

Duration of Dual Antiplatelet Therapy in Patients with CKD and Drug-Eluting Stents

A Meta-Analysis

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Abstract

Background and objectives Whether prolonged dual antiplatelet therapy (DAPT) is more protective in patients with CKD and drug-eluting stents compared with shorter DAPT is uncertain. The purpose of this meta-analysis was to examine whether shorter DAPT in patients with drug-eluting stents and CKD is associated with lower mortality or major adverse cardiovascular event rates compared with longer DAPT.

Design, setting, participants, & measurements A Medline literature research was conducted to identify randomized trials in patients with drug-eluting stents comparing different DAPT duration strategies. Inclusion of patients with CKD was also required. The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke, or stent thrombosis (definite or probable). Major bleeding was the secondary outcome. The risk ratio (RR) was estimated using a random-effects model.

Results Five randomized trials were included (1902 patients with CKD). Short DAPT (≤ 6 months) was associated with a similar incidence of the primary outcome, compared with 12-month DAPT among patients with CKD (48 versus 50 events; RR, 0.93; 95% confidence interval [95% CI], 0.64 to 1.36; $P=0.72$). Twelve-month DAPT was also associated with a similar incidence of the primary outcome compared with extended DAPT (≥ 30 months) in the CKD subgroup (35 versus 35 events; RR, 1.04; 95% CI, 0.67 to 1.62; $P=0.87$). Numerically lower major bleeding event rates were detected with shorter versus 12-month DAPT (9 versus 13 events; RR, 0.69; 95% CI, 0.30 to 1.60; $P=0.39$) and 12-month versus extended DAPT (9 versus 12 events; RR, 0.83; 95% CI, 0.35 to 1.93; $P=0.66$) in patients with CKD.

Conclusions Short DAPT does not appear to be inferior to longer DAPT in patients with CKD and drug-eluting stents. Because of imprecision in estimates (few events and wide confidence intervals), no definite conclusions can be drawn with respect to stent thrombosis.

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Introduction

Dual antiplatelet therapy (DAPT) is an effective treatment to prevent major cardiovascular and cerebral ischemic events including stent thrombosis in patients treated with drug-eluting stents. Concomitant use of aspirin and P2Y₁₂ inhibitors is beneficial because these agents block independent signals of platelet activation (1). The duration of this therapy in patients with drug-eluting stents—whether it should be less than or equal to 6, 12, or >12 months—has been studied in several randomized, controlled trials (RCTs) (2–14). Despite this evidence, optimal duration of DAPT remains controversial and depends on the setting of stent insertion and patient characteristics, as highlighted by several recent meta-analyses (15–20). On the basis of this information, recent practice guidelines from the American College of Cardiology/American Heart Association and the European Society of Cardiology

recommend at least 6 months of DAPT in patients with stable coronary disease who receive a drug-eluting stent and suggest DAPT beyond 6 months for patients who are not at high bleeding risk (21,22).

Patients with CKD are at higher risk for major adverse cardiovascular events compared with non-CKD patients (23,24). This observation has been attributed to a prothrombotic risk associated with CKD that has not been thoroughly explained. At the same time, patients with CKD have higher tendency to bleed (24,25), and a higher risk for major or minor bleeding events has been reported in patients with CKD who are prescribed antiplatelet agents (26).

It is unknown whether prolonged DAPT is more protective in patients with CKD with drug-eluting stents compared with shorter DAPT due to the higher prothrombotic risk of these patients or whether it increases bleeding complications in a susceptible population

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and should be avoided. The purpose of this meta-analysis was to examine whether shorter DAPT in patients with drug-eluting stents and CKD is associated with lower mortality or major adverse cardiovascular event rates compared with longer DAPT. We also examined whether shorter versus longer DAPT in patients with CKD affects the incidence of bleeding.

Materials and Methods

The protocol for this meta-analysis was prespecified and registered in the international prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>, CRD42016052906). Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 checklist (27). Because this meta-analysis included unpublished data from various RCTs shared with the principal investigators, it was approved by the Partners Institutional Review Board. The study was conducted according to the Helsinki declaration for medical research in humans.

Search Strategy

A Medline literature research was conducted in PubMed including manuscripts published from January of 1960 through December of 2016. The reference lists of all selected studies and available meta-analyses were also reviewed. The following search terms, as free text, were used: (duration OR shortened DAPT OR prolonged DAPT OR extended DAPT OR premature cessation OR early discontinuation) AND ((DAPT OR dual antiplatelet therapy) OR ((clopidogrel OR Plavix OR thienopyridine OR P2Y12 OR ADP receptor antagonist OR prasugrel OR Effient OR ticagrelor OR Brilinta) AND aspirin)). The search was limited to clinical trials or meta-analyses and English or French language articles. Given the recent publication of several RCTs exploring the effect of DAPT on clinical outcomes (2–14), we did not include non-randomized observational cohort trials.

Two authors (T.A.M. and K.G.) independently reviewed the literature and selected the studies on the basis of the eligibility criteria cited below. There were no discrepancies between the authors. The primary investigator (or a designee) of each trial included in this meta-analysis extracted and submitted relevant data using a standardized digital spreadsheet. Data sought included relevant baseline characteristics (listed in Tables 1 and 2) and information on eligibility criteria (listed below).

Eligibility Criteria

The following criteria were required for inclusion: (1) Study population: patients with coronary artery disease, after implantation of a drug-eluting stent, on DAPT. Patients who had bare metal stents were excluded. Inclusion of patients with CKD was also required. Because the DAPT trial recorded whether serum creatinine was ≥ 2 mg/dl but did not record the actual value, CKD was defined as an elevated baseline creatinine (≥ 2 mg/dl) or being on dialysis for the DAPT study and as an eGFR < 60 ml/min per 1.73 m² (CKD Epidemiology Collaboration equation) for all of the other trials. (2) Intervention: duration of DAPT (short versus long). Short was the

minimal duration of DAPT after which the second antiplatelet agent was discontinued and patients were treated with aspirin only. Long was the period of prolonged DAPT in each clinical trial. The exact duration of DAPT in each study arm had to be reported. (3) Study design: RCTs, published in the form of a manuscript. (4) At least one of the following outcomes had to be reported: (1) all-cause or cardiovascular mortality; (2) major bleeding or any bleeding events rate; (3) incidence of myocardial infarction, stroke, or definite or probable stent thrombosis.

End Points and Quality Assessment

Most of the identified RCTs had not published CKD-specific results in the drug-eluting stent-specific population. Therefore, the principal investigator from each study was contacted to provide relevant baseline data and clinical outcomes. Because the DAPT and Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trials also included patients with bare metal stents, we specifically requested outcomes only in patients with drug-eluting stents. The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke, and stent thrombosis (definite or probable). The secondary outcome was major bleeding. Major bleeding definitions in each trial are depicted in Supplemental Table 1. Tertiary outcomes were the components of the primary outcome, cardiovascular mortality, repeat revascularization (target lesion), any bleeding events, and a composite outcome including the primary and the secondary outcome. The Jadad score was used to assess the quality of each study (28). Overall risk of bias was considered “not serious.” The GRADE approach was used to rate confidence in estimates of effect (29).

Statistical Analyses

Outcomes were reported at the maximum available follow-up for DAPT, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice (OPTIMIZE), and OPTimal DUAL antiplatelet therapy (OPTIDUAL) trials, and at 12 and 24 months for PRODIGY and Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel (ITALIC) trials. The principal summary measure was the risk ratio (RR).

The RR for each outcome was estimated using a random-effects model. To quantify heterogeneity and assess inconsistency, the I^2 index was used.

We prespecified an additional analysis of patients without CKD (eGFR ≥ 60 ml/min per 1.73 m² or below the respective creatinine cutoff). A *post-hoc* secondary analysis was performed comparing short (≤ 12 months) versus long (≥ 24 months) DAPT. This analysis included the DAPT trial, PRODIGY (24-month outcomes), OPTIDUAL, and ITALIC (24-month outcomes), but not OPTIMIZE (both short and long arm ≤ 12 months).

A supplementary analysis was conducted pooling hazard ratios using the generic inverse variance method and a random-effects model.

Analyses were performed using Review Manager 5.3.5 (The Cochrane Collaboration, Copenhagen). A P value < 0.05 was considered significant.

Table 1. Characteristics and risk of bias of the included trials

Characteristic	Trial									
	PRODIGY		OPTIMIZE		ITALIC		DAPT		OPTIDUAL	
Arm	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
DAPT duration, mo	6	24	3	12	6	24	12	30	12	48
Country	Italy		Brazil		France, Poland, Hungary, Norway, Bahrain, UAE		USA, Canada, Australia, Czech Republic, France, Germany, Hungary, New Zealand, Poland, Romania, UK		France	
Number of centers	3		33		45		256		48	
Inclusion criteria	Elective, urgent, or emergent angioplasty		PCI, zotarolimus-eluting stents		Any PCI, except primary PCI or left main treatment		PCI with stent deployment		PCI with ≥1 DES	
CAD type	Stable CAD or ACS		Stable CAD or low-risk ACS		Stable CAD or ACS		Stable CAD or ACS		Stable angina, silent ischemia, ACS	
Second antiplatelet	Clopidogrel		Clopidogrel		Clopidogrel/prasugrel/ticagrelor ^a		Clopidogrel/prasugrel ^b		Clopidogrel	
Drug-eluting stent type	Everolimus-, paclitaxel-, and zotarolimus-eluting stent		Zotarolimus-eluting stent		Everolimus-eluting stent		Sirolimus-, zotarolimus-paclitaxel-, and everolimus-eluting stent		Any type	
Jadad score	2		3		3		4		2	
Risk of bias	Serious		Not serious		Not serious		Not serious		Serious	

PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; ITALIC, Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel; DAPT, dual antiplatelet therapy; OPTIDUAL, OPTImal DUAL antiplatelet therapy; UAE, United Arab Emirates; USA, United States of America; UK, United Kingdom; PCI, percutaneous coronary intervention; DES, drug-eluting stent; CAD, coronary artery disease; ACS, acute coronary syndrome.

^a15 patients on prasugrel and one on ticagrelor.

^b35% of patients on prasugrel.

Table 2. Baseline characteristics of patients with CKD

Characteristic	Trial									
	PRODIGY		OPTIMIZE		ITALIC		DAPT		OPTIDUAL	
	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
Arm										
Number of patients	202	205	300	280	139	137	197	223	117	102
Presenting with ACS	153 (76)	152 (74)	81 (27)	74 (26)	34 (25)	33 (24)	35 (18)	50 (22)	46 (39)	25 (25)
Age, yr	75±9	74±9	67±10	68±10	70±9	69±10	66±10	67±10	72±10	72±10
Male sex	133 (66)	140 (68)	170 (57)	146 (52)	99 (71)	92 (67)	140 (71)	161 (72)	80 (68)	73 (72)
Black race	0	0	47 (16)	54 (19)	N/A	N/A	17 (9)	17 (8)	N/A	N/A
Diabetes	61 (30)	67 (33)	127 (42)	107 (38)	63 (45)	67 (49)	96 (49)	115 (52)	52 (44)	38 (37)
Hypertension	160 (79)	169 (82)	280 (93)	263 (94)	117 (84)	113 (83)	183 (93)	204 (91)	92 (79)	80 (78)
Dyslipidemia	109 (54)	121 (59)	196 (65)	192 (69)	104 (75)	98 (72)	N/A	N/A	80 (68)	73 (72)
Smoking (current)	30 (15)	24 (12)	38 (13)	31 (11)	16 (12)	19 (14)	33 (17)	26 (12)	60 (51)	50 (49)
Smoking (never)	120 (59)	122 (60)	157 (52)	151 (54)	79 (57)	81 (59)	N/A	N/A	N/A	N/A
Prior MI	73 (36)	77 (38)	109 (36)	93 (33)	21 (15)	21 (15)	49 (25)	66 (30)	25 (21)	19 (19)
Prior stroke	0	2 (1)	8 (3)	13 (5)	9 (7)	5 (4)	10 (5)	18 (8)	6 (5)	10 (10)
Previous PCI	52 (26)	52 (25)	65 (22)	44 (16)	32 (23)	37 (27)	88 (45)	89 (40)	41 (35)	25 (25)
Previous CABG	28 (14)	25 (12)	24 (8)	30 (11)	13 (9)	11 (8)	44 (22)	45 (20)	9 (8)	7 (7)
Major bleeding history	3 (1)	2 (1)	0 (0)	1 (0)	N/A	N/A	3 (2)	6 (3)	1 (1)	1 (1)
Creatinine, mean, mg/dl	1.5±1.1	1.7±1.4	1.7±1.3	1.6±1.3	1.4±1.0	1.7±1.5	N/A	N/A	1.5±0.7	1.6±0.8
Creatinine, median, mg/dl	1.3 (1.2–1.5)	1.3 (1.2–1.5)	1.4 (1.2–1.6)	1.4 (1.2–1.5)	1.4 (1.2–1.7)	1.3 (1.2–1.6)	N/A	N/A	1.3 (1.2–1.5)	1.4 (1.2–1.6)
eGFR, ml/min per 1.73 m ²	47±12	45±12	45±12	47±12	46±11	47±13	N/A	N/A	48±11	45±13

Results are presented as mean ± SD, median (interquartile range), or cases (%). CKD was defined as an elevated baseline creatinine (≥ 2 mg/dl) or being on dialysis for the DAPT study and as an eGFR < 60 ml/min per 1.73 m² (Chronic Kidney Disease Epidemiology Collaboration equation) for all other trials. Short was the minimal duration of DAPT after which the second antiplatelet agent was discontinued and the patients were treated with aspirin only. Long was the period of prolonged DAPT in each clinical trial. PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; ITALIC, Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel; DAPT, dual antiplatelet therapy; OPTIDUAL, OPTimal DUAL antiplatelet therapy; ACS, acute coronary syndrome; N/A, not available; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation.

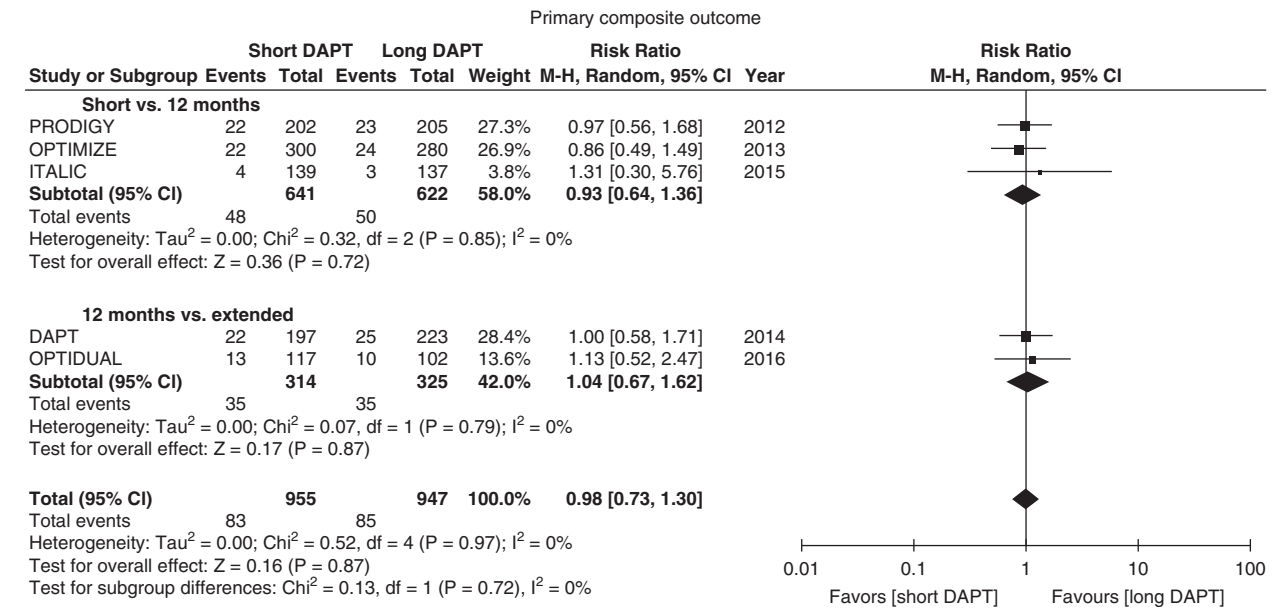


Figure 1. | Forest plot showing a similar incidence of the primary outcome, a composite of all-cause mortality, myocardial infarction, stroke, and stent thrombosis (definite or probable), with short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy in patients with CKD. Data are presented with risk ratios with 95% confidence intervals. A random effects model was used. 95% CI, 95% confidence interval; DAPT, dual antiplatelet therapy; ITALIC, Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel; M-H, Mantel-Haenszel; OPTIDUAL, OPTIMAL DUAL antiplatelet therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study.

Results

Study and Patient Characteristics

A total of 148 articles were identified and screened. Forty-four articles were retrieved for full text review and 13 eligible RCTs were identified (Supplemental Figure 1). Eight RCTs had to be excluded because the investigators did not respond despite multiple attempts ($n=5$) (10–14) or because baseline creatinine data and CKD status were not available for study participants ($n=3$) (7–9). Five trials were included in this meta-analysis (1902 patients with CKD and 15,085 patients without CKD) (2–6). Characteristics and risk of bias of the five included trials are shown in Table 1.

Baseline characteristics of patients with and without CKD from the five selected RCTs are shown in Table 2 and Supplemental Table 2. Patients with any degree of kidney impairment or normal kidney function were included in these studies. In four of the five trials included in this meta-analysis, clopidogrel was the second antiplatelet agent. The DAPT trial enrolled patients on clopidogrel or prasugrel (35%), whereas none of the trials included patients on ticagrelor. The DAPT and ITALIC trials included more patients with diabetes compared with the other studies. The DAPT trial enrolled more patients who had undergone surgical revascularization, whereas in the PRODIGY trial the majority of patients presented with acute coronary syndrome. Patients with CKD were older and had higher prevalence of diabetes and hypertension than those with preserved kidney function.

Primary Outcome

Short DAPT (≤ 6 months) was associated with a similar incidence of the primary outcome, a composite of death

from any cause, myocardial infarction, stroke, or stent thrombosis, compared with 12-month DAPT among patients with CKD: 48 versus 50 events; RR, 0.93; 95% confidence interval (95% CI), 0.64 to 1.36; $P=0.72$ (Figure 1). Similarly, 12-month DAPT was associated with a similar incidence of the primary outcome compared with extended DAPT (≥ 30 months) in the CKD subgroup: 35 versus 35 events; RR, 1.04; 95% CI, 0.67 to 1.62; $P=0.87$. In contrast, 12-month DAPT was less protective against the primary outcome compared with extended DAPT in patients without CKD: 290 versus 205 events; RR, 1.43; 95% CI, 1.20 to 1.71; $P<0.001$ (Table 3). No heterogeneity was detected in either analysis in the CKD and non-CKD subgroups ($I^2=0\%$).

Secondary and Tertiary Outcomes

A nonsignificant, numerically lower rate of major bleeding was evident with shorter compared with 12-month DAPT (9 versus 13 events; RR, 0.69; 95% CI, 0.30 to 1.60; $P=0.39$) and 12-month versus extended (≥ 30 months) DAPT (9 versus 12 events; RR, 0.83; 95% CI, 0.35 to 1.93; $P=0.66$) in patients with CKD (Figure 2, Table 3). No heterogeneity was detected ($I^2=0\%$). A similar numerically lower rate was identified for any bleeding events, which was statistically significant in favor of 12-month versus extended DAPT (Supplemental Figure 2, Table 3).

Numerically lower (protective), albeit nonsignificant, event rates in favor of short compared with 12-month DAPT were detected for all-cause mortality, cardiovascular mortality, myocardial infarction, stent thrombosis, and the composite outcome of death from any cause, myocardial infarction, stroke, stent thrombosis, or major bleeding

Table 3. Pooled clinical outcomes by DAPT duration in patients with and without CKD

Outcome	CKD Status	≤6 versus 12 mo	12 mo versus Extended	Short versus Long	Quality of Evidence
		RR (95% CI)	RR (95% CI)	RR (95% CI)	
Primary composite	CKD	0.93 (0.64 to 1.36)	1.04 (0.67 to 1.62)	0.98 (0.73 to 1.30)	Moderate ^a
	No CKD	1.09 (0.79 to 1.50)	1.43 (1.20 to 1.71)	1.35 (1.15 to 1.57)	High
Major bleeding	CKD	0.69 (0.30 to 1.60)	0.83 (0.35 to 1.93)	0.76 (0.42 to 1.37)	Low ^b
	No CKD	0.71 (0.33 to 1.52)	0.62 (0.46 to 0.83)	0.63 (0.47 to 0.83)	Moderate ^c
Tertiary composite	CKD	0.86 (0.60 to 1.22)	0.95 (0.64 to 1.42)	0.90 (0.69 to 1.17)	Moderate ^a
	No CKD	1.01 (0.75 to 1.36)	1.17 (1.00 to 1.36)	1.13 (0.99 to 1.30)	Moderate ^a
All-cause mortality	CKD	0.89 (0.57 to 1.40)	0.84 (0.45 to 1.55)	0.87 (0.61 to 1.25)	Moderate ^a
	No CKD	1.07 (0.69 to 1.68)	0.98 (0.52 to 1.85)	0.92 (0.71 to 1.18)	Moderate ^d
CV mortality	CKD	0.66 (0.32 to 1.34)	1.10 (0.51 to 2.40)	0.79 (0.49 to 1.27)	Moderate ^a
	No CKD	1.41 (0.81 to 2.48)	1.06 (0.70 to 1.61)	1.17 (0.84 to 1.64)	Moderate ^a
MI	CKD	0.80 (0.43 to 1.51)	1.61 (0.79 to 3.29)	1.09 (0.68 to 1.75)	Moderate ^a
	No CKD	1.19 (0.77 to 1.84)	2.03 (1.60 to 2.59)	1.53 (1.05 to 2.24)	Moderate ^e
Stent thrombosis	CKD	0.65 (0.18 to 2.33)	1.62 (0.20 to 13.11)	0.83 (0.28 to 2.48)	Low ^f
	No CKD	1.33 (0.56 to 3.14)	1.02 (0.05 to 22.44)	1.63 (0.65 to 4.08)	Low ^g
Target-lesion revascularization	CKD	0.93 (0.36 to 2.38)	1.74 (0.45 to 6.79)	1.10 (0.57 to 2.11)	Moderate ^d
	No CKD	1.05 (0.74 to 1.48)	0.74 (0.44 to 1.24)	0.94 (0.69 to 1.27)	Moderate ^a
Stroke	CKD	0.98 (0.28 to 3.45)	0.61 (0.14 to 2.66)	0.80 (0.31 to 2.08)	Low ^f
	No CKD	0.28 (0.07 to 1.14)	1.31 (0.85 to 2.03)	0.96 (0.45 to 2.04)	Moderate ^d
Any bleeding	CKD	0.75 (0.43 to 1.31)	0.55 (0.31 to 1.00)	0.65 (0.43 to 0.98)	Moderate ^h
	No CKD	0.61 (0.40 to 0.94)	0.81 (0.31 to 2.10)	0.64 (0.45 to 0.91)	Low ⁱ

The summary measure was the RR. The primary outcome was a composite of all-cause mortality, MI, stroke, and stent thrombosis (definite or probable). The secondary outcome was major bleeding. The tertiary composite outcome included the primary and the secondary outcomes. Short was the minimal duration of DAPT after which the second antiplatelet agent was discontinued and the patients were treated with aspirin only. Long was the period of prolonged DAPT in each clinical trial. The reference group was respectively 12-mo DAPT, extended DAPT, and long DAPT. DAPT, dual antiplatelet therapy; RR, risk ratio; 95% CI, 95% confidence interval; CV, cardiovascular; MI, myocardial infarction.

^aDue to serious imprecision. Serious imprecision: confidence interval includes no difference.

^bDue to serious imprecision and serious indirectness. Serious imprecision: confidence interval includes no difference. Serious indirectness: variable definition of major bleeding.

^cDue to serious indirectness. Serious indirectness: variable definition of major bleeding.

^dDue to serious imprecision and borderline inconsistency. Serious imprecision: confidence interval includes no difference. Borderline inconsistency: no serious limitation.

^eDue to serious inconsistency and borderline imprecision. Borderline imprecision: no serious limitation. Serious inconsistency: $I^2=40\%$.

^fDue to very serious imprecision. Very serious imprecision: very few events and large confidence intervals.

^gDue to serious imprecision and serious inconsistency. Serious imprecision: confidence interval includes no difference. Serious inconsistency: $I^2=52\%$.

^hDue to serious indirectness and borderline imprecision. Serious indirectness: the clinical effect of these events is not clear; it was not clear how this outcome was ascertained. Borderline imprecision: no serious limitation.

ⁱDue to serious indirectness, serious inconsistency, and borderline imprecision. Serious indirectness: the clinical effect of these events is not clear; it was not clear how this outcome was ascertained. Serious inconsistency: $I^2=40\%$. Borderline imprecision: no serious limitation.

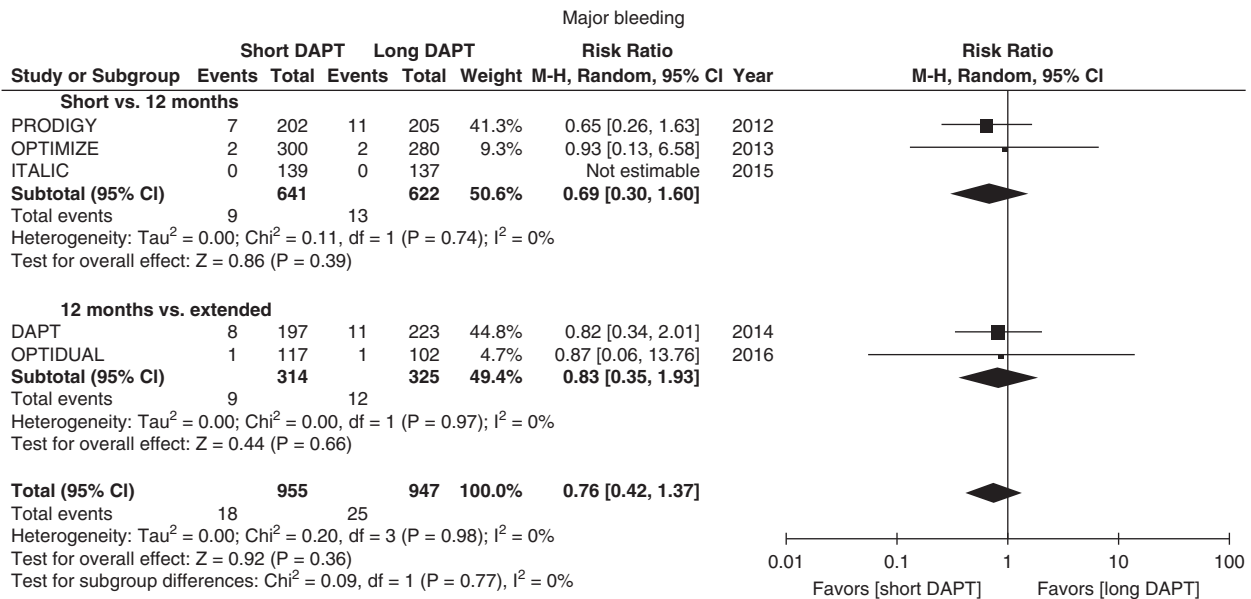


Figure 2. | Forest plot showing numerically lower major bleeding event rates with short (≤ 6 months) versus 12-month, and 12-month versus extended (≥ 30 months) dual antiplatelet therapy in patients with CKD. Data are presented with risk ratios with 95% confidence intervals. A random effects model was used. 95% CI, 95% confidence interval; DAPT, dual antiplatelet therapy; ITALIC, Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel; M-H, Mantel-Haenszel; OPTIDUAL, OPTimal DUAL antiplatelet therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study.

among patients with CKD (Figures 3 and 4, Supplemental Figures 3 and 4, Table 3). On the contrary, point estimates were in favor of 12-month DAPT in patients without CKD. Heterogeneity was undetectable or mild for all outcomes. Incidence of stroke and target lesion revascularization was similar in the short and 12-month DAPT arms (Supplemental Figures 5 and 6, Table 3).

Certainty in effect estimates, as assessed by the GRADE approach, is shown in Table 3. The secondary analysis, comparing ≤ 12 -month versus ≥ 24 -month DAPT (Supplemental Table 3), yielded comparable results to the main analysis (Table 3). Similarly, using the hazard ratio instead of the RR and a random effects model provided identical results (Supplemental Table 4).

Discussion

This is the first meta-analysis examining optimal DAPT duration in patients with CKD treated with drug-eluting stents, using data from five RCTs, including 1902 patients with CKD. We were unable to detect evidence of a benefit from extended DAPT (≥ 30 months) with respect to myocardial infarction or stent thrombosis compared with 12-month DAPT among individuals with CKD, in contrast to what was observed in the non-CKD subgroup. Conversely, the point estimates were consistent with a higher incidence of major and any bleeding events with extended DAPT compared with 12-month DAPT, as well as with 12-month DAPT compared with short DAPT (≤ 6 months) among individuals with CKD. Finally, there was no difference for all outcomes tested with short DAPT in patients with CKD, compared with 12-month DAPT.

Benefit versus Risk with Prolonged DAPT

The lack of efficacy in preventing ischemic events that we observed with extended DAPT is relevant in patients with CKD where the risks of bleeding may be important. In an individual patient data meta-analysis from six RCTs, Palmerini *et al.* (30) showed that bleeding was independently associated with mortality. A persistent risk was observed beyond 1 year after the index event, possibly related to the subjects with comorbid conditions being more likely to bleed, and additionally could be attributed to the event itself or the interruption of antiplatelet therapy and other medications (angiotensin-converting enzyme inhibitors, β -blockers) in the setting of bleeding. In addition, a secondary analysis from the DAPT trial demonstrated that bleeding events were associated with a high risk of mortality (21.5 per 100 person-years versus 27.2 for ischemic events), highlighting the prognostic importance of severe and moderate bleeding (31).

Previous studies have attempted to evaluate subjects with CKD treated with varying durations of DAPT after percutaneous coronary intervention. A recently published cohort study from Taiwan, examining the incidence of death or myocardial infarction in adult patients on maintenance hemodialysis who were treated with ≤ 6 -month versus > 6 -month DAPT (aspirin and clopidogrel) post-drug-eluting stent implantation, did not detect any significant difference for this outcome between the two treatment groups (32). Our results are also in accordance with the CKD-subgroup analysis of the PRODIGY trial as well as a previously published meta-analysis of antiplatelet agents in CKD with respect to bleeding outcomes (24,26).

Clopidogrel was the second antiplatelet agent in four of the five trials included in this meta-analysis, whereas none

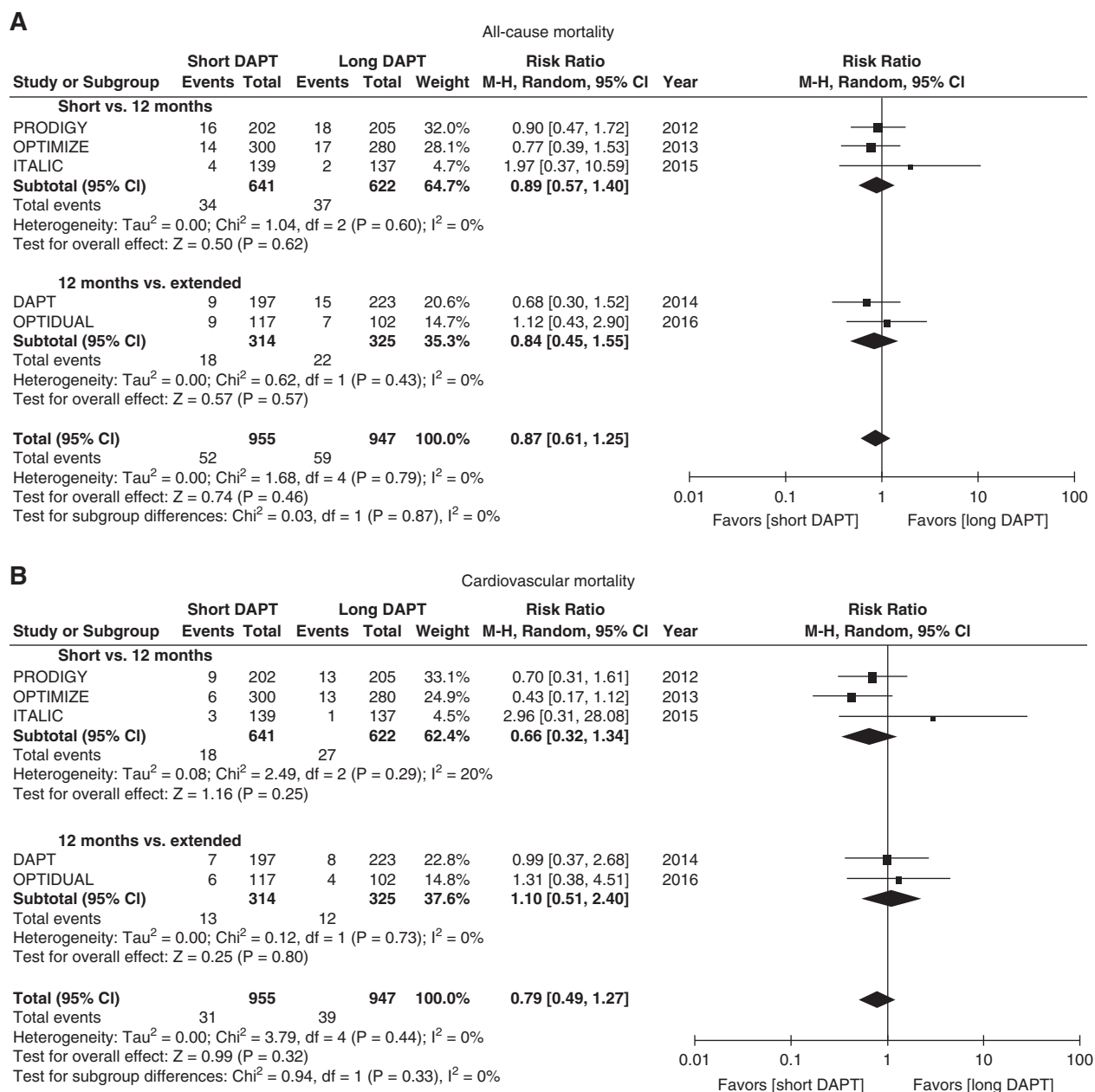


Figure 3. | Forest plot showing similar all-cause mortality (A) and cardiovascular mortality (B) event rates with short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy in patients with CKD. Data are presented with risk ratios with 95% confidence intervals. A random effects model was used. 95% CI, 95% confidence interval; DAPT, dual antiplatelet therapy; ITALIC, Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel; M-H, Mantel-Haenszel; OPTIDUAL, OPTImal DUAL antiplatelet therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study.

of the trials included patients on ticagrelor. The DAPT trial was the only study to enroll patients on prasugrel (35%). Whether our observations could be explained by a CKD-specific attenuation of clopidogrel efficacy and whether results might have been different with ticagrelor or prasugrel remain to be determined (33–35).

Both presence of diabetes and the degree of diabetic control can affect clopidogrel metabolism, as well as platelet inhibition by clopidogrel (36,37). Benefit from extended DAPT has been shown to be attenuated in patients with

diabetes compared with individuals without diabetes mellitus (38). Furthermore, body mass index is often higher among patients with diabetes mellitus and may affect the degree of platelet inhibition by clopidogrel (39,40). Thus, significant differences in both the prevalence of diabetes mellitus and obesity may confound this analysis, suggesting a differential treatment effect of clopidogrel by CKD status.

It should be noted that the majority of point estimates did not achieve statistical significance. We cannot rule out the

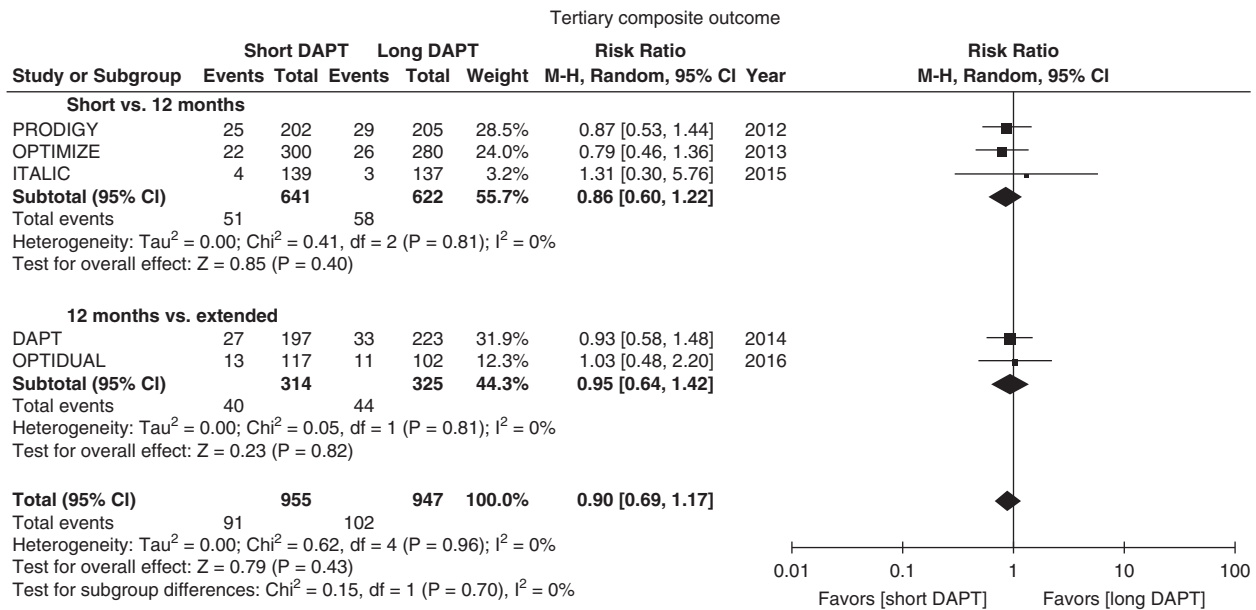


Figure 4. | Forest plot showing a similar incidence of the tertiary outcome, a composite of all-cause mortality, myocardial infarction, stroke, stent thrombosis (definite or probable), and major bleeding, with short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy in patients with CKD. Data are presented with risk ratios with 95% confidence intervals. A random effects model was used. 95% CI, 95% confidence interval; DAPT, dual antiplatelet therapy; ITALIC, Is There A Life for Drug Eluting Stents after Discontinuation of Clopidogrel; M-H, Mantel-Haenszel; OPTIDUAL, OPTImal DUAL antiplatelet therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment with the Zotarolimus-Eluting Stent in Real-World Clinical Practice; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study.

possibility that a larger set of studies including a greater number of individuals with CKD might detect benefits. However, it should be noted that our study represents the largest reported collection of patients with CKD randomized to divergent durations of DAPT therapy. Because of imprecision (very few events and large confidence intervals), no definite conclusion can be drawn from this meta-analysis with respect to stent thrombosis in patients with CKD. Our point estimates were consistent with higher risks of bleeding (with a significant *P* value in the pooled analysis comparing risk of any bleeding with ≤ 12 months of DAPT compared with ≥ 24 months). Point estimates were also clustered around a relative risk of 1 for the primary efficacy end point while suggesting higher all-cause mortality for longer DAPT. This stands in contrast to the analysis of individuals with preserved kidney function (Table 3) in whom there was a suggestion of greater efficacy with longer DAPT. Our data thus clearly demonstrate the urgent need for additional studies (preferably RCTs) powered to assess the efficacy and safety of DAPT within the CKD population. Until then, we believe that caution should be used before prescribing prolonged DAPT to individuals with moderate or advanced CKD.

Individualized Treatment Decisions

Suggesting shorter DAPT regimens for patients with CKD with a drug-eluting stent should not be misinterpreted to imply a “one size fits all strategy.” Some patients may benefit from shorter duration and others may need longer therapy. Several factors should be taken into account, including individual thrombotic and bleeding risk, stent

localization, burden of cardiovascular disease, various comorbidities, and patient preference. Clinical decision tools may prove useful in guiding individualized treatment decisions (41–45).

Study Limitations

Our study has important limitations. We lacked sufficient data to explore effect modification by acute coronary syndrome (although 36% of our population was admitted with acute coronary syndrome) or generation of drug-eluting stent. Analyses in the CKD population have suggested that extended DAPT with aspirin and ticagrelor beyond 12 months post-acute coronary syndrome has been associated with four-fold absolute risk reduction in cardiovascular mortality, myocardial infarction, or stroke, despite higher rates of drug discontinuation (46). Similarly, in the Swedish heart disease registry, patients with an eGFR ≤ 60 ml/min per 1.73 m² who were treated with prolonged DAPT (beyond 3 months through year 1) after an acute coronary syndrome had significantly lower death, reinfarction, or ischemic stroke rates compared with 3-month DAPT, without any significant increase in incidence of major bleeding (47). Given the potentially higher platelet reactivity among acute coronary syndrome patients with CKD, results might differ according to presentations (48). Conversely, the new generation of polymers used in contemporary drug-eluting stents may be associated with lower risks of stent thrombosis, making DAPT less beneficial (49). Future studies to analyze the effects of these factors are warranted.

Baseline creatinine values were not available for all patients in the ITALIC and OPTIMIZE trials. Five of the potentially eligible RCTs, all of them conducted either in Korea or in China, could not be included in this meta-analysis because their authors did not respond to multiple requests to participate (10–14). Furthermore, CKD in the DAPT trial was defined as creatinine ≥ 2 mg/dl or need for dialysis, excluding patients with less advanced CKD, whereas the exact proportion of patients who were dialysis dependent was not provided. In the other four trials, CKD was defined on the basis of serum creatinine alone, because albuminuria data were not available. Individual patient data were not available for most studies and interaction *P* values by CKD status could not be calculated. Therefore, it is not clear whether the true effects of prolonged DAPT actually differ from the larger non-CKD group or whether the apparent lack of benefit with shorter DAPT in CKD is a chance observation due to insufficient power. Moreover, heterogeneity by drug could not be assessed. In addition, all analyses assessed relative risk, whereas absolute risks and benefits were not generated. However, comparison of absolute risks is the most useful approach to guide individualized decision making.

In the three trials comparing short with 12-month DAPT, patients were randomized at the time of or 1 month after percutaneous coronary intervention including events occurring while both groups were on DAPT, thus potentially diluting treatment effects. Adjudication of bleeding events can be challenging, and bleeding definition was not uniform across different studies. Older trials included patients with first generation drug-eluting stents, associated with higher thrombotic risk, and most patients were on clopidogrel rather than the novel antiplatelet agents with better efficacy profile. Our analysis also shares the limitations of the underlying individual trials including open-label design, low event rates, inadequate power for most end points, heterogeneous primary outcomes, and loss to follow-up. Finally, there were relatively few patients with advanced CKD (stage 4–5), precluding meaningful analysis according to the severity of CKD. However, inclusion of 1902 patients with CKD from studies with different inclusion criteria, representing a diverse population; inclusion of end point events occurring only during the on-treatment study period; exclusion of patients treated with bare metal stents; absence of heterogeneity for studied outcomes; and similar results in various analyses constitute unique strengths of our analysis.

Although large studies with the power for definitive estimates are clearly desirable, our data provide the best estimates to date of the risks and benefits of DAPT in the setting of CKD. On the basis of our analysis, short DAPT (≤ 6 months) seems to be a reasonable strategy and, given the point estimates, it is unlikely to be inferior to longer DAPT (12 or >12 months) in patients with CKD treated with a drug-eluting stent. Treatment should be individualized in this patient subgroup. Additional, CKD-specific RCTs of short compared with longer DAPT using the newer antiplatelet agents are warranted.

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Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12901018/-/DCSupplemental>.

Supplemental Table 1. Major bleeding definitions in the clinical trials included in this meta-analysis.

Supplemental Table 2. Baseline characteristics of patients without CKD.

Supplemental Table 3. Pooled clinical outcomes by DAPT duration (≤ 12 months versus ≥ 24 months) in patients with and without CKD (secondary analysis).

Supplemental Table 4. Pooled clinical outcomes by DAPT duration in patients with and without CKD (hazard ratios).

Supplemental Figure 1. Study selection flow chart.

Supplemental Figure 2. Forest plot showing the effect of short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy on any bleeding in patients with CKD.

Supplemental Figure 3. Forest plot showing the effect of short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy on myocardial infarction in patients with CKD.

Supplemental Figure 4. Forest plot showing the effect of short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy on stent thrombosis in patients with CKD.

Supplemental Figure 5. Forest plot showing the effect of short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy on stroke in patients with CKD.

Supplemental Figure 6. Forest plot showing the effect of short (≤ 6 months), 12-month, and extended (≥ 30 months) dual antiplatelet therapy on target lesion revascularization in patients with CKD.

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