It seemed that a general worse survival of patients with CKD shadowed the benefits of DES-II implantation. Moreover, we had previously shown that the use of DES-II versus DES-I in patients with anemia is associated with the same risk of MACCE and TVR at the 1-year follow-up [28], but in diabetic patients DES-II has a lower risk of ST and similar MACCE rate compared to DES-I [29].

Study Limitations

There are several limitations of the study. First of all, it was not a randomized, but a retrospective study. On the other hand, in our opinion, the limitation is offset (at least in part) by the “all-comer” inclusion criteria, 100% follow-up rate and conformation of the endpoints by the National Health Service database. Secondly, data about the pharmacotherapy before the admission and data about the adherence to dual antiplatelet therapy after PCI were unavailable.

Conclusion

CKD patients had an increased risk of in-hospital bleeding requiring blood transfusion and had a higher risk of death at the 12-month follow-up. Unfortunately, the use of second-generation DES did not decrease the risk of MACCE in CKD patients.

Statement of Ethics

The Institutional Ethics Committee has been approached and their decision was that the registry does not require formal approval. The patients' data were anonymized and as such processed and statistically analyzed. The patients' data were protected according to the requirements of Polish law and hospital SOPs.

Disclosure Statement

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