Interventional Cardiology

Embolic Protection and Platelet Inhibition During Renal Artery Stenting

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Background—Preservation of renal function is an important objective of renal artery stent procedures. Although atheroembolization can cause renal dysfunction during renal stent procedures, whether adjunctive use of embolic protection devices or glycoprotein IIb/IIIa inhibitors improves renal function is unknown.

Methods and Results—One hundred patients undergoing renal artery stenting at 7 centers were randomly assigned to an open-label embolic protection device, Angioguard, or double-blind use of a platelet glycoprotein IIb/IIIa inhibitor, abciximab, in a 2×2 factorial design. The main effects of treatments and their interaction were assessed on percentage change in Modification in Diet in Renal Disease–derived glomerular filtration rate from baseline to 1 month using centrally analyzed creatinine. Filter devices were analyzed for the presence of platelet-rich thrombus. With stenting alone, stenting and embolic protection, and stenting with abciximab alone, glomerular filtration rate declined (P<0.05), but with combination therapy, it did not decline and was superior to the other allocations in the 2×2 design (P<0.01). The main effects of treatment demonstrated no overall improvement in glomerular filtration rate; although abciximab was superior to placebo (0±27% versus −10±20%; P<0.05), embolic protection was not (−1±28% versus −10±20%; P=0.08). An interaction was observed between abciximab and embolic protection (P<0.05), favoring combination treatment. Abciximab reduced the occurrence of platelet-rich emboli in the filters from 42% to 7% (P<0.01).

Conclusions—Renal artery stenting alone, stenting with embolic protection, and stenting with abciximab were associated with a decline in glomerular filtration rate. An unanticipated interaction between Angioguard and abciximab was seen, with combination therapy better than no treatment or either treatment alone. (Circulation. 2008;117:2752-2760.)

Key Words: kidney □ peripheral vascular disease □ platelets □ stenosis □ stents

Renal artery stenosis resulting from atherosclerosis, an important cause of secondary hypertension1,2 and renal failure,3,4 is increasingly recognized as imaging improves and the population ages.5 Renal stenting has become the dominant revascularization therapy, although acutely worsening renal function sometimes occurs, resulting in end-stage renal disease.6 Several causes have been implicated, including atheroembolization. Recently, filters and occlusion devices have been developed to prevent embolization of atheromatous material. During renal stenting, material is often captured with embolic protection devices (EPDs), and several recent studies have suggested that renal function may be improved compared with historical control subjects.7-9 Whether this strategy is effective for preventing declines in renal function after stenting is not known.

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Platelet glycoprotein IIb/IIIa inhibitors reduce the incidence of myocardial necrosis and adverse cardiac events during coronary stenting. Abciximab is a human-murine genetic reconstruction that prevents platelet aggregation and is effective in coronary procedures.10 In animal models, platelet activation contributes to ischemic glomerular injury,11 whereas inhibition reduces injury.12 Whether abciximab confers a benefit during renal stenting is untested. In addition, the utility of abciximab combined with EPDs remains unclear.

The aim of this phase II study, conducted in patients with atherosclerotic renal artery stenosis undergoing stenting, was to determine whether embolic protection, platelet inhibition,
or combination treatment improved renal function 1 month after the procedure and was safe.

Methods

The study (ClinicalTrials.gov identifier NCT00234585) was conducted by the Clinical Coordinating Center at the University of Toledo (Ohio) with funding provided by the sponsors, with study conduct, analysis, and reporting performed independently of the sponsors. International Conference on Harmonization good clinical practice guidelines were followed, with patients providing informed consent in an Institutional Review Board–approved protocol. A total of 100 patients were recruited from 7 sites. Inclusion required a history of hypertension, renal insufficiency, heart failure, or angina with poorly controlled hypertension and the presence of ≥1 renal artery stenoses ≥50% and <100% treatable with the EPD.

Exclusion Criteria

Patients with the following were excluded: age <18 years, pregnancy, life expectancy ≤6 months, dialysis, kidney transplant, stenosis not amenable to stent, allergy to study agents, unrelated renal disease, untreated aortic aneurysm, kidney size <8 cm, restenosis, vessel dimensions out of range for study devices, treatment of a side branch or distal stenosis, active bleeding, stroke within 2 years or with a significant residual neurological deficit, international normalized ratio >1.2 times control, thrombocytopenia, major surgery or trauma within 6 weeks, intracranial neoplasm, arteriovenous malformation or aneurysm, vasculitis, or a nonstudy procedure within 24 hours.

Preprocedural Care

Use of acetaminophen, sodium bicarbonate, or other agents to prevent contrast nephropathy was initiated at the discretion of the clinical centers. Before double-blinded administration of abciximab or placebo, systolic blood pressure was lowered to ≤160 mm Hg. The target activated clotting time was 275 seconds; if randomized to the EPD, an activated clotting time of >300 seconds was required. A bolus of 0.25 mg/kg abciximab (or placebo) was administered 5 minutes before crossing the lesion and was followed by an infusion at 0.125 μg · kg⁻¹ · min⁻¹ (maximum 10 μg/min) for 12 hours.

Interventional Procedure

Predilatation was permitted to facilitate the Angioguard short-tip emboli capture guidewire EPD delivery. After positioning the EPD, predilatation of the stenosis was performed before treatment with a Genesis stent. The goal of stenting was to achieve 1:1 sizing of the treated lesion compared with a normal-appearing distal segment.

Blood Pressure Assessment

Systemic hypertension was defined ≥140/90 mm Hg. Baseline and follow-up blood pressures were monitored with office measurements performed in a quiet room in subjects who had been seated for 5 minutes and were measured in triplicate with an oscillometric automatic device or a mercury sphygmomanometer. The arm recorded in the baseline visit was used for subsequent measurements. All antihypertensive medications were continued throughout the study and during blood pressure evaluations.

Central Laboratory Analyses

Stenoses were measured centrally, with comparisons performed between minimal luminal diameter within the stenosis and a normal reference segment. Angiographic analyses were performed by a single blinded investigator; intraobserver agreement was 97% for all measurements. For ostial stenoses, the reference segment was considered to be a normal-appearing distal segment unaffected by poststenotic dilatation. The blinded analysis of EPD contents was performed by the CVPath core laboratory (Gaithersburg, Md). Platelet emboli consisted of layered platelet aggregates with various amounts of entrapped leukocytes and fibrin as evidenced on hematoxylin and eosin–stained sections.

Glomerular filtration rate (GFR), calculated from the modified Modification in Diet in Renal Disease (MDRD) equation, was used as the primary measure of renal function. Creatinine was measured by a modified Jaffe reaction using the isotope dilution mass spectrometry–traceable assay at the University of Minnesota Core Laboratory. Antihypertensive medications were continued during the evaluation except for diuretics, which were held that morning. Nonsteroidal antiinflammatory drugs (except aspirin), cimetidine, ranitidine, and trimethoprim were withheld for 7 days. Patients were instructed to drink ≥1-L water the day before and ≥500-mL water on the morning of assessment.

Bleeding Classification

Bleeding classification was adapted from the Thrombolysis in Myocardial Infarction scale and was described as major, minor, or insignificant. Major bleeding included intracranial bleeding, a hemoglobin decrease ≥5 g/dL, or transfusion. Minor bleeding was spontaneous gross hematuria or hematemesis or a hemoglobin decrease ≥3 g/dL. Insignificant bleeding did not meet these criteria.

Study Plan

This phase II study was designed to evaluate the safety and efficacy of the EPD and/or drug in preventing renal injury 1 month after stenting. One month was selected as the optimal observation period to avoid acute changes in renal function associated with hydration or contrast use and later changes related to restenosis. The study addressed the following hypotheses: AngioGuard improves the change in MDRD-estimated GFR from baseline to 1 month; abciximab improves the change in MDRD-estimated GFR from baseline to 1 month; AngioGuard and abciximab are safe alone and in combination; and an interaction occurs between AngioGuard and abciximab for change in MDRD-estimated GFR.

Randomization

The 2 × 2 randomization plan was generated from computer-based pseudorandom number generators with the following allocations: half to Angioguard and half to no Angioguard, and half to abciximab and half to placebo infusion. This yielded 4 groups: control, Angioguard only, abciximab only, and Angioguard with abciximab. Randomization was stratified by baseline creatinine ≥1.6 mg/dL and enrolling center.

Sample Size Estimate

The study was designed to evaluate a difference between Angioguard and no Angioguard and between abciximab and placebo on the change in MDRD-estimated GFR from baseline to 1 month at an α error of 5% for each comparison. A total of 85 evaluable subjects provided 80% power to detect a difference of 5 mL · min⁻¹ · 1.73 m⁻² between each of the main contrasts, with an expected SD of 8. One hundred subjects were recruited with an expected loss to follow-up rate for the primary end point assessment of 15%, providing 85 evaluable subjects. Similarly, the sample of 85 individuals yields 80% power to detect a difference of 8% in relative GFR assuming an SD of 13%, with both values corresponding to the assumptions made for the absolute difference.

Statistical Analysis

Study data are presented as continuous (mean ± SD) and categorical data. Because absolute GFR change was not normally distributed, the 4 allocations were contrasted by nonparametric methods. For this reason, percentage change was used as the principal analysis variable for determining the study main effects and their interaction to approximate better a normal distribution of the study data needed for analysis of interaction. In SAS, 2-way ANOVA was used to test for the effect of Angioguard and abciximab; their interaction was analyzed with Tukey’s multiple-comparison adjustment for the least-squares means. In the presence of a significant interaction, analysis of adjusted means was performed with the 4 groups: control, Angioguard, abciximab, and Angioguard with abciximab. All analyses were performed in SAS or JMP (SAS Inc, Cary, NC).
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
In total, 100 patients were enrolled at 7 centers, with 28 randomized to neither Angioguard nor abciximab, 22 to Angioguard only, 25 to abciximab only, and 25 to both (Figure 1). Nine could not be evaluated for the primary end point because of withdrawal of consent (n=110052), refusal of 1-month assessment (n=110052), and inadequate sample collection at baseline (n=110053) or 1 month (n=110052). The groups were well matched for baseline characteristics (Table 1).

Study Treatments
Angioguard use was successful in all patients attempted. Abciximab was used in all allocated patients, although 2 placebo and 2 abciximab infusions were discontinued before completion. No patients received a glycoprotein IIb/IIIa inhibitor off protocol.

Procedural Outcomes
Genesis stent implantation improved percentage stenosis and minimal luminal diameter, with no differences noted between groups (Table 2). Contrast use was somewhat lower in control subjects, although this difference was not significant (P=0.08). Activated clotting times were longest in patients randomized to Angioguard in accordance with the protocol. Four procedural complications occurred: dissection in 1 patient randomized to no Angioguard and placebo, distal embolization in 1 patient allocated to Angioguard and abciximab, and renal artery spasm in 1 patient treated with Angioguard and in 1 patient treated with Angioguard and abciximab.

Renal Function Assessment
Analysis of renal function was conducted in 91 evaluable subjects with baseline and follow-up values (Table 2 and Figure 2). The absolute GFR change over 1 month favored combination treatment (P<0.05). The percentage change in GFR over 1 month also favored combination treatment (P<0.01) and is displayed in Figure 3A for the 4 potential allocations in the 2×2 design. MDRD-estimated GFR declined from baseline to 1 month in patients treated with stenting alone (59±29 to 52±20 mL/min; P<0.05), with stenting and Angioguard (61±29 to 52±22 mL/min; P<0.05), and with stenting and abciximab (66±20 to 58±20 mL/min; P<0.05) but not stenting with Angioguard and abciximab (52±18 to 54±17 mL/min; P=NS.) A positive interaction was observed between abciximab and Angioguard use on percentage change in GFR (P<0.05).

In the analysis of percentage change in MDRD-estimated GFR from baseline to 1 month, the main effect of Angioguard (with or without abciximab) was not superior to treatment without Angioguard (with or without abciximab) (−1±28% versus −10±20%; P=0.08; Figure 3B). Abciximab (with or without Angioguard) was superior to placebo (with or without Angioguard) (0±27% versus −10±20%; P<0.05; Figure 3B). One patient receiving neither Angioguard nor abciximab developed progressive renal dysfunction after stenting requiring dialysis.
Filter Contents

Analysis of Angioguard contents was performed in 42 of 47 patients (89%) randomized to Angioguard. Abciximab markedly reduced the occurrence of platelet-rich thrombi (42 versus 7%; P<0.01), but no difference was observed in the capture of atheromatous debris (21 versus 17%; P=NS) or fibrin-based thrombi. A greater decline in GFR was observed with platelet-rich emboli compared with those without, although this difference was not significant (−9±19% versus 1±31%; P=NS). Capture of atheromatous debris was not associated with differences in GFR.

Blood Pressure

Systolic pressure declined 1 month after the procedure (158±30 versus 147±30 mm Hg; P<0.001), but diastolic pressure did not (74±16 versus 72±13 mm Hg; P=NS). Angioguard did not affect systolic or diastolic pressure. Abciximab was associated with a greater reduction in diastolic pressure compared with placebo (−4±12 versus 1±14 mm Hg; P<0.05) but not systolic pressure (−16±28 versus −7±28 mm Hg; P=NS). No interaction was observed between Angioguard and abciximab on blood pressure.

Bleeding

Both major and minor bleeding events were relatively common in all treatment groups (Table 2). All patients who had a major bleeding event required transfusion; none had intracranial hemorrhage. Neither abciximab nor the Angioguard device significantly increased bleeding rates.

Discussion

Stenting is the dominant mode of renal artery revascularization because of its ability to achieve patency with low restenosis rates while avoiding the morbidity and mortality associated with...
surgical revascularization. The use of stents, albeit somewhat controversial, is often advocated to improve blood pressure, to manage nephropathy, or to control heart failure symptoms. In this setting, considerable interest exists in identifying strategies that improve renal outcomes. A strong association is present between renal function and survival after renal artery stenting, with 1 report suggesting that improvement in renal function after the procedure occurs in ≈ 20% of patients, infrequently resulting in end-stage kidney disease.

Several mechanisms are implicated in postprocedural declines in renal function, including contrast nephrotoxicity and atheroembolization. This has led to interest in using EPDs to capture emboli liberated during stenting. Two recent studies suggest that embolic protection was associated with better directional changes in renal function compared with historical controls. However, EPDs increase procedural complexity, and their effectiveness is not established. No study has evaluated a platelet-inhibiting strategy during renal revascularization.

**Effect of Angioguard and Abciximab During Renal Intervention**

The present study sought to identify whether an EPD or a glycoprotein IIb/IIIa inhibitor improves renal function. Importantly, when the main study hypotheses were tested, abciximab was superior to placebo, although it was not associated with improvement compared with renal function before the procedure (Figure 3B). However, in subsequent analysis, the benefit of abciximab appeared to be attributed mostly to the subgroup of patients who received both abciximab and Angioguard (Figure 3A). Alone, each therapy was not beneficial, whereas their combination appeared to be. It is sobering to note that in patients treated with either therapy alone or neither therapy, a fall in GFR was observed.

<table>
<thead>
<tr>
<th>Table 2. Procedural and 1-Month Outcomes for Randomized Patients</th>
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<tr>
<td><strong>Procedural outcomes</strong></td>
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<tr>
<td>Control (n=26)</td>
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<tr>
<td>Renal artery stenoses, n</td>
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<tr>
<td>Angiographic thrombus, n</td>
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<tr>
<td>Pretreatment</td>
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<tr>
<td>Stenosis, %</td>
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<td>Reference diameter, mm</td>
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<td>Lesions treated, n</td>
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<td>Stenosis, %</td>
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<td>MLD, mm</td>
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<td><strong>GFR estimations</strong></td>
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<td>MDRD</td>
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<td>At 1 mo</td>
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<td>Change, %</td>
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<td>Change in GFR</td>
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<td><strong>Clinical events</strong></td>
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<tr>
<td>Renal, n (%)</td>
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<tr>
<td>Dialysis</td>
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<td>Bleeding, %</td>
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<tr>
<td>Major</td>
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<td>Minor</td>
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<td>Insignificant</td>
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Control indicates neither Angioguard nor abciximab; AG, Angioguard; Drug, abciximab; MLD, minimum lumen diameter; and ACT, activated clotting time. Values are mean±SD.

*P<0.05 using 1-way ANOVA among groups; P<0.01 vs each of the control, AG only, and drug only groups using Fisher protected least-significant difference post hoc test.

†P<0.05 using Kruskal-Wallis among groups; P<0.05 vs each of the control, AG only, and drug only groups using the Mann–Whitney U test.

‡P<0.05 using paired t test between baseline and 1-month GFR.
Figure 2. Line charts of individual patient MDRD-calculated GFR matched at baseline and 1 month. Comparisons between baseline and 1 month.
Interaction of Angioguard and Abciximab

It was an unanticipated finding that patients receiving both therapies concurrently had modest improvements in both the percentage and absolute changes in GFR compared with patients treated with either treatment alone or those receiving neither treatment. The lack of efficacy of the EPD in improving GFR, despite capturing debris, raises concerns about the possibility of emboli before or after filter deployment or an alternative mechanism of renal injury offsetting prevention of atheroembolization. The observed interaction with glycoprotein IIb/IIIa inhibition may suggest such a mechanism.

Figure 3. A, Percentage change in adjusted means MDRD-calculated GFR from baseline to 1 month in 4 randomly assigned groups of patients: control, Angioguard only, abciximab only, or Angioguard with abciximab. Overall comparison, \( P < 0.01 \), with \( P < 0.01 \) for all post hoc comparisons of combined treatment against control, Angioguard only, or abciximab only groups. B, Percentage change in MDRD-calculated GFR from baseline to 1 month comparing no embolic protection (−) and embolic protection (+) with the Angioguard device and placebo vs abciximab platelet glycoprotein IIb/IIIa inhibition. Data are displayed as means with 95% confidence intervals.

Concurrent use of EPDs and glycoprotein IIb/IIIa inhibitors is common in vein graft intervention and is associated with conflicting results. The vein graft studies are confounded by presumed selection bias, with higher-acuity patients receiving treatment with glycoprotein inhibition. The present study is the first to randomize patients to both treatments concurrently and suggests a potential biological interaction between treatments. Despite aggressive anticoagulation with heparin, aspirin, and a high rate of thienopyridine use, platelet-rich thrombi were evident in 40% of filters without concurrent abciximab. This relatively high rate of platelet-rich emboli was unanticipated and
is significant, considering the absence of angiographic thrombus before or during the procedures and the relatively rare occurrence of thrombotic events during renal intervention. Whether platelet-derived thrombi also occur before, off, or after use of EPDs is not known. Certainly, the observation that glycoprotein IIb/IIIa inhibition markedly decreases the occurrence of platelet-rich emboli and is associated with a trend toward improved renal function supports this construct. Thus, prevention of platelet activation concurrently with capture of embolic debris may be useful for preservation of kidney function.

The importance of these findings to other vascular beds is unknown. Certainly, the renal circulation is sensitive to microvascular events, presumably because of the vascular architecture of the cortical glomeruli and the microvasculature of the peritubular medulla. Now it appears that prior work suggesting a role for platelet activation in ischemia-induced renal dysfunction11,12 may have relevance to stenting. It also raises concerns that capturing emboli may not be an adequate surrogate for clinical outcome. In contrast, capturing emboli may be offset by other factors, presumably platelet activation.

The present study demonstrated lower blood pressure after revascularization, a common finding in most renal stent studies. However, several trials have demonstrated similar reductions in patients randomized to either renal angioplasty or medical therapy.30 Of interest was the decrease in diastolic pressure with abciximab. Although platelet activation within the kidney might result in microvascular events that raise blood pressure, the association of abciximab use with lowered diastolic pressure may simply represent a chance association in an end point that was not prespecified.

Finally, the present study did not demonstrate an excess of bleeding events with abciximab treatment; however, the sensitivity was limited by the small sample size and relatively infrequent occurrence of these events. Certainly, patients with renal artery stenosis may be at higher risk as a result of coexisting and severe hypertension; for this reason, the protocol required that blood pressure be lowered to ≤160 mm Hg before and during abciximab treatment. Finally, it is possible that abciximab therapy could increase the risk of perirenal hemorrhage from wire trauma, although this was not observed.

Study Limitations
The present study was designed as an initial test of the 2 treatment strategies on renal function changes occurring within 1 month. Thus, the findings, although of biological interest, do not constitute proof of the long-term effectiveness of either strategy alone or in combination. Furthermore, although treatment interaction was prospectively assessed, the observed interaction was unexpected. It remains to be identified whether these effects can be replicated and, if so, whether the benefit is maintained over long-term follow-up. In addition, the present study does not establish whether stenting is superior to medical therapy for the prevention of cardiovascular or renal events, the subject of the ongoing National Institutes of Health–funded Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial.31

Conclusion
The present study was designed to test the effects of Angioguard embolic protection and abciximab in a 2 × 2 randomized factorial design. Although a modest benefit of abciximab was observed over placebo, an unanticipated interaction was observed between therapies. Renal artery stenting alone, stenting with Angioguard, and stenting with abciximab were associated with similar declines in GFR at a 1-month follow-up; however, allocation to both Angioguard embolic protection and abciximab was not associated with a decline in GFR and was superior to the other 3 allocations. Further work is needed to confirm these findings and to determine the longer-term clinical relevance.

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References
CLINICAL PERSPECTIVE

Atherosclerotic renal artery stenosis, an important cause of secondary hypertension and chronic kidney disease, is increasingly recognized as imaging improves and the population ages. Renal stenting has become the dominant revascularization therapy, although worsening renal function after stenting sometimes occurs and may result in end-stage renal disease. Several causes of renal injury have been implicated, including atheroembolization. Recently, filters and occlusion devices have been developed to prevent embolization of atheromatous material. Whether embolic protection or use of a platelet glycoprotein IIb/IIIa inhibitor is effective in preventing declines in renal function after stenting is not known. In the present study, patients undergoing renal artery stenting were randomly assigned to an open-label embolic protection device, Angioguard, or use of a platelet glycoprotein IIb/IIIa inhibitor, abciximab. Although a benefit of abciximab was observed over placebo, an unanticipated interaction was observed between treatment with abciximab and embolic protection. Renal artery stenting alone, stenting with Angioguard embolic protection, and stenting with abciximab were associated with similar and modest declines in glomerular filtration rate at a 1-month follow-up; however, allocation to both Angioguard embolic protection and abciximab was not associated with a decline in glomerular filtration rate and was superior to the other 3 allocations for the prevention of declines in kidney function. Further work is needed to confirm these findings and to determine the longer-term clinical relevance.
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