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Impact of chronic kidney disease and diabetes on clinical outcomes in women undergoing PCI

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KEYWORDS

- death
- diabetes
- drug-eluting stent
- miscellaneous
- renal insufficiency

Abstract

Background: For women undergoing drug-eluting stent (DES) implantation, the individual and combined impact of chronic kidney disease (CKD) and diabetes mellitus (DM) on outcomes is uncertain.

Aims: We sought to assess the impact of CKD and DM on prognosis in women after DES implantation.

Methods: We pooled patient-level data on women from 26 randomised controlled trials comparing stent types. Women receiving DES were stratified into 4 groups based on CKD (defined as creatine clearance <60 mL/min) and DM status. The primary outcome at 3 years after percutaneous coronary intervention was the composite of all-cause death or myocardial infarction (MI); secondary outcomes included cardiac death, stent thrombosis and target lesion revascularisation.

Results: Among 4,269 women, 1,822 (42.7%) had no CKD/DM, 978 (22.9%) had CKD alone, 981 (23.0%) had DM alone, and 488 (11.4%) had both conditions. The risk of all-cause death or MI was not increased in women with CKD alone (adjusted hazard ratio [adj. HR] 1.19, 95% confidence interval [CI]: 0.88-1.61) nor DM alone (adj. HR 1.27, 95% CI: 0.94-1.70), but was significantly higher in women with both conditions (adj. HR 2.64, 95% CI: 1.95-3.56; interaction p-value <0.001). CKD and DM in combination were associated with an increased risk of all secondary outcomes, whereas alone, each condition was only associated with all-cause death and cardiac death.

Conclusions: Among women receiving DES, the combined presence of CKD and DM was associated with a higher risk of the composite of death or MI and of any secondary outcome, whereas alone, each condition was associated with an increase in all-cause and cardiac death.

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Abbreviations

ACS	acute coronary syndrome
BMS	bare metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCS	chronic coronary syndrome
CKD	chronic kidney disease
CrCl	creatinine clearance
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DM	diabetes mellitus
HR	hazard ratio
KDIGO	Kidney Disease Improving Global Outcomes
MI	myocardial infarction
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
ST	stent thrombosis
TLR	target lesion revascularisation
TWILIGHT	Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention
WIN-DES	Women in Innovation and Drug-Eluting Stents

Introduction

Chronic kidney disease (CKD) and diabetes mellitus (DM) are 2 common comorbid conditions in patients undergoing percutaneous coronary intervention (PCI) and are associated with increased morbidity and mortality, especially when both are present[1-3]. Among CKD patients, concomitant DM is frequent and one of the main causes of CKD[4]. Additionally, patients with DM frequently develop CKD due to DM-related microvascular changes within the kidney, an entity referred to as diabetic kidney disease[5].

Women undergoing PCI sustain poorer clinical outcomes than men, due to their older age and a higher burden of comorbidities, including CKD and DM[6]. Prior studies assessing how the presence of DM and CKD affect cardiovascular outcomes in women undergoing PCI have considered the prognostic impact of these conditions separately and not in combination[7-10].

The WIN-DES (Women in Innovation and Drug-Eluting Stents) database was formed by pooling patient-level data of women treated with coronary stents from 26 randomised controlled trials (RCTs) to obtain new sex-specific evidence concerning drug-eluting stents (DES) and to address the underrepresentation of women in RCTs[11].

In this study, we sought to examine the individual as well as the combined effects of CKD and DM on adverse events among women undergoing PCI included in this large pooled dataset.

Methods

STUDY POPULATION

The study design and rationale of the WIN-DES database have been previously described[11]. In summary, patient-level data of female participants from 26 randomised trials comparing different stent types (bare metal stent [BMS], first-generation or current-generation drug-eluting stents [DES]) in patients with acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) undergoing PCI were pooled. Characteristics of the included trials are described in **Supplementary Table 1**. Dual antiplatelet therapy (DAPT) duration ranged from 2 to 24 months. All included studies complied with the provisions of the Declaration of Helsinki, and the institutional review board at each site approved the study protocol. All patients provided written informed consent before enrolment in each study.

For the purpose of the present analysis, women who received either first- or current-generation DES were stratified into 4 groups based on the presence of CKD and DM at baseline: 1) without CKD/DM, 2) with CKD alone, 3) with DM alone, and 4) with both CKD and DM. CKD was defined as baseline creatinine clearance (CrCl) <60 mL/min/1.73 m^2 at the time of enrolment, according to the Kidney Disease Improving Global Outcomes (KDIGO) definition[12]. Patients were labelled as diabetic if this condition was present at baseline and irrespective of the type of antidiabetic treatment. Patients who received BMS or had no available data on baseline CrCl or DM were excluded.

CLINICAL OUTCOMES

The primary outcome was the composite of all-cause death or myocardial infarction (MI) at 3-year follow-up after index PCI. Secondary outcomes included the individual components of the primary outcome, cardiac death, definite or probable stent thrombosis (ST), and target lesion revascularisation (TLR). The endpoint definitions used in each included study are listed in **Supplementary Table 2**.

STATISTICAL ANALYSIS

A prespecified extraction sheet was used for the collection of patient-level data from all 26 randomised trials. Baseline clinical and procedural characteristics were compared across all 4 groups using the chi-square test for categorical variables and the Student's t-test for continuous variables. The Kaplan-Meier method was used to estimate the cumulative event rates for the primary and secondary endpoints, and the log-rank test was used to compare the event rates across the 4 groups. Multivariable Cox proportional hazards regression models were used to calculate the risk of primary and secondary endpoints using patients without DM and CKD as the reference group. The models included a frailty term (γ) to assess random effects in the trials[13,14]. Risks were expressed as hazard ratios (HR) and 95% confidence intervals (CI). The multivariable model was adjusted for the following clinically relevant characteristics: age, body mass index (BMI), hypertension, hypercholesterolaemia, prior MI, prior revascularisation (including PCI or coronary artery bypass graft [CABG] surgery), indication for PCI (CCS vs ACS), stent type (first- vs current-generation DES), number of stents implanted, and multivessel disease. A p-value for interaction between DM/CKD status was calculated. The total follow-up time was defined as the time from index procedure until death or last follow-up

date (whichever occurred first). In addition, a sensitivity analysis was performed to assess risks associated with CKD or DM individually according to their severity (based on CrCl and on concomitant insulin treatment, respectively). We reported 2-sided p-values and considered p-values <0.05 to be significant. The consistency of the effect across the 4 groups was assessed with an interaction test. All analyses were performed with STATA version 16.0 (Stata Corp).

Results

STUDY POPULATION

A total of 11,557 women were included in the pooled dataset of 26 RCTs. After exclusion of 1,108 patients who received BMS and 6,180 with missing data on CrCl or DM, 4,269 women were included in this analysis **(Figure 1)**. The mean age was 67.7±10.5 years, 45.1% presented with ACS, 27.3% had multivessel disease, and 50.6% received a newer-generation DES. Within the included population, 1,822 (42.7%) had no CKD/DM, 978 (22.9%) had CKD alone, 981 (23.0%) had DM alone, and 488 (11.4%) had both CKD and DM. The prevalence of insulin-dependent DM and CKD severity were similar in the groups that included DM or CKD patients, respectively **(Table 1)**.

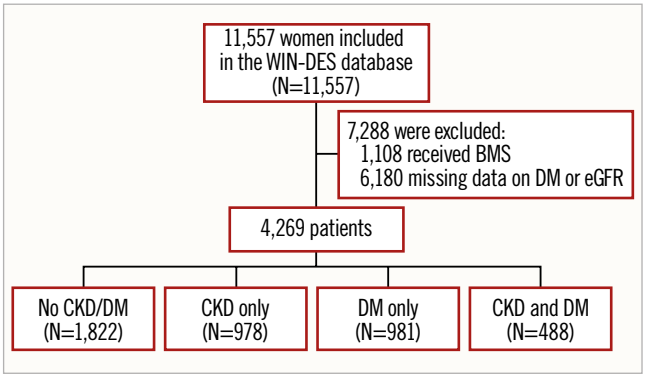

Figure 1. *Patient flowchart. BMS: bare metal stent; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; WIN-DES: Women in Innovation and Drug-Eluting Stents*

CLINICAL OUTCOMES AT 3-YEAR FOLLOW-UP

In the transition from patients without CKD/DM to those with CKD or DM alone and to patients with both these conditions, a significant stepwise increase in 3-year rates was observed for all-cause death or MI (7.2%, 11.9%, 8.8% and 23.4%, respectively; p<0.001) **(Figure 2)**, all-cause death (2.4%, 7.6%, 4.5%, 15.7%; p<0.001) **(Figure 3)** and cardiac death (1.2%, 4.0%, 2.3%, 10.1%; p<0.001). Rates of MI were similar between women without CKD/DM (5.1%), with CKD only (5.7%) and DM only (5.4%) but significantly higher in patients with CKD and DM (12.4%) **(Figure 3)**. Similarly, definite or probable ST was generally rare in patients without CKD or DM (1.0%) or with only one of these conditions (CKD only: 0.9%; DM only: 1.6%) but significantly increased in patients with both CKD and DM (4.0%). TLR occurred in 5.0% of women without CKD/DM or with CKD only; however, the incidence of TLR was significantly increased in patients with DM only (9.1%) and those with both CKD and DM (9.4%) **(Figure 4)**.

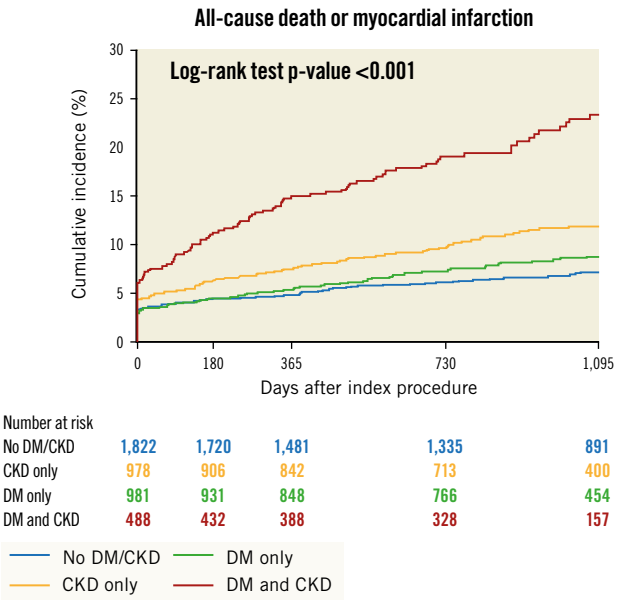

Figure 2. *Kaplan-Meier curves for all-cause death or myocardial infarction at 3 years. CKD: chronic kidney disease; DM: diabetes mellitus*

Women with CKD were on average 10 years older, with lower BMI and higher creatinine values irrespective of concomitant DM. As compared to the group without CKD/DM, women with CKD and/or DM were more likely to have hypertension, hypercholesterolaemia, established coronary artery disease (i.e., prior MI, prior PCI or prior CABG), multivessel disease, type B2 or C lesions or lesions with moderate or severe calcification, and to have a greater total stent length implanted, particularly in women with both CKD and DM **(Table 1)**. Presentation with CCS at the time of index PCI was more common in diabetic patients with or without CKD. Current-generation DES were implanted in about 50% of women across the 4 groups.

After multivariable adjustment for potential confounders, DM and CKD in combination were independently associated with an increased risk of all-cause death or MI (HR 2.64, 95% CI: 1.95-3.56; p<0.001), MI (HR 2.00, 95% CI: 1.36-2.94; p<0.001) and definite or probable ST (HR 3.28, 95% CI: 1.51-7.16; p=0.003) at 3 years **(Figure 4)**. The risk of all-cause death and cardiac death was increased by about 2-fold in the presence of CKD or DM alone and by about 5- and 6-fold, respectively, in women with both conditions. The risk of TLR was enhanced in women with DM, irrespective of the concomitant presence of CKD. The increase in all-cause or cardiac death associated with CKD alone was largely determined by women with moderate/severe CKD **(Supplementary Table 3)**. The

Table 1. Baseline and procedural characteristics.

Variable	No DM/CKD n=1,822	CKD only n=978	DM only n=981	DM and CKD n=488	*p*-value
Baseline characteristics					
Age, years	63.8±9.9	75.1±7.8	64.2±9.3	74.6±8.3	<0.01
BMI, kg/m^2	28.2±5.2	24.4±4.1	31.0±6.2	26.3±5.0	<0.01
Hypertension	1,227 (67.3)	778 (79.6)	831 (84.7)	438 (89.8)	<0.01
Hypercholesterolaemia	1,208 (66.3)	645 (66)	740 (75.4)	346 (70.9)	<0.01
Insulin-dependent DM	0 (0)	0 (0)	307 (31.3)	161 (33.0)	<0.01
Smoking	793 (43.5)	259 (26.5)	313 (31.9)	81 (16.6)	<0.01
Family history of CAD	697 (39.3)	263 (28.1)	321 (34.3)	104 (22.7)	<0.01
Prior MI	323 (17.7)	209 (21.4)	218 (22.2)	123 (25.2)	<0.01
Prior PCI	277 (15.2)	204 (20.9)	240 (24.5)	160 (32.8)	<0.01
Prior CABG	54 (3.0)	63 (6.4)	68 (6.9)	38 (7.8)	<0.01
Creatinine, mg/dL	0.8±0.2	1.2±1.0	0.8±0.2	1.5±1.5	<0.01
Chronic kidney disease	0 (0)	978 (100)	0 (0)	488 (100)	<0.01
Mild (CrCl 45-59 mL/min)	0 (0)	565 (57.8)	0 (0)	246 (50.4)	<0.01
Moderate-severe (CrCl <45 mL/min)	0 (0)	381 (39.0)	0 (0)	222 (45.5)	<0.01
LVEF, %	52.5±23.2	54.9±18.0	54.2±19.6	53.0±17.8	0.06
Indication for PCI					0.04
ACS	835 (46.5)	447 (47)	404 (42.7)	195 (41.2)	
CCS	960 (53.5)	505 (53)	543 (57.3)	278 (58.8)	
Procedural characteristics					
Multivessel disease	379 (20.8)	292 (29.9)	285 (29.1)	209 (42.8)	<0.01
Lesions per patient	1.3±0.6	1.3±0.6	1.3±0.6	1.4±0.7	<0.01
Number of stents per patient	1.5±0.9	1.5±0.9	1.5±0.9	1.6±1.0	<0.01
Mean stent diameter, mm	3.0±0.4	2.9±0.4	2.9±0.4	2.9±0.4	<0.01
Mean stent length, mm	29.0±19.8	29.9±19.5	29.8±19.0	33.2±22.7	<0.01
Moderate/severe calcification	410 (24.2)	283 (33.5)	246 (26.8)	139 (32.3)	<0.01
At least one type B2 or C lesion	1,042 (58.1)	635 (66.5)	602 (62.6)	344 (72.7)	<0.01
At least one bifurcation lesion	120 (22.3)	72 (20.1)	81 (23.0)	46 (21.0)	0.78
Type of stent implanted					
First-generation DES	870 (47.7)	506 (51.7)	491 (50.1)	244 (50.0)	0.23
Current-generation DES	952 (52.3)	472 (48.3)	490 (49.9)	244 (50.0)	

Data are presented as n (%) or mean±SD. ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCS: chronic coronary syndrome; CKD: chronic kidney disease; CrCl: creatinine clearance; DES: drug-eluting stent; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation

risks associated with DM alone were consistent, irrespective of concomitant insulin treatment **(Supplementary Table 4)**.

Discussion

In this pooled analysis of patient-level data of 4,269 women from 26 randomised coronary stent trials, we evaluated the independent and combined impact of DM and CKD on adverse outcomes at 3 years after PCI.

The key findings for women undergoing PCI are as follows:

1) more than 50% had CKD or DM, and approximately 11% had both these conditions;
2) CKD and DM in combination were associated with an increased risk of death or MI and of any secondary outcomes;
3) CKD and DM in isolation predicted a higher risk of all-cause death and cardiac death;
4) DM was related to an increased risk of TLR irrespective of the CKD status.

Although the individual effect of DM and CKD on cardiac complications following PCI has been well demonstrated in women-specific cohorts, to date no report has examined the joint prognostic impact of these 2 conditions[7-10].

The prevalence of DM and CKD in combination in our women-only cohort (11.4%) was in keeping with that reported in prior male-predominant observational studies (10-22%)[2,3,15] and slightly higher than in previous RCTs (5-8%)[16-18], in which no more than 30% of participants were women. As previously observed,

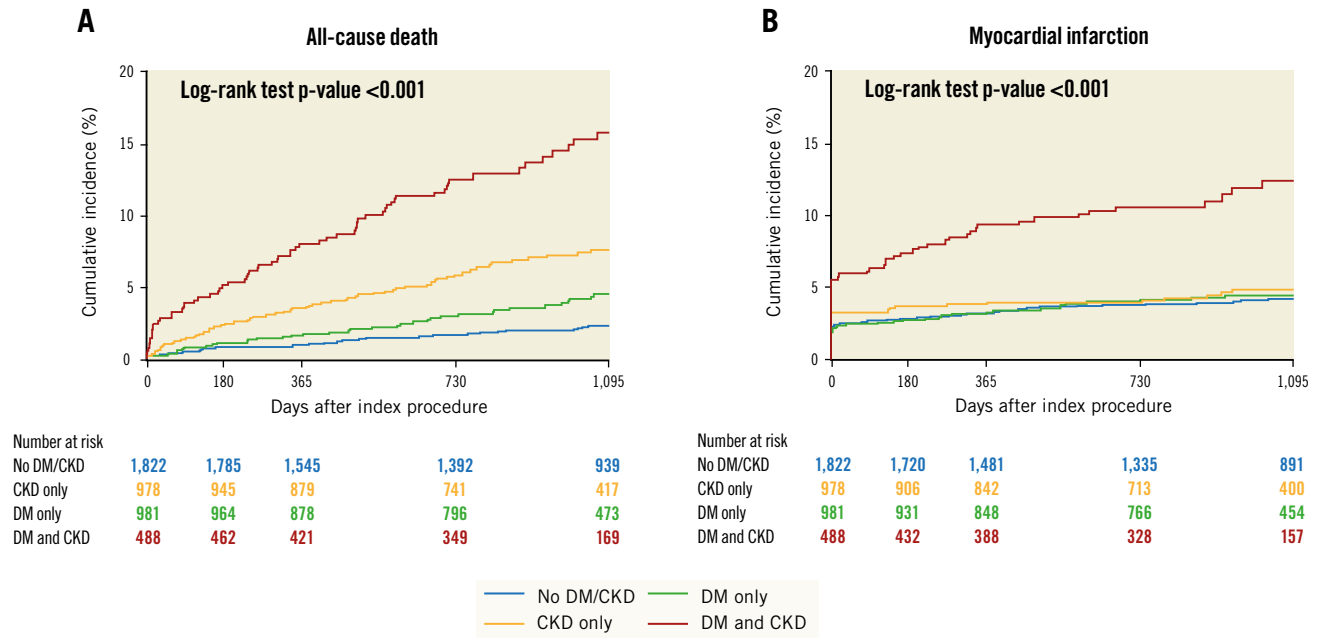

Figure 3. *Kaplan-Meier curves for 3-year outcomes. Kaplan-Meier curves for all-cause death (A) and myocardial infarction (B). CKD: chronic kidney disease; DM: diabetes mellitus*

CKD patients were on average 10 years older than those without CKD[3,15,17]. Women with CKD, DM or both conditions had a higher burden of comorbidities and were more likely to present with multivessel disease or complex lesions. The combination of CKD and DM conferred a significantly higher risk of the composite of all-cause death or MI and its individual components, of cardiac death, definite or probable ST and TLR at 3 years. Conversely, CKD or DM individually were associated with a 2-fold greater risk of all-cause or cardiac death, but were not related to an increased risk of the primary outcome, MI or ST. In women with DM, the hazard of TLR was significantly increased, irrespective of concomitant CKD status. The risks associated with CKD were largely determined by women with moderate/severe CKD.

Our results suggest that poor outcomes in women with either CKD or DM are largely driven by those with both coexisting conditions[7-10]. The additive effect of CKD and DM observed in the present study is consistent with previous observational reports and RCTs enrolling predominantly men[2,3,15-18]. In addition, pharmacodynamic studies revealed that the combination of DM and CKD confers a synergistic effect on residual platelet reactivity when compared to either condition alone[19,20].

Conversely, the prognostic effect of CKD alone and DM alone noted in the present women-specific analysis partly differs from previous studies that included mostly men. Indeed, in the present study, CKD alone as compared to DM alone was associated with higher crude rates of all-cause death (7.6% vs 4.5%) and cardiac death (4.0% vs 2.3%); however, after adjustment for baseline imbalances (including age), both CKD and DM were associated with a similar risk increase (about 2-fold) for these two outcomes. These findings are in keeping with one previous RCT that provided adjusted risks for adverse outcomes[16] but are in contrast with observational studies in which CKD remained, after adjustment, a more relevant predictor of mortality than DM[2,3,15]. Additionally, in the present analysis, DM alone was related to a higher risk of ST and TLR than CKD alone, whereas in previous observational studies, CKD alone and DM alone had a similar impact on these complications[2,3,15].

These discrepancies are mostly explained by the exclusion of CKD patients with advanced disease (i.e., glomerular filtration rate [GFR] <30 mL/min) from most of the RCTs, in which the CKD groups had a better prognosis. In the present study, moderate and severe CKD (i.e., GFR <45 mL/min) was associated with a higher mortality than mild CKD (i.e., GFR 45-59 mL/min) or DM alone. These differences in prior non-women-specific studies might also be due to a different prognostic impact of CKD and DM in women, but the mechanism is unclear.

In aggregate, our observations suggest that even though DM and CKD are interrelated and share common pathophysiological mechanisms that lead to accelerated atherosclerosis and enhanced blood thrombogenicity[21,22], DM alone might induce a faster progression of coronary artery disease (CAD) and be a stronger risk factor for stent-related complications than CKD alone. However, since the risks of MI and ST were not significantly increased in women with CKD or DM alone, the higher all-cause and cardiac mortality in these patients is probably explained by sudden cardiac death, heart failure or non-cardiac causes. Among CKD patients, anaemia, volume overload, and hypertension may also have a relevant impact on mortality[23,24].

Optimal medical therapy together with percutaneous or – especially in diabetic patients with extended CAD – surgical coronary

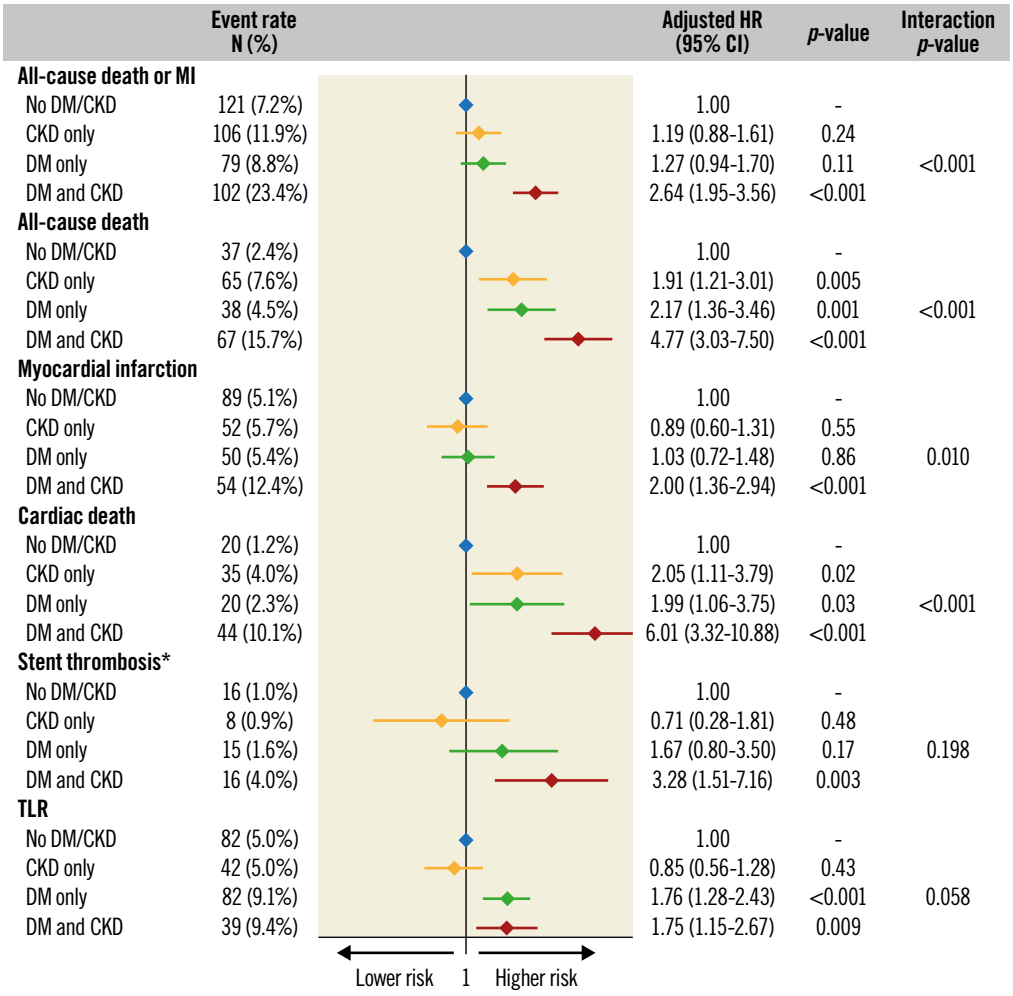

Figure 4. *Adjusted risk of adverse events at 3 years. *definite or probable. CI: confidence interval; CKD: chronic kidney disease; DM: diabetes mellitus; HR: hazard ratio; MI: myocardial infarction; TLR: target lesion revascularisation*

revascularisation have been demonstrated to decrease morbidity and mortality related to CAD, irrespective of concomitant DM or CKD[25,26]. A recent analysis of the TWILIGHT trial showed that ticagrelor monotherapy results in fewer bleeding complications without increasing ischaemic risk in patients with CKD, DM or both conditions[16]. Other interventions that attenuate the risks of adverse events in patients with CKD or DM include lipid-lowering agents, sodium-glucose cotransporter-2 inhibitors[27,28], as well as the use of new stent technologies like the ABLUMINUS DES+ (Concept Medical; a biodegradable polymer sirolimus-eluting stent)[29].

In summary, our study provides valuable insights on how the prognosis of women undergoing PCI is affected by the interaction between DM and CKD and highlights the utility of stratifying women according to these 2 comorbidities for decision-making on therapy and further management.

Limitations

The study findings should be interpreted in light of the following limitations. First, since data were pooled from 26 RCTs mostly excluding patients with severe CKD, the prognostic impact of this condition might have been underestimated. Secondly, even if we had included "trial" as a random effect in our adjusted analyses, differences between the pooled RCTs concerning study design, inclusion/exclusion criteria, follow-up duration and enrolment at different time periods might have affected the results. Thirdly, despite adjusting for several clinically relevant baseline characteristics, residual confounding may still exist. For example, data on the type or duration of antithrombotic therapy, as well as adherence during follow-up, were lacking. Similarly, some confounders that reflect disease severity (e.g., haemoglobin A1C in DM) were not available. Of note, about 50% of the women included received a first-generation DES, devices that are no longer used in contemporary practice given their inferior safety and efficacy as compared to the current-generation stents. Therefore, the absolute rates of adverse events might be slightly higher than expected because of the use of first-generation DES. However, it is unlikely that the CKD- and DM-related risks have been significantly biased by the high proportion of these devices, the use of which was similar across the 4 CKD/DM categories. Furthermore, data on bleeding

events were not available. Finally, these results apply only to women undergoing PCI with DES implantation.

Conclusions

Among women receiving DES, the combined presence of CKD and DM was associated with a higher risk of the composite of death or MI and of any secondary outcome. Each of these conditions alone increased the risk of all-cause and cardiac death, but had no impact on MI or ST. In addition, DM alone enhanced the risk of TLR.

The presence or absence of DM and CKD provides valuable information on the risk of adverse events in women undergoing PCI.

Impact on daily practice

Among women receiving drug-eluting stents (DES), the combination of CKD and DM was associated with a higher risk of all-cause death, cardiac death, MI, ST or TLR. CKD or DM alone were associated with a higher risk of all-cause and cardiac death, but were not predictors of MI or ST. DM alone increased the risk of TLR. The presence or absence of DM and CKD provides valuable information on the risk of adverse events in women undergoing DES implantation.

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Conflict of interest statement

A. Spirito received a research grant from the Swiss National Science Foundation (SNSF). R.V. Jeger reports research and educational grants to the institution from Abbott, Amgen, AstraZeneca, Bayer, Biosense Webster, B. Braun Melsungen AG, Biotronik, Boston Scientific, Bristol-Myers Squibb, Cordis, Daiichi Sankyo, Edwards Lifesciences, GE Medical Systems, MCM Medsys, Medtronic, Novartis, Pfizer, Terumo, and Vascular Medical GmbH. G.W. Stone has received speaker honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, and Abbott; has served as a consultant to Daiichi Sankyo, Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore, Amgen, Adona Medical, and Millennia Biopharma; and has equity/options from Ancora, Cagent, Applied Therapeutics, the Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; his daughter is an employee at IQVIA. G.W. Stone's employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Philips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-Wave. P.G. Steg reports receiving research grants from Amarin, Bayer, Sanofi, and Servier; compensation for work on clinical trials (steering committee, clinical events committee or data safety and monitoring board) from Amarin, AstraZeneca, Bayer, Bristol-Myers Squibb, Idorsia, Novartis, PhaseBio, Pfizer, Sanofi, and Servier; for consulting or speaking from Amarin, Amgen, BMS/Myokardia, Merck, Novo Nordisk, and Regeneron; and is a Senior Associate Editor at Circulation. S. Windecker reports research, travel or educational grants to the institution from Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardinal Health, CardioValve, CorFlow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, and V-Wave; and serves as advisory board member and/or member of the steering/

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Supplementary data

Supplementary Table 1. Summary of the included trials.

Supplementary Table 2. Definitions of clinical endpoints used in the included trials.

Supplementary Table 3. Adjusted risk for adverse events at 3 years in women with CKD only stratified by disease severity.

Supplementary Table 4. Adjusted risk for adverse events at 3 years in women with diabetes stratified by insulin treatment.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00086

Supplementary data

Supplementary Table 1. Summary of the included trials.

Trial Name (year)	Year of Publication	Sample size	Number of Women	% of Women	Stents Used	Stable CAD	UA	Non STEMI	STEMI	Additional inclusion criteria	Min DAPT Duration
RAVEL (2002)	2002	238	57	24%	Cypher, BMS	√	√			Single De-Novo Lesion	2 months
SIRIUS	2003	1058	307	29%	Cypher, BMS	√	√			Single De-Novo Lesion	3 months
E-SIRIUS	2003	352	103	29%	Cypher, BMS	√	√			Single De-Novo Lesion	2 months
C-SIRIUS	2004	100	31	31%	Cypher, BMS	√	√			Single De-Novo Lesion	3 months
TAXUS I	2003	61	7	11%	Taxus, BMS	√	√			Single De-Novo Lesion	6 months
TAXUS II SR	2003	267	67	25%	Taxus, BMS	√	√			Single De-Novo Lesion	6 months
TAXUS IV	2004	1314	367	28%	Taxus, BMS	√	√			Single De-Novo Lesion	6 months
TAXUS V	2005	1156	353	31%	Taxus, BMS	√	√			Single De-Novo Lesion	6 months
SIRTAX	2005	1012	231	23%	Cypher, Taxus	√	√	√	√		12 months
ENDEAVOR II	2006	1197	283	24%	Endeavor, BMS	√	√			Single De-Novo Lesion	3 months
ENDEAVOR III	2006	436	133	31%	Endeavor, Cypher	√	√			Single De-Novo Lesion	6 months
ENDEAVOR IV	2009	1548	500	32%	Endeavor, Taxus	√	√			Single De-Novo Lesion	6 months
PROTECT	2012	8709	2061	24%	Endeavor, Cypher	√	√	√	√		12 months
RESOLUTE AC	2010	2292	529	23%	Resolute, Xience	√	√	√	√		6 months

Trial Name	Year of Publication	Sample size	Number of Women	% of Women	Stents Used	Stable CAD	UA	Non STEMI	STEMI	Additional inclusion criteria	Min DAPT Duration
TWENTE	2012	1391	382	27%	Resolute, Xience	√	√	√			12 months
SPIRIT II	2006	300	81	27%	Xience, Taxus	√	√			Max2 De-Novo Lesions	6 months
SPIRIT III	2008	1002	314	31%	Xience, Taxus	√	√			Max 2 De-Novo Lesions	6 months
SPIRIT IV	2010	3687	1189	32%	Xience, Taxus	√	√			Max 3 De-Novo Lesions	12 months
COMPARE	2010	1800	527	29%	Xience, Taxus	√	√	√	√		12 months
BASKET-PROVE	2010	2314	565	24%	Xience, Cypher, BMS	√	√	√	√	Target Vessel Diameter ≥3.0mm	12 months
EXCELLENT	2011	1443	512	35%	Xience/Promus, Cypher	√	√	√			6 months
RESET	2012	3197	742	23%	Xience, Cypher	√	√	√	√		3 months
PRODIGY	2012	2013	473	23%	Xience/Promus, Endeavor, Taxus, BMS	√	√	√	√		6 months
LEADERS	2008	1707	430	25%	Biomatrix, Cypher	√	√	√	√		12 months
COMPARE-2	2013	2707	693	26%	Nobori, Xience/Promus	√	√	√	√		12 months
ISAR-TEST 4	2009	2603	623	24%	Yukon, Xience, Cypher	√	√	√	√		6 months

BMS: bare metal stent; CAD: coronary artery disease; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: unstable angina

Supplementary Table 2. Definitions of clinical endpoints used in the included trials.

Trial Name	Myocardial Infarction	Target lesion revascularization	Stent Thrombosis
RAVEL	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2* ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
SIRIUS	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2* ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
E-SIRIUS	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2* ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
C-SIRIUS	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2* ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
TAXUS I	Development of Q waves in ≥2 contiguous leads with CK and CK-MB levels above normal	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
TAXUS II SR	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
TAXUS IV	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
TAXUS V	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
SIRTAX	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB or troponin I	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria

Trial Name	Myocardial Infarction	Target lesion revascularization	Stent Thrombosis
ENDEAVOR II	Development of Q waves in ≥2 contiguous leads or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
ENDEAVOR III	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
ENDEAVOR IV	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK levels ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
PROTECT	II Universal Definition (Thygesen K et al. Circulation 2007): Periprocedural MI: cardiac biomarkers increase ≥ 3*ULN; Spontaneous: Typical rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value > URL and at least 1 of the following: symptoms, ST-T chances at ECG, pathological Q waves, or imaging evidence of ischemia	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
RESOLUTE AC	Extended historical definition (Vranckx et al. Eurointervention 2010). In summary: development of Q waves in ≥2 contiguous leads and elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2*ULN and increased level of CK-MB or troponin. In patients with acute MI at baseline: if cardiac biomarkers still raising new chest pain of ischemia equivalent and rise in cardiac biomarkers > 50% previous level; if cardiac biomarkers have returned to normal, CK level ≥ 2*ULN	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
TWENTE	Extended historical definition (Vranckx et al. Eurointervention 2010). In summary: development of Q waves in ≥2 contiguous leads and elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2*ULN and increased level of CK-MB or troponin. In patients with acute MI at baseline: if cardiac biomarkers still raising new chest pain of ischemia equivalent and rise in cardiac biomarkers > 50% previous level; if cardiac biomarkers have returned to normal, CK level ≥ 2*ULN	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria

Trial Name	Myocardial Infarction	Target lesion revascularization	Stent Thrombosis
SPIRIT II	Development of Q waves in ≥ 2 contiguous leads or, in the absence of Q waves, a typical rise and fall of CK-MB (if non-procedural/spontaneous MI, CK-MB > 2 times upper limit of normal; if post PCI, CK-MB > 3 times upper limit of normal; if post CABG, CK-MB > 5 times upper limit of normal)	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
SPIRIT III	Development of Q waves in ≥2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2* ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
SPIRIT IV	Development of Q waves in ≥ 2 contiguous leads with elevated cardiac enzymes or, in the absence of Q waves, increase in the CK level ≥ 2*ULN and increased level of CK-MB	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
COMPARE	Periprocedural MI (in patients without acute MI at baseline): any elevation in concentrations of CK ≥ 2*ULN and increase in CK-MB or troponin. Spontaneous MI: typical rise and fall of troponin or CK-MB with at least one of the following: ischemic symptoms, development of pathological Q waves, ischemic ECG changes, or pathological finding of an acute MI	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
BASKET-PROVE	Typical rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value > URL and at least 1 of the following: symptoms, ST-T changes at ECG, pathological Q waves, or recent angioplasty	Target vessel revascularization was used	Academic Research Consortium Criteria
EXCELLENT	Academic Research Consortium criteria (Cutlip DE et al. Circulation 2007). In summary: Periprocedural MI: troponin > 3* URL or CK-MB > 3* URL if baseline cardiac biomarkers < URL, stable or decreasing values on 2 sample followed by 20% increase if baseline cardiac biomarkers > URL. Spontaneous MI: troponin > URL or CK-MB > URL	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
RESET	Periprocedural MI: CK-MB ≥ 3*ULN or CK ≥ 3*ULN in the absence of CKMB measurement. Spontaneous MI: Academic Research Consortium criteria (Cutlip DE et al. Circulation 2007): troponin > URL or CK-MB > URL	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria

Trial Name	Myocardial Infarction	Target lesion revascularization	Stent Thrombosis
PRODIGY	II Universal Definition (Thygesen K et al. Circulation 2007): Periprocedural MI: cardiac biomarkers increase ≥ 3*ULN; Spontaneous: Typical rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value > URL and at least 1 of the following: symptoms, ST-T chances at ECG, pathological Q waves, or imaging evidence of ischemia	Target vessel revascularization was used	Academic Research Consortium Criteria
LEADERS	Development of Q waves in ≥ 2 contiguous leads or, in the absence of Q waves, increase in the CK level ≥ 2*ULN and increased level of CK-MB or troponin I	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
COMPARE-2	Periprocedural MI (in patients without acute MI at baseline): any elevation in concentrations of CK ≥ 2*ULN and increase in CK-MB or troponin. Spontaneous MI: typical rise and fall of troponin or CK-MB with at least one of the following: ischemic symptoms, development of pathological Q waves, ischemic ECG changes, or pathological findings of an acute MI	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria
ISAR-TEST 4	Periprocedural MI: CK-MB (or CK) ≥ 3*ULN and at least 50% over the most recent pre-PCI levels, or the development of new ECG changes consistent with MI and CK-MB (CK) elevation > ULN at 2 measurements for patients with stable angina pectoris or NSTE-ACS and falling or normal CK-MB (CK levels). Recurrent chest pain lasting .30 min with either new ECG changes consistent with second MI or next CK-MB (CK) level at least 8-12 hours after PCI elevated at least 50% above the previous level was considered procedural-related MI for patients presenting with elevated CK-MB (CK) level prior PCI. Spontaneous MI: any CK-MB increase with or without the development of Q-waves on ECG	Revascularization for ischemia for stenosis of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent	Academic Research Consortium Criteria

BMS: bare metal stent; CABG: Coronary artery bypass graft surgery; CAD: coronary artery disease; CK: creatine kinase; CK-MB: Creatine kinase-MB; ECG: electrocardiogram; MI: Myocardial infarction; NSTE-ACS: Non-ST elevation-acute coronary syndrome; PCI: Percutaneous coronary intervention; ULN: upper limit of normal; URL: upper reference limit

Supplementary Table 3. Adjusted risk for adverse events at 3 years in women with CKD only stratified by disease severity.

	No. of patients	No. of event (%)	Adjusted HR (95% CI)	p-value	p-value between CKD stages
Death or MI					
No DM/CKD	1822	121 (7.2%)	Ref.		
CKD only, mild*	565	44 (8.6%)	0.94 (0.63 - 1.38)	0.742	0.001
CKD only, moderate or severe#	381	60 (17.2%)	1.85 (1.24 - 2.77)	0.003	
All-cause death					
No DM/CKD	1822	37 (2.4%)	Ref.		
CKD only, mild*	565	22 (4.5%)	0.98 (0.54 - 1.78)	0.956	<.001
CKD only, moderate or severe#	381	42 (12.8%)	2.47 (1.38 - 4.45)	0.002	
Myocardial infarction					
No DM/CKD	1822	89 (5.1%)	Ref.		
CKD only, mild*	565	25 (4.9%)	0.88 (0.53 - 1.44)	0.600	0.193
CKD only, moderate or severe#	381	26 (7.2%)	1.28 (0.74 - 2.21)	0.380	
Cardiac death					
No DM/CKD	1822	20 (1.2%)	Ref.		
CKD only, mild*	565	13 (2.6%)	1.01 (0.47 - 2.19)	0.973	0.055
CKD only, moderate or severe#	381	22 (6.5%)	2.05 (0.93 - 4.52)	0.075	
Stent thrombosis					
No DM/CKD	1822	16 (1.0%)	Ref.		
CKD only, mild*	565	2 (0.5%)	0.26 (0.06 - 1.23)	0.090	0.086
CKD only, moderate or severe#	381	6 (1.6%)	1.10 (0.34 - 3.58)	0.879	
TLR					
No DM/CKD	1822	82 (5.0%)	Ref.		
CKD only, mild*	565	28 (5.6%)	0.94 (0.58 - 1.53)	0.801	0.370
CKD only, moderate or severe#	381	14 (4.2%)	0.70 (0.36 - 1.34)	0.277	

CKD: chronic kidney disease; DM: diabetes mellitus; MI: myocardial infarction; TLR: target lesion revascularization
* CrCl 45-59 mL/min
# CrCl <45 mL/min

Supplementary Table 4. Adjusted risk for adverse events at 3 years in women with diabetes stratified by insulin treatment.

	No. of patients	No. of event (%)	Adjusted HR (95% CI)	p-value	p-value between DM groups
Death or MI					
No DM/CKD	1822	121 (7.2%)	Ref.		
DM only, non-insulin dependent	674	58 (9.3%)	1.34 (0.98 - 1.84)	0.070	0.447
DM only, insulin dependent	307	21 (7.5%)	1.08 (0.68 - 1.72)	0.737	
All-cause death					
No DM/CKD	1822	37 (2.4%)	Ref.		
DM only, non-insulin dependent	674	26 (4.6%)	1.89 (1.15 - 3.13)	0.013	0.824
DM only, insulin dependent	307	12 (4.4%)	1.93 (1.01 - 3.70)	0.048	
Myocardial infarction					
No DM/CKD	1822	89 (5.1%)	Ref.		
DM only, non-insulin dependent	674	38 (5.9%)	1.19 (0.81 - 1.74)	0.375	0.331
DM only, insulin dependent	307	12 (4.1%)	0.85 (0.46 - 1.55)	0.593	
Cardiac death					
No DM/CKD	1822	20 (1.2%)	Ref.		
DM only, non-insulin dependent	674	15 (2.6%)	2.09 (1.07 - 4.10)	0.031	0.653
DM only, insulin dependent	307	5 (1.7%)	1.56 (0.58 - 4.16)	0.375	
Stent thrombosis					
No DM/CKD	1822	16 (1.0%)	Ref.		
DM only, non-insulin dependent	674	11 (1.7%)	1.86 (0.86 - 4.01)	0.113	0.418
DM only, insulin dependent	307	4 (1.3%)	1.49 (0.50 - 4.45)	0.477	
TLR					
No DM/CKD	1822	82 (5.0%)	Ref.		
DM only, non-insulin dependent	674	59 (9.6%)	1.90 (1.36 - 2.66)	<.001	0.478
DM only, insulin dependent	307	23 (8.0%)	1.67 (1.05 - 2.66)	0.030	

CKD: chronic kidney disease; DM: diabetes mellitus; MI: myocardial infarction; TLR: target lesion revascularization