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Original article

A randomized unblinded trial to compare effects of intensive versus conventional lipid-lowering therapy in patients undergoing renal artery stenting

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ABSTRACT

Background: Although current guidelines recommend the use of statins for severe atherosclerotic renal artery stenosis (ARAS), the renal protection of intensive lipid-lowering therapy in patients with ARAS who underwent stent placement remains uncertain. The aim of this study was to compare the renal-protective effect of intensive lipid lowering with that of conventional lipid lowering in patients with ARAS undergoing stent placement.

Methods: A total 150 patients with severe ARAS undergoing stent placement were randomly (1:1) assigned to receive intensive lipid lowering [target low-density lipoprotein cholesterol (LDL-C) <70 mg/dL] or conventional lipid lowering (target LDL-C ≥70 mg/dL, <128 mg/dL). All patients received rosuvastatin. We adjusted LDL-C to the goal within two months after renal stenting and maintained stability. The primary endpoint was the change in estimated glomerular filtration rate (eGFR) at 12 months.

Results: During the study period, LDL-C was lower in the patients with intensive lipid lowering than with conventional lipid lowering (at 12 months 58.0 ± 11.6 vs 85.1 ± 15.5 mg/dL, $p < 0.001$). At 12-month follow-up, eGFR (91.8 ± 30.2 vs 78.5 ± 19.5) mL/min·1.73 m^2, $p = 0.002$) and the increase in eGFR compared to baseline [14.8(IQR, 4.1, 26.7) vs −0.4(IQR, −9.5, 8.0) mL/min·1.73 m^2, $p < 0.001$] were higher in the patients with intensive lipid lowering than with conventional lipid lowering. Urinary albumin–creatinine ratio [42.2(IQR, 20.0, 60.9) vs 60.8(IQR, 26.8, 121.6) mg/g, $p = 0.032$] was lower and the decrease in urinary albumin–creatinine ratio compared to baseline [27.4(IQR, 3.0, 53.8) vs −3.1(IQR, −17.3, 30.9) mg/g, $p = 0.001$] was higher in the patients with intensive lipid lowering than with conventional lipid lowering. The restenosis rate (3.1% vs 3.4%, $p = 0.711$) and major clinical events (6.8% vs 11.0%, $p = 0.37$) were similar between the two groups.

Conclusions: In patients with severe ARAS undergoing stent placement, intensive lipid lowering showed significant benefits in renal protection over conventional lipid-lowering therapy.

Introduction

Renal artery stenosis, which can lead to renovascular hypertension and renal dysfunction, is most commonly caused by atherosclerosis [1]. The reported prevalence of clinically manifested atherosclerotic renal artery stenosis (ARAS) in the hypertensive population is 1–3%. Antihypertensive drugs are often effective in lowering blood pressure in patients with renal artery stenosis. On the other hand, salvage of renal function has become a key target of revascularization. Although percutaneous renal artery stenting (PRAS) has been applied in the management of atherosclerotic renal artery stenosis for decades, its clinical efficacy is still controversial. Some randomized clinical trials showed the lack of additional benefit for PRAS compared with sole medical therapy, and was unable to reverse kidney damage [2,3]. However,

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these trials presented a number of limitations [4]. Further evidence is therefore required to investigate the actual efficacy of PRAS plus optimal medication.

Statins competitively inhibit hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase, resulting in reduced plasma total and low-density lipoprotein cholesterol (LDL-C) levels. Furthermore, it has been shown that statins exert potentially important effects independent of lipid lowering (e.g. improve endothelial function, reduce oxidant stress, and have direct anti-inflammatory, plaque-stabilizing, and antithrombotic effects). A meta-analysis indicated the renal-protective effect of statins [5]. It has been shown that intensive lipid-lowering therapy can reduce the risk for cardiovascular events and mortality and provides significant clinical benefit beyond that afforded by conventional lipid lowering [6,7]. Although expert consensuses recommend the use of statins in the treatment of ARAS in such patients, the related investigation focused on renal protection by intensive lipid-lowering therapy is scant, and the optimal target level for lipid reduction remains uncertain.

Therefore, we hypothesized that intensive lipid lowering could offer more benefits with respect to renal function in the patients with PRAS. We conducted a prospective randomized unblinded trial to compare the renal-protective effect of intensive lipid lowering with that of conventional lipid lowering in patients with ARAS undergoing PRAS.

Materials and methods

Study participants

Patients with ARAS undergoing PRAS, within the age range 40–80 years, were screened for enrollment between June 2013 and December 2014 at Fuwai Hospital (Beijing, China). Inclusion criteria were: (a) angiographic evidence of severe ARAS (diameter reduction $\geq$70%) with $\geq$20 mmHg systolic translesional gradient or positive captopril renography in the target kidney; (b) sustained systolic blood pressure $\geq$180 mmHg, and/or diastolic blood pressure $\geq$110 mmHg while not receiving drug therapy or systolic blood pressure $\geq$140 mmHg, and/or diastolic blood pressure $\geq$90 mmHg while taking standard triple-drug combination treatment (including one diuretic); (c) estimated glomerular filtration rate (eGFR) $\geq$10 mL/min 1.73 m^2 (eGFR = 186 $\times$ [serum creatinine, SCr]$^{-1.154}$ $\times$ [age]$^{-0.203}$ $\times$ [0.742 if female]) [8] with longitudinal kidney length $\geq$7 cm supplied by target artery; (d) SCr level $<$264 μmol/L; (e) urine protein $\leq$1+. Exclusion criteria were: (a) allergy to rosuvastatin; (b) myopathy; (c) active liver disease or alanine aminotransferase and/or aspartate aminotransferase levels $\geq$ three times the upper limit of normality; (d) serious perioperative complications; (e) severe chronic congestive heart failure (New York Heart Association functional class IV); (f) patients who should be excluded based on physician discretion. This study was registered at clinicaltrials.gov as NCT03521700. The protocol and consent forms were approved by the ethics committee of Fuwai Hospital and conformed to the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Baseline data collection

Baseline information on social and demographic factors (e.g. gender, age, smoking status), and medical history (e.g. antihypertensive medications prescribed by physicians, the history of diabetes, hyperlipidemia, stroke, etc.) were collected. Clinical physical examination (including height, weight, and blood pressure) and laboratory measurements (SCr, LDL-C, fasting serum glucose, urinary albumin–creatinine ratio, alanine aminotransferase, aspartate aminotransferase, etc.) were also recorded.

Intervention and drug treatment

The revascularization procedure (angioplasty with stenting) was applied to all patients; the method has been previously described by Jiang et al. [9]. The procedural success of PRAS was defined as $<$30% residual stenosis in diameter and no serious complications associated with the procedure. Before the procedure, all patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) for at least 2 days. If patients were previously not on clopidogrel, a loading dose of clopidogrel (150 mg) was given. After the procedure, the long-term maintenance of aspirin (100 mg/d) was recommended, and clopidogrel (75 mg/d) was taken for at least 3 months. Appropriate medications were prescribed to control glucose and blood pressure levels in accordance with guidelines and our previous study [10,11], which were comparable between the two groups.

Randomization

Patients with ARAS undergoing PRAS were randomly assigned to receive intensive lipid lowering or conventional lipid lowering in a 1:1 ratio with the use of a computerized minimized-randomization procedure. On the first postoperative day, all previously prescribed lipid-regulating drugs were discontinued. For patients who were assigned to receive intensive lipid lowering, 10 mg/d rosuvastatin was initially prescribed and target LDL-C was $<$70 mg/dL. For patients who were assigned to receive conventional lipid lowering, 5 mg/d rosuvastatin was initially prescribed and target LDL-C was $\geq$70 mg/dL, $<$128 mg/dL. The lipid-lowering drug rosuvastatin used in the study was produced by Chia Tai Tianqing Pharmaceutical CO., LTD, Nanjing, China. In order to achieve target LDL-C levels, the dose of rosuvastatin was titrated within 2 months after the procedure and the appropriate treatment was maintained during subsequent follow-up.

Follow-up

Follow-up visits were scheduled 1, 2, 3, 6, and 12 months after randomization. Clinical blood pressure, LDL-C, SCr, alanine aminotransferase, aspartate aminotransferase, and urinary albumin–creatinine ratio were assessed at every visit. At 6 and 12 months after randomization renal artery color duplex scanning was performed. When clinical symptoms (no benefit in blood pressure control or blood pressure rebounded after post-procedure improvement) and duplex ultrasonography suggested significant restenosis (peak systolic velocity $>$ 180 cm/s), confirmatory angiogram or computed tomography angiogram was performed. Adverse events were recorded.

Outcome measures

The primary outcome was the change in eGFR at 12 months. The secondary outcomes were the changes in urinary albumin-creatinine ratio, the number of antihypertensive medications, the clinic blood pressure, the restenosis rate, and major clinical events at 12 months. Restenosis was defined as recurrence of hypertension and renal artery stenosis $>$50% diameter evaluated by confirmatory angiogram or computed tomography angiogram [12]. Major clinical events included death from cardiovascular or renal causes, myocardial infarction (MI), hospitalization for congestive heart failure, stroke, and a relative increase in SCr from baseline of $\geq$50%. The improvement in eGFR was defined as a more than 10% increase in eGFR.

Statistical analysis

The sample size was calculated for 80% power and a two-sided significance level of 0.05 to detect a reduction of 10 mL/min 1.73 m^2 in terms of eGFR. It was assumed that the standard deviation (SD) of eGFR was 25 mL/min/1.73 m^2 and the correlation coefficient of repeated measurements (eGFR) was 0.8 [13]. Allowing for a dropout rate of 10%, it was calculated that 150 patients (75 patients per group) would need to be enrolled.

All analyses were performed according to the intention-to-treat principle. All participants who underwent randomization were included in the intention-to-treat analyses. Continuous variables were presented as mean ± SD or median and interquartile range (IQR). And categorical variables were presented as frequencies and percentages. When between-group differences were evaluated, the chi-square test or Fisher exact test was used for categorical and the Student test or Mann–Whitney test was used for continuous variables. The effect of treatment on eGFR over time was estimated with the use of a repeated-measures analysis. Univariate and multivariate logistic regression analyses were applied to assess the independent predictors of the improvement in eGFR at 12 months and to adjust for confounding factors. All reported *p*-values are two-tailed. Values of $p < 0.05$ were considered to be statistically significant. The statistical package SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

From June 2013 through December 2014, a total of 150 patients were enrolled (75 in each study group) (Fig. 1). Baseline clinical characteristics of the patients are shown in Table 1. The two groups were well matched in baseline characteristics.

Level of LDL-C over time

The baseline LDL-C did not differ significantly between the two groups. LDL-C was lower in the intensive lipid-lowering group than that in the conventional lipid-lowering group at 1, 2, 3, 6, and 12 months post procedure (at 12 months 58.0 ± 11.6 vs 85.1 ± 15.5 mg/dL, $p < 0.001$) (Fig. 2).

Renal function over time

At final follow-up, eGFR significantly increased from baseline values in the intensive lipid-lowering group (91.8 ± 30.2 vs 77.7 ± 26.2 mL/min 1.73 m^2, $p < 0.001$). However, there were no significant increases above baseline in the conventional lipid-lowering group (78.5 ± 19.5 vs 79.9 ± 24.3 mL/min 1.73 m^2, $p = 0.512$). eGFR in the intensive lipid-lowering group was higher than that in the conventional lipid-lowering group at 2 months (88.1 ± 29.4 vs 79.2 ± 21.2 mL/min 1.73 m^2, $p = 0.036$), 6 months (92.0 ± 29.3 vs 79.5 ± 19.4 mL/min 1.73 m^2, $p = 0.002$), and 12 months (91.8 ± 30.2 vs 78.5 ± 19.5 mL/min 1.73 m^2, $p = 0.002$) post procedure (Fig. 3A). The increases in eGFR compared to baseline were higher in the intensive lipid-lowering group at 2 months [10.7(3.2, 17.2) vs −0.2(−8.3, 5.5) mL/min 1.73 m^2, $p < 0.001$], 3 months [13.8(2.0, 23.7) vs 4.5(−5.1, 11.9) mL/min 1.73 m^2, $p < 0.001$], 6 months [16.7(3.6, 24.6) vs 1.5(−9.5, 8.7) mL/min 1.73 m^2, $p < 0.001$], and 12 months [14.8(4.1, 26.7) vs −0.4 (−9.5, 8.0) mL/min 1.73 m^2, $p < 0.001$] post procedure compared

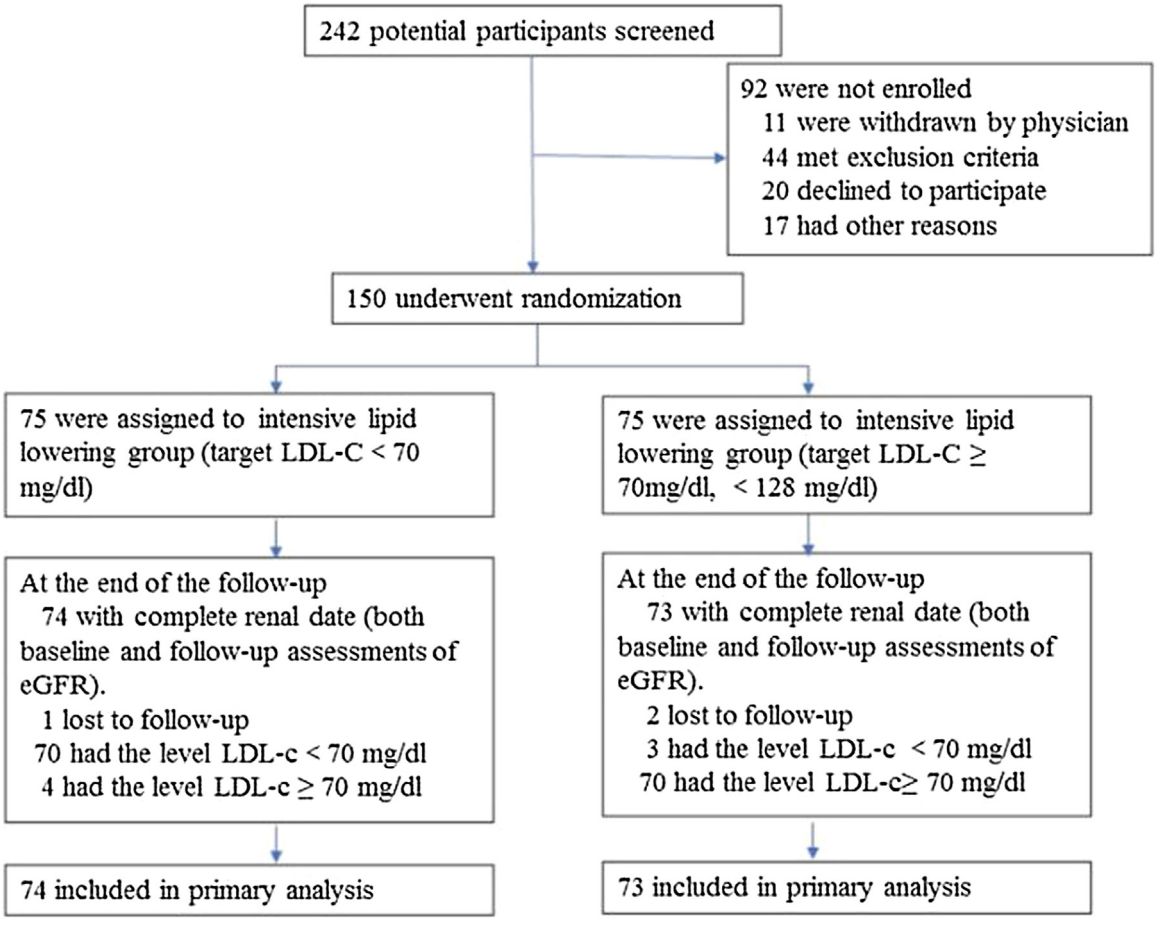

Fig. 1. Screening, randomization, and follow-up. LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 1
Baseline clinical characteristics of the patients.

Variable	Intensive lipid-lowering group ($n = 75$)	Conventional lipid-lowering group ($n = 75$)	p-Value
Female, n (%)	27 (36.0)	30 (40.0)	0.613
Age, years	64.3 ± 10.2	63.2 ± 11.2	0.532
Smoking, n (%)	35 (46.7)	29 (38.7)	0.320
Diabetes, n (%)	19 (25.3)	20 (26.7)	0.848
Hyperlipidemia, n (%)	50 (66.7)	48 (64.0)	0.734
Heart failure, n (%)	8 (10.7)	7 (9.3)	0.785
Stroke, n (%)	13 (17.3)	7 (9.3)	0.149
No. of antihypertensive drugs	2.45 ± 0.7	2.36 ± 0.8	0.451
SBP, mmHg	157.6 ± 17.7	156.9 ± 18.8	0.827
DBP, mmHg	85.8 ± 11.2	85.1 ± 14.6	0.752
BMI, kg/m^2	24.9 ± 3.5	25.7 ± 3.0	0.153
LDL-C, mg/dL	119.9 ± 30.9	123.7 ± 34.8	0.495
HDL-C, mg/dL	44.5 ± 13.5	42.9 ± 10.8	0.464
Fasting plasma glucose, mmol/L	6.0 ± 1.8	6.2 ± 2.5	0.523
Hs-CRP, mg/L	3.9 ± 3.4	4.1 ± 4.2	0.713
Serum creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.3	0.648
eGFR, mL/min·1.73 m^2	77.7 ± 26.2	79.9 ± 24.3	0.599
Levels of eGFR, n (%)			1.000
<30 mL/min·1.73 m^2	0	2 (2.7)	
45–60 mL/min·1.73 m^2	20 (27.0)	16 (21.3)	
>60 mL/min·1.73 m^2	55 (73.0)	57 (76.0)	
Urinary albumin–creatinine ratio, mg/g	63.8(IQR, 28.6, 100.0)	66.5(IQR, 14.6, 123.0)	0.673
Bilateral renal artery stenosis, n (%)	25 (33.3)	24 (32.0)	0.857
Stenosis rate, %	80.8 ± 11.7	82.3 ± 9.2	0.330
Contrast medium volume, mL	67.4 ± 13.7	68.0 ± 17.4	0.826
Baseline statin use, n (%)	65(86.7)	67(89.3)	0.802

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

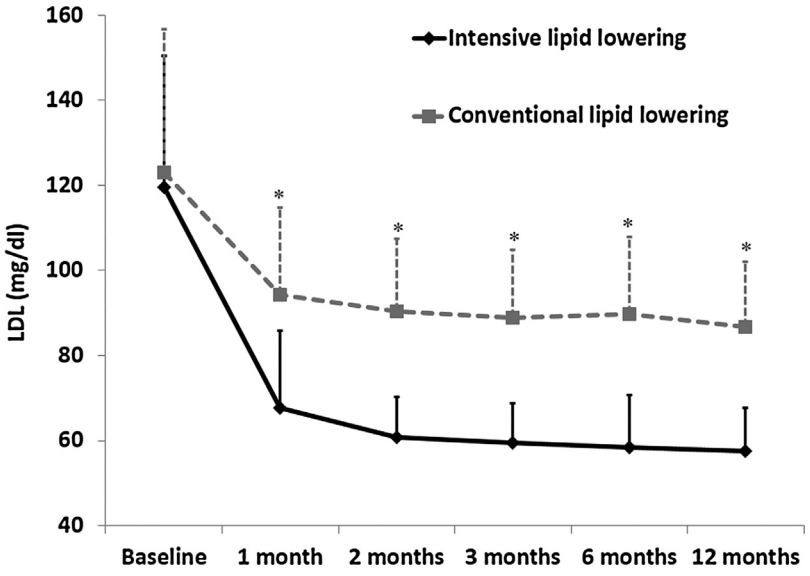

Fig. 2. Dynamic changes in LDL-C during follow-up. LDL-C, low-density lipoprotein cholesterol; *$p < 0.05$ when between-group differences were evaluated.

to the conventional lipid-lowering group (Fig. 3B). The improvement in eGFR at 12 months was more common in the intensive lipid-lowering group than that in the conventional lipid-lowering group (63.5% vs 31.5%, $p < 0.001$).

Only intensive lipid-lowering therapy could independently predict the improvement in eGFR at 12 months (OR, 4.253, 95%CI: 2.029–8.917; $p < 0.001$) by multivariate analysis (Table 2).

At final follow-up, urinary albumin–creatinine ratio significantly decreased from baseline values in the intensive lipid-lowering group [42.2(20.0, 60.9) vs 63.8(28.6, 100.0) mg/g, $p < 0.001$]. However, there were no significant differences in the conventional lipid-lowering group [60.8(26.8, 121.6) vs 66.5(14.6, 123.0) mg/g, $p = 0.83$]. Urinary albumin–creatinine ratio in the intensive lipid-lowering group was lower compared to the conventional lipid-lowering group at 2 months [45.1(23.2, 78.1) vs 58.0(32.1, 130.2) mg/g, $p = 0.023$], 3 months [33.3(21.4, 70.9) vs 50.0(31.0, 127.3) mg/g, $p = 0.007$], 6 months [45.3(19.8, 64.0) vs 55.4(26.0, 121.8) mg/g, $p = 0.037$], and 12 months [42.2(20.0, 60.9) vs 60.8(26.8, 121.6) mg/g, $p = 0.032$] post procedure (Fig. 3C). The decrease in urinary albumin–creatinine ratio compared to baseline was higher in the intensive lipid-lowering group than that in the conventional lipid-lowering group at 2 months [19.2(3.5, 44.0) vs −9.0(−20.2, 24.1) mg/g, $p < 0.001$], 3 months [28.1(6.6, 45.0) vs −10.0(−24.2, 33.3) mg/g, $p < 0.001$], 6 months [31.7 (2.3, 54.4) vs −6.6 (−17.6, 31.1) mg/g, $p = 0.001$], and 12 months [27.4(3.0, 53.8) vs −3.1(−17.3, 30.9) mg/g, $p = 0.001$] post procedure (Fig. 3D).

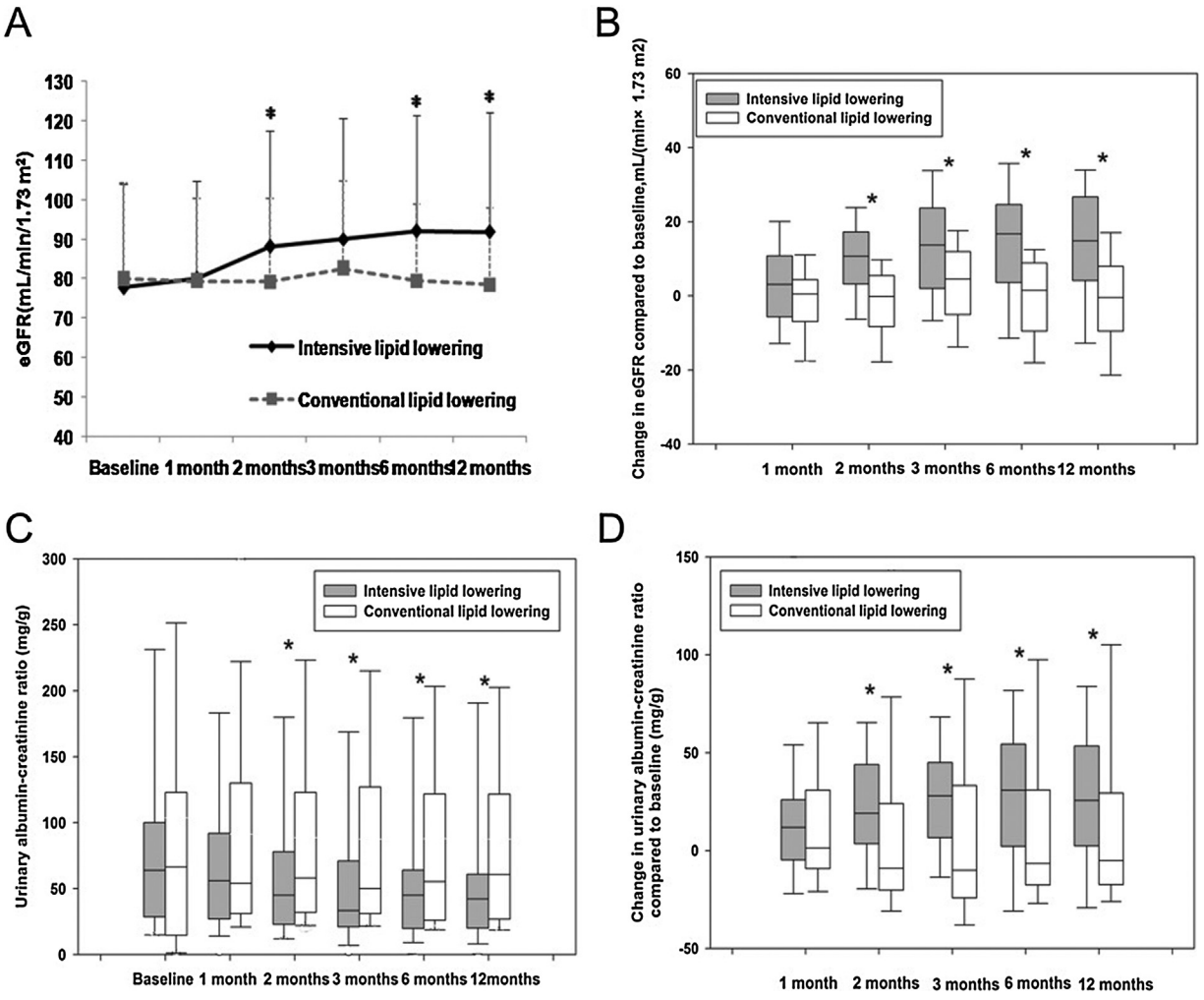

Fig. 3. Renal function over time. (A) Dynamic changes in eGFR during follow-up; (B) increase in eGFR compared to baseline; (C) dynamic changes in urinary albumin–creatinine ratio during follow-up; (D) decrease in urinary albumin–creatinine ratio compared to baseline. eGFR, estimated glomerular filtration rate. $^{*}p < 0.05$ when between-group differences were evaluated.

Table 2
The factors predicting improvement in eGFR[a] at 12 months by logistic regression analysis.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Female	0.781	0.401–1.522	0.468	0.663	0.286–1.536	0.338
Age	1.024	0.993–1.056	0.133	1.020	0.984–1.057	0.276
Smoking	0.943	0.490–1.817	0.861	0.714	0.304–1.676	0.439
Diabetes mellitus	0.923	0.443–1.923	0.831	0.787	0.337–1.842	0.582
Body mass index	0.996	0.904–1.098	0.940	1.019	0.911–1.140	0.745
Baseline strain use	1.592	0.547–4.635	0.394	1.649	0.485–5.610	0.423
Baseline LDL-C levels	0.752	0.507–1.115	0.156	0.791	0.508–1.231	0.299
Baseline eGFR >60 mL/min/1.73 m^2	0.661	0.315–1.389	0.275	0.670	0.273–1.642	0.381
Baseline ejection fraction	1.023	0.965–1.084	0.450	1.051	0.983–1.124	0.146
Contrast medium volume	1.015	0.993–1.037	0.181	1.015	0.989–1.041	0.262
Changes in hs-CRP at 12 months	0.903	0.780–1.047	0.176	0.914	0.774–1.080	0.291
Intensive lipid-lowering therapy	3.783	1.909–7.500	<0.001	4.253	2.029–8.917	<0.001

LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.
[a] The improvement in eGFR was defined as a more than 10% increase in eGFR.

Blood pressure and high-sensitivity C-reactive protein over time

As for blood pressure, during the follow-up systolic blood pressure, diastolic blood pressure and the number of antihypertensive medications significantly decreased from baseline values in both groups (Fig. 4), but there was no significant difference between the two groups.

At final follow-up, high-sensitivity C-reactive protein (hs-CRP) significantly decreased from baseline values in the intensive lipid-lowering group (3.3 + 2.9 vs 3.9 + 3.4 mg/L, $p < 0.001$). However,

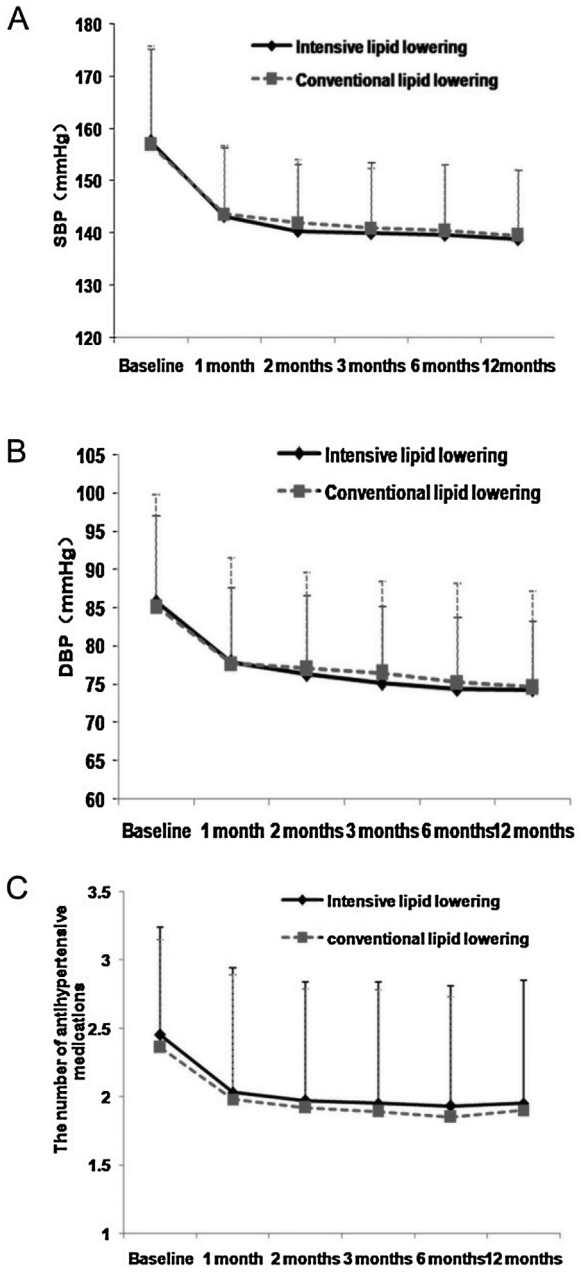

Fig. 4. Blood pressure over time. Dynamic changes in SBP (A), DBP (B), and the number of antihypertensive medications (C) during follow-up. SBP, systolic blood pressure; DBP, diastolic blood pressure. There was no significant difference between the two groups.

there was no significant difference in the conventional lipid-lowering group (3.7 + 3.2 vs 4.1 + 4.2 mg/L, $p = 0.216$). There was no significant difference in the levels of hs-CRP at baseline (3.9 ± 3.4 vs 4.1 ± 4.2 mg/L, $p = 0.713$) and the changes in levels of hs-CRP at 12 months (-0.6 ± 1.8 vs -0.4 ± 2.6 mg/L, $p = 0.713$) between intensive lipid-lowering group and conventional lipid-lowering group. The changes in hs-CRP at 12 months could not predict the improvement in eGFR at 12 months by the multivariate analysis (Table 2).

The dose of rosuvastatin and the side effects

At final follow-up, the dose of rosuvastatin was 15.3 ± 4.0 mg in the intensive lipid-lowering group and 6.4 ± 2.7 mg in the conventional lipid-lowering group, $p < 0.001$. In the intensive lipid-lowering group, four patients had a level of LDL-C ≥70 mg/dL. And in the conventional lipid-lowering group 3 patients had a level of LDL-C <70 mg/dL. Slight elevations in liver function enzymes (alanine aminotransferase and/or aspartate aminotransferase less than three times the upper limit of normality) were reported in 3 patients (4.1%), myalgia in 1 patient (1.4%) in the intensive lipid-lowering group. Slight elevations in liver function enzymes were reported in two patients (2.7%) in the conventional lipid-lowering group ($p = 0.681$). These enzymes gradually returned to normal when the dosage of rosuvastatin was reduced 50%. In no patients was it necessary to discontinue taking rosuvastatin (Supplementary Table 1).

Restenosis rate and major clinical events

At 12 months post procedure, restenosis occurred in 3 (3.1%) lesions in the intensive lipid-lowering group and in 4 (3.4%) lesions in the conventional lipid-lowering group. There was no significant difference between the two groups ($p = 0.711$). In the intensive lipid-lowering group, stroke occurred in 1 patient (1.4%) and hospitalization for congestive heart failure in 2 patients (2.7%), MI in 1 (1.4%) patient, and there was a relative increase in SCr from baseline of ≥50% in 1 patient (1.4%). In the conventional lipid-lowering group, MI occurred in 2 patients (2.7%), stroke in 2 patients (2.7%), hospitalization for congestive heart failure in 1 patient (1.4%), and there was a relative increase in SCr from baseline of ≥50% in 3 patients (4.1%). The two groups did not differ significantly in the occurrence of the primary composite clinical events (6.8% vs 11.0%, $p = 0.37$) (Supplementary Table 2).

Discussion

This study demonstrates that intensive lipid lowering had significant benefits with respect to renal function over conventional lipid lowering in patients with severe ARAS undergoing PRAS. At 12-month follow-up, the intensive lipid lowering showed significant benefits with respect to eGFR over the conventional lipid lowering. Only intensive lipid-lowering therapy could independently predict the improvement in eGFR at 12 months. This is in line with several previous studies. Koren et al. reported intensive lipid-lowering strategy (atorvastatin) prevented the anticipated decline in renal function and modified the progression of CKD during the 4 years of the trial when compared with usual care [14]. Shepherd et al. reported in a randomized double-blind trial a total of 10,001 patients with coronary heart disease were randomly assigned to therapy with 10 or 80 mg/d atorvastatin. eGFR improved in both groups but was significantly greater with 80 mg than with 10 mg [15]. Our results were different from those in the ASTRAL and CORAL trial because of multi-factors, including study population, operative procedures, and intensive statin therapy. *First, study population*. In the present study, only renal artery stenosis ≥70% with ≥20 mmHg systolic translesional gradient or positive captopril renography in the target kidney was included. The mean renal artery stenosis (80.8%) was more severe than those in ASTRAL (76.0%) and CORAL (72.5%) trial [2,3]. In ASTRAL trial, approximately 40% of patients in renal stenting group had a renal artery stenosis of less than 70% [2]. In the CORAL trial, 210 patients who were convinced of the clinical benefit of the stenting procedure, were excluded by physicians [3]. *Second, operative procedure*. All patients in our study underwent stenting procedures by only one operator (Dr Jiang) during a period of 1.5 years. Only mean one and eleven patients per year were recruited and underwent renal stenting in each center in ASTRAL and CORAL trial, respectively [2,3]. Therefore, low procedure-related complications due to adequate operation experience in our study might partly explain the improvement in eGFR. *Third,*

intensive statin therapy. The proportion of patients with CKD stages 1–3 was 100% and 97.3% in intensive lipid-lowering group and conventional lipid-lowering group, respectively in our study. In the ASTRAL trial, 22% and 25% patients had a baseline eGFR of <25 mL/min·1.73 m^2 and >50 mL/min·1.73 m^2 in renal revascularization group [2]. In the CORAL trial, 49.6% patients had a baseline eGFR of <60 mL/min·1.73 m^2 in stenting plus medical therapy [3]. Meta-analysis showed that statins could reduce the decline in eGFR for patients with CKD stages 1–3 and decrease pathologic proteinuria moderately [16,17]. However, with regard to severe CKD patients, the effect of strain usage on renal function remains in dispute [18,19]. In a meta-analysis by Zhang et al., strains did not effectively slow the CKD progression in patients with non-end stage CKD [18]. Sanguankeo et al. revealed that high-intensity statins were found to improve a decline in eGFR in a population with CKD not requiring dialysis compared with control, but moderate- and low-intensity statins were not [19]. Based on the above analysis, baseline eGFR of >30 mL/min·1.73 m^2 not >60 mL/min·1.73 m^2 may predict the improvement in eGFR of patients with statin therapy. However, the proportion of patients with eGFR <30 mL/min·1.73 m^2 in our study was low, therefore no statistical analysis was performed. Further studies of renal revascularization with stricter inclusion criteria, adequate operation experience, and more patients with CKD stages 4–5 might be essential to analyze the effect of statin therapy on the improvement in eGFR.

The present study suggested an intensive lipid-lowering strategy helps to stabilize and improve renal function. Current guidelines recommend the use of high-dosage statin treatment to achieve lower target LDL-cholesterol levels for optimal prevention of cardiovascular events [20]. Our results were consistent with the trend in guidelines. In addition, in the present study the heightened renal benefit of the intensive lipid-lowering strategy was achieved without increased risk or additional safety concerns and was in line with previous studies which have shown high-dosage rosuvastatin to be safe and well tolerated [21].

The mechanisms that are involved in the nephroprotective effect of statins have been explored. There are several potential explanations. For example, (a) statin treatment could prevent the development of renal injury mediated by a decrease in total cholesterol exposure level and prevention of LOX-1 expression in atherosclerotic arteries [22]. (b) Statins also could attenuate the inflammatory expression in the kidney cortex [23]. In the present study, the changes in levels of hs-CRP at 12 months between intensive lipid-lowering group and conventional lipid-lowering group did not achieve significant difference. The possible reasons were as follows: first, the proportion of baseline statin use was high at baseline (86.7% in intensive lipid-lowering group vs 89.3% in conventional lipid-lowering group, $p = 0.802$). The levels of hs-CRP might have a significant decrease due to previous statin use, therefore, the further intensive statin therapy could not achieve significant difference, compared with that in conventional lipid-lowering group. Second, as a systemic biomarker, hs-CRP may not reflect the level of the local renal inflammation. More accurate indicators of renal inflammation such as neutroplil gelatinase associated lipocalin, kidney injury molecule-1, liver type fatty acid binding protein, etc., should be investigated in further studies [24]. (c) Statins have beneficial renal hemodynamic effects by increasing renal blood flow, preserve renal function after ischemia/reperfusion injury [25,26]. (d) Statins prevent the downregulation of vascular eNOS, inhibit oxidative stress, and protect against end-organ injury [27]. In the intensive lipid-lowering group, the effect of rosuvastatin discussed above might be stronger than that in the conventional lipid-lowering group, which might be the reason for an improvement in renal function gained in the intensive lipid-lowering group. Intensive lipid-lowering therapy may be an important approach to improve the efficacy of PRAS.

Study limitations

There were several limitations in the present study. First, although the distribution of antihypertensive medications was similar in the two groups, the information on the use of other medications that affect GFR and proteinuria was not collected in the present study, which might be potential confounding factors. However, our randomized study design might make potential confounding factors comparable in the two groups and help to rule out some bias. Second, a blinded analysis was not performed in the study, which might have led to biases. However, the main indicator of this study, eGFR, was calculated based on objective variables. Third, duplex ultrasonography was used for routine follow-up, not all patients underwent angiography follow-up, and the rate of restenosis may be underestimated.

Conclusions

In conclusion, in patients with ARAS undergoing PRAS, the intensive lipid lowering showed significant benefits with respect to renal function over the conventional lipid lowering. The findings deserve confirmation in a blinded clinical trial.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.04.010.

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