Effects of Rosuvastatin and Atorvastatin on Renal Function – Meta-Analysis –

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Background: Several clinical trials have reported inconsistent findings for the effects of rosuvastatin (RSV) and atorvastatin (ATV) on renal function. The aim of this meta-analysis was to investigate the effects of these 2 statins on glomerular filtration rate (GFR) and proteinuria respectively, and determine which is better.

Methods and Results: PubMed, CENTRAL, Web of Knowledge, and ClinicalTrials.gov website were searched for randomized controlled trials. Eligible studies reported GFR and/or proteinuria during treatment with RSV or ATV compared with control (placebo, no statins, or usual care), or RSV compared with ATV head to head. Trials that enrolled dialysis participants and teenagers were excluded. Statistical heterogeneity was assessed using the I^2 statistic, and pooled results using the random-effects model. The standardized mean differences (SMD) and ratio of means (ROM) were measured, respectively, to analyze GFR and proteinuria. Sixteen trials with a total number of 24,278 participants were identified. Compared with control, changes in the SMD of GFR were 0.04 (95% confidence interval [CI]: 0.01–0.07) and 0.59 (95%CI: 0.12–1.06) for RSV and ATV, respectively. The ROMs of proteinuria were 0.59 (95%CI: 0.46–0.74) for RSV vs. the control group, and 1.23 (95%CI: 1.05–1.43) in the head-to-head comparison.

Conclusions: Both RSV and ATV improve GFR, and ATV seems to be more effective in reducing proteinuria. The validity and clinical significance require high-quality intensive studies with composite clinic endpoints of kidney and death. (*Circ J* 2012; **76**: 1259–1266)

Key Words: Atorvastatin; Glomerular filtration rate; Proteinuria; Rosuvastatin

Chronic kidney disease (CKD) and renal replacement treatment are important global public health problems associated with a high risk of cardiovascular disease (CVD) and high health-care costs.^{1,2} Dyslipidemia is one of the risk factors (the others are hypertension, diabetes, and smoking) associated with the development and progression of CKD.^{3,4} Clinical trials have indicated the powerful effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) on lipid lowering, which is independently associated with the decrease of all cause mortality and cardiovascular mortality.^{5,6} Several studies and meta-analyses have shown the renoprotective effects of statins.^{7–12} The roles of 2 strong statins (rosuvastatin [RSV] and atorvastatin [ATV]) on renal function, however, still need to be clarified considering the conflicting results.

In the PLANET 1 and PLANET 2 trials, diabetic and non-

diabetic patients with moderate proteinuria were assigned to RSV or ATV for 1 year.^{13,14} It was found that ATV significantly reduced proteinuria without affecting glomerular filtration rate (GFR), whereas RSV was associated with a significant decline in GFR and had no effect on proteinuria. In contrast, Abe et al reported that RSV reduced proteinuria significantly in patients with diabetic nephropathy,¹⁵ and another study by Sawara et al showed that RSV had beneficial roles both on GFR and proteinuria in CKD patients.¹⁶ The previous meta-analysis by Sandhu et al reported significant decrease in the rate of GFR reduction by a mean of 1.22 ml·min⁻¹·year⁻¹ and meta-regression showed that ATV was associated with a significantly larger beneficial effect on the rate of decline in GFR than other statins.⁹ A Cochrane systematic review by Navaneethan et al, however, showed that statins did not improve the decline in renal function as measured by cre-

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Study	Year	Country	Subjects	Sample size	Follow-up (months)	Lost to follow-up (%)	Blinding
Abe et al ¹⁵	2011	Japan	Diabetic nephropathy	104	6	3	Open-label
JUPITER ²³	2011	USA	Healthy adult and HTN	16,279	12	NR	Double-blind
Sawara et al ¹⁶	2008	Japan	CKD	38	12	0	Open-label
Verma et al ²⁴	2005	USA	CKD	91	5	9	Open-label
ALLIANCE ²⁵	2009	USA	CVD	2,442	24	21	Open-label
Bianchi et al ²⁶	2003	Italy	CKD	56	12	NR	Open-label
CARDS ²⁷	2009	UK	DM	2,313	46.8	18	Double-blind
Dalla et al ²⁸	2003	Italy	DM	25	12	0	Open-label
Goicoechea et al ²⁹	2006	Spain	CKD	66	6	5	Open label
GREACE ³⁰	2004	Greece	CVD	1,486	48	NR	Open label
LORD ³¹	2010	Australia	CKD	132	30	7	Double-blind
ATOROS ³²	2006	Greece	Relatively healthy adults	120	6	0	Open-label
PATROL ³³	2011	Japan	Hyperlipidemia	192	4	0	Open-label
PLANET1 ¹³	2010	USA	DM with proteinuria	353	12	21.8	Double-blind
PLANET2 ¹⁴	2010	USA	Non-DM with proteinuria	237	12	20.3	Double-blind
URANUS ³⁴	2006	Sweden	DM with hyperlipidemia	344	4	NR	Double-blind

HTN, hypertension; NR, not reported; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus.

atinine clearance, but may decrease urinary protein excretion (UPE).¹² To resolve the uncertainty, we performed this meta-analysis to address 2 issues: whether RSV and ATV have renoprotective effects on the parameters of GFR and proteinuria; and which is better.

Methods

Data Source, Search Strategy and Selection Criteria

We searched PubMed, Cochrane Central Register of controlled Trials (CENTRAL), Web of Knowledge, and the ClinicalTrials.gov website for all relevant studies published in

Table 2. Baseline Participant Characteristics

Study (year)	Intervention	Age (years)	Baseline cholesterol (mmol/L), (mean $\pm$ SD)	Baseline GFR (ml/min), (mean $\pm$ SD)	Baseline ACR (mg/g), (mean $\pm$ SD)	Baseline UPE [†] (mg/d)
Abe et al ¹⁵ (2011)	RSV 2.5–10 mg	65	5.87 $\pm$ 0.59	70.4 $\pm$ 11.9	141 $\pm$ 86	NR
	Usual care	65	5.79 $\pm$ 0.65	69.3 $\pm$ 9.50	142 $\pm$ 83	NR
JUPITER ²³ (2011)	RSV 20 mg	66	NR	75.4 $\pm$ 17.5	NR	NR
	Placebo	66	NR	75.4 $\pm$ 17.1	NR	NR
Sawara et al ¹⁶ (2008)	RSV 2.5 mg	64	5.91 $\pm$ 1.23	50.7 $\pm$ 18.7	NR	170 $\pm$ 290
	No statins	67	5.31 $\pm$ 0.73	57.3 $\pm$ 16.2	NR	120 $\pm$ 300
Verma et al ²⁴ (2005)	RSV 10 mg	73	5.79 $\pm$ 1.58	42.3 $\pm$ 11.1	NR	NR
	No statins	74	5.25 $\pm$ 0.88	49.4 $\pm$ 11.9	NR	NR
ALLIANCE ²⁵ (2009)	ATV 10–80 mg	61	NR	73.0 $\pm$ 17.8	NR	NR
	Usual care	61	NR	72.6 $\pm$ 17.9	NR	NR
Bianchi et al ²⁶ (2003)	ATV 10–40 mg	57	8.14 $\pm$ 0.16	50.8 $\pm$ 1.8	NR	2,500 $\pm$ 1,850
	No statins	57	7.91 $\pm$ 0.08	50.0 $\pm$ 1.9	NR	1,900 $\pm$ 1,410
CARDS ²⁷ (2009)	ATV 10 mg	62	5.35 $\pm$ 0.83	64.3 $\pm$ 10.3	10.1 $\pm$ 13.9	NR
	Placebo	62	5.33 $\pm$ 0.80	64.1 $\pm$ 10.3	9.4 $\pm$ 15.7	NR
Dalla et al ²⁸ (2003)	ATV 10 mg	66	6.10 $\pm$ 1.37	NR	NR	5.8 $\pm$ 16
	Placebo	63	5.25 $\pm$ 0.70	NR	NR	7.2 $\pm$ 11.74
Goicoechea et al ²⁹ (2006)	ATV 20 mg	66	5.93 $\pm$ 0.64	42.8 $\pm$ 24.9	NR	NR
	No statins	70	5.73 $\pm$ 0.96	44.2 $\pm$ 25.9	NR	NR
GREACE ³⁰ (2004)	ATV 10–80 mg	58	NR	76 $\pm$ 13	NR	NR
	Usual care	58	NR	77 $\pm$ 10	NR	NR
LORD ³¹ (2010)	ATV 10 mg	60	5.42 $\pm$ 1.20	31.9 $\pm$ 11.0	NR	1,430 $\pm$ 2,280
	Placebo	60	5.75 $\pm$ 1.50	29.1 $\pm$ 12.8	NR	1,180 $\pm$ 1,610
ATOROS ³² (2006)	RSV 10–20 mg	54	7.37 $\pm$ 0.78	85 $\pm$ 26	70 $\pm$ 40 [†]	NR
	ATV 20–40 mg	53	7.37 $\pm$ 1.11	85 $\pm$ 20	70 $\pm$ 40 [†]	NR
PATROL ³³ (2011)	RSV 2.5–5 mg	62	NR	73.1 $\pm$ 16.2	52.7 $\pm$ 250	NR
	ATV 10–20 mg	62	NR	75.7 $\pm$ 13.8	82.3 $\pm$ 443	NR
PLANET1 ¹³ (2010)	RSV 10–40 mg	NR	NR	70.8 $\pm$ 25.0	1,059 $\pm$ 726.8	NR
	ATV 80 mg	NR	NR	72.2 $\pm$ 24.9	1,143.2 $\pm$ 779.5	NR
PLANET2 ¹⁴ (2010)	RSV 10–40 mg	NR	NR	77.5 $\pm$ 29.3	1,102.7 $\pm$ 804	NR
	ATV 80 mg	NR	NR	71.5 $\pm$ 30.0	1,069.1 $\pm$ 720.8	NR
URANUS ³⁴ (2006)	RSV 10–40 mg	64	6.20 $\pm$ 0.89	73.9 $\pm$ 13.8	NR	44.9 $\pm$ 159.8
	ATV 10–80 mg	66	6.22 $\pm$ 0.91	76.2 $\pm$ 13.2	NR	39.6 $\pm$ 224.6

[†]PCR, not ACR, measured. [‡]All the data extracted were measured by UPE; UAE was not measured.

GFR, glomerular filtration rate; ACR, albumin-to-creatinine ratio; UPE, urinary protein excretion; RSV, rosuvastatin; NR, not reported; ATV, atorvastatin; PCR, protein-to-creatinine ratio; UAE, urinary albumin excretion.

English between 1966 and June 2011 using the search items proteinuria, UPE, albuminuria, urinary albumin excretion (UAE), renal function, GFR, kidney disease, RSV, and ATV. We limited our search to randomized controlled trials in adults >18 years.

We had a standard approach to the study search, data extraction, and quality assessment, which were undertaken independently by 2 authors (Y. Wu and Y. Wang). Disagreements were resolved by discussion and/or consultation with a third reviewer (F. An). Included studies met the following criteria: (1) prospective, randomized, controlled; (2) compared RSV with control (placebo, no statins or usual care); compared ATV with control (placebo, no statins or usual care); compared RSV with ATV head-to-head; and (3) provided baseline and follow-up data on GFR measured by creatinine clearance or estimated GFR (eGFR; using the formula of Modification of Diet in Renal Disease Study Group or Cockcroft-Gault); proteinuria and/or albuminuria measured on 24-h urine collection or urinary albumin-to-creatinine ratio (ACR). We excluded studies in which the participants were <18 years old, and we also excluded studies that enrolled dialysis patients.

Data Extraction and Quality Assessment

Published reports with full text were obtained for all included studies except 2 trials from the ClinicalTrials.gov website.^{13,14} Two reviewers (Y. Wu and Y. Wang), independently extracted and recorded the following information: study characteristics (year, country, sample size, loss to follow-up, blinding), participants (age, clinical population, baseline data for total cholesterol, GFR, UPE, UAE, protein-to-creatinine ratio [PCR], ACR), intervention (doses of RSV and ATV, duration of follow-up), outcomes (follow-up data of GFR, UPE, UAE, PCR, and ACR).

Study quality was assessed using the Cochrane collaboration's tool for assessing risk of bias (adequate sequence generation, allocation concealment, blinding, incomplete data addressed, free of selective reporting and free of other bias).¹⁷

Statistical Analysis

We measured change in the standardized mean differences (SMD) of GFR from baseline to follow-up. When data for change from baseline were available in the included trials, we directly extracted them from the literature. When only base-

line and final data were available, we imputed the mean and SD of the change from baseline according to the Cochrane Handbook.¹⁸ We obtained the mean change by subtracting the final mean from the baseline mean.¹⁸ The missing SD was calculated on the basis of reported P-values, if available.¹⁸ When P-value was not provided, we imputed the missing SD by using the correlation coefficient obtained from other include trials.¹⁸ We replaced missing mean with median, and missing SD with the width of interquartile range divided by 1.35.¹⁹ The SMD, which expresses the size of the difference in means in each trial relative to the variability observed in that trial, and the 95% confidence interval (CI) were measured considering the different units of reported data (ml/min , $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, and $\text{ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$). We undertook sensitivity analysis to test the impact of imputation.

For the treatment effect on proteinuria, we used the final data to decrease the bias because the raw data were insufficient and transformation of these data might cause huge errors. Proteinuria was measured via 24-h urine collection and urinary ACR. Although it was difficult to convert these 2 measurements, there was a linear correlation between them.²⁰ We therefore used the ratio of means (ROM) as the treatment effects to summarize the different measurement units.²¹ Moreover, the distribution of proteinuria data was highly skewed, suggesting a logarithmic transformation of the data before analysis. We therefore analyzed the log-transformed data and then reverse transformed to the original scale to obtain ROM (the ratio of the average treatment effect in the experimental

group to the control groups).

We assessed statistical heterogeneity between included trials using the I^2 statistic.²² We pooled the results using a random-effects model instead of a fixed-effects model considering the differences expected between studies (clinical population, doses of RSV and ATV). Publication bias is represented graphically with funnel plots.

All statistical analysis was performed using Review Manager 5.0.25. Statistical significance was set at $P < 0.05$.

Sensitivity Analysis

We tried different values of correlation coefficients to assess the impact of the imputation for the missing SD. We conducted another sensitivity analysis by pooling the results of GFR and proteinuria using both a random-effects model and a fixed-effects model to estimate the change of effect size. We did additional sensitivity analysis to measure the SMD of proteinuria, and observed whether it was consistent with ROM.

Results

Search Results

The literature search yielded 408 articles from which we identified 16 randomized controlled trials for inclusion (Figure 1).^{13–16,23–34} Four trials compared RSV with control,^{15,16,23,24} 7 trials compared ATV with control,^{25–31} and 5 trials compared RSV with ATV.^{13,14,32–34} In total, 24,278 individuals were enrolled: for 24,194 of whom the outcomes of

Figure 3. Ratio of means for RSV vs. control (placebo, no statins, usual care), ATV vs. control (placebo, no statins, usual care), and RSV vs. ATV. ATV, atorvastatin; CI, confidence interval; RSV, rosuvastatin.

GFR were reported from 15 trials;^{13–16,23–27,29–34} for 961 of whom PCR/ACR from 5 trials were reported;^{13–15,32,33} and for 586 of whom, UPE were reported from 5 trials.^{16,26,28,31,34} We excluded most of the studies that did not examine RSV or ATV therapy, that compare RSV or ATV with other statins head-to-head or examine the different dose effect of RSV and ATV, or did not provide adequate outcomes data.

Details of the included studies and baseline characteristics of participants are presented in [Tables 1,2](#). Follow-up of trials ranged from 4 months to 48 months and the mean age of the participants ranged from 53 years to 74 years. All the trials were randomized and controlled and were done in the USA, Japan, Italy, and so on. Six trials enrolled participants with CKD, 5 trials enrolled participants with diabetes mellitus (DM), 2 trials, with CVD and the remaining trials enrolled relatively healthy adults with hypertension or hyperlipidemia. Nine trials measured GFR or proteinuria as a priori outcomes,^{13–16,24,26,28,29,31} 2 trials as safety parameters,^{32,33} and the remaining trials as outcomes of post-hoc analysis from major randomized trials.

Trial Quality

The methodological quality of some enrolled trials was sub-optimal. Sequence generation was adequate in 10 trials (63%) and unclear in the remainder. Allocation concealment was adequate only in 3 trials (19%) and unclear in the remainder. Double-blinding was undertaken in 6 trials (38%) and the remainder were open-labeled. Incomplete data were addressed in 11 trials (69%) and unclear in the remainder. Selective reporting of outcomes was free in 15 trials (94%) and unclear in 1 (6%). Six trials (38%) were free of other bias, 2 trials (13%) had bias because of early termination, and the remainder were unclear.

Quantitative Data Analysis

Effects of RSV and ATV on GFR Compared with control (placebo, no statins, or usual care), both RSV and ATV improved GFR significantly ([Figure 2](#)): the change in the SMD of GFR was 0.04 (95%CI: 0.01–0.07; I²=0%; P=0.01) for RSV vs. control and 0.59 (95%CI: 0.12–1.06; I²=98%; P=0.01) for ATV vs. control. For the head-to-head comparison of RSV with ATV, the SMD in change from baseline for GFR was –0.01 (95% CI: –0.18 to 0.16; I²=51%; P=0.89).

Effects of RSV and ATV on Proteinuria Compared with control (placebo, no statins, or usual care), the ROM was 0.59 (95%CI: 0.46–0.74; I²=0%; P<0.0001) for RSV and 0.73 (95%CI: 0.52–1.04; I²=0%; P=0.08) for ATV ([Figure 3](#)). The ROM for head-to-head comparison of RSV with ATV was 1.23 (95%CI: 1.05–1.43; I²=14%; P=0.009).

Publication Bias

We used funnel plots to assess the publication bias. The funnel plots for GFR and proteinuria suggested no evidence of publication bias visually.

Sensitivity Analysis

When we used different values of correlation coefficients (0.4 and 0.6) to calculate the missing SD, the results of analysis were robust. The pooled treatment effects of RSV and ATV on GFR and proteinuria did not change when we used a fixed-effects model instead of a random-effects model. We also measured the SMD of proteinuria with 2 kinds of units separately: mg/day for UPE, and mg/gCr for PCR/ACR. The SMD of ACR was 0.19 (95%CI: 0.05–0.33; P=0.008) for RSV compared with ATV head to head, which similarly demonstrated the strength of ATV on proteinuria.

Discussion

The present meta-analysis found that both RSV (SMD, 0.04; 95%CI: 0.01–0.07; $P=0.01$) and ATV (SMD, 0.59; 95%CI: 0.12–1.06; $P=0.01$) improved GFR significantly when compared with control groups, and there was no significant difference in the head-to-head comparison. For the treatment effect on proteinuria, RSV was beneficial and the ATV effect was not significant, whereas head-to-head comparison showed that ATV was better than RSV at reducing proteinuria (ROM, 1.23; 95%CI: 1.05–1.43; $P=0.009$). The cause of these seemingly contradictory results may come from the LORD trial comparing ATV with placebo, which enrolled participants with severe CKD with a low baseline GFR (approximately 30 ml/min). When we excluded this trial, ATV treatment became effective for proteinuria compared with control (ROM, 0.66; 95%CI: 0.44–0.99; $P=0.04$). Because the small number of trials restricted our ability to run subgroup analysis, we cannot reach a conclusion as to whether the renoprotective effects of ATV or RSV were different according to the different stages of CKD.

Heterogeneity existed in the comparison of ATV vs. control and in that of RSV vs. ATV for the outcome of GFR. The former could be due to the large treatment effect observed in the Bianchi et al study and the GREACE trial.^{26,30} The SMD in change from baseline for GFR was 0.07 (95%CI: 0.01–0.12; $I^2=0\%$; $P=0.02$) when these 2 trials were excluded. The latter could be due to the stronger treatment effect of ATV rather than RSV in the PLANET 1 trial.¹³ When this trial was excluded, the change of SMD for GFR was 0.07 (95%CI: –0.06 to 0.21; $I^2=0\%$; $P=0.29$). Bianchi et al enrolled patients with idiopathic chronic glomerulonephritis who had significant proteinuria, and that trial estimated the effect of ATV on renal function in comparison with no statins after 12 months treatment of angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB).²⁶ Previous research has demonstrated that ACEI and ARB delay or prevent the progression of CKD.³⁵ For the GREACE trial, we extracted the baseline and final data for participants treated with ATV with structured care in comparison with no statins with usual care.³⁰ From the PLANET 1 trial, we found that high-dose ATV (80 mg) was better than RSV (10 mg and 40 mg) on GFR and proteinuria in diabetic patients with moderate proteinuria and hyperlipidemia.¹³ This suggests that the heterogeneity could be attributed to the different health condition of participants, cause of CKD, usage of ACEI or ARB, doses of ATV and RSV or any other confounding of study design.

Dyslipidemia is not only a risk factor for CVD, but also a risk factor for the progression of CKD.³⁶ Several clinical studies reported that dyslipidemia accelerated the progression of renal function both in CKD patients and in relatively healthy adults.^{37,38} Experimental studies demonstrate that re-absorption of lipoproteins by kidney tubules accelerates tubulo-interstitial inflammation, and that deposition of lipoprotein in the glomerular mesangium also promotes glomerulosclerosis.³⁶ The renoprotective effects of statins have been established in experiments³⁹ and clinical trials,^{7,8} which showed that these beneficial effects were related to the pleiotropic effects of statins.⁴⁰ These effects result in the attenuation of endothelial dysfunction and oxidative stress, anti-inflammation, anti-proliferation of mesangial cells, and protection of podocyte.^{41,42} Researchers came to similar conclusions about the effects of RSV and ATV on renoprotection.^{43–46}

The powerful effects of statins on lipid lowering have been proved, and they were independently associated with the de-

crease of all cause mortality and cardiovascular morbidity and mortality in the general population.^{5,6} CKD patients have a high rate of CVD, which was found to be an independent risk factor for worsening of renal function.⁴⁷ In recent guidelines for the management of dyslipidemia, low-density lipoprotein cholesterol (LDL-C) reduction is recommended as the primary target in order to reduce the CVD risk in CKD subjects (stage 2–4).⁴⁸ Clinical endpoint results for statins, however, are conflicting in CKD patients. The SHARP trial suggested that simvastatin plus ezetimibe reduced the risk of major atherosclerosis events both in dialysis- and in non-dialysis-dependent CKD patients, but that they had no effect on the progression of end-stage renal disease (ESRD).⁴⁹ The CARDS trial and JUPITER trial reported that RSV and ATV reduced the number of major CVD events in non-dialysis-dependent CKD patients,^{27,50} but the AURORA trial and 4D trial did not show this positive effect in dialysis patients.^{51,52} In the present meta-analysis, we have proved the beneficial effects of statins (RSV and ATV) on the parameters of GFR and proteinuria. These 2 parameters both are significant predictors of CVD, ESRD, and mortality.^{53,54} As an established risk factor for progressive renal function loss,⁵⁵ proteinuria or albuminuria is a target in treatment of diabetic kidney disease.⁵⁶ In the general population, proteinuria is an important marker of endothelial injury and an independent risk factor for cardiovascular morbidity and mortality.⁵⁷ A collaborative meta-analysis by Kidney Disease: Improving Global Outcomes (KDIGO) reported that eGFR less than of equal to $60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ and ACR less than of equal to 10 mg/g were independent predictors for mortality in the general population.⁵⁸ To determine whether the subtle changes of GFR and proteinuria, attributed to the renoprotective effects of RSV and ATV, are associated with clinical benefits or not, we need further studies both in patients with and without CKD.

Before the present meta-analysis there were several that discussed the effects of statins on renal outcome. The meta-analysis by Sandhu et al concluded that statins therapy reduced the rate of decline in eGFR by a mean of $1.22 \text{ ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$, and meta-regression found that ATV use was associated with a significantly larger beneficial effect on the rate of decline in eGFR than other statins, but not RSV.⁹ Another meta-analysis of randomized placebo-controlled trials by Douglas et al reported that statins were associated with statistically significant reduction in pathologic level of albuminuria and proteinuria.¹⁰ The present results are consistent with the previous meta-analysis. To our knowledge, this is the first reported meta-analysis to pool the effects of RSV on renal function and compare RSV with ATV on kidney outcome.

There were several limitations in the present meta-analysis, however. First, considerable variation was found in the patients (CKD, DM, CVD, hyperlipidemia, etc.), intervention (doses of RSV and ATV), outcomes (estimates of GFR and proteinuria), and follow-up (from 4 months to 48 months). These variations may be the cause of heterogeneity between studies on the outcome of GFR. We concluded that ATV can improve GFR (SMD, 0.59; 95%CI: 0.12–1.06; $I^2=98\%$; $P=0.01$). Although we used a random-effects model to pool the data, this result should be interpreted with caution. Second, the small number of trials restricted the ability to run subgroup analysis and the statistical power was limited. Meanwhile, the number of high-quality randomized controlled trials was relatively low. Third, in the comparison of RSV vs. control, the sample size was unbalanced among the trials. Fourth, given the different kinds of units, we used relative effect size (SMD and ROM) to measure the treatment effects,

which should be interpreted with caution. Finally, although we searched several databases and included 2 studies from the ClinicalTrials.gov website,^{13,14} the possibility of publication bias still exists. Outcome reporting bias was also inevitable because we found that several trials reported baseline GFR or proteinuria but not final data.²⁷

The present meta-analysis suggests that both RSV and ATV improve GFR, and that ATV may be more effective on reducing proteinuria than RSV. The results should be confirmed, however, by further larger, high-quality, multiple-center studies with a longer follow-up. Head-to-head studies of RSV vs. ATV that measure GFR and proteinuria as a priori efficacy outcomes but not potential adverse events are needed. Although the protective effects of RSV and ATV on kidney outcome have been proved in the present meta-analysis, the clinical benefits of these subtle changes still need to be studied in patients with normal kidney function and with impaired renal function at different stages. In other words, further trials are required to clarify the roles of RSV and ATV both on renal function and on the composite clinic endpoint of death, CVD, progression of ESRD, and doubling of serum creatinine.

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Disclosures

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Supplemental Files

Supplemental File 1

Figure S1. Funnel plots for included studies in the meta-analysis of glomerular filtration rate show the standardized mean differences (SMD) vs. the standard error (SE) of SMD.

Figure S2. Funnel plots for included studies in the meta-analysis of proteinuria show the ratio of means (ROM) vs. the standard error (SE) for the logarithm of ROM.

Figure S3. Changes in the standardized (Std.) mean differences of glomerular filtration rate when we used correlation coefficient ($r=0.4$) to impute the missing SDs.

Figure S4. Changes in the standardized (Std.) mean differences of glomerular filtration rate when we used correlation coefficient ($r=0.6$) to impute the missing SDs.

Figure S5. Changes in the standardized (Std.) mean difference of glomerular filtration rate with fixed-effects model.

Figure S6. Ratio of means of proteinuria with fixed-effects model.

Figure S7. Standardized (Std.) mean differences of proteinuria measured by urinary protein excretion.

Figure S8. Standardized (Std.) mean differences of proteinuria measured by albumin-to-creatinine ratio or protein-to-creatinine ratio.

Please find supplemental file(s);
<http://dx.doi.org/10.1253/circj.CJ-11-1385>