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Angiotensin II receptor blocker and long-acting calcium channel blocker combination therapy decreases urinary albumin excretion while maintaining glomerular filtration rate

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Angiotensin II receptor blocker and long-acting calcium channel blocker combination therapy decreases urinary albumin excretion while maintaining glomerular filtration rate

Running title: Combination therapy with ARB and long-acting CCB

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Abstract

Microalbuminuria is a recognized risk factor and predictor for cardiovascular events in patients with hypertension. We analyzed changes in hypotensive effect, urinary albumin excretion (UAE), and estimated glomerular filtration rate (eGFR) in subjects with hypertension and microalbuminuria as a subanalysis of the results of the NICE Combi (Nifedipine and Candesartan Combination) Study. A total of 86 subjects with essential hypertension with microalbuminuria (UAE <300 $mg \cdot g^{-1}$ creatinine) were randomly assigned in a double-blind manner to a combination therapy group (standard-dose candesartan at 8 mg/day plus controlled-release (CR) nifedipine 20 mg/day) (n=42) or an up-titrated monotherapy group (candesartan 12 mg/day) (n=44) for 8 weeks of continuous treatment after initially receiving standard-dose candesartan (8 mg/day) monotherapy for 8 weeks (initial treatment). After 8weeks, blood pressure was significantly reduced in both groups compared with at the end of initial treatment. UAE also showed a significant decrease in the combination therapy group, while there was no significant change of eGFR in either group. A significant positive correlation was seen between blood pressure reduction and UAE after 8 weeks of double-blind treatment in both groups, whereas no significant association was found between ΔUAE and ΔeGFR in either group. These findings show that combination therapy with standard-dose candesartan and nifedipine CR is more effective than up-titrated candesartan monotherapy for reducing blood pressure and improving UAE while maintaining eGFR, and strongly suggest that the

combination of an angiotensin II receptor blocker and long-acting calcium channel blocker is beneficial in patients with hypertension and microalbuminuria.

Key words: combination therapy, controlled-release nifedipine, candesartan, estimated glomerular filtration rate, urinary albumin excretion

Introduction

The purpose of antihypertensive therapy for patients with chronic kidney disease (CKD) is to inhibit the development of renal dysfunction by decreasing blood pressure and preventing the onset or recurrence of cardiovascular disease. The renal protective effects of renin angiotensin system (RAS) inhibitors have been demonstrated in many studies,[1-3] and clinical practice guidelines uniformly recommend an angiotensin-converting enzyme inhibitor (ACEI) or Angiotensin II type 1 receptor blocker (ARB) is first-line treatment for CKD.[4-6] A calcium channel blocker (CCB) or diuretic is recommended as a second-line agent in combination with a RAS inhibitor. However, it still remains unclear which agent is more effective in slowing the progression of renal insufficiency in CKD patients in the context of changes in the glomerular filtration rate (GFR).

We previously reported that standard-dose combination therapy with an ARB plus controlled-release (CR) nifedipine is superior to up-titrated ARB treatment in lowering blood pressure and reducing urinary albumin excretion (UAE) in the NICE-Combi study. [7] In this study, which involves a subanalysis of the results of the NICE-Combi study, we used the Japanese equation proposed by the Japanese Society of Nephrology [8] to calculate eGFR and examine the association of ΔeGFR with ΔUAE to determine whether UAE reduction is associated with a decline in the eGFR.

Methods

Study population

The methods of the NICE-Combi study were reported previously.[7] In this subanalysis, we included 86 subjects with microalbuminuria (UAE <300 mg•g^{-1} creatinine) at the start of the study from the 258 subjects enrolled with essential hypertension. The reference value of microalbuminuria was ≥22 mg•g^{-1} creatinine for men and ≥31 mg•g^{-1} creatinine for women, according to the European Society of Hypertension-European Society of Cardiology (ESH/ESC) 2003 guideline.[9] Patients with overt nephropathy with a baseline UAE ≥300 mg•g^{-1} creatinine were excluded from this study.

BP and renal function measurements

We estimated the glomerular filtration rate with a modified modification of diet in renal disease equation for Japanese: glomerular filtration rate (ml•min^{-1}•1.73 m^{-2}) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 for females).[8] We examined changes in blood pressure, UAE, and eGFR measured on the designated appointment day (at trough before administration) again in the up-titrated monotherapy group (candesartan dosage increase to 12 mg/day) and the combination therapy group (candesartan 8 mg plus nifedipine CR 20 mg), to which patients had been randomly assigned using a double-blind design after initial treatment with candesartan (8 mg/day) monotherapy for 8 weeks. UAE and eGFR were measured before initial treatment, at the end of

initial treatment, and at the end of double-blind treatment, with UAE adjusted for urinary creatinine using the first urine in the morning. For blinding, we put tablets into opaque capsules to prevent the study drugs from being identified.

Statistical analysis

We compared the demographics of patients in the up-titrated monotherapy group and the combination therapy group by analysis of categorical variables, including gender and eGFR distribution, using the $\chi 2$ test and Fisher's exact test, and continuous variables such as blood pressure, UAE, serum creatinine, and eGFR, using Student's *t*-test or the Wilcoxon rank-sum test. Changes in blood pressure over 4 weeks and in UAE and eGFR for 8 weeks, in each group were analyzed using a linear mixed model with Bonferroni correction. In addition, the interactions between changes in blood pressure, UAE, and eGFR in both groups were determined using the Type III test using a linear mixed model, and differences between groups at each time of measurement were evaluated using the Wilcoxon rank-sum test.

Values are expressed as the mean ± standard deviation, except for those of UAE and eGFR, which are given as median values (midpoint between 25th and 75th percentiles). We reviewed correlations between UAE and blood pressure achieved at the end of double-blind treatment in each treatment group using Spearman's rank correlation coefficient. We then calculated the coefficients of

correlation and regression equations for the levels and ΔeGFR and ΔUAE during initial and double-blind treatment. If a normal distribution was not found, we used Spearman's rank correlation coefficient. Furthermore, we compared rates of progress and improvement with changes in UAE or eGFR as a category in the two groups using the $\chi 2$ test. All statistical analyses were two-sided, with a level of significance of α-0.05, and performed with SAS software version 2010 (SAS Institute, Cary, North Carolina, USA).

Results

Subject demographics

The demographics of the 86 subjects (42 in the combination therapy group, and 44 in the up-titrated monotherapy group) at the end of initial treatment are shown in Table 1. No significant differences were seen between groups (mean eGFR 70.9 ± 23.2 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ in the combination therapy group and 64.6 ± 17.5 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ in the up-titrated monotherapy group; and mean UAE 81.0 ± 66.9 $mg \cdot g^{-1}$ creatinine in the combination therapy group and 85.6 ± 69.5 $mg \cdot g^{-1}$ creatinine in the up-titrated monotherapy group). In addition, no differences were seen between groups in blood pressure or eGFR distribution by age.

Changes in blood pressure

Changes of blood pressure from initial treatment to the end of double-blind treatment in the two groups are shown in Fig. 1. Although no significant hypotensive effect for either systolic blood pressure (SBP) or diastolic blood pressure (DBP) was seen during initial treatment with candesartan 8 mg/day for 8 weeks, there was a significant decrease in blood pressure in the up-titrated candesartan group (from 160.2 ± 1.8/98.2 ± 1.0 mmHg to 153.7 ± 2.1/95.0 ± 1.2 mmHg, P=0.01/0.07) only at the end of the double-blind treatment. On the other hand, significant decreases were seen in blood pressures in the combination therapy group after 4 weeks of double-blind

treatment, as well as at the end of treatment (from 153.9 ± 2.0/97.3±1.0 mmHg to 144.1 ± 2.4/92.0 ± 1.3 mmHg, P<0.001/<0.001). Furthermore, blood pressures after 4 weeks and at the end of double-blind treatment were significantly lower in the combination therapy group than in the up-titrated monotherapy group (P<0.001/0.042, 0.003/0.104). When we examined changes in blood pressure in patients stratified by eGFR ≥60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ (eGFR ≥60) and eGFR <60 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ (eGFR <60), there were significant decreases of SBP and DBP after 4 weeks and at the end of double-blind treatment only in subjects from the combination therapy group with eGFR ≥60 but not in those with eGFR <60.

Changes in urinary albumin excretion

Changes of UAE from initial treatment to the end of double-blind treatment in the two groups are shown in Fig. 2a. In all subjects, a significant increase in UAE was observed after 8 weeks of initial treatment (p<0.01) (42 subjects in the combination therapy group: median from 40.1 to 56.7, P=0.055; 44 in the up-titrated monotherapy group: median from 31.5 to 51.1, P<0.05). Although there was no significant decrease in UAE in the up-titrated monotherapy group during double-blind treatment, a significant decrease was seen in UAE in the combination therapy group (P<0.05), and the reduction at the end of the study was significant in comparison to the up-titrated monotherapy group (P<0.05). When we examined changes in UAE in patients stratified at an

eGFR of 60 ml•min^{-1}•1.73 m^{-2}, the change was significantly lower in the combination therapy group (26.1 mg•g^{-1} creatinine) than in the up-titrated monotherapy group (50.7 mg•g^{-1} creatinine, $P<0.05$) at the end of double-blind treatment in subjects with eGFR ≥60 (Fig.2b), but similar in the combination therapy group (40.5 mg•g^{-1} creatinine) and the up-titrated monotherapy group (63.2 mg•g^{-1} creatinine, $P=0.252$) in subjects with eGFR <60 (Fig. 2c).

Changes in eGFR

Changes of eGFR from initial treatment to the end of double-blind treatment in the two groups are shown in Fig. 2d. No significant changes were seen in both group between baseline and the end of the study. Similar results were obtained in patients stratified by eGFR ≥60 and <60. In addition, examination of changes in eGFR according to subject age group revealed no significant difference between treatment groups for any stratum between before and after randomized treatment (Table 2).

Relationships between blood pressure, UAE, and eGFR

Correlations between UAE and SBP at the end of double-blind treatment are shown in Fig. 3. Significant positive correlations were seen in both the combination therapy group ($\gamma=0.453$, $P<0.01$) and up-titrated monotherapy group ($\gamma=0.334$, $P<0.05$). There were only weak positive correlation

(not significant) between ΔUAE and ΔSBP among subjects stratified by eGFR ≥60 and eGFR <60 from both the combination therapy group and the up-titrated monotherapy group.

We then examined the correlations between ΔeGFR and ΔUAE before and after double-blind treatment. No significant correlation was seen between ΔUAE and ΔeGFR during double-blind treatment in either the combination therapy group (γ=-0.195, P=0.217) or the up-titrated monotherapy group (γ=0.214, P=0.164) (Fig. 4). In the combination therapy group, 27 of 35 subjects (77%) with an increase of UAE during initial treatment showed a decrease of UAE during double-blind treatment, whereas 22 of 38 subjects (58%) with increased UAE during initial treatment showed a decrease during double-blind treatment in the up-titrated monotherapy group. Comparison between groups revealed a strong tendency to improvement in UAE in the combination therapy group (P=0.080).

Discussion

In this study, which involved a subanalysis of the results of the NICE-Combi study, we demonstrated the following: (1) blood pressure level was significantly decreased in both groups with intensive antihypertensive treatment, but blood pressure reduction was significantly earlier and greater in the combination therapy group than in the up-titrated monotherapy group; (2) eGFR did not change significantly in either group, although UAE decreased significantly in the combination therapy group alone in parallel with blood pressure reduction during 8 weeks of double-blind treatment. Recently, the GUARD study in the U.S.[10]showed treatment with an ACEI (benazepril) plus a diuretic (hydrochlorothiazide) in patients with diabetic nephropathy reduced albuminuria to a greater extent than an ACEI plus CCB (amlodipine). These results called into question whether a diuretic or CCB is more suitable as a second-line agent with a RAS inhibitor. However, treatment with ACEI plus CCB (-2.03 $ml \cdot min^{-1} \cdot yr^{-1}$) was superior to ACEI plus diuretic (-13.64 $ml \cdot min^{-1} \cdot yr^{-1}$) for maintenance of eGFR, apparently because reduction of UAE with the latter treatment was caused by a decline in eGFR. In general, eGFR can decrease temporarily in patients with CKD who are placed on a strict antihypertensive treatment regimen for a short period of time. However, in the analysis of renal events in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study,[11, 12] combined treatment with ARB plus ACEI significantly reduced UAE in comparison to monotherapy with either agent alone, but eGFR reduction (-6.11

ml•min^{-1}•yr^{-1}) and renal events were significantly greater, suggesting that renal events cannot be prevented by UAE reduction if there is an excessive decline of the eGFR. Therefore, the characteristics of antihypertensive therapy should be examined in relation to changes of the eGFR.

In the present study, we found that the blood pressure reduction was greater in the combination therapy group than in the up-titrated monotherapy group, and that UAE declined significantly in the combination therapy group alone, while eGFR was unchanged over 8 weeks of intensive antihypertensive treatment and no significant correlation was found between ΔGFR and ΔUAE in either group. Furthermore, the percentage of subjects with improved UAE after double-blind treatment was higher in the combination therapy group than in the up-titrated monotherapy group, although the difference was not significant. When we examined changes of UAE in subjects stratified at an eGFR of 60 ml•min^{-1}•1.73m^{-2}, marked improvement was seen in subjects from the combination therapy group with eGFR ≥60, suggesting that combination therapy with nifedipine CR reduces UAE without affecting the eGFR, so that the improvement of UAE may be attributed to increased tubular protein reabsorption. There was a weak positive correlation (not significant) between ΔUAE and ΔSBP in subjects both eGFR >60 and eGFR <60 from both therapy groups, probably because the number of subjects in each stratified group was too small.

A meta-analysis found that a higher rate of achievement of an SBP <130 mmHg, or a decrease in blood pressure, in patients with CKD leads to decreased impairment in eGFR and

prevention of end-stage renal disease.[13] As shown in Fig. 3, we found greater improvement of UAE in subjects who reached a lower blood pressure in both the combination therapy group and the up-titrated monotherapy group, suggesting that UAE is worsen by standard dosage ARB treatment but can be improved by the intensive antihypertensive treatment. Basic studies have reported that nifedipine CR not only has stronger antihypertensive effects than other CCBs, but also strongly inhibits activation and secretion of aldosterone through a mineralocorticoid receptor, and that the strength of effect on aldosterone activation varies between CCB.[14] Previous studies have shown that nifedipine reduces levels of expression of monocyte chemoattractant protein-1, transforming growth factor-β, type III collagen and receptors for advanced glycation end products (AGE) in AGE-exposed human cultured mesangial cells,[15] and may act as an anti-inflammatory and anti-fibrogenic agent against AGE via mineralocorticoid antagonistic activity.[16] These studies indicate that combination therapy with an ARB plus nifedipine CR may have strong blood pressure-decreasing effects and organ protective effects, and may thus improve renal function.

Recently, several studies comparing use of a CCB or diuretic with an RAS inhibitor have been published. Initially, in the Antihypertensive and Lipid Lowering treatment to prevent Heart ATtack (ALLHAT) [17] conducted in 30,000 patients with hypertension, amlodipine was found to be superior to ACEI and diuretics in delaying the decline in renal function and maintaining GFR in terms of the serum creatinine level (inverse/year), an indicator of renal function. Secondly, the

International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT) study [18, 19] compared the effects on renal function in patients with high-risk hypertension between once-daily nifedipine formulations and combined co-amilozide (hydrochlorothiazide plus amiloride) groups, and reported that the former treatment significantly inhibited decline in GFR in comparison to the latter. Most recently, a subanalysis of renal outcome data in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study[20] demonstrated a significantly slower decline in eGFR after 2.9 years of treatment in the benazepril (ACEI) plus amlodipine (CCB) group (-0.88 $ml \cdot min^{-1} \cdot 1.73m^{-2}$) than in the benazepril plus hydrochlorothiazide (diuretic) group (-4.22 $ml \cdot min^{-1} \cdot 1.73m^{-2}$; p=0.01) in some 11,500 patients at high cardiovascular risk. It has also been reported that CCBs, especially those of the dihydropyridine class, increase urinary sodium and water excretion, partly by decreasing proximal tubular sodium reabsorption.[21, 22] In addition, CCBs have been proven to be effective in preventing arteriosclerosis,[23, 24] whereas diuretics can damage the sugar/fat metabolism system, [25, 26] a possible factor in exacerbation of atherosclerosis.

This study has several limitations. One limitation of the NICE-Combi study is its lack of direct comparison with diuretics, since we did not include a treatment arm with ARB plus diuretic. The effects of combination treatment including ARB, long-acting CCBs, and diuretics in patients with CKD require examination in large randomized studies. In addition, it has been reported in a

clinical study that protective effects on organs may differ among CCBs,[27-29] and a controlled trial is needed to investigate antihypertensive effects and protection of organs in patients with CKD. Secondly, the up-titrated dose of candesartan was 12 mg/day, which is the maximum recommended dose in Japan, so the achieved systolic blood pressure significantly differed by about 10 mmHg between the two groups. There is still be a possibility that other ARB monotherapy up-titrated to doubled the standard dose could reduce blood pressure and UAE to the same extent as the combination therapy. Thirdly, our subjects were all Japanese, and several studies have reported racial/ethnic differences in BP responses to antihypertensive therapy.[30] Finally, 8 weeks of double-blind treatment was relatively short period to estimate of long-term improvement of renal function. Further studies are needed to clarify these issues in large number of patients and long-term administration.

In conclusion, it appears that ARB plus nifedipine CR treatment can provide rapid and greater hypotensive effects and contribute to the preservation/improvement of renal function, in which UAE is reduced while maintaining eGFR. Our findings strongly suggest that early use of nifedipine CR is effective in patients with hypertension and microalbuminuria.

Conflict of interest

Drs Kikuchi and Hasebe report receiving advisory board fees from Bayer Yakuhin Ltd, Osaka, Japan.

The remaining authors declare no conflict of interest.

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Figure legends

Figure 1 Changes in blood pressure

Changes in blood pressure (BP) during initial treatment with candesartan 8 mg/day, and double-blind treatment with nifedipine controlled release 20 mg/day plus candesartan 8 mg/day combination therapy (○, n = 42), or with candesartan 12 mg/day up-titrated monotherapy (●, n = 44). Data are expressed as mean ± SD. $P < 0.05$: *compared to the end of initial treatment (8 weeks) in each treatment group; # comparison between two treatment groups.

Figure 2 Changes in urinary albumin excretion and estimated glomerular filtration rate

(a) Changes in urinary albumin excretion (UAE; measured as the ratio of albumin to creatinine) before and after double-blind treatment in all patients (□, combination therapy, n = 42; ■, up-titrated monotherapy, n = 44), (b) in patients with baseline eGFR ≥60 $ml \cdot min^{-1} \cdot 1.73m^{-2}$ (□, combination therapy, n = 27; ■, up-titrated monotherapy, n = 23) and (c) in patients with baseline eGFR <60 $ml \cdot min^{-1} \cdot 1.73m^{-2}$. (d) Changes in estimated glomerular filtration rate (eGFR) before and after double-blind treatment in all patients (□, combination therapy, n = 42; ■, up-titrated monotherapy, n = 44). [a]Wilcoxon signed rank test using Bonferroni correction; [b]Wilcoxon Rank-Sum test.

Figure 3 Correlation between urinary albumin excretion and systolic blood pressure after double-blind treatment

Correlation between urinary albumin excretion (UAE) and systolic blood pressure (SBP) after double-blind treatment in (a) the combination therapy group (n = 42), and (b) the up-titrated monotherapy group (n = 44). r_S, Spearman's rank correlation coefficient.

Figure 4 Correlation between ΔeGFR and ΔUAE during double-blind treatment

Correlation between delta change of estimated glomerular filtration rate (eGFR) and urinary albumin excretion (UAE) during double-blind treatment in (a) the combination therapy group (n = 42), and (b) the up-titrated monotherapy group (n = 44). r_S: Spearman's rank correlation coefficient.

Table 1　Demographic characteristics of patients randomly allocated to groups at baseline

	All (n=86)	Nifedipine CR ＋candesartan combination therapy (n=42)	Candesartan up-titrated monotharapy (n=44)	P
Sex				
male	51 (59.3%)	25 (59.5%)	26 (59.1%)	0.967
female	35 (40.7%)	17 (40.5%)	18 (40.9%)	
Age				
20～59 years	50 (58.1%)	27 (64.3%)	23 (52.3%)	0.312
60～69 years	25 (29.1%)	9 (21.4%)	16 (36.4%)	
70～80 years	11 (12.8%)	6 (14.3%)	5 (11.4%)	
All	57.7 ± 9.9	57.2 ± 10.7	58.1 ± 9.1	0.674
SBP/DBP (mmHg)				
20～59 years	153.9 ± 12.9/98.5 ± 6.6	151.7 ± 13.7/97.6 ± 6.3	156.4 ± 11.6/99.4 ± 7.0	0.201/0.341
60～69 years	160.0 ± 10.7/97.3 ± 6.5	154.9 ± 9.4/98.8 ± 8.5	162.9 ± 10.5/96.5 ± 5.2	0.069/0.481
70～80 years	165.0 ± 10.2/95.7 ± 5.4	162.0 ± 10.5/93.7 ± 2.5	168.6 ± 9.7/98.2 ± 7.2	0.311/0.179
All	157.1 ± 12.5/97.8 ± 6.4	153.9 ± 12.7/97.3 ± 6.5	160.2 ± 11.6/98.2 ± 6.4	0.018/0.512
Heart rate (beats/min)	73.9 ± 8.8	71.4 ± 6.6	76.3 ± 10.0	0.009
Serum creatinine (mg/dL)	0.87 ± 0.23	0.85 ± 0.23	0.90 ± 0.23	0.261
eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)				
≥90	11 (12.8%)	7 (16.7%)	4 (9.1%)	0.413
60 to 90	39 (45.3%)	20 (47.6%)	19 (43.2%)	
＜60	36 (41.9%)	15 (35.7%)	21 (47.7%)	
All	67.7 ± 20.6	70.9 ± 23.2	64.6 ± 17.5	0.16
UAE (mg•g-1 creatinine)	83.3 ± 67.9	81.0 ± 66.9	85.6 ± 69.5	0.759

Variables are presented as mean ± SD, or number (percentage). SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion.

Table 2 Changes in estimated glomerular filtration rate (stratified by age)

Age (year)	Treatment group	After baseline treatment (8w) ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	After double-blind treatment (16w) ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	Paired t	Unpaired t
20-59	Combination (n=27)	77.2 ± 4.9	74.3 ± 4.2	0.513	0.43
	Up-titrated (n=23)	70.0 ± 2.9	70.4 ± 2.6	1.000	
60-69	Combination (n=9)	64.2 ± 3.6	60.9 ± 3.9	0.475	0.936
	Up-titration (n=16	60.7 ± 5.5	61.6 ± 6.4	1.000	
≥70	Combination (n=6)	52.4 ± 4.9	54.7 ± 5.9	1.000	0.73
	Up-titrated (n=5)	52.4 ± 1.8	52.3 ± 2.7	1.000	

Variables are presented as mean ± SEM.

Figure 1 Changes in blood pressure

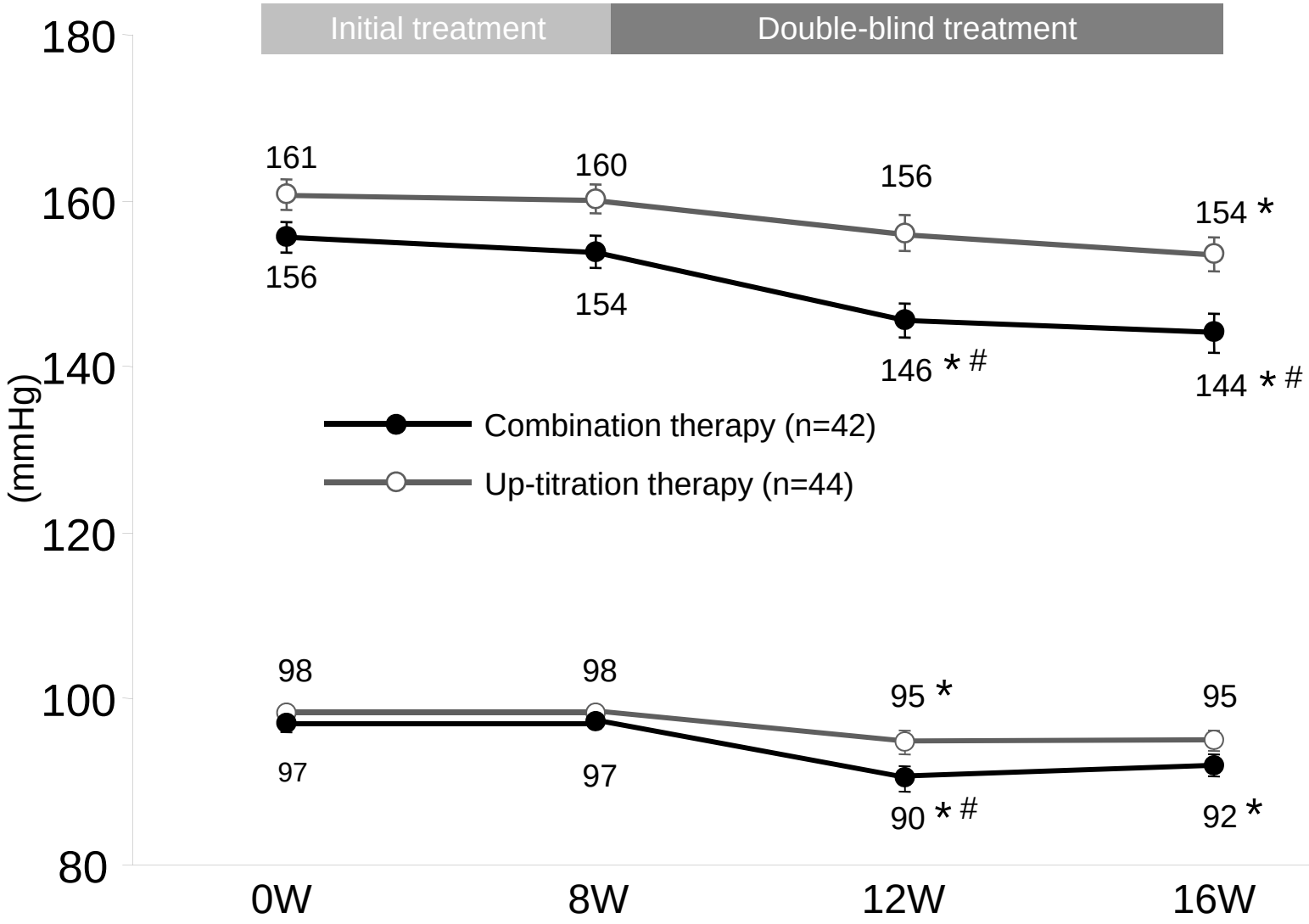

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Figure 2a Changes in urinary albumin excretion in all subjects

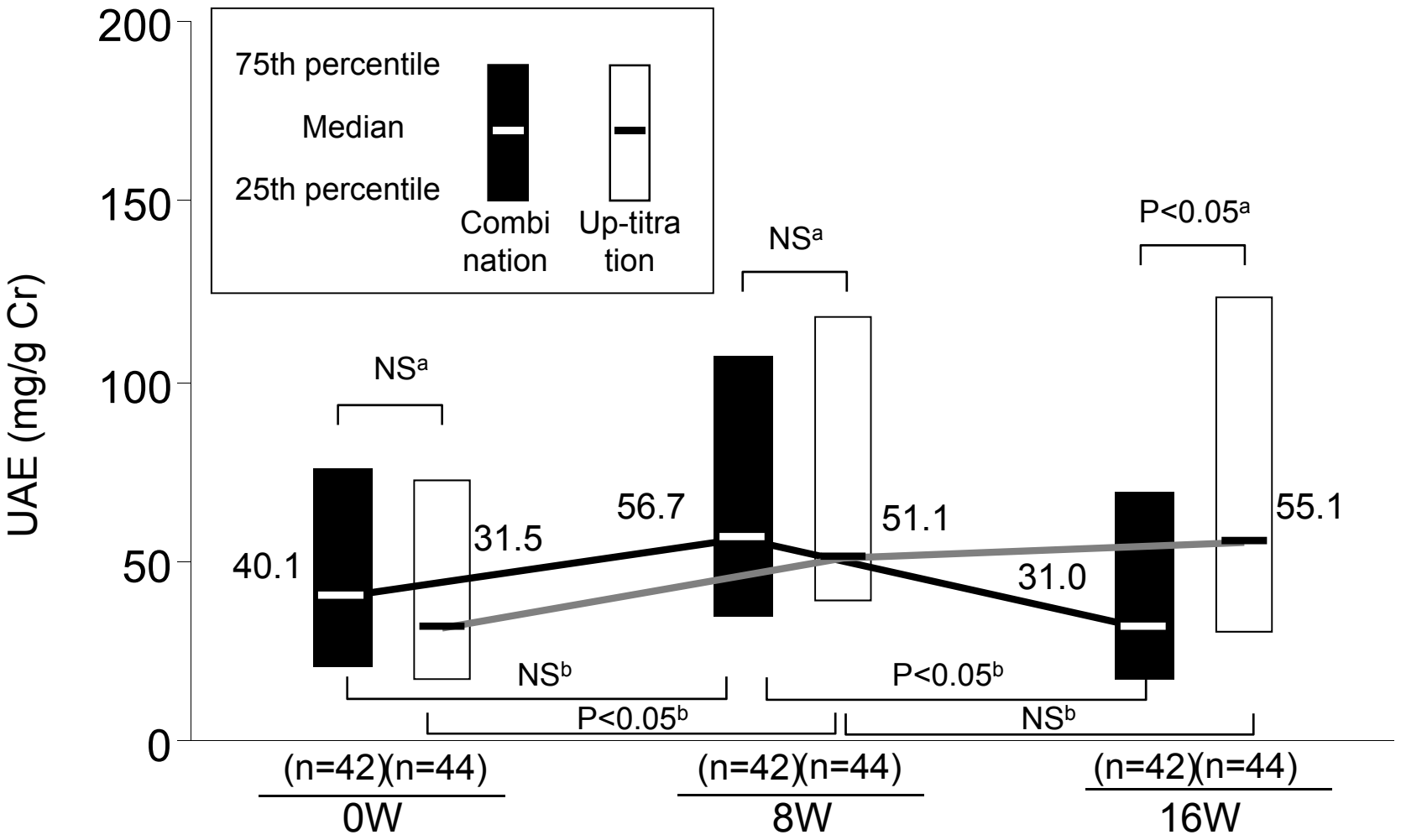

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Figure 2b Changes in urinary albumin excretion in subjects with eGFR ≥60 mL•min^{-1}•1.73 m^{-2}

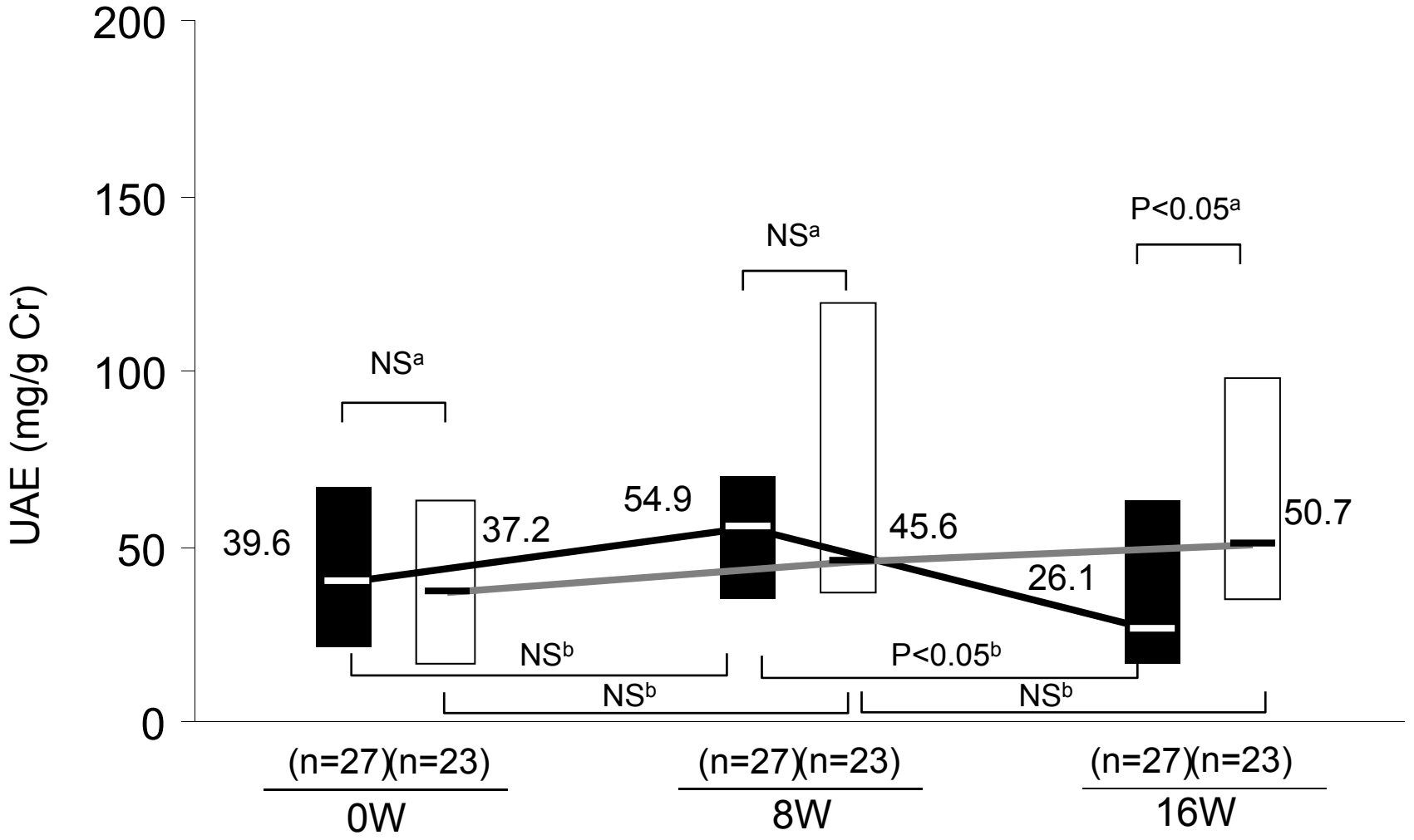

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Figure 2c Changes in urinary albumin excretion in patients with estimated glomerular filtration rate <60 mL•min^{-1}•1.73 m^{-2}

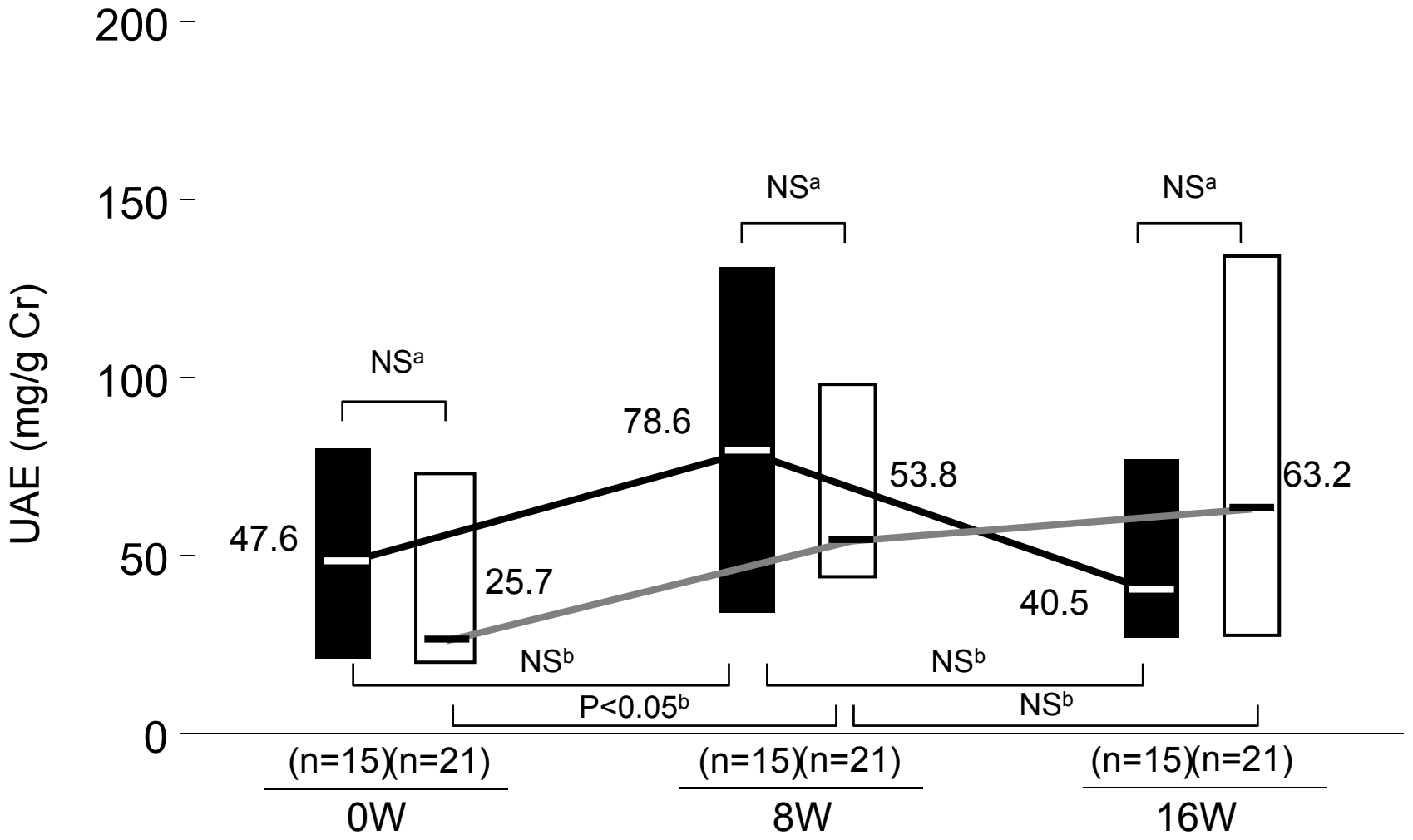

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Figure 2d Changes in estimated glomerular filtration rate in all patients

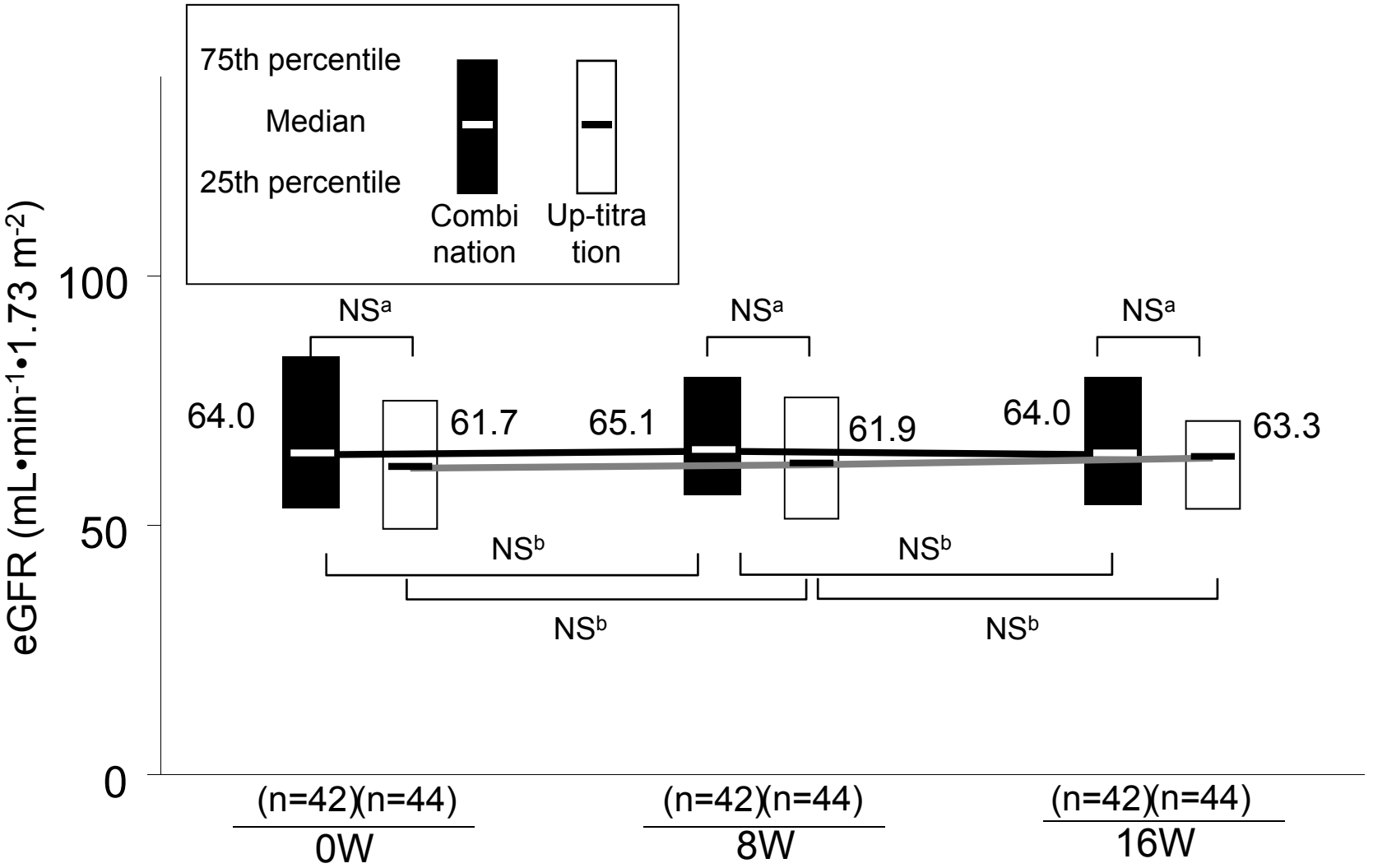

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Figure 3 Correlation between urinary albumin excretion and systolic blood pressure after double-blind treatment

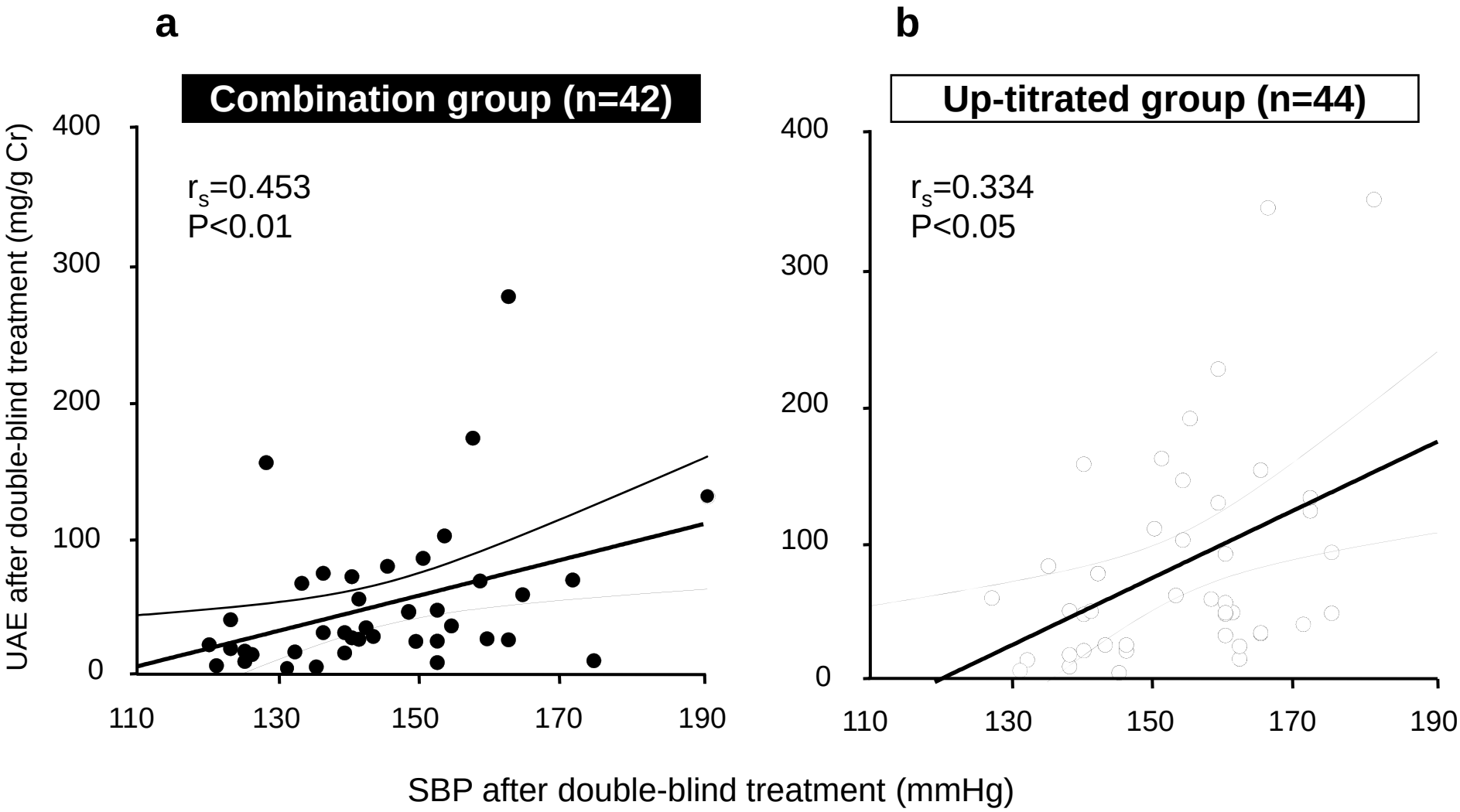

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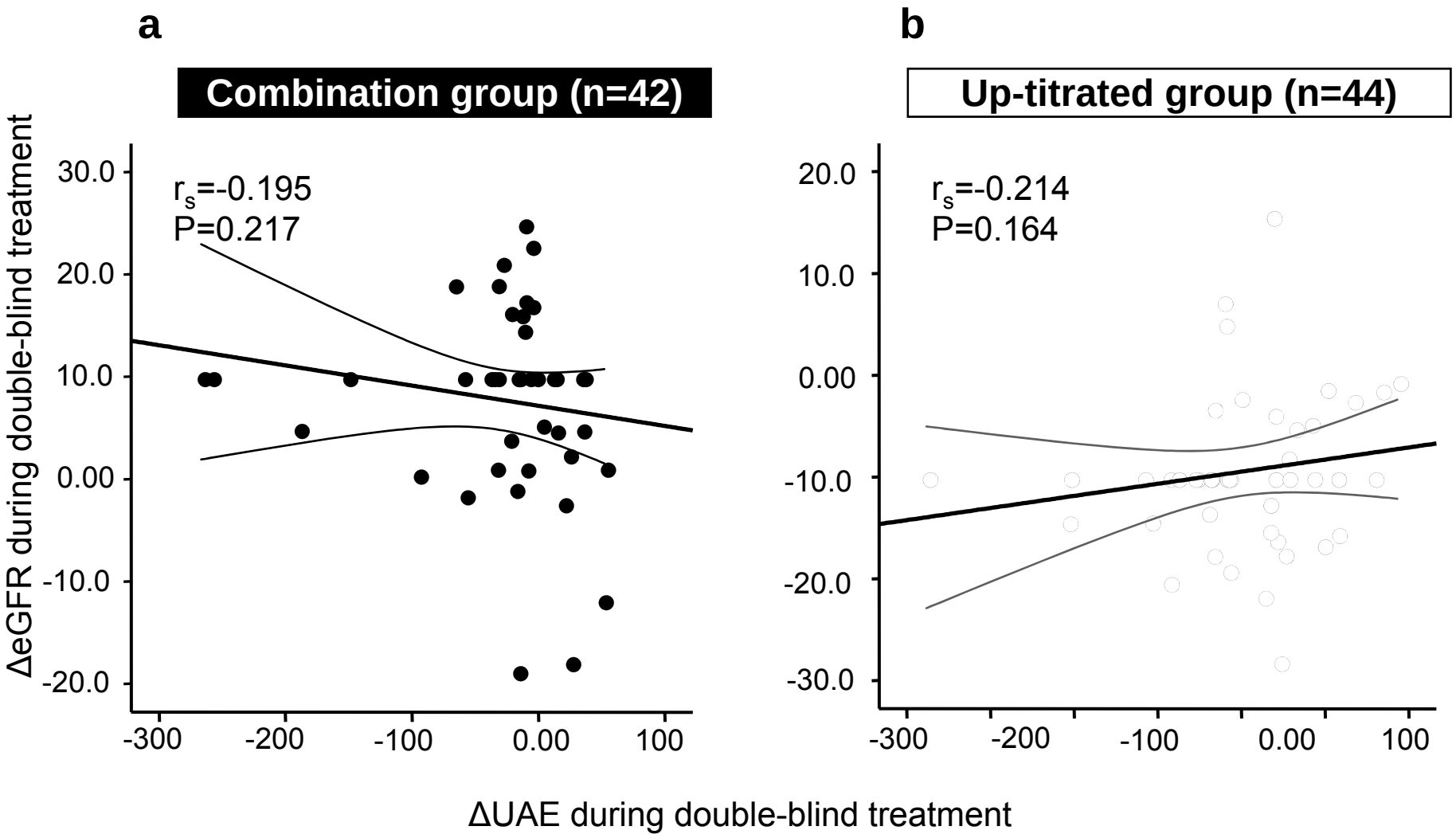
Figure 4 Correlation between ΔeGFR and ΔUAE during double-blind treatment



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