Duration of dual antiplatelet therapy in patients with CKD and drug-eluting stents: a meta-analysis

Mavrakanas, Thomas A; Chatzizisis, Yiannis S; Gariani, Karim; Kereiakes, Dean J; Gargiulo, Giuseppe; Helft, Gérard; Gilard, Martine; Feres, Fausto; Costa, Ricardo A; Morice, Marie-Claude; Georges, Jean-Louis; Valgimigli, Marco; Bhatt, Deepak L; Mauri, Laura [**and 1 more**]

How to cite

MAVRAKANAS, Thomas A et al. Duration of dual antiplatelet therapy in patients with CKD and drug-eluting stents: a meta-analysis. In: Clinical Journal of the American Society of Nephrology, 2019, vol. 14, n° 6, p. 810–822. doi: 10.2215/CJN.12901018

This publication URL: https://archive-ouverte.unige.ch/unige:143073
Publication DOI: 10.2215/CJN.12901018

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

A Meta-Analysis

Thomas A. Mavrakanas,[1,2] *Yiannis S. Chatzizisis*,[3] *Karim Gariani*,[4] *Dean J. Kereiakes*,[5] *Giuseppe Gargiulo*,[6,7] *Gérard Helft*,[8] *Martine Gilard*,[9] *Fausto Feres*,[10] *Ricardo A. Costa*,[10] *Marie-Claude Morice*,[11] *Jean-Louis Georges*,[12] *Marco Valgimigli*,[6] *Deepak L. Bhatt*,[13] *Laura Mauri*,[14] *and David M. Charytan*[1,15,16]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Thomas A. Mavrakanas, Renal Division, Brigham and Women's Hospital, 1620 Tremont Street, Boston, MA 02120. Email: tmavrakanas@gmail.com

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.

CJASN 14: 810–822, 2019. doi: https://doi.org/10.2215/CJN.12901018

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 $P2Y_{12}$ 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

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 nonrandomized 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 m^2 (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 m^2 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.

[a]15 patients on prasugrel and one on ticagrelor.

[b]35% of patients on prasugrel.

Table 2. Baseline characteristics of patients with CKD

Characteristic	Trial									
	PRODIGY		OPTIMIZE		ITALIC		DAPT		OPTIDUAL	
Arm	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
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 m^2 (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.

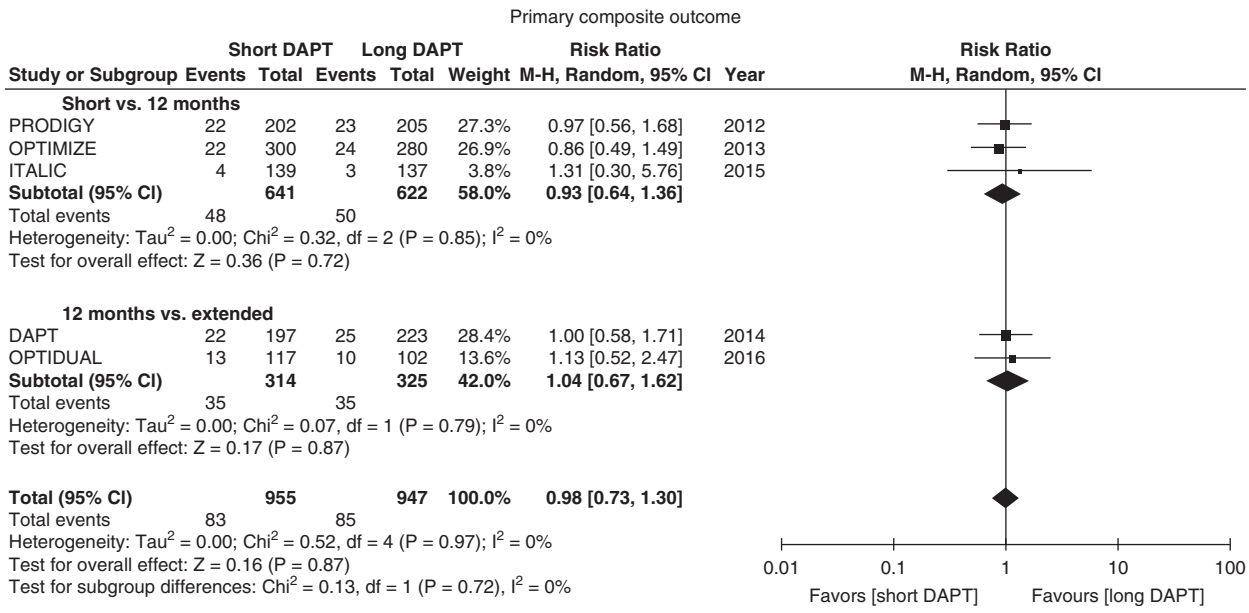

Figure 1. | Forest plot showing a similar incidence of the primary outcome, a composite of all-cause mortality, myocardial infarction, stroke, and stent thrombosis (definite or probable), with short (≤6 months), 12-month, and extended (≥30 months) dual antiplatelet therapy in patients with CKD. Data 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 RR (95% CI)	12 mo versus Extended RR (95% CI)	Short versus Long RR (95% CI)	Quality of Evidence
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.

[a]Due to serious imprecision. Serious imprecision: confidence interval includes no difference.

[b]Due to serious imprecision and serious indirectness. Serious imprecision: confidence interval includes no difference. Serious indirectness: variable definition of major bleeding.

[c]Due to serious indirectness. Serious indirectness: variable definition of major bleeding.

[d]Due to serious imprecision and borderline inconsistency. Serious imprecision: confidence interval includes no difference. Borderline inconsistency: no serious limitation.

[e]Due to serious inconsistency and borderline imprecision. Borderline imprecision: no serious limitation. Serious inconsistency: I^2=40%.

[f]Due to very serious imprecision. Very serious imprecision: very few events and large confidence intervals.

[g]Due to serious imprecision and serious inconsistency. Serious imprecision: confidence interval includes no difference. Serious inconsistency: I^2=52%.

[h]Due 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.

[i]Due 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.

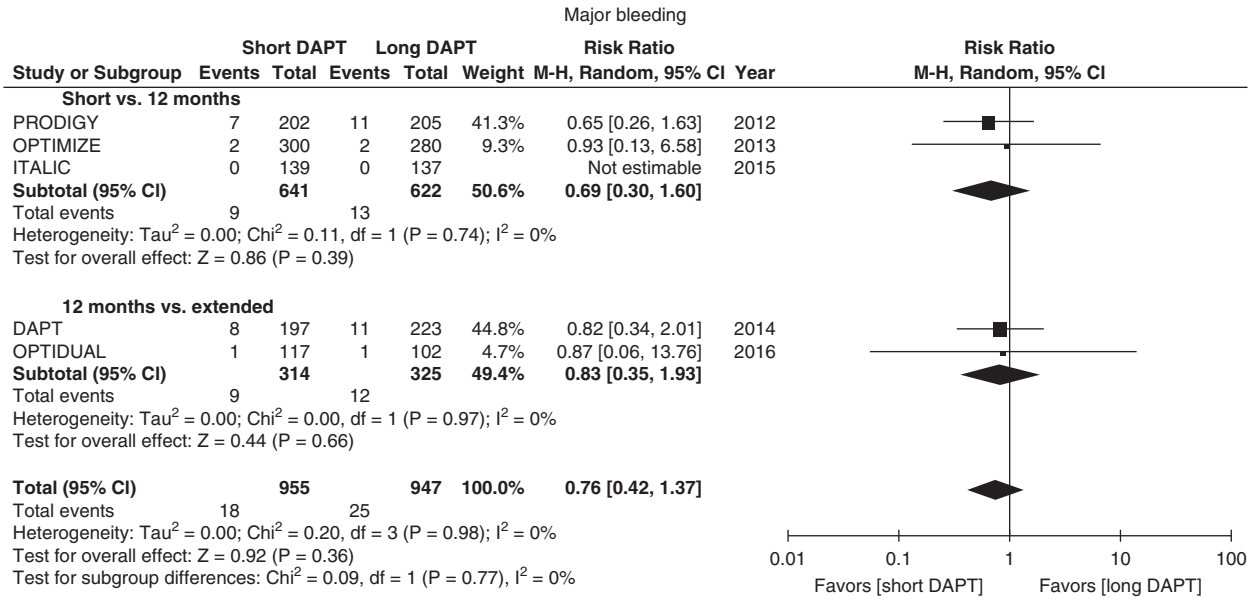

Figure 2. | Forest plot showing numerically lower major bleeding event rates with short (≤6 months) versus 12-month, and 12-month versus extended (≥30 months) dual antiplatelet therapy in patients with CKD. Data are presented with risk ratios with 95% confidence intervals. A random effects model was 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

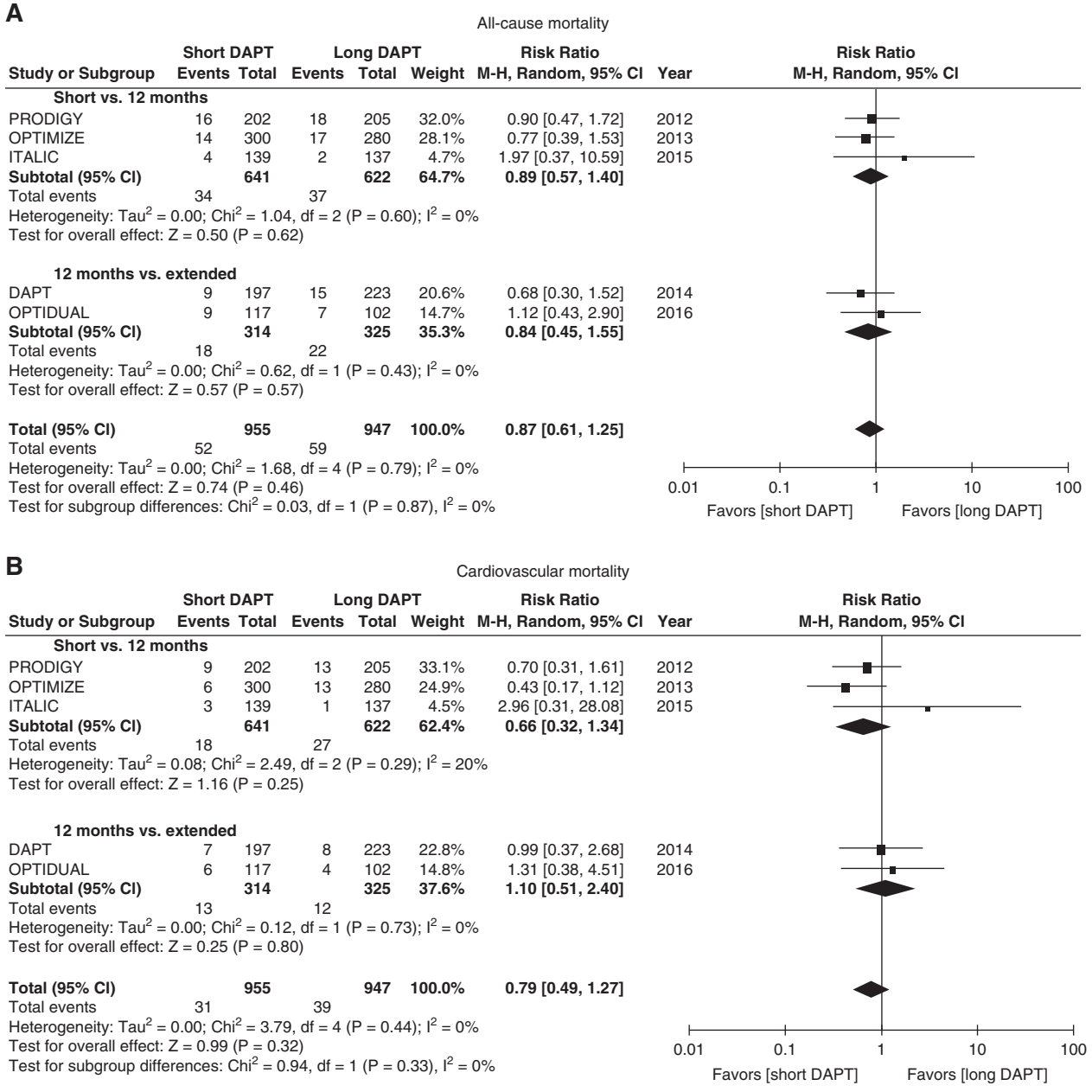

Figure 3. | Forest plot showing similar all-cause mortality (A) and cardiovascular mortality (B) event rates with short (≤6 months), 12-month, and extended (≥30 months) dual antiplatelet therapy in patients with CKD. Data are presented with risk ratios with 95% confidence intervals. A random effects 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

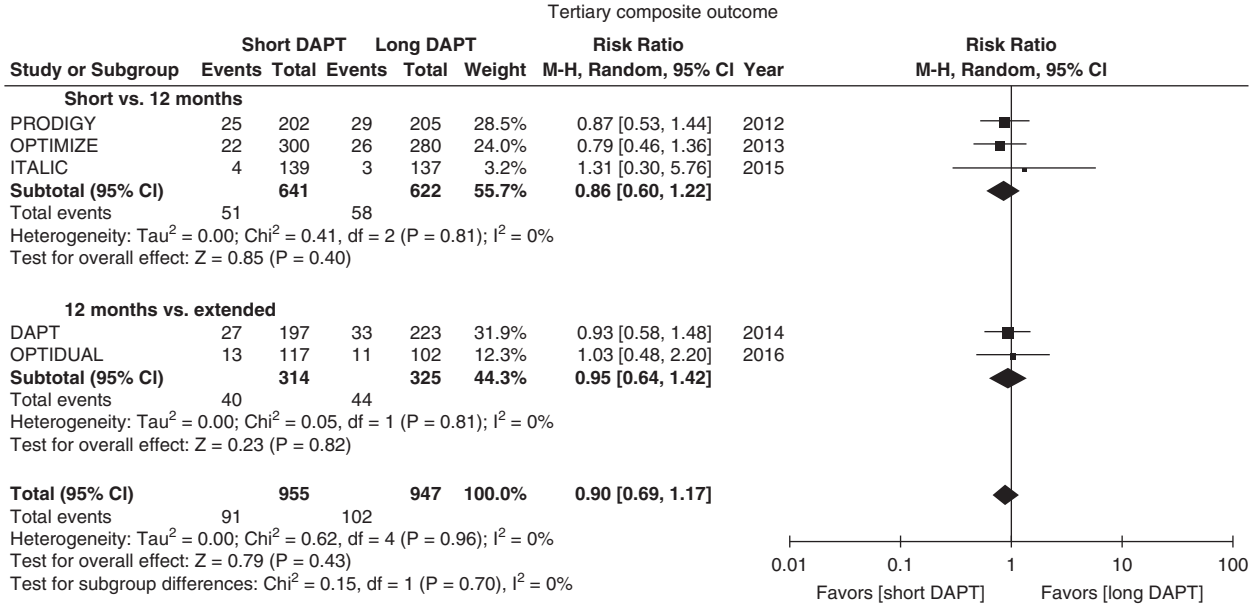

Figure 4. | Forest plot showing a similar incidence of the tertiary outcome, a composite of all-cause mortality, myocardial infarction, stroke, stent thrombosis (definite or probable), and major bleeding, with short (≤6 months), 12-month, and extended (≥30 months) dual antiplatelet therapy in patients 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 m^2 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.

Acknowledgments

Part of this work was presented in the form of a poster at the 2018 Kidney Week of the American Society of Nephrology in San Diego.

Disclosures

Dr. Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston Veteran Affairs Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the Portico Transcatheter Heart Valve and Delivery Systems trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, American College of Cardiology Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Healthcare Made Practical Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the Cardiovascular Outcomes for People Using Anticoagulation Strategies operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (Continuous Medical Education steering committees); Other: Clinical Cardiology (Deputy Editor), National Cardiovascular Data Registry Steering Committee (Chair), Veteran Affairs Clinical Assessment Reporting and Tracking Program, Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Coinvestigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. Dr. Charytan has received grants from Public Limiting Company (PLC) Medical and Medtronic/Covidien, and personal fees from Public Limiting Company (PLC) Medical, Astra Zeneca, Allena Pharmaceuticals, Medtronic/Covidien, Amgen, Merck, Zoll Medical, Fresenius, Daichio Sankyo, and Janssen Pharmaceuticals. Dr. Gargiulo has received research grant support from Cardiopath PhD program at University Federico II of Naples. Dr. Georges has received institutional research grants from AstraZeneca France, and personal fees from AstraZeneca France and Sanofi-Aventis. Dr. Mauri reports employment by Medtronic since June of 2018, outside of the submitted work. Dr. Valgimigli has received grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Biosensors, and personal fees from Idorsia, outside of the submitted work. The remaining authors have nothing to disclose.

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.

References

1. Patrono C, Morais J, Baigent C, Collet JP, Fitzgerald D, Halvorsen S, Rocca B, Siegbahn A, Storey RF, Vilahur G: Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. *J Am Coll Cardiol* 70: 1760–1776, 2017
2. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators: Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: A randomized multicenter trial. *Circulation* 125: 2015–2026, 2012
3. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB 3rd, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ Jr., Nicolela EL Jr., Perin MA, Devito FS, Labrunie A, Salvadori D Jr., Gusmão M, Staico R, Costa JR Jr., de Castro JP, Abizaid AS, Bhatt DL; OPTIMIZE Trial Investigators: Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: The OPTIMIZE randomized trial. *JAMA* 310: 2510–2522, 2013
4. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice MC: 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: The randomized, multicenter ITALIC trial. *J Am Coll Cardiol* 65: 777–786, 2015
5. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators: Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 371: 2155–2166, 2014
6. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, Furber A, Leclercq F, Eltchaninoff H, Falquier JF, Henry P, Cattan S, Sebagh L, Michel PL, Tuambilangana A, Hammoudi N, Boccara F, Cayla G, Douard H, Diallo A, Berman E, Komajda M, Metzger JP, Vicaut E; OPTImal DUAL Antiplatelet Therapy Trial Investigators: Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: The OPTIDUAL randomized trial. *Eur Heart J* 37: 365–374, 2016
7. Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, Cuisset T, Elhadad S, Schiele F, Lhoest N, Ohlmann P, Carrié D, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Beygui F, Vicaut E, Montalescot G; ARCTIC Investigators: Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): A randomised trial. *Lancet* 384: 1577–1585, 2014
8. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, Menozzi A, Pucci E, Mauri J, Cesana BM, Giustino G, Sardella G: Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: The SECURITY randomized clinical trial. *J Am Coll Cardiol* 64: 2086–2097, 2014
9. Schulz-Schüpke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tölg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wöhrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schömig A, Mehilli J, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators: ISAR-SAFE: A randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 36: 1252–1263, 2015
10. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS: Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 125: 505–513, 2012
11. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y; RESET Investigators: A new strategy for discontinuation of dual antiplatelet therapy: The RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 60: 1340–1348, 2012
12. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Han S, Lee SG, Seong IW, Rha SW, Jeong MH, Lim DS, Yoon JH, Hur SH, Choi YS, Yang JY, Lee NH, Kim HS, Lee BK, Kim KS, Lee SU, Chae JK, Cheong SS, Suh IW, Park HS, Nah DY, Jeon DS, Seung KB, Lee K, Jang JS, Park SJ: Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: A randomized, controlled trial. *Circulation* 129: 304–312, 2014
13. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, Li X, Zhao X, Wang H, Zhao X, Li X, Yu P, Zang H, Wang Z, Cao X, Zhang J, Pang W, Li J, Yang Y, Dangas GD: Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: Randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv* 9: e003145, 2016
14. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Her AY, Kim YH, Jang Y, Hong MK; IVUS-XPL Investigators: 6-Month versus 12-Month dual-antiplatelet therapy following long everolimus-eluting stent implantation: The IVUS-XPL Randomized Clinical Trial. *JACC Cardiovasc Interv* 9: 1438–1446, 2016
15. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW: Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: A pairwise and Bayesian network meta-analysis of randomised trials. *Lancet* 385: 2371–2382, 2015
16. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD: Duration of dual antiplatelet

therapy after drug-eluting stent implantation: A systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 65: 1298–1310, 2015
17. Navarese EP, Andreotti F, Schulze V, Kołodziejczak M, Buffon A, Brouwer M, Costa F, Kowalewski M, Parati G, Lip GY, Kelm M, Valgimigli M: Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ* 350: h1618, 2015
18. Gargiulo G, Valgimigli M, Capodanno D, Bittl JA: State of the art: Duration of dual antiplatelet therapy after percutaneous coronary intervention and coronary stent implantation - past, present and future perspectives. *EuroIntervention* 13: 717–733, 2017
19. Bonaca MP, Sabatine MS: Antiplatelet therapy for long-term secondary prevention after myocardial infarction. *JAMA Cardiol* 1: 627–628, 2016
20. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee CW, Mauri L, Valgimigli M, Park SJ, Montalescot G, Sabatine MS, Braunwald E, Bhatt DL: Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: A collaborative meta-analysis of randomized trials. *Eur Heart J* 37: 390–399, 2016
21. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr.: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 68: 1082–1115, 2016
22. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies: 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 39: 213–254, 2018
23. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP: Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *Lancet* 382: 339–352, 2013
24. Gargiulo G, Santucci A, Piccolo R, Franzone A, Ariotti S, Baldo A, Esposito G, Moschovitis A, Windecker S, Valgimigli M: Impact of chronic kidney disease on 2-year clinical outcomes in patients treated with 6-month or 24-month DAPT duration: An analysis from the PRODIGY trial. *Catheter Cardiovasc Interv* 90: E73–E84, 2017
25. Molnar AO, Bota SE, Garg AX, Harel Z, Lam N, McArthur E, Nesrallah G, Perl J, Sood MM: The risk of major hemorrhage with CKD. *J Am Soc Nephrol* 27: 2825–2832, 2016
26. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, Copetti M, Graziano G, Tognoni G, Jardine M, Webster A, Nicolucci A, Zoungas S, Strippoli GF: Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: A systematic review and meta-analysis. *Ann Intern Med* 156: 445–459, 2012
27. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* 62: 1006–1012, 2009
28. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 17: 1–12, 1996
29. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336: 924–926, 2008
30. Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Ahn JM, Park SJ, Schüpke S, Kastrati A, Montalescot G, Steg PG, Diallo A, Vicaut E, Helft G, Biondi-Zoccai G, Xu B, Han Y, Genereux P, Bhatt DL, Stone GW: Bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. *J Am Coll Cardiol* 69: 2011–2022, 2017
31. Secemsky EA, Yeh RW, Kereiakes DJ, Cutlip DE, Cohen DJ, Steg PG, Cannon CP, Apruzzese PK, D'Agostino RB Sr., Massaro JM, Mauri L; Dual Antiplatelet Therapy (DAPT) Study Investigators: Mortality following cardiovascular and bleeding events occurring beyond 1 year after coronary stenting:A Secondary Analysis of the Dual Antiplatelet Therapy (DAPT) study. *JAMA Cardiol* 2: 478–487, 2017
32. Chen YT, Chen HT, Hsu CY, Chao PW, Kuo SC, Ou SM, Shih CJ: Dual antiplatelet therapy and clinical outcomes after coronary drug-eluting stent implantation in patients on hemodialysis. *Clin J Am Soc Nephrol* 12: 262–271, 2017
33. Dasgupta A, Steinhubl SR, Bhatt DL, Berger PB, Shao M, Mak KH, Fox KA, Montalescot G, Weber MA, Haffner SM, Dimas AP, Steg PG, Topol EJ; CHARISMA Investigators: Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance [CHARISMA] trial). *Am J Cardiol* 103: 1359–1363, 2009
34. Montalescot G, Silvain J: Ticagrelor in the renal dysfunction subgroup: Subjugated or substantiated? *Circulation* 122: 1049–1052, 2010
35. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, Harrington RA, Horrow J, Katus H, Keltai M, Lewis BS, Parikh K, Storey RF, Szummer K, Wojdyla D, Wallentin L: Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: Results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 122: 1056–1067, 2010
36. Singla A, Antonino MJ, Bliden KP, Tantry US, Gurbel PA: The relation between platelet reactivity and glycemic control in diabetic patients with cardiovascular disease on maintenance aspirin and clopidogrel therapy. *Am Heart J* 158: 784.e1–784.e6, 2009
37. Angiolillo DJ, Jakubowski JA, Ferreiro JL, Tello-Montoliu A, Rollini F, Franchi F, Ueno M, Darlington A, Desai B, Moser BA, Sugidachi A, Guzman LA, Bass TA: Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. *J Am Coll Cardiol* 64: 1005–1014, 2014
38. Meredith IT, Tanguay JF, Kereiakes DJ, Cutlip DE, Yeh RW, Garratt KN, Lee DP, Steg PG, Weaver WD, Holmes DR Jr., Brindis RG, Trebacz J, Massaro JM, Hsieh WH, Mauri L; DAPT Study Investigators: Diabetes mellitus and prevention of late myocardial infarction after coronary stenting in the randomized Dual Antiplatelet Therapy study. *Circulation* 133: 1772–1782, 2016
39. Ang L, Palakodeti V, Khalid A, Tsimikas S, Idrees Z, Tran P, Clopton P, Zafar N, Bromberg-Marin G, Keramati S, Mahmud E: Elevated plasma fibrinogen and diabetes mellitus are associated with lower inhibition of platelet reactivity with clopidogrel. *J Am Coll Cardiol* 52: 1052–1059, 2008
40. Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Büttner HJ, Neumann FJ: Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol* 55: 2427–2434, 2010
41. Levine GN, Bates ER: It is time to end the dualistic short versus long duration of dual antiplatelet therapy debates. *Circulation* 135: 2451–2453, 2017
42. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L; DAPT Study Investigators: Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 315: 1735–1749, 2016
43. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler

B, Weisz G, Steg PG, Pocock S: Coronary thrombosis and major bleeding after PCI with drug-eluting stents: Risk scores from PARIS. *J Am Coll Cardiol* 67: 2224–2234, 2016
44. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators: Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: A pooled analysis of individual-patient datasets from clinical trials. *Lancet* 389: 1025–1034, 2017
45. Chatzizisis YS, Stefanadis C: Clash of oral $P2Y_{12}$ receptor inhibitors in acute coronary syndromes. *J Am Coll Cardiol* 71: 382–385, 2018
46. Magnani G, Storey RF, Steg G, Bhatt DL, Cohen M, Kuder J, Im K, Aylward P, Ardissino D, Isaza D, Parkhomenko A, Goudev AR, Dellborg M, Kontny F, Corbalan R, Medina F, Jensen EC, Held P, Braunwald E, Sabatine MS, Bonaca MP: Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: Insights from the PEGASUS-TIMI 54 trial. *Eur Heart J* 37: 400–408, 2016
47. Carrero JJ, Varenhorst C, Jensevik K, Szummer K, Lagerqvist B, Evans M, Spaak J, Held C, James S, Jernberg T: Long-term versus short-term dual antiplatelet therapy was similarly associated with a lower risk of death, stroke, or infarction in patients with acute coronary syndrome regardless of underlying kidney disease. *Kidney Int* 91: 216–226, 2017
48. Mavrakanas TA, Alam A, Reny JL, Fontana P: Platelet reactivity in stable cardiovascular patients with chronic kidney disease. *Platelets* 29: 455–462, 2018
49. Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, Kereiakes DJ, Waksman R, Mauri L, Meredith IT, Finn AV, Kim HS, Kubica J, Suryapranata H, Aprami TM, Di Pasquale G, von Birgelen C, Kedhi E: Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: Comprehensive network meta-analysis. *BMJ* 347: f6530, 2013

Received: October 31, 2018 **Accepted:** March 27, 2019

Published online ahead of print. Publication date available at www.cjasn.org.

AFFILIATIONS

[1]Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Department of Medicine, Geneva University Hospitals, Geneva, Switzerland; [3]Cardiovascular Division, University of Nebraska Medical Center, Omaha, Nebraska; [4]Division of Diabetes and Endocrinology, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland; [5]The Christ Hospital Heart and Vascular Center and The Lindner Center for Research and Education, Cincinnati, Ohio; [6]Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland; [7]Department of Advanced Biomedical Sciences, University Federico II of Naples, Naples, Italy; [8]Institute of Cardiology, University Hospitals Pitié-Salpêtrière- Charles Foix (Public Assistance- Hospitals of Paris), Sorbonne University, Paris, France; [9]Division of Cardiology, Regional University Hospital La Cavale Blanche, Brest, France; [10]Institute Dante Pazzanese de Cardiologia, Sao Paulo, Sao Paulo, Brazil; [11]Private Hospital Jacques Cartier, Ramsay Générale de Santé, Massy, France; [12]Hospital of Versailles, Le Chesnay, France; [13]Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, Massachusetts; [14]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [15]Baim Institute for Clinical Research, Boston, Massachusetts; and [16]Division of Nephrology, New York University Langone Medical Center, New York, New York