

Effect of Estimated Glomerular Filtration Rate Decline on the Efficacy and Safety of Clopidogrel With Aspirin in Minor Stroke or Transient Ischemic Attack

CHANCE Substudy (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events)

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Background and Purpose—Patients with chronic kidney disease (CKD) are at a particularly high risk for ischemic and bleeding events. Limited data exist as to the efficacy and safety of clopidogrel in stroke patients with renal dysfunction. Therefore, we sought to assess the impact of decreased kidney function on clinical outcomes for stroke patients on clopidogrel–aspirin treatment.

Methods—Patients in the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) were randomized to clopidogrel–aspirin or aspirin-alone treatment. The primary efficacy outcome was new stroke during 90 days, whereas bleeding was the safety outcome. Patients were stratified according to estimated glomerular filtration rate.

Results—Dual clopidogrel–aspirin therapy was associated with a marked reduction in new strokes compared with the therapy of aspirin alone in patients with normal renal function (hazard ratio, 0.77; 95% confidence interval, 0.60–0.98; $P=0.02$) and mild CKD (hazard ratio, 0.60; 95% confidence interval, 0.45–0.79; $P<0.01$), whereas in patients with moderate CKD, no significant benefit from clopidogrel therapy was detected (hazard ratio, 1.00; 95% confidence interval, 0.43–2.35; $P=0.99$). There was no clear difference in bleeding episodes by treatment assignment across categories of renal impairment.

Conclusions—Clopidogrel plus aspirin could decrease new stroke in patients with normal kidney function and mild CKD, but no extra benefit was observed in those with moderate CKD. Bleeding risk from the dual therapy did not seem to increase in mild or moderate CKD patients.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00979589.

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Key Words: chronic kidney disease ■ clopidogrel ■ stroke

Chronic kidney disease (CKD) is associated with a high prevalence of stroke,^{1,2} and reduced estimated glomerular filtration rate (eGFR) can be a strong predictor of higher recurrence, comorbidity, and mortality among patients with acute ischemic

stroke.³⁻⁵ As the backbone of P2Y₁₂ inhibition,⁶ clopidogrel is often recommended for preventing stroke, especially in patients with noncardioembolic ischemic stroke.⁷ However, specific recommendations for antiplatelet therapy in patients with ischemic

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stroke plus CKD are not available, although there have been a few investigations in the field of acute coronary syndrome (ACS).

CKD is characterized as a state with a prothrombotic tendency where excessive platelet activation and dysfunction plays a pivotal role. On the contrary, the risk of all-cause major hemorrhage increased in a graded fashion across all stages of CKD.⁸ Bleeding complications may occur in patients even with a normal coagulation profile or elevated coagulation factors.² Therefore, assessment of the efficacy and safety of dual antiplatelet therapy with clopidogrel and aspirin for treating and preventing cerebrovascular diseases in the setting of CKD is of great significance.^{2,9}

The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was designed to determine the protection effect against stroke and bleeding risk of combination therapy of clopidogrel plus aspirin compared with aspirin alone among patients with minor stroke or transient ischemic attack (TIA).^{10,11} On the basis of the CHANCE trial, we aimed to investigate whether declined eGFR would be associated with altered efficacy and safety of dual antiplatelet therapy.

Methods

Study Population

CHANCE was a randomized, double-blind, placebo-controlled clinical trial conducted at 114 clinical centers in China. Details about the CHANCE study design and results have been published elsewhere.¹⁰⁻¹² Within 24 hours after the onset of minor ischemic stroke or high-risk TIA, patients were randomly assigned to either clopidogrel plus aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per

day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) or placebo plus aspirin (75 mg per day for 90 days) group.

Between October 2009 and July 2012, the CHANCE trial enrolled 5170 eligible patients, who met the following inclusion criteria: age ≥ 40 years; diagnosis of an acute minor ischemic stroke or high-risk TIA; and ability to start the study drug within 24 hours after symptom onset. Acute minor stroke was defined as the National Institutes of Health Stroke Scale value ≤ 3 at the time of randomization. High-risk TIA was defined as a neurological deficit lasting < 24 hours caused by focal brain ischemia plus a moderate-to-high risk of stroke recurrence (ABCD2 [scores assessing the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes mellitus] at the time of randomization ≥ 4). Other eligibility criteria were provided in the study protocol.¹⁰ Venous blood samples were obtained at randomization and were sent for laboratory analysis of creatinine concentration. It should be noted that patients with severe renal dysfunction, defined as serum creatinine > 1.5 times of upper limit of normal value, were excluded.

The trial was approved by the ethics committee at each study center. Written informed consent was obtained from all the participants or their legal proxies. This study was registered at ClinicalTrials.gov (registration number NCT00979589).

Calculation of eGFR

eGFR was calculated by the CKD-EPI China equation with adjusted coefficient of 1.1 for the Chinese population¹³: $eGFR_{CKD-EPI(CN)} = 141 \times \min(SCr/k, 1)^{\alpha} \times \max(SCr/k, 1)^{-1.209} \times 0.993^{\Delta_{age}} \times 1.018$ (if female) $\times 1.1$, where SCr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1. Patients were divided into the following groups: eGFR ≥ 90 mL/min per 1.73 m² (normal renal function), 60 to 89 mL/min per 1.73 m² (mild CKD), and < 60 mL/min per 1.73 m² (moderate CKD) based on the NKF-KDOQI guidelines (National Kidney Foundation Kidney Disease Outcomes Quality Initiative).^{14,15}

Table 1. Baseline Characteristics According to eGFR Category

Characteristics	eGFR < 60 mL/min per 1.73 ² (n=354)	eGFR 60–89 mL/min per 1.73 ² (n=2064)	eGFR ≥ 90 mL/min per 1.73 ² (n=2732)	P Value
Demographics				
Age, median (IQR), y	73.35 (65.59–77.15)	69.00 (60.15–75.02)	57.52 (51.29–64.12)	< 0.001
Female sex, n (%)	158 (44.63)	698 (33.82)	887 (32.47)	< 0.001
Medical history, n (%)				
Ischemic stroke	88 (24.86)	473 (22.92)	465 (17.02)	< 0.001
TIA	18 (5.08)	64 (3.10)	91 (3.33)	0.16
Myocardial infarction	13 (3.67)	49 (2.37)	34 (1.24)	< 0.001
Angina	20 (5.65)	84 (4.07)	79 (2.89)	0.008
Congestive heart failure	10 (2.82)	37 (1.79)	32 (1.17)	0.027
Known atrial fibrillation	13 (3.67)	60 (2.91)	23 (0.84)	< 0.001
Valvular heart disease	1 (0.28)	11 (0.53)	2 (0.07)	0.010
Hypertension	278 (78.53)	1395 (67.59)	1715 (62.77)	< 0.001
Diabetes mellitus	85 (24.01)	431 (20.88)	572 (20.94)	0.39
NIHSS, median (IQR)	2.00 (0.00–3.00)	1.00 (0.00–2.00)	2.00 (0.00–2.00)	0.21
eGFR (mL/min per 1.73 ²), median (IQR)	52.45 (45.81–56.68)	80.06 (71.81–85.76)	100.25 (94.99–106.15)	< 0.001
Qualifying event, n (%)				
Minor stroke	258 (72.88)	1494 (72.38)	1964 (71.89)	0.89
TIA	96 (27.12)	570 (27.62)	768 (28.11)	...

eGFR indicates estimated glomerular filtration rate; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

Efficacy and Safety Outcomes

The primary efficacy outcome was a new stroke event (ischemic or hemorrhagic) within 90 days. The secondary efficacy outcome was a combined vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death). The safety outcome was mild-to-severe bleeding event.¹⁶ Mild bleeding referred to bleeding not requiring transfusion and not causing hemodynamic compromise requiring intervention (eg, subcutaneous bleeding, mild hematomas, and oozing from puncture sites). Moderate hemorrhage was defined as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention. Severe hemorrhage was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention, according to the GUSTO definition (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries).¹⁷ All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was blinded to the study group assignments.

Statistical Methods

Categorical variables were presented as percentages, whereas continuous variables were presented as medians with interquartile ranges. The study population was divided according to levels of kidney function. Comparisons across groups were calculated by 1-way ANOVA or Kruskal–Wallis test. Kaplan–Meier methods were used to estimate event rates between subgroups based on kidney function and were compared with a log-rank test. Hazard ratios and their corresponding 95% confidence intervals were estimated using Cox proportional hazards models to assess the efficacy and safety of treatment stratified by renal function categories. To exclude impact of confounding factors, baseline characteristics, including age, sex, current or previous smoking, medical history of hypertension, ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation, valvular heart disease, National Institutes of Health Stroke Scale score at 1 day after randomization, and qualifying event, were considered for adjustment in the multivariable Cox regression analysis. All analyses were performed using SAS software version 9.4 (SAS Institute).

Results

Baseline Characteristics

A total of 5170 eligible patients were enrolled at 114 medical centers in China. Among them, 5150 (99.61%) subjects with

renal parameters and 90-day outcome data were analyzed in this study. Overall, 354 (6.9%), 2064 (40.1%), and 2732 (53.0%) patients had eGFR <60 mL/min per 1.73² (moderate CKD), 60 to 89 mL/min per 1.73² (mild CKD), and ≥90 mL/min per 1.73² (normal renal function), respectively. Baseline eGFR were 52.45 (45.81–56.68), 80.06 (71.81–85.76), and 100.25 (94.99–106.15) mL/min per 1.73² in the moderate CKD, mild CKD, and normal renal function groups, respectively.

Compared with the subjects with mild CKD and normal kidney function, those with moderate CKD were older and more likely to be men and to have history of ischemic stroke, myocardial infarction, angina, congestive heart failure, known atrial fibrillation, valvular heart disease, and hypertension (Table 1).

Clinical Outcomes

Ninety-Day Efficacy Outcomes

As shown in Table 2 and Figure, at 90 days, combination therapy of clopidogrel and aspirin reduced the incidence of new stroke compared with aspirin alone in patients with normal kidney function (8.6% versus 11.2%; hazard ratio, 0.74; 95% confidence interval, 0.58–0.95; *P*=0.02) and mild CKD group (7.5% versus 10.1%; hazard ratio, 0.59; 95% confidence interval, 0.44–0.78; *P*<0.001). Similarly, in normal renal function group and mild CKD group, clopidogrel–aspirin therapy was associated with significant lower rates of combined vascular events in comparison with the aspirin group.

However, in patients with moderate CKD, no significant benefit from clopidogrel therapy was again found. The new stroke events occurred in 10.1% of patients in the aspirin therapy group and in 9.1% of patients in the clopidogrel–aspirin therapy group (hazard ratio, 1.00; 95% confidence interval, 0.43–2.35; *P*=0.99).

Ninety-Day Safety Outcomes

As shown in Table 3, in the subgroup of patients with normal renal function, mild CKD, and moderate CKD, moderate or

Table 2. Effects of Combination Therapy of Clopidogrel and Aspirin on 90-d Efficacy Outcomes Based on eGFR Levels

eGFR, mL/min per 1.73 ²	Outcome	Aspirin Event Rate, %	Clopidogrel –Aspirin Event Rate, %	Crude		Multivariable Adjusted*	
				HR (95% CI)	<i>P</i> Value	HR (95% CI)	<i>P</i> Value
≥90 (n=2732)	Stroke	147 (10.70)	117 (8.62)	0.77 (0.60–0.98)	0.036	0.74 (0.58–0.95)	0.017
	Ischemic stroke	144 (10.48)	115 (8.47)	0.77 (0.60–0.99)	0.039	0.74 (0.58–0.95)	0.019
	Combined vascular events†	149 (10.84)	118 (8.69)	0.77 (0.60–0.98)	0.032	0.74 (0.57–0.94)	0.015
60–89 (n=2064)	Stroke	135 (13.08)	77 (7.46)	0.60 (0.45–0.79)	<0.001	0.59 (0.44–0.78)	<0.001
	Ischemic stroke	130 (12.60)	72 (6.98)	0.58 (0.43–0.77)	<0.001	0.56 (0.42–0.76)	<0.001
	Combined vascular events†	136 (13.18)	80 (7.75)	0.60 (0.46–0.80)	<0.001	0.60 (0.45–0.79)	<0.001
<60 (n=354)	Stroke	17 (10.12)	17 (9.14)	1.06 (0.50–2.25)	0.88	1.00 (0.43–2.35)	0.99
	Ischemic stroke	17 (10.12)	16 (8.60)	1.06 (0.50–2.25)	0.88	1.00 (0.43–2.35)	0.99
	Combined vascular events†	18 (10.71)	17 (9.14)	0.99 (0.47–2.07)	0.97	0.93 (0.40–2.16)	0.87

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

*Adjusted for age, sex, current or previous smoking, medical history of hypertension, ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation, valvular heart disease, National Institutes of Health Stroke Scale score at 1 d after randomization, and qualifying event.

†Combined vascular events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death.

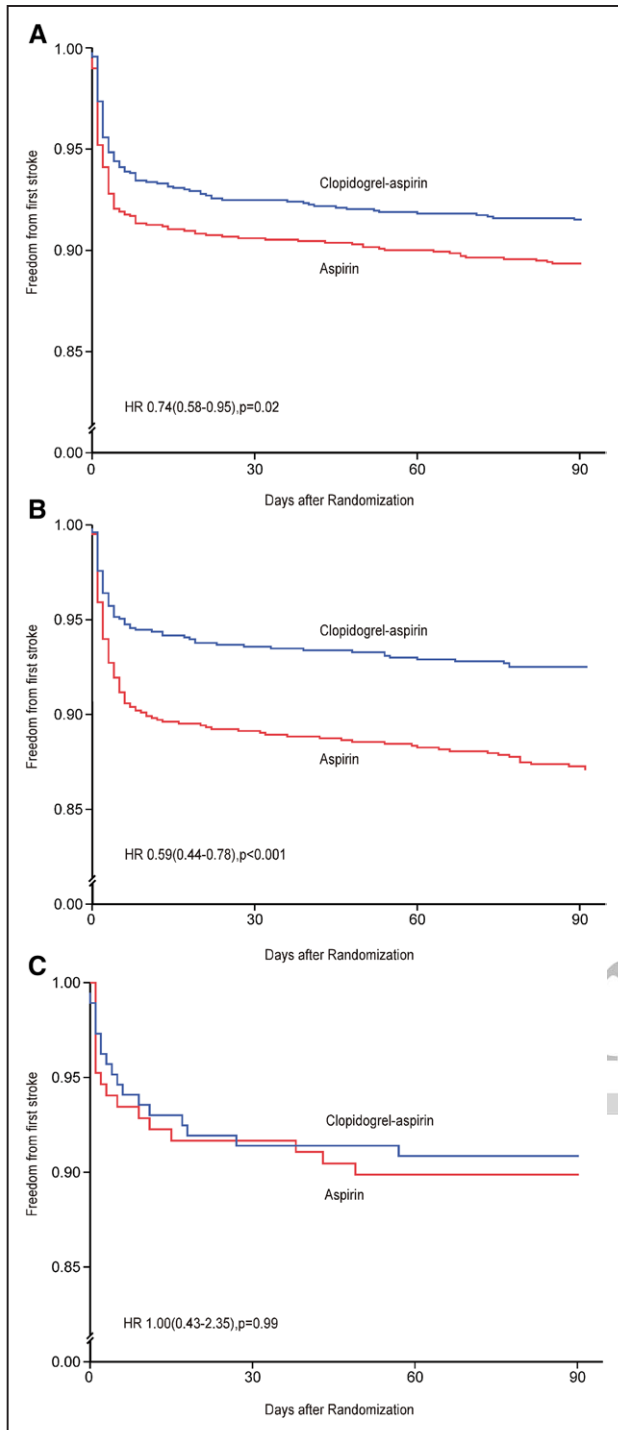


Figure. Probability of survival free of stroke in the subjects based on eGFR levels of ≥ 90 mL/min per 1.73^2 (A), 60 to 89 mL/min per 1.73^2 (B), and < 60 mL/min per 1.73^2 (C).

severe hemorrhage occurred in 3 patients (0.22%), 3 patients (0.29%), and 1 patient (0.54%), respectively, on clopidogrel-aspirin therapy and in 4 patients (0.29%), 4 patients (0.38%), and 0 patient on aspirin therapy. With respect to mild bleeding, it occurred in 16 patients (1.18%), 11 patients (1.07%), and 3 patients (1.61%) in the subgroups, respectively, on clopidogrel-aspirin therapy and 7 patients (0.51%), 12 patients (1.16%), and 0 patient on aspirin therapy. There was

no significant interaction between eGFR subgroup and antiplatelet therapy in their effects on mild, moderate, and severe bleeding events.

Discussion

There are 2 major findings in this post hoc analysis of the CHANCE trial. First, clopidogrel plus aspirin compared with aspirin alone in patients with normal renal function and mild renal insufficiency resulted in a significant reduction in new stroke events and combined vascular events at 90 days of follow-up, but this benefit was not apparent in moderate CKD patients. Second, clopidogrel did not seem to increase bleeding more in mild or moderate CKD patients than it did in those with normal renal function.

In patients with normal renal function and mild renal insufficiency, our results were in accordance with those of the overall cohort of the CHANCE study. The significance of this subgroup study is that even in mild CKD, the combination of clopidogrel and aspirin was superior to aspirin alone for reducing the risk of stroke among patients with minor stroke or TIA in the first 90 days. However, no extra benefit from clopidogrel therapy was observed in those with moderate CKD. To our knowledge, there were no trials that have evaluated the effect of clopidogrel in terms of decreasing the risk of cerebrovascular events in patients with CKD. As opposed to our results, subgroup analysis of the CURE trial (Clopidogrel in Unstable angina to prevent Recurrent Events) showed that clopidogrel add-on resulted in a similar beneficial effect in all 3 groups stratified according to eGFR (< 64 , $64-81.2$, and > 81.3 mL/min).¹⁸ Post hoc analysis of the CREDO trial (Clopidogrel for the Reduction of Events During Observation) suggested that clopidogrel did not decrease mortality or improve cardiovascular outcomes in mild or moderate CKD patients with ACS after percutaneous coronary intervention.¹⁵

The reasons why no benefit of clopidogrel was observed in patients with moderate CKD in the present study were not absolutely clear. Clopidogrel resistance might partly account for this result. Clopidogrel induces antiplatelet effect to be highly variable, and the individuals who have poor antiplatelet effects are defined as clopidogrel resistant.¹⁹ Clopidogrel resistance is a multifactorial phenomenon, and the underlying mechanisms involve clinical, cellular, and genetic aspects.^{20,21} Previous studies have shown that patients with CKD exhibited significantly higher platelet activation and on-treatment residual ADP-inducible platelet reactivity than patients without renal insufficiency.^{20,22-24} Moreover, a low response to clopidogrel might be an independent predictor of the poorer outcomes in these CKD patients. Nowadays, the use of higher than usual clopidogrel doses (600 mg as loading dose and 150 mg as maintenance dose),²⁵ longer therapy duration (beyond 12 months),²⁶ or alternative more potent thienopyridine agents such as prasugrel^{27,28} or ticagrelor²⁹ have been proposed as ways to overcome the clopidogrel resistance in CKD. However, patients with CKD also have higher bleeding tendency. So special consideration should be given to balance the benefit-risk ratio among CKD patients.⁹

Several previous studies³⁰⁻³² demonstrated that in patients with ACS, CKD increased gastrointestinal bleeding or serious

Table 3. Effects of Combination Therapy of Clopidogrel and Aspirin on 90-d Safety Outcomes Based on eGFR Levels

	eGFR \geq 90 mL/min per 1.73 ² (n=2732)		eGFR 60–89 mL/min per 1.73 ² (n=2064)		eGFR <60 mL/min per 1.73 ² (n=354)		P Value*
	Aspirin Event Rate, %	Clopidogrel –Aspirin Event Rate, %	Aspirin Event Rate, %	Clopidogrel –Aspirin Event Rate, %	Aspirin Event Rate, %	Clopidogrel –Aspirin Event Rate, %	
Mild bleeding	7 (0.51)	16 (1.18)	12 (1.16)	11 (1.07)	0	3 (1.61)	0.34
Moderate bleeding	2 (0.15)	2 (0.15)	2 (0.19)	1 (0.10)	0	0	0.81
Severe bleeding	2 (0.15)	1 (0.07)	2 (0.19)	2 (0.19)	0	1 (0.54)	0.99

eGFR indicates estimated glomerular filtration rate.

*P values for interaction of eGFR subgroup by treatment assignment.

bleeding in clopidogrel users. Although in another study conducted in patients with end-stage renal disease undergoing dialysis, no association was found between increased hemorrhagic risks and use of aspirin or clopidogrel.³³ In our trial, clopidogrel did not seem to increase bleeding more in mild or moderate CKD patients than it did in those with normal renal function. Although the exact mechanism underlying the conflicting results were not absolutely elucidated, and possible explanations for the difference were as follows. First, populations targeted in these studies were highly heterogeneous, and the definitions and assessment of bleeding outcomes were different. Second, compared with previous studies including patients with more severe strokes, our trial targeted a population at a relative low risk for bleeding. Third, compared with studies conducted in patients with ACS including percutaneous coronary intervention, the treatment paradigm was different in the CHANCE trial. In patients with ACS, the dual antiplatelet therapy was lasted for at least 9 to 12 months under normal circumstances. However, in our trial, clopidogrel plus aspirin was administered for just 21 days, followed by clopidogrel alone for a total of 90 days.

There were several limitations in the study. First, because the patients with creatinine >1.5 times the upper normal limit were excluded from the CHANCE trial and the eGFR of the patients enrolled ranged from 31.8 to 146.2 mL/min per 1.73 m², it would be difficult to make generalizations to patients with more severe renal insufficiency such as stage 4 or 5 CKD. Second, the sample size was imbalanced between the defined CKD subgroups, in particular, much less patients in the moderate renal dysfunction group (n=354). Therefore, cautions are needed when we interpret the efficacy and safety of dual antiplatelet treatment in the defined CKD patients plus stroke based on statistical analyses in this study. However, because specific recommendations for antiplatelet therapy in patients with CKD plus ischemic stroke are not available, the present study may provide some valuable information for this special population. A prospective and well-designed study in CKD with stroke would be needed for further evaluation. Third, we did not perform the platelet function test such as residual ADP-inducible platelet reactivity; thus, we could not directly evaluate the relationship between clopidogrel resistance and CKD. However, many investigations have confirmed this relationship in ACS and stroke.

To sum up, the present study is the first to investigate the effect of renal function on efficacy of clopidogrel in the setting of cerebrovascular events. In this cohort of patients with minor ischemic stroke or high-risk TIA in CHANCE, dual

antiplatelet therapy was associated with improved outcomes in patients with normal renal function and mild CKD, whereas in those with moderate CKD, no extra benefit was observed. With respect to safety, bleeding risk of the dual therapy did not seem to increase with declined eGFR. Taken together, these observations support the use of dual antiplatelet therapy among patients with minor ischemic stroke or TIA with normal to mild renal insufficiency. While for those with moderate-to-severe CKD, further studies would be needed to explore how to optimize antiplatelet treatment according to renal function to improve the clinical outcomes.

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Disclosures

None.

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