The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: Results from the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial

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Background Mild and moderate chronic kidney disease (CKD) is associated with decreased survival and increased adverse events after a percutaneous coronary intervention (PCI). Therapy with clopidogrel decreases adverse events in large patient populations. Therefore, we sought to determine the efficacy and safety of long-term clopidogrel therapy in patients with CKD.

Methods Two thousand two patients from the CREDO trial in whom an elective PCI of a single or multiple vessels was planned were analyzed. Patients were randomly assigned to a 300-mg loading dose of clopidogrel before PCI followed by clopidogrel 75 mg/d for a year versus a placebo loading dose at the time of the PCI procedure and clopidogrel 75 mg/d for 28 days and placebo for the remainder of a year. Patients were categorized by their estimated creatinine clearance (>90 [normal, n = 999], 60-89 [mild CKD, n = 672], <60 mL/min [moderate CKD, n = 331]).

Results Diminished renal function was associated with worse outcomes. Patients with normal renal function who received 1 year of clopidogrel had a marked reduction in death, myocardial infarction, or stroke compared with those who received placebo (10.4% vs 4.4%, $P < .001$), whereas patients with mild and moderate CKD did not have a significant difference in outcomes with clopidogrel therapy versus placebo (mild: 12.8% vs 10.3%, $P = .30$; moderate: 13.1% vs 17.8%, $P = .24$). Clopidogrel use was associated with an increased relative risk of major or minor bleeding, but this increased risk was not different based on renal function (relative risk 1.2, 1.3, 1.1).

Conclusions Clopidogrel in mild or moderate CKD patients may not have the same beneficial effect as it does in patients with normal renal function, but was not associated with a greater relative risk of bleeding based on renal function. Further studies are needed to define the role of clopidogrel therapy in patients with CKD. (Am Heart J 2008;155:687-93.)

In patients 1 year after a successful percutaneous coronary intervention (PCI), mortality is twice as high in mild chronic kidney disease (CKD) patients than in those with normal renal function; and in those with moderate CKD, mortality is 4 times higher.[1] Accelerated plaque progression and rupture may contribute to the increased mortality from cardiovascular causes in this population. Aggressive risk factor modification and other medical therapies are warranted in these patients, although few therapies have been tested specifically among patients with CKD. Dual antiplatelet therapy with aspirin and clopidogrel reduces long-term major adverse cardiovascular events after PCI and among patients with an acute coronary syndrome.[2-4] However, minimal data are available on the efficacy of clopidogrel in the CKD population.

Because CKD results in a complex hemostatic disorder manifested by increased bleeding and thrombosis, the use of antiplatelet therapy has the potential for both benefit and harm. Reduced platelet aggregation, intrinsic platelet dysfunction, and abnormalities in platelet-endothelial interactions are found in CKD and may in part account for the increased bleeding risk with PCI in these patients.[5-7] However, a prothrombotic state is present in CKD patients manifest by increases in fibrinogen, von Willebrand factor, and tissue factor and reductions in antithrombin III.[5,8-10] Thus, it is unclear whether dual

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antiplatelet therapy with aspirin and clopidogrel is beneficial and safe in CKD.

Therefore, using the CREDO data, we hypothesized that mildly to moderately reduced renal function would be associated with altered safety and efficacy of dual antiplatelet therapy.

Methods

Patient population

In the CREDO trial, 2116 patients in whom an elective PCI was planned or considered likely were enrolled.[4] Patients were excluded from this analysis if a serum creatinine was not available at study entry (n = 114, 5%). All other CREDO patients were included in this analysis.

Randomization and treatment

In CREDO, patients were randomly assigned to receive clopidogrel (300 mg) or placebo 3 to 24 hours before PCI, followed by 75 mg/d of clopidogrel after the procedure and once daily for 28 days. After 28 days, patients who received pretreatment with the loading dose of clopidogrel continued to receive 75 mg/d of clopidogrel for a year, whereas patients who received a placebo loading dose received placebo for 1 year. All patients received aspirin 325 mg/d for the first 28 days then 81 to 325 mg/d for 1 year.

Creatinine clearance

The creatinine clearance was estimated using the Cockroft-Gault formula[11]; and patients were divided into the following groups: creatinine clearance ≥90 mL/min (normal renal function), 60 to 90 mL/min (mild CKD), and <60 mL/min (moderate CKD) based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative stages of CKD (stage 1, stage 2, and stages 3-5 combined).[12]

Outcomes

The primary end point was a composite of death, myocardial infarction, or urgent target vessel revascularization at 28 days, based on intention to treat. Secondary end points included individual components of the composite end point or any other revascularization procedures, and major bleeding at 28 days and 1 year after study enrollment, as well as the composite of death, myocardial infarction, or stroke at 1 year. Any revascularization was defined as PCI or coronary artery bypass graft (CABG), or any peripheral or cerebral revascularization procedure. Bleeding was defined using a modification of the Thrombolysis in Myocardial Infarction bleeding criteria.

Statistical methods

Patient demographics are presented as the means, medians, SDs, and the 25th and 75th quartiles for continuous variables, and percentages for discrete variables. Comparisons across groups were made with the Wilcoxon rank sum test, χ^2 test, or Fisher exact test. Kaplan-Meier methods were used to estimate event rates between CKD groups and were compared with a log-rank test. The incidence of bleeding was compared using the χ^2 test. Relative risk reductions (RRRs), hazard ratios (HR), and their corresponding 95% CIs were estimated using Cox proportional hazards models. A multivariate analysis was performed for 1-year death/MI/stroke using a Cox proportional hazards model. All baseline characteristics were considered for adjustment. Variables that attained a P value < .05 were kept in the multivariate model. All analyses were performed using SAS software version 8.0 (SAS Institute Inc, Cary, NC).

Table I. Baseline characteristics of patients in CREDO based on renal function

Characteristic	Creatinine clearance (mL/min) >90 (n = 999)	60-89 (n = 672)	<60 (n = 331)	P
Age in years ± SD	55.4 ± 8.7	65.3 ± 8.9	73.5 ± 8.1	<.001
Male sex, %	80.7	65.5	54.4	<.001
Weight in kg ± SD	96.6 ± 18.1	81.4 ± 13.6	73.7 ± 13.8	<.001
BMI >30, %	58.7	33.8	18.1	<.001
Diabetes mellitus, %	26.7	25.6	27.5	.804
Hypertension, %	66.4	68.1	76.6	.002
History of smoking, %	40.5	24.2	14.8	<.001
Hyperlipidemia, %	80.1	74.7	72.6	.004
Family history CAD, %	56.7	45.4	32.0	<.001
Previous CABG, %	16.3	23.2	27.4	<.001
Previous PCI, %	39.1	34.4	36.2	.193
Previous MI, %	34.6	34.1	36.8	.706
Peripheral vascular disease, %	5.7	8.8	17.0	<.001
Mean LVEF, % ± SD	55.8 ± 11.3	54.7 ± 12.5	54.2 ± 12.9	.361
Congestive heart failure, %	6.2	8.4	17.0	<.001
Treatment after initial angiogram, %				
PCI	84.4	87.0	89.9	.033
Medical therapy	2.3	2.8	3.7	.413
CABG	3.7	4.2	3.0	.671

CAD, Coronary artery disease; *MI*, myocardial infarction; *LVEF*, left ventricular ejection fraction.

Results

Baseline characteristics

Of the 2002 study patients, those with moderate CKD were older and more likely to be female and to have hypertension, peripheral vascular disease, and congestive heart failure (Table I). They were less likely to smoke, to be obese, to have hyperlipidemia, or to have a family history of coronary artery disease. Most of the patients had unstable angina (53%) as the indication for intervention, 14% had a recent myocardial infarction, and 28% had stable angina. There were no differences in these indications between the creatinine clearance groups. Before enrollment, medical therapy was administered in similar frequencies to patients of all the groups. There were no differences in any of the

Table II. Procedural characteristics of patients in CREDO study undergoing PCI based on renal function

Characteristic	Creatinine clearance (mL/min) >90 (n = 841)	60-89 (n = 582)	<60 (n = 295)	P
Stent length, mm, median (Q1, Q3)	18.0 (15.0, 31.0)	18.0 (13.0, 30.0)	18.0 (13.0, 27.0)	.131
Balloon angioplasty only, %	5.6	9.1	5.8	.026
Stent, %	90.4	86.8	90.2	.082
GpIIb/IIIa antagonist use, %				
Prespecified	23.9	26.3	19.7	.094
Bailout	22.8	22.0	18.3	.266
Maximum ACT, s, mean ± SD	276.1 ± 77.8	282.3 ± 79.1	293.2 ± 82.8	.012
Heparin use, IU, mean ± SD	7793 ± 5872	7328 ± 6111	7478 ± 7463	<.001
Heparin use (IU)/weight (kg), mean ± SD	69.5 ± 65.0	79.3 ± 72.1	93.6 ± 111.3	<.001

Gp, Glycoprotein; *ACT;* activated clotting time.

baseline characteristics between those who received clopidogrel and placebo within any of the creatinine clearance groups.

There were no differences in any of the procedure characteristics between those who received clopidogrel and placebo within any of the creatinine clearance groups (Table II).

Outcomes

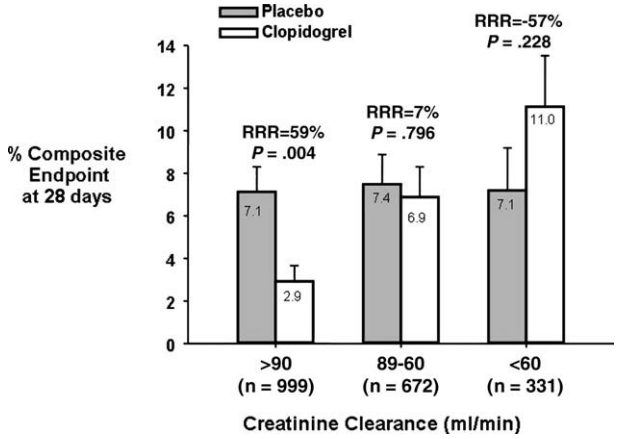
Twenty-eight–day end point. Decreased creatinine clearance was associated with worse outcomes. At 28 days, the combined end point of death, MI, or stroke occurred in 5.1%, 7.8%, and 9.8% of patients with normal, mild, and moderate CKD ($P = .12$); and death, MI or urgent revascularization occurred in 5.8%, 7.9%, and 10.4%, respectively ($P = .014$).

At 28 days, clopidogrel therapy was associated with a significant reduction in the composite end point of death, myocardial infarction, and stroke in patients with normal renal function (7.1% vs 2.9%, $P = .004$). However, in mild or moderate CKD patients, the RRR of randomization to clopidogrel diminished with worsening renal function (Figure 1). Clopidogrel therapy was associated with a significant reduction in the original CREDO primary 28-day composite end point in the patients with normal renal function (7.9% vs 3.7%, $P = .004$). In the mild or moderate CKD patients, the RRR of clopidogrel decreased with decreasing renal function (mild CKD: 8% vs 7.8%, $P = .93$; moderate CKD: 9.5% vs 11.0%, $P = .65$).

One-year end point. Decreased renal function was associated with adverse outcomes at 1 year. The combined end point of death, MI, or stroke occurred in 8.0%, 12.4%, and 15.9% of patients with normal, mild, and moderate CKD ($P < .001$) at 1 year.

Clopidogrel therapy was associated with a significant reduction in the composite end point of death, myocardial infarction, and stroke in patients with normal renal function (10.4% vs 4.4%, HR = 0.42, 95% CI 0.26-0.69, $P = .001$). However, in mild or moderate CKD patients, less benefit from clopidogrel therapy was again found (HR = 0.80, 95% CI 0.51-1.25, $P = .32$ in those with mild CKD; HR = 1.41, 95% CI 0.81-2.45, $P = .23$ in those with moderate CKD) (Figure 2).

Figure 1

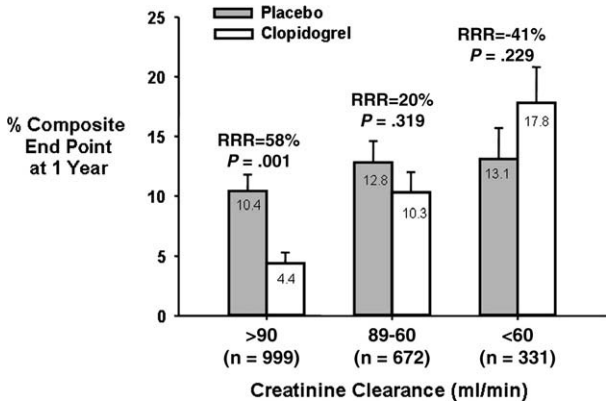


The effect of clopidogrel therapy on the composite end point of death, myocardial infarction, and stroke at 28 days in all 3 creatinine clearance groups.

In a multivariate model of each renal function group, patients with normal renal function had an HR = 0.47 ($P = .003$) for the use of clopidogrel and an HR = 2.2 for a history of peripheral vascular disease ($P = .037$). In the mild CKD group, clopidogrel use had an HR = 0.84 ($P = .485$), whereas age ≥70 years had an HR = 1.2 ($P < .001$) and recent myocardial infarction had an HR = 2.4 ($P = .003$). In patients with moderate CKD, the HR for the use of clopidogrel was 1.7 ($P = .073$), age ≥70 years had an HR = 1.1 ($P = .87$), and recent myocardial infarction had an HR = 2.5 ($P = .006$).

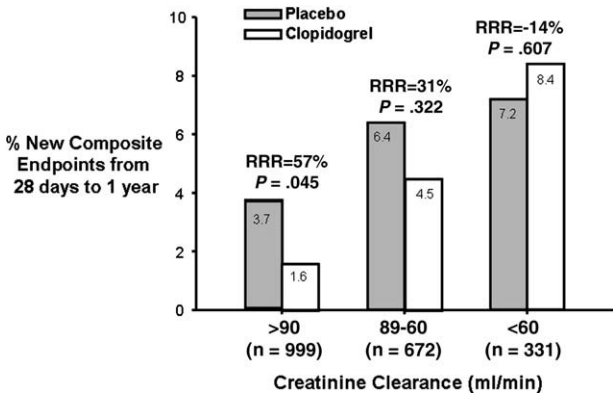
The difference in the new events of the combined end point of death, myocardial infarction, or stroke

Figure 2



The effect of clopidogrel therapy on the composite end point of death, myocardial infarction, and stroke at 1 year in all 3 creatinine clearance groups.

Figure 3



The effect of clopidogrel therapy on new composite events of death, myocardial infarction, and stroke between 28 days and 1 year in all 3 creatinine clearance groups.

between 28 days and 1 year still favored clopidogrel therapy in the normal renal function group (3.7% vs 1.6%, P = .045) (Figure 3). A similar absolute reduction was seen in those with mild CKD (6.4% vs 4.5%, P = .322). However, in individuals with moderate CKD, a trend in the opposite direction was found (7.2% vs 8.4%, P = .607).

In a multivariate model of the whole cohort (Table III), the HR for the composite end point during follow-up was highest in those patients with a recent myocardial infarction and those on calcium-channel blockers at baseline. Because the treatment effects in normal renal function and mild CKD groups were similar, they were combined together for this multivariate model. The statistically significant interaction between the use of clopidogrel and patients with moderate CKD (HR = 2.5, P = .007) indicates that patients with moderate CKD who were on clopidogrel were at an increased risk of experiencing an event at 1 year.

Table III. Multivariate model for the composite end point of death, myocardial infarction, and stroke at 1 year

Variable	HR (95% confidence limits)	P
Clopidogrel versus placebo	0.58 (0.42-0.81)	.001
Age >70 y	1.09 (1.05-1.14)	<.001
Recent myocardial infarction	1.87 (1.33-2.63)	<.001
Baseline calcium-channel blockers	1.41 (1.05-1.90)	.021
Creatinine clearance <60 mL/min	0.71 (0.42-1.20)	.200
Creatinine clearance <60 mL/min and clopidogrel interaction	2.45 (1.28-4.70)	.007

Bleeding

At 1 year, the incidence of major and minor bleeding was, in general, greater in the lower creatinine clearance groups. There was no significant increase in the individual outcomes of major bleeding, minor bleeding, or transfusions with clopidogrel use in any of the creatinine clearance groups (Table IV). However, there was a slight increase in the composite of major or minor bleeding among patients randomized to long-term clopidogrel therapy in the mild and moderate CKD groups (Figure 4). Between 28 days and 1 year, in the normal renal function group, major and minor bleeding was not different between placebo and clopidogrel (5.1% vs 5.5%, P = .76). There also was no difference in the mild CKD group (5.9% vs 9.5%, P = .82) or in the moderate CKD group (9.8% vs 5.1%, P = .106).

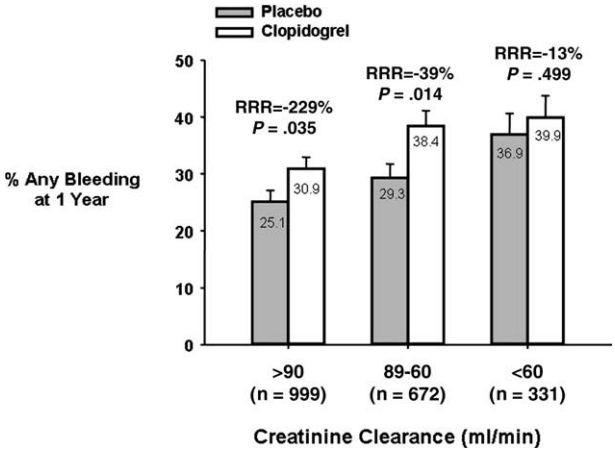
Discussion

The current study, a post hoc analysis of the CREDO trial, demonstrates that although long-term clopidogrel use in patients with normal renal function resulted in a significant reduction in major adverse cardiovascular events at 28 days and 1 year, this benefit was less apparent in mild CKD and not apparent at all in moderate CKD patients. This finding was surprising given that, as in patients in prior studies, patients with mild and moderate CKD in CREDO had a 2- to 4-fold higher frequency of death and 2-fold higher risk of a myocardial infarction during 1 year of follow-up. Despite the platelet and coagulation abnormalities associated with CKD, clopidogrel did not increase bleeding more in mild or moderate CKD patients than it did in those with normal renal function.

Table IV. Relative risk for bleeding at 1 year for patients who received clopidogrel versus those who did not based on creatinine clearance

Relative risk of bleeding with clopidogrel	Creatinine clearance, mL/min (95% CI)		
	≥90	60-89	<60
Major bleeding	1.168 (0.741, 1.841)	1.595 (0.970, 2.621)	1.124 (0.511, 2.476)
Minor bleeding	0.929 (0.498, 1.732)	1.579 (0.883, 2.825)	0.546 (0.250, 1.189)
Major or minor bleeding	1.235 (1.010, 1.511)	1.310 (1.058, 1.622)	1.081 (0.822, 1.420)
Transfusions	1.233 (0.980, 1.551)	1.241 (0.965, 1.595)	1.265 (0.890, 1.798)

Figure 4



The effect of clopidogrel on any bleeding at 1 year in all 3 creatinine clearance groups.

Several studies support the long-term use of clopidogrel with or without aspirin in patients with vascular disease and without marked elevations in serum creatinine. In the CAPRIE trial, clopidogrel was more effective than aspirin in reducing major adverse cardiovascular events in patients with atherosclerotic vascular disease.[13] Among diabetics, the benefit of clopidogrel therapy compared with aspirin was even greater.[14] In the CURE trial, long-term clopidogrel therapy in patients with non–ST-elevation acute coronary syndromes reduced major adverse cardiovascular events.[2,3,15] The CREDO trial also demonstrated benefit from long-term therapy with clopidogrel and aspirin compared with aspirin alone in patients undergoing PCI.[4] Interestingly, in the CHARISMA trial, there was no benefit from adding clopidogrel to aspirin in the overall trial, particularly in the cohort without established disease. Although no analysis including renal function in CHARISMA has been reported, >40% of this cohort was classified as having a diabetic nephropathy.[16]

Chronic kidney disease is a strong risk factor for cardiovascular events and is associated with a doubling of mortality in mild CKD patients 1 year after a PCI, a 5-fold increase in mortality in moderate CKD patients, and a 12-fold increase in mortality in severe CKD patients.[1] As is the case among patients with diabetes, CKD patients have the potential to derive greater benefit from therapies that reduce subsequent cardiovascular events. Unfortunately, few studies have directly addressed treatment options specifically in CKD patients, although current guidelines nonetheless support aggressive medical therapy and secondary prevention methods in these patients.[12]

This study demonstrated that patients with mild or moderate CKD might not derive the same level of benefit from clopidogrel therapy as patients with normal renal function. Most of the difference in the clopidogrel treatment effect between the creatinine clearance groups was seen in the first 28 days. The specific reasons for these findings are unknown, but may relate to alterations in the clopidogrel metabolism and bioavailability in CKD patients. Only small prospective studies have been performed to evaluate the effectiveness of clopidogrel therapy to alter platelet aggregation in CKD patients. Although a small series of 9 dialysis patients suggested a similar degree of platelet inhibition from a standard dose of clopidogrel as is achieved in patients with normal kidney function,[17] other studies found that the level of the major nonactive metabolite of clopidogrel is lower in severe CKD patients. Although these lowered metabolites in CKD patients are inactive, other studies have demonstrated that they correlate with platelet inhibition and may suggest differences in the pharmacokinetics in CKD patients.[18] The dose requirement of clopidogrel may be greater in patients with CKD, or it may take longer for clopidogrel loading therapy to adequately cause platelet inhibition. Indeed, several recent studies even among patients with normal renal function have documented lack of responsiveness to clopidogrel in a subset of patients that may be more pronounced in patients with CKD.[19] Thus, this post hoc analysis leads to the hypothesis that there is an interaction between renal function and clopidogrel effect. Only 1 other post hoc analysis has evaluated the interaction of renal function and clopidogrel effect.[20] Although the authors of this study found no interaction of renal function by glomerular filtration rate (GFR) tertile with clopidogrel therapy (*P* for heterogeneity = .11), they found no significant improvement in outcomes with clopidogrel therapy in the lowest GFR tertile (RR = 0.89 [0.76-

1.05]), whereas there was a significant reduction in adverse events in the middle and upper GFR tertiles (middle GFR tertile: RR = 0.68, 95% CI 0.56-0.89; upper GFR tertile: RR 0.74, 95% CI 0.60-0.93). Our study not only showed reduced benefit in the lowest creatinine clearance group, we also had an increased RR of events with clopidogrel therapy in this group. These differences may represent marked differences in the patient population between the studies and may be suggestive of differences in the attainment of pretreatment benefit in the normal renal function patients, but not in those with CKD. In addition, these studies have biases because they are post hoc analyses; and thus, the results have limitations. Further studies specifically studying the interaction between creatinine clearance and clopidogrel effect will be needed to definitively define this interaction, as subgroup analyses have inherent flaws and are ideally intended to be hypothesis generating.[21]

Chronic kidney disease is characterized by complex hemostatic properties with both an increased thrombotic risk that might make long-term clopidogrel therapy more efficacious and also an increased bleeding propensity.[5-10,22] Few studies have evaluated the appropriate dosing of antithrombotic agents or anticoagulants in patients with CKD.[23] Prior studies including CURE demonstrated an increased risk of major bleeding (3.7% vs 2.7%) with long-term clopidogrel therapy compared with placebo.[3] In the overall CREDO study, there was also a trend for increased major bleeding at 1 year with long-term clopidogrel therapy compared with placebo; but this did not reach statistical significance (8.8% vs 6.7%, $P = .07$). In this study, we examined the bleeding risk from long-term clopidogrel therapy in mild and moderate CKD patients and found that the relative and absolute increase in bleeding was less among patients with moderate CKD than in those with mild and no CKD. Thus, despite the theoretical risk of a larger increase in bleeding from clopidogrel therapy in CKD patients, this therapy appears to be safe.

Limitations

A potential limitation of the study relates to there having been only a single measurement of creatinine at the start of the study. Therefore, the possibility exists that patients with acute renal disease that was not clinically recognized may have been classified as chronic CKD. There are also limitations to the use of estimated renal function, such as the Cockroft-Gault equation. This is particularly true in obese patients, where the Cockroft-Gault formula overestimates renal function. Furthermore, this is a post hoc analysis of a prospective study, which therefore has inherent limitations. Notably, patients with CKD have greater risk factors for coronary artery disease and have less utilization of proven therapy such as glycoprotein IIb/IIIa inhibitors. Although we attempted to correct for these difference by multivariate analysis, some bias may still exist. In addition, there were a small number of moderate CKD patients because those with a creatinine >3 mg/dL were excluded from the CREDO trial.

Conclusion

Although clopidogrel was overall highly effective at reducing adverse cardiovascular events in CREDO, this effect seemed to be greatest in patients with normal renal function, whereas patients with mild and in particular moderate CKD appeared to have experienced less of a benefit. Major bleeding was not increased from clopidogrel to a greater degree in CKD patients than in others. This finding represents an outlier compared with other aspirin-clopidogrel trials, such that confirmation of the effect of CKD is thus far lacking. More studies are needed to determine the optimal use of clopidogrel therapy in patients with CKD.

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