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Reviewer's Summary Evaluation

Reviewer 1

For decades the investigation of the treatment of arterial hypertension in randomized controlled trials has consisted of the theoretical comparison of two monotherapies to which later on and if required one, two, or more drugs were added in a nonrandomized way. In many of those studies different combination therapies were used during the trial coming to complicate the final conclusions of those trials. The present study compares two combinations using olmesartan as a common drug that combines either with a diuretic or with a calcium cannel blocker. This type of study design initiated with the ACCOMPLISH study is, in my opinion, the most adequate to test the capacity of what the great majority of patients with arterial hypertension require for the control of BP, combination therapy.

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Research Paper

Comparison of the Antialbuminuric Effects of Benidipine and Hydrochlorothiazide in Renin-Angiotensin System (RAS) Inhibitor-Treated Hypertensive Patients with Albuminuria: the COSMO-CKD (COmbination Strategy on Renal Function of Benidipine or Diuretics TreatMent with RAS inhibitOrs in a Chronic Kidney Disease Hypertensive Population) Study

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Abstract

Objective: This study evaluated the non-inferiority of renoprotection afforded by benidipine versus hydrochlorothiazide in hypertensive patients with chronic kidney disease (CKD).

Methods: In this prospective, multicenter, open-labeled, randomized trial, the antialbuminuric effects of benidipine and hydrochlorothiazide were examined in renin-angiotensin system (RAS) inhibitor-treated patients with blood pressure (BP) readings of ≥ 130/80 mmHg and ≤ 180/110 mmHg, a urinary albumin to creatinine ratio (UACR) of ≥ 300 mg/g, and an estimated glomerular filtration rate (eGFR) of ≥ 30 ml/min/1.73m^2. Patients received benidipine (n = 176, final dose: 4.8 mg/day) or hydrochlorothiazide (n = 170, 8.2 mg/day) for 12 months.

Results: Benidipine and hydrochlorothiazide exerted similar BP- and eGFR-decreasing actions. The UACR values for benidipine and hydrochlorothiazide were 930.8 (95% confidence interval: 826.1, 1048.7) and 883.1 (781.7, 997.7) mg/g at baseline, respectively. These values were reduced to 790.0 (668.1, 934.2) and 448.5 (372.9, 539.4) mg/g at last observation carried forward (LOCF) visits. The non-inferiority of benidipine versus hydrochlorothiazide was not demonstrated (benidipine/hydrochlorothiazide ratio of LOCF value adjusted for baseline: 1.67 (1.40, 1.99)).

Conclusions: The present study failed to demonstrate the non-inferiority of the antialbuminuric effect of benidipine relative to that of hydrochlorothiazide in RAS inhibitor-treated hypertensive patients with macroalbuminuria.

Key words: chronic kidney disease, hypertension, renin-angiotensin system inhibitor; L-/N-/T-type calcium channel blocker, thiazide diuretic, urinary albumin.

Introduction

Considerable clinical evidence suggests that renin-angiotensin system (RAS) inhibitors (e.g., ramipril and benazepril) are beneficial as first-line agents for the treatment of hypertension in patients with chronic kidney disease (CKD) [1-4]. However, by themselves, RAS inhibitors are unable to maintain an adequate blood pressure (BP) in these individuals. To maintain the BP, second-line depressor agents are therefore required. Accordingly, dihydropyridine-type calcium channel blockers (CCBs) (e.g., felodipine and amlodipine) are frequently used in combination with RAS inhibitors in hypertensive patients with CKD because of their strong BP-lowering properties and minimal adverse effects [5].

However, CCBs are not always able to protect against kidney injury. For example, in the REnoprotection In patients with Nondiabetic chronic renal disease (REIN)-2 trial [6], felodipine did not decrease the incidence of end-stage renal disease in ramipril-treated patients with CKD, despite further lowering the BP. Furthermore, the GaUging Albuminuria Reduction with lotrel in Diabetic patients with hypertension (GUARD) trial [7] showed that the antialbuminuric effect of amlodipine was weaker than that of hydrochlorothiazide, a thiazide diuretic, in benazepril-treated hypertensive patients with type 2 diabetic nephropathy. In addition, urinary protein was not significantly decreased in a meta-analysis of the antiproteinuric effects of dihydropyridine CCBs [8].

On the other hand, certain CCBs, including benidipine (a multifunctional L-type (long-lasting)/T-type (transient)/N-type (neural) CCB), cilnidipine (a dual L-type/N-type CCB), and azelnidipine (an L-type and sympatholytic CCB), have stronger antialbuminuric effects than others. For example, benidipine decreased urinary protein levels to a greater extent than amlodipine (an L-type CCB) in RAS inhibitor-treated hypertensive patients with stage 3–5 CKD [9]. Benidipine was also more effective than amlodipine in terms of reducing urinary albumin in patients with mild to moderate stage CKD and albuminuria [10]. A more pronounced antiproteinuric effect of benidipine compared to amlodipine has also been reported in hypertensive patients with early-stage CKD [11].

The above studies provide comparisons among CCBs, but not between CCBs and other types of antihypertensives, such as the thiazide diuretics. As noted above, the GUARD trial [7] indicated the inferiority of amlodipine versus hydrochlorothiazide in benazepril-treated hypertensive patients with type 2 diabetic nephropathy. However, there is a paucity of data concerning the non-inferiority of other so-called "renoprotective" CCBs such as benidipine relative to the antihypertensive diuretics. For this reason, we set out to clarify whether benidipine, with demonstrated renoprotective actions in patients with CKD [9-11], could decrease urinary albumin with similar efficacy as hydrochlorothiazide. Hydrochlorothiazide is often used together with an angiotensin receptor blocker (ABR) and/or a thiazide diuretic in CKD patients. Hence, the goal of this study was to examine the non-inferiority of benidipine compared with hydrochlorothiazide when administered to RAS inhibitor-treated hypertensive patients with CKD and macroalbuminuria.

Methods

A prospective, multicenter, open-labeled, randomized trial, the COmbination Strategy on renal function of benidipine or diuretics treatMent with RAS inhibitOrs in Chronic Kidney Disease hypertensive population (COSMO-CKD) trial, was performed in clinics and hospitals in Japan from July 2009 to March 2013. The trial was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) under trial identification number UMIN000002143. The trial was approved by the Institutional Review Board of the University of Tokyo Clinical Research Center (reference number P2008042-11X) and by the review boards of all other participating medical facilities. The trial was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participating patients after they received oral and written explanations about the study protocol.

Participants

Hypertensive patients with albuminuria under treatment with an RAS inhibitor (ARB or angiotensin-converting enzyme (ACE) inhibitor) were recruited for this study. The inclusion criteria were: 1) outpatient systolic and diastolic BP readings of ≥ 130/80 mmHg; 2) a pretreatment urinary albumin to creatinine ratio (UACR) (the average of two measured values) of ≥ 300 mg/g; 3) an estimated glomerular filtration rate (eGFR) [12] of ≥ 30 ml/min/1.73m^2; 4) between 20 and 80 years of age; 5) a duration of antihypertensive treatment with RAS inhibitors of ≥ 3 months prior to enrollment; and 6) no treatment with CCBs or diuretics of any kind for at least 3 months prior to enrollment. The exclusion criteria were: 1) outpatient systolic and diastolic BP readings of ≥ 180/110 mmHg; 2) a hypertensive emergency requiring intravenous administration of any antihypertensive agent; 3) administration of an adrenocorticosteroid or an immunosuppressant, or long-term (≥ 2

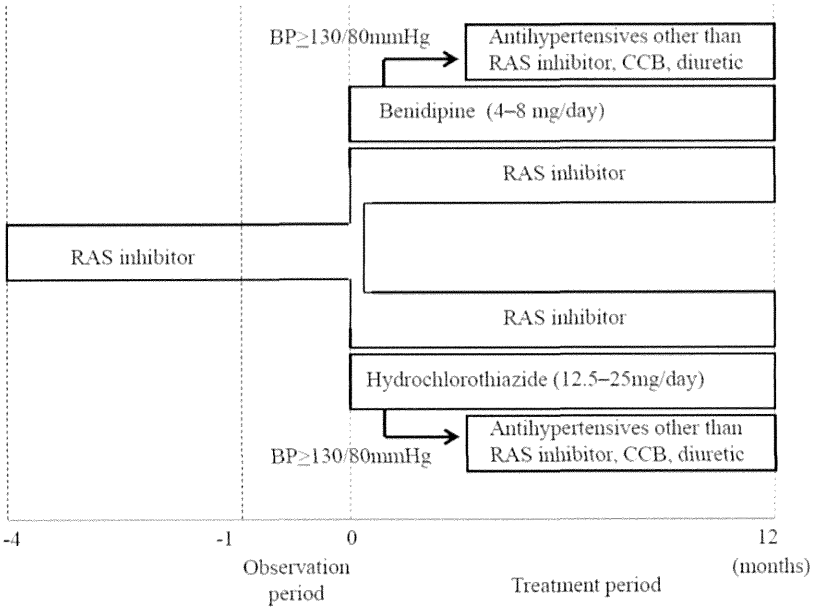

Figure 1. Study protocol. BP, blood pressure; CCB, calcium channel blocker; RAS, renin-angiotensin system.

weeks) administration of nonsteroidal anti-inflammatory drugs (NSAIDs); 4) a past history of severe adverse reaction to CCBs, thiazide diuretics, ARBs, or ACE inhibitors; 5) type 1 diabetes or type 2 diabetes requiring hospitalization due to high hemoglobin A1c content (≥ 9.0%), extremely high blood glucose, or diabetic ketoacidosis; 6) cerebrovascular disease occurring within 6 months of enrollment; 7) severe heart failure (New York Heart Association (NYHA) class ≥ III), severe arrhythmia (frequent ventricular or atrial extrasystole, prolonged ventricular tachycardia, atrial tachyarrhythmia with severe tachycardia, atrial fibrillation or flutter with severe tachycardia, sick sinus syndrome with severe bradycardia, or atrio-ventricular block with severe bradycardia), angina, or myocardial infarction within 6 months of enrollment; 8) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of > 5 times the upper limit; and 9) pregnancy, the possibility of pregnancy, or a desire to become pregnant.

Interventions

After confirming patient eligibility during the observation period (**Figure 1**), each individual was randomly allocated to one of two groups, the benidipine group or the hydrochlorothiazide group. Benidipine was initiated at 4 mg/day, followed by adjustment to 4–8 mg/day, while hydrochlorothiazide was initiated at 6.25 mg/day, followed by adjustment to 6.25–12.5 mg/day. Each drug was given in combination with one or more RAS inhibitors (an ARB and/or an ACE inhibitor) during the treatment period (**Figure 1**), and the dose of the ARB or the ACE inhibitor was not changed during the treatment period.

The following factors were used for stratified randomization: 1) systolic BP (< 140 mmHg, ≥ 140 mmHg) and 2) UACR (< 1000 mg/g, ≥ 1000 mg/g). The target BP was < 130/80 mmHg. If benidipine or hydrochlorothiazide plus the RAS inhibitor failed to reduce BP to the target level, additional antihypertensive drugs of a different type (i.e., not a CCB, diuretic, or RAS inhibitor) were administered. The treatment period in each case was 12 months.

Outcome measures

The primary endpoint was the change in the UACR (mg/g) from the baseline to the endpoint (endpoint/baseline ratio). The UACR at endpoint was determined in spot urine samples after 12 months of benidipine or hydrochlorothiazide treatment, and the UACR at baseline (the average of two consecutive measurements) was determined during a 4-week pretreatment period. The resulting endpoint/baseline ratios were then compared between the benidipine and hydrochlorothiazide arms. Laboratory tests were performed at a central laboratory (Mitsubishi Chemical Medicine Inc., Tokyo, Japan). The urinary albumin level was measured by using the Bromcresol green photometric method (IatroFine ALB II), and the urinary creatinine level was measured by using an enzymatic colorimetric assay (IatroLQ CRE(A) II).

Secondary outcomes included the absolute values of the UACR at each time point; the eGFR, calculated according to the modified "Modification of Diet in Renal Disease (MDRD)" formula set forth by the Japanese Society of Nephrology (male: eGFR (ml/min/1.73 m^2) = 194 × $age^{-0.287}$ × serum $creatinine^{-1.094}$; female: same as for male, with further multiplication by a factor of 0.739) [12]; the CKD stage [13]; urinary liver-type free fatty acid-binding protein (L-FABP) levels; serum creatinine and blood urea nitrogen (BUN) content; BP readings; renal events (initiation of dialysis or renal transplantation); cerebro-cardiovascular events (cerebro-cardiovascular death (fatal myocardial infarction, fatal heart failure, sudden death, fatal stroke, or death due to other cardiovascular causes) or hospitalization due to a cerebro-cardiovascular disease (nonfatal myocardial infarction, angina, heart failure, cerebral bleeding, cerebral infarction, or transient cerebral ischemic attack)); and other adverse events.

Statistical Analysis

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). The safety of the treatment assignments was assessed in a safety analysis set. The efficacy of the treatment assignments were analyzed in the full analysis set. Subjects who did not meet the eligibility criteria, who were not administered the assigned drugs (benidipine or hydrochlorothiazide), or who had no relevant data after randomization were excluded from the full analysis. All data are given as the mean ± standard deviation (SD) or the mean together with the 95% confidence interval.

For the analysis of the non-inferiority of the antialbuminuric effect of benidipine versus hydrochlorothiazide when prescribed in combination with RAS inhibitors, the value of the endpoint/baseline ratio of the UACR in the benidipine group was divided by that of the UACR in the hydrochlorothiazide group. An inferiority margin was assumed as ≥ 0.80 or ≤ 1.25. One-hundred-and-seventy patients were required in each treatment group for a power of 80% with a significance level of 2.5% (one-sided test) to detect the non-inferiority of benidipine when the SD of the natural logarithm of the UACR was assumed to be 0.73. With the added expectation of 15% of the patients withdrawing from the study, a plan was formulated to recruit approximately 200 patients to each group. In actuality, 585 patients were recruited, and 365 were randomized.

Results

As noted above, 585 patients were recruited into the COSMO-CKD trial. Of these 585 individuals, 365 were randomized. Nineteen individuals were not administered an allocated drug and were therefore eliminated from the trial. Data corresponding to the remaining 346 patients (benidipine, n = 176; hydrochlorothiazide, n = 170) were used for the analysis of drug safety. However, only 344 of these individuals (benidipine, n = 175; hydrochlorothiazide, n = 169) were included in the analysis of efficacy (**Table 1**), because two patients (benidipine group, n = 1; hydrochlorothiazide group, n = 1) did not meet the eligibility criteria. Furthermore, only 277 of 346 subjects (benidipine, n = 143; hydrochlorothiazide, n = 134) completed the study regimen. The patient characteristics at baseline (n = 344) are shown in **Table 1**. The baseline data were almost identical between the two groups.

Baseline UACR was 930.8 (95% confidence interval, 826.1, 1048.7) mg/g in the benidipine group and 883.1 (781.7, 997.7) mg/g in the hydrochlorothiazide group (**Figure 2a**). After 12 months of drug treatment, the UACR values were reduced to 783.1 for benidipine and 383.6 mg/g for hydrochlorothiazide. The last observation carried forward (LOCF) value of the UACR was 790.0 (668.1, 934.2) mg/g for benidipine and 448.5 (372.9, 539.4) mg/g for hydrochlorothiazide, resulting in endpoint/baseline UACR ratios of 0.85 (0.76, 0.95) (benidipine group) and 0.51 (0.44, 0.58) (hydrochlorothiazide group). The ratio (benidipine/hydrochlorothiazide) of the endpoint/baseline data sets was 1.67 (1.40, 1.99). Thus, the non-inferiority of benidipine versus hydrochlorothiazide was not demonstrated (**Figure 2b**).

Table 1. Patient Characteristics.

	Benidipine	Hydrochlorothiazide	P value
n	175	169	
Male/female	124/51	111/58	0.354*
Age (years)	59.5 ± 11.5	58.4 ± 12.1	0.380**
BMI (kg/m²)	26.07 ± 5.44	25.83 ± 4.48	0.654**
Systolic BP (mmHg)	144.4 ± 12.5	143.7 ± 12.5	0.641**
Diastolic BP (mmHg)	83.6 ± 8.9	84.5 ±9.0	0.332**
Pulse rate (bpm)	75.8 ± 10.8	76.5 ± 10.7	0.513**
Serum total cholesterol (mg/dl)	200.4 ± 35.3	200.8 ± 36.9	0.919**
Serum LDL cholesterol (mg/dl)	117.8 ± 35.4	114.7 ± 32.2	0.403**
Serum HDL cholesterol (mg/dl)	56.8 ± 15.9	55.3 ± 15.1	0.371**
Serum triglycerides (mg/dl)	182.4 ± 143.4	193.1 ± 145.0	0.493**
Blood sugar (mg/dl)	141.5 ± 53.0	140.5 ± 54.5	0.864**
Hemoglobin A1c (%)	6.37 ± 1.16	6.22 ± 1.12	0.226**
AST (IU/l)	25.7 ± 14.1	24.8 ± 10.9	0.510**
ALT (IU/l)	25.4 ± 17.5	25.5 ± 21.2	0.962**
γ-GTP (IU/l)	39.7 ± 33.7	47.8 ± 52.3	0.088**
Serum sodium (mEq/l)	140.5 ± 2.7	140.2 ± 2.5	0.286**
Serum potassium (mEq/l)	4.36 ± 0.40	4.36 ± 0.48	1.000**
Antihypertensive agents			
ARB	161	159	
ACE inhibitor	27	23	
α blocker	3	7	
β blocker	5	6	
Others	6	4	
Renal disease			
Diabetic nephropathy	99	78	
Glomeruronephritis	40	56	
Others	35	37	
Complications			
Dyslipidemia	100	79	
Diabetes	112	88	
Liver dysfunction	16	10	
Cerebrovascular disease	3	6	
Myocardial infarction	0	0	
Angina pectoris	2	2	
Heart failure	0	1	

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; γ-GTP, gamma-glutamyl transpeptidase; HDL, high density lipoprotein; LDL, low density lipoprotein.
* Fisher's exact test, ** *t*-test.

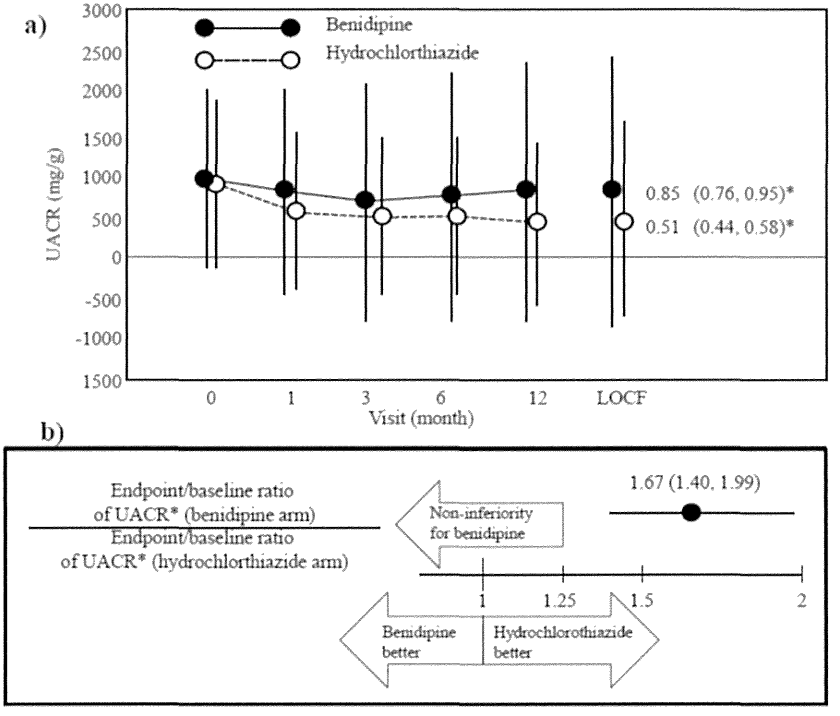

Figure 2. Changes in the urinary albumin/creatinine ratio (UACR). **a)** The decrease in UACR was greater in the hydrochlorothiazide group than in the benidipine group, as indicated by the endpoint/baseline ratio of the UACR for each drug. Data (black and white circles) are given as the mean ± the standard deviation (SD). LOCF, last observation carried forward. * The endpoint/baseline ratio of the UACR for each drug is given as the mean (95% confidence interval). **b)** The endpoint/baseline data are given as the ratio of the benidipine arm/hydrochlorothiazide arm (mean and 95% confidence interval). The non-inferiority of benidipine was not demonstrated.

Serum creatinine levels were similar at baseline (0.961 (0.919, 1.005) mg/dl, benidipine; 0.967 (0.922, 1.014) mg/dl, hydrochlorothiazide) and at the LOCF (1.039 (0.986, 1.096) mg/dl, benidipine; 1.054 (0.998, 1.114) mg/dl, hydrochlorothiazide). However, serum creatinine levels were slightly and similarly increased by both treatments (**Figure 3a**). By contrast, eGFR values were also similar at baseline (57.91 (55.31, 60.64) ml/min/1.73m^2, benidipine; 57.01 (54.05, 54.05) ml/min/1.73m^2, hydrochlorothiazide) and at the LOCF (52.81 (49.94, 55.84) ml/min/1.73m^2, benidipine; 51.55 (43.36, 54.95) ml/min/1.73m^2, hydrochlorothiazide) (**Figure 3b**), but the eGFR values were slightly and similarly decreased.

Table 2 shows that the distribution of CKD stages, as assessed by the eGFR, was largely comparable between baseline and the LOCF for both drug groups. CKD staging was also similar between the two groups at each time point. However, a marked increase (from 1.2 (0.1, 4.2)% at baseline to 10.1 (6.0, 15.7)% at the LOCF) was observed in the number of stage 4 patients after hydrochlorothiazide treatment. At the same time point, the number of stage 4 patients in the benidipine group increased from 1.2 (0.1, 4.2)% at the baseline to 5.3 (2.4, 9.8)% at the LOCF.

Table 2. CKD stages due to the eGFR at baseline and at the LOCF.

	Benidipine			Hydrochlorothiazide			
N	171			168			P value*
	N	%	95% CI	n	%	95% CI	
Baseline							
Stage 1	9	5.3	2.4, 9.8	16	9.5	5.5, 15.0	0.150
Stage 2	78	45.6	38.0, 53.4	61	36.3	29.0, 44.1	0.098
Stage 3	82	48.0	40.3, 55.7	89	53.0	45.1, 60.7	0.386
Stage 4	2	1.2	0.1, 4.2	2	1.2	0.1, 4.2	1.000
Stage 5	0	0.0	0.0, 2.1	0	0.0	0.0, 2.2	-
LOCF							
Stage 1	7	4.1	1.7, 8.3	12	7.1	3.7, 12.1	0.246
Stage 2	66	38.6	31.3, 46.3	50	29.8	23.0, 37.3	0.109
Stage 3	88	51.5	43.7, 59.2	88	52.4	44.5, 60.1	0.914
Stage 4	9	5.3	2.4, 9.8	17	10.1	6.0, 15.7	0.105
Stage 5	1	0.6	0.0, 3.2	1	0.6	0.0, 3.3	1.000

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LOCF, last observation carried forward.
* Fisher's exact test.

BUN values were similar between the two drugs at baseline (17.57 (16.85, 18.32) mg/dl, benidipine; 17.28 (16.49, 18.11) mg/dl, hydrochlorothiazide) and at the LOCF (18.14 (17.31, 19.01) mg/dl, benidipine; 18.84 (17.84, 19.89) mg/dl, hydrochlorothiazide). However, although BUN levels did not appreciably change over the course of the study in the benidipine group (endpoint/baseline ratio, 1.02 (0.98, 1.07)), they were slightly albeit significantly increased in the hy-

drochlorothiazide group (1.09 (1.05, 1.13)). Hence, the non-inferiority of benidipine was demonstrated in terms of BUN content (benidipine arm/hydrochlorothiazide arm, 0.98 (0.89, 1.00)).

Urinary L-FABP values were also comparable between the two drug groups at baseline (15.20 (12.92, 17.88) μg/g, benidipine; 13.94 (11.70, 16.60) μg/g, hydrochlorothiazide) and at the LOCF (18.67 (15.47, 22.53) μg/g, benidipine; 13.44 (11.22, 16.11) μg/g, hydrochlorothiazide). L-FABP levels showed a slight but significant increase in the benidipine group (endpoint/baseline ration, 1.27 (1.10, 1.46)), but not in the hydrochlorothiazide group (endpoint/baseline ratio, 0.98 (0.84, 1.13)). The non-inferiority of benidipine was not suggested (benidipine arm/hydrochlorothiazide arm, 1.30 (1.06, 1.59)).

Systolic and diastolic BP readings showed similar baseline values between the two drug groups. The systolic BP was 144.4 (142.5, 146.2) mmHg for benidipine and 143.7 (141.9, 145.6) mmHg for hydrochlorothiazide, and the diastolic BP was 83.6 (82.2, 84.9) mmHg for benidipine and 84.5 (83.1, 85.9) mmHg for hydrochlorothiazide, respectively. Systolic and diastolic BP both decreased with drug treatment, and their decrements were similar between the two groups (**Figure 4**).

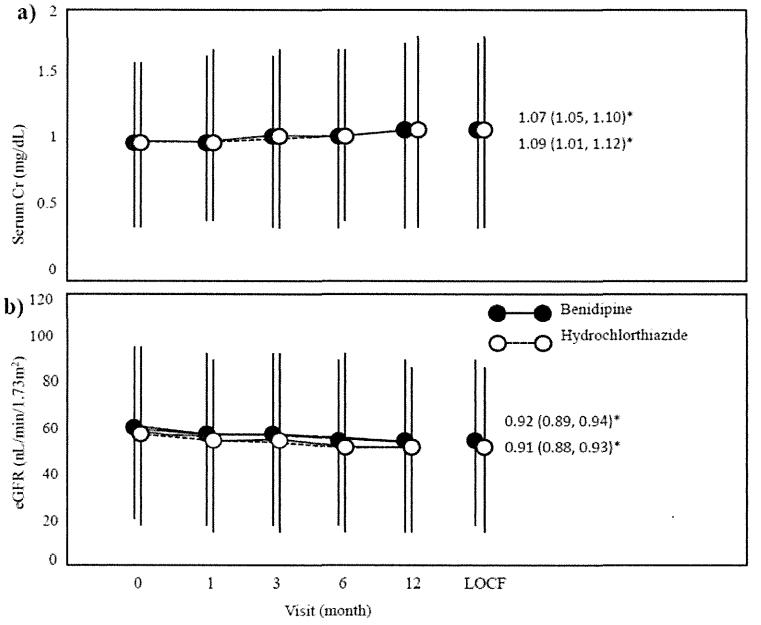

Figure 3. Changes in serum creatinine **(a)** and estimated glomerular filtration rate (eGFR) **(b)**. Data (black and white circles) are given as the mean ± the standard deviation (SD). LOCF, last observation carried forward. * The endpoint/baseline ratios for benidipine and hydrochlorothiazide are each given as the mean (95% confidence interval).

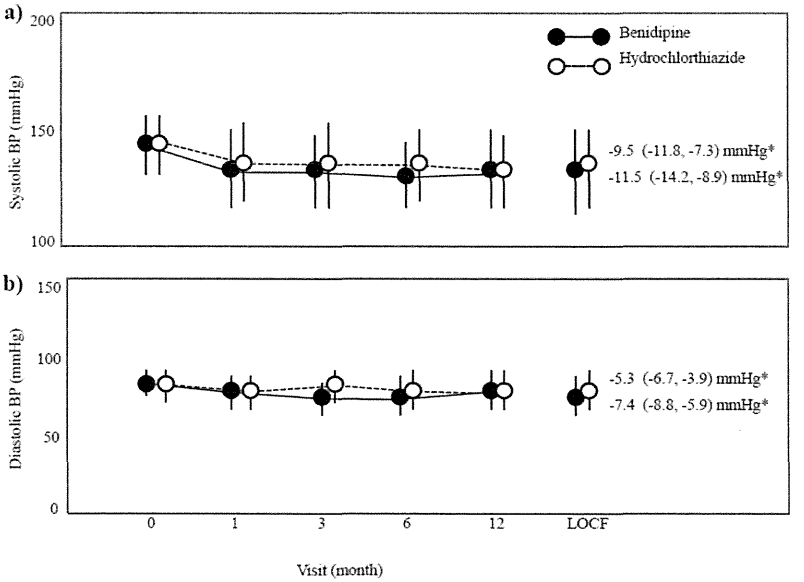

Figure 4. Changes in systolic and diastolic blood pressure (BP). Data are given as the mean ± the standard deviation (SD). LOCF, last observation carried forward. * Changes in the BP from the baseline to the endpoint are shown as the mean (95% confidence interval).

Adverse events occurred in 65 of 176 patients (36.9%) in the benidipine group and 74 of 170 patients (43.5%) in the hydrochlorothiazide group. Severe adverse events included one case of vitreous hemorrhage with aggravation of diabetic retinopathy and one case of cerebral bleeding in the benidipine group, and one case each of arteriosclerotic obliteration, gangrene of right third toe, and cerebral infarction with death in the hydrochlorothiazide group. There were no patients in whom renal events occurred, serious or otherwise.

Discussion

The present study failed to demonstrate the non-inferiority of the antialbuminuric effect of benidipine versus hydrochlorothiazide in RAS inhibitor-treated hypertensive patients with macroalbuminuria. The effect of benidipine appeared to be rather inferior to that of hydrochlorothiazide in terms of UACR (Figure 2b), even though the previous studies report that benidipine decreases urinary albumin/protein more efficaciously in patients with a wide range of CKD stages than other CCBs, such as amlodipine [9-11]. Therefore, although we did not directly compare antialbuminuric actions between benidipine and amlodipine, the current investigation together with the previous data [9-11] suggest that the potency of benidipine to decrease urinary albumin might be intermediate between the less effective CCBs and the more effective thiazide diuretics.

Benidipine and hydrochlorothiazide decreased the eGFR to a similar extent in the present COSMO-CKD trial, although its actions of both drugs on the kidney were fairly weak. On the other hand, amlodipine had a slightly but significantly lower propensity than hydrochlorothiazide to decrease the eGFR in the GUARD study [7]. These results indirectly suggest that amlodipine, but not benidipine, exclusively dilates the afferent artery via L-type calcium channel blockade to increase glomerular pressure, as shown previously [14]. Hence the blockade of T- and N-type calcium channels by benidipine, aside from its L-type calcium channel-blocking effects, may dilate both afferent and efferent arteries, leading to decreasing glomerular pressure, which might protect kidney. However, weaker antialbuminuric effect of benidipine than hydrochlorothiazide suggest that benidipine is less beneficial on the kidney, although both drugs did similarly reduce office systolic and diastolic BP.

Thus, thiazide diuretics may have a potent effect to decrease urinary albumin. Recently, the combination of losartan and hydrochlorothiazide decreased morning BP to a greater extent than high-dose losartan. The combination was also associated with a larger decrease in the UACR [15]. Furthermore, the effects of the thiazide diuretic to ameliorate circadian BP (from a non-dipper pattern to a dipper pattern) and to suppress proteinuria have been demonstrated in RAS inhibitor-treated patients with immunoglobulin A nephropathy [16]. Daytime salt retention is proposed to cancel the normal nighttime reduction in the BP; nighttime high BP accelerates pressure natriuresis to excrete sodium retained during the day. However, diuretics are thought to attenuate daytime sodium retention, resulting in reduced nighttime BP. Nonetheless, daytime and nighttime BP were not examined in the present study. At any rate, thiazide diuretics, which have a different mechanism of action from RAS inhibitors to decrease urinary albumin, may confer greater renoprotective in combination with RAS inhibitors than L-/T-/N-type CCBs such as benidipine, which has a similar renoprotective mechanism (efferent arteriole vasodilation) as RAS inhibitors.

Another recent study [17] demonstrated the non-inferiority of the antialbuminuric effect of azelnidipine, another so-called "renoprotective" CCB [18], compared with the thiazide diuretic, trichloromethiazide. Because several different mechanisms have been attributed to the "renoprotective" CCBs (e.g., T-type calcium channel blockade (benidipine), N-type calcium channel blockade (benidipine and cilnidipine), and sympatholytic effects (azelnidipine)), the extent of antialbuminuric action might be different among these agents.

In addition, the subjects of the present study and the above-mentioned study [17] showed different degrees of albuminuria; ≥ 300 mg/g and 30–600 mg/g, respectively. Recently, Ogawa et al. demonstrated that the antialbuminuric effects of ARB were weakened in patients with ≥1,000 mg/g of UACR [19]. Thus, amelioration of glomerular microcirculation may not effectively decrease urinary albumin in CKD patients with the advanced renal dysfunction. Therefore, the non-inferiority of benidipine versus hydrochlorothiazide might be observed in RAS inhibitor-treated CKD patients with lower UACR values.

Another consideration is that the majority of the patients included in the present study had diabetes (Table 1). Macroalbuminuric patients with diabetes may have advanced diabetic vascular damage, which might also suppress the effectiveness of other "renoprotective" CCB [20]. In addition, there are few reports that compare the antialbuminuric effects between so-called "renoprotective" CCB and thiazide diuretics. Moreover, future investigations are required to examine whether the antiproteinuric effect of benidipine and other "renoprotective" CCBs diuretic is non-inferior compared with thiazides in pa-

tients with microalbuminuria.

The present study has several limitations. First, UACR values in spot urine samples can vary with each measurement, even in the same patient with the same drug treatment. In this regard, measurement of urinary albumin excretion in samples collected over a 24-h period or repeated measurements of the first morning void sample may be more accurate than a spot sample. Second, sample size estimation was done in the absence of previous reports comparing the antialbuminuric effects of "renoprotective" CCBs and thiazide diuretics. For this reason, we cannot guarantee that the sample size was sufficient.

In conclusion, the COSMO-CKD trial failed to demonstrate the non-inferiority of the antialbuminuric effect of benidipine relative to hydrochlorothiazide. Several previous studies showed the renoprotective actions of benidipine in CKD patients with various stages of disease, as well as its potentially beneficial actions on glomerular microcirculation. Thus, the renoprotective effect of benidipine might be limited compared with more potent thiazide diuretics, but more pronounced than that of other CCBs. Further studies are required to clarify in the subset of CKD patients in which benidipine most effectively decreases urinary albumin content.

Acknowledgments

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Competing Interests

The first author (K.A.) is endowed by Daiichi-Sankyo, Co., Ltd. (Tokyo, Japan). The last author (T.F.) is endowed by Mochida Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., MSD Co., Ltd., Toray Industries, Inc., and Terumo Cooperation (all in Tokyo, Japan).

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ORIGINAL ARTICLE

Budget impact analysis of chronic kidney disease mass screening test in Japan

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Abstract
Background Our recently published cost-effectiveness study on chronic kidney disease mass screening test in Japan evaluated the use of dipstick test, serum creatinine (Cr) assay or both in specific health checkup (SHC). Mandating the use of serum Cr assay additionally, or the continuation of current policy mandating dipstick test only was found cost-effective. This study aims to examine the affordability of previously suggested reforms.
Methods Budget impact analysis was conducted assuming the economic model would be good for 15 years and applying a population projection. Costs expended by social insurers without discounting were counted as budgets.
Results Annual budget impacts of mass screening compared with do-nothing scenario were calculated as ¥79–¥−1,067 million for dipstick test only, ¥2,505–¥9,235 million for serum Cr assay only and ¥2,517–¥9,251 million for the use of both during a 15-year period. Annual budget impacts associated with the reforms were calculated as ¥975–¥4,129 million for mandating serum Cr assay in addition to the currently used mandatory dipstick test, and ¥963–¥4,113 million for mandating serum Cr assay only and abandoning dipstick test.
Conclusions Estimated values associated with the reform from ¥963–¥4,129 million per year over 15 years are considerable amounts of money under limited resources.

On behalf of the Japanese Society of Nephrology Task Force for the Validation of Urine Examination as a Universal Screening.

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The most impressive finding of this study is the decreasing additional expenditures in dipstick test only scenario. This suggests that current policy which mandates dipstick test only would contain medical care expenditure.

Keywords CKD · Budget impact · Dipstick test · Mass screening · Proteinuria · Serum creatinine assay

Introduction

A consensus has been established that chronic kidney disease (CKD) is a worldwide public health problem [1, 2]. The effectiveness of its early detection and treatment to prevent progression to end-stage renal disease (ESRD) and premature death from cardiovascular disease has become widely accepted [3], while the strategy of its screening is still under debate [4]. Whereas high-risk strategies such as routine screening for diabetes patients and as a part of initial evaluation of hypertension patients are pursued in Western countries [5, 6], some argue that population strategies, such as mass screening, could be adopted in Asian countries where CKD prevalence is high [7].

Japan has a long history of mass screening programme for kidney diseases targeting school children and adults since the 1970s. Both urinalysis and measurement of serum creatinine (Cr) level have been mandated to detect glomerulonephritis in annual health checkup provided by workplace and community for adults aged ≥40-year old since 1992 [8]. However, glomerulonephritis was replaced by diabetic nephropathy as the leading cause of ESRD in 1998, and the focus of mass screening policy for adults was shifted to the control of lifestyle-related diseases. In 2008, the Japanese government launched a programme, specific health checkup (SHC) and Specific Counselling Guidance, focusing on metabolic syndrome to control lifestyle-related diseases, targeting all adults between the ages of 40 and 74 years [9]. This is a combined programme of mass screening followed by health education or referral to physicians. During the process of this development of SHC, different types of screening test for kidney diseases were discussed in the health policy arena [10]. Abandonment of dipstick test to check proteinuria was initially proposed by the Ministry of Health, Labour and Welfare, which was opposed by nephrologists who emphasised the significance of CKD. As a consequence, serum Cr assay was alternatively dropped and dipstick test remained in the list of mandatory test items [11]. From the viewpoint of CKD control, the current SHC and Specific Counselling Guidance are not adequate. Therefore, to present evidence regarding CKD screening test for the revision of SHC, which was due in 5 years from its start in 2008, the Japanese Society of Nephrology set up the Task Force for the Validation of Urine Examination as a Universal Screening. Since cost-effectiveness analysis provides crucial information for organising public health programmes such as mass screening, the task force conducted an economic evaluation as a part of their mission, which had been published elsewhere [12]. It concludes that the current policy which mandates dipstick test only is cost-effective, while a policy that mandates serum Cr assay is also cost-effective.

However, it is said that there are five hurdles to overcome in the nationwide application of health intervention: quality, safety, efficacy, cost-effectiveness and affordability (Fig. 1) [13, 14]. Among these hurdles, 'cost-effective' in the economic evaluation framework means that it is acceptable for the society to sacrifice the total value of cumulative costs with discount over the time horizon to gain additional health outcomes brought by the suggested public health programme, whereas it does not directly mean affordability that the government or the third party payer such as social insurers are able to expend required cash to implement the policy. Prevention including mass screening always accompanies costs in advance and effectiveness in the future, which instantly raises a question about its impact on health care financing over time. This paper aims to examine the fifth hurdle, that is, affordability of CKD mass screening test under Japan's health system by estimating its impact on public health care expenditure [15]. The results would have implications for CKD screening programmes not only in Japan but also for other populations with high prevalence of CKD such as Asian countries [16, 17].

Methods

We conducted a budget impact analysis of CKD screening test in SHC based on our previous economic model reporting cost-effectiveness [12]. As shown in Fig. 1, the budget impact analysis is to demonstrate budget changes in terms of cash flows, in which payer's perspective is always taken; health outcomes are excluded; and financial costs are included.

As the summary of the economic model constructed in our previous cost-effectiveness analysis is shown in Table 1, it evaluated two reform policy options based on

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the economic model comparing do-nothing scenario with dipstick test only, serum Cr assay only, and both. The two policies were: mandate the use of serum Cr assay in addition to the current dipstick test (Policy 1); or mandate the use of serum Cr assay only and abandon dipstick test (Policy 2). Policy 1 meant that the current SHC practice, which was a mandatory 100 % use of dipstick test with 60 % use of serum Cr assay at discretion, would become a mandatory 100 % use of both dipstick test and serum Cr assay; while Policy 2 meant that the current practice would switch to the mandatory 100 % use of serum Cr assay and no use (0 %) of dipstick test. The latter assumption was made by the change in diagnosis criterion of diabetes [18], in which a blood test to check the level of haemoglobin A1c instead of a dipstick test to check urinary sugar level had become pivotal. And the model estimator comparing

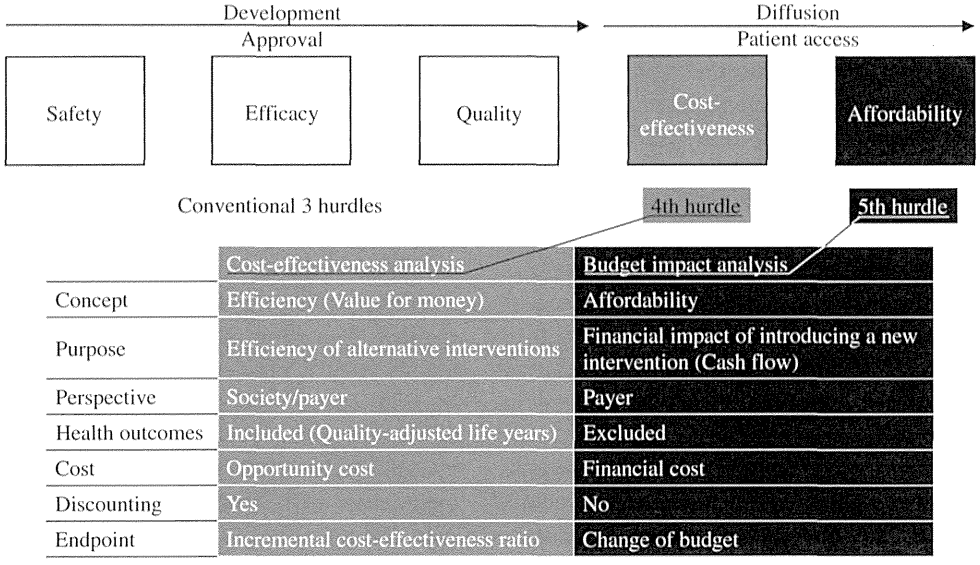


Fig. 1 In addition to conventional three hurdles for approval through development phase, two modern hurdles for patient access through diffusion phase are widely recognised these years: 4th hurdle for cost-effectiveness and 5th hurdle for affordability. These hurdles are appraised by cost-effectiveness analysis and budget impact analysis, respectively. Cost-effectiveness analysis concerns efficiency of resources use based on the valuations of cost and effectiveness at the same time comparing technical alternatives, while budget impact analysis concerns affordability of the government or the third party payer by demonstrating changes of cash flows as a result of making an intervention accessible for the population

Table 1 Summary of cost-effectiveness of chronic kidney disease (CKD) screening test in Japan

Objective The study aims to assess the cost-effectiveness of population strategy, i.e. mass screening, for CKD control and Japan's health checkup reform

Methods Cost-effectiveness analysis was carried out to compare test modalities in the context of reforming Japan's mandatory annual health checkup for adults. A decision tree and Markov model with societal perspective were constructed to compare dipstick test to check proteinuria only, serum creatinine (Cr) assay only, or both

Results Number of screened patients and incremental cost-effectiveness ratios (ICERs) of mass screening compared with do-nothing were calculated as 832 patients out of 100,000 participants and ¥1,139,399/QALY (US $12,660/QALY) for dipstick test only; 3,448 patients and ¥8,122,492/QALY (US $90,250/QALY) for serum Cr assay only; and 3,898 patients and ¥8,235,431/QALY (US $91,505/QALY) for both. Number of additionally screened patients and ICERs associated with the reform were calculated as 1,061 (3,898 from 2,837) patients out of 100,000 participants and ¥9,325,663/QALY (US $103,618/QALY) for mandating serum Cr assay in addition to the currently used mandatory dipstick test (Policy 1), and 611 (3,448 from 2,837) patients ¥9,001,414/QALY (US $100,016/QALY) for mandating serum Cr assay and applying dipstick test at discretion (Policy 2). The decrease of new haemodialysis patients compared with do-nothing in the fifth year and tenth year were estimated as 0.293 %/1.128 % for dipstick test only, 5.092 %/4.380 % for serum Cr assay only, and 5.094 %/4.380 % for both. The decrease of new haemodialysis patients associated with the reform was 1.249 %/1.346 % for Policy 1 and 1.251 %/1.346 % for Policy 2

Conclusions Taking a threshold to judge cost-effectiveness according to World Health Organization's recommendation, i.e. three times gross domestic product per capita of ¥11.5 million/QALY (US $128 thousand/QALY), a policy that mandates serum Cr assay is cost-effective. The choice of continuing the current policy which mandates dipstick test only is also cost-effective. Results suggest that a population strategy for CKD detection such as mass screening using dipstick test and/or serum Cr assay can be justified as an efficient use of health care resources in a population with high prevalence of the disease

Source Kondo et al. [12]

do-nothing scenario with dipstick test only scenario reflected the choice of continuing the current policy. Our budget impact analysis evaluated these policy options.

Health care budget impact is defined as a forecast of rates of use (or changes in rates of use) with their consequent short- and medium-term effects on budgets and other resources to help health service managers plan such changes [19]. We took the following three steps in our analysis: (1) the estimation of annual incremental budget per person, (2) the estimation of annual number of adults who would uptake SHC and (3) the estimation of budget impact by combining the results from (1) and (2).

The first step (1) was implemented on our economic model assuming that the annual economic model would be good for 15 years (Table 2). It included costs borne by adults and social insurers from the societal perspective, while costs of sectors other than health and productivity losses were uncounted. Costs expended by social insurers without discounting were counted as budgets. Costs for screening were fully borne by social insurers, and costs for further detailed examination and treatment at health facilities were 70 % reimbursed except in case of dialysis. Fixed co-payment for dialysis patients, ¥10,000 (US$100, US$1 =¥100) per month, was subtracted from the total cost. Assumed annual budgets per person are shown in Table 2.

In the second step (2), we used a population projection for Japan [20], and sex and age structure was applied to our annual economic model. We assumed that the uptake of SHC was fixed at 41.3 % for 15 years [21]. In the third step (3), estimated annual incremental budgets per person were multiplied by estimated annual number of adults who would uptake SHC.

Table 2 Assumptions for budget impact analysis

1. The annual economic model is good for 15 years	
2. Annual budgets per person (costs in the economic model [12])	
Screening	
Dipstick test only	¥ 267 (¥267)
Serum Cr assay only	¥138 (¥138)
Dipstick test and serum Cr assay	¥342 (¥342)
Detailed examination at clinic or hospital	¥17,500 (¥25,000)
CKD treatment	
Stage 1	¥84,000 (¥120,000)
Stage 2	¥102,900 (¥147,000)
Stage 3	¥235,900 (¥337,000)
Stage 4	¥555,100 (¥793,000)
Stage 5	¥691,600 (¥988,000)
ESRD treatment	¥5,880,000 (¥6,000,000)
Heart attack treatment	
1st year	¥1,946,000 (¥2,780,000)
2nd year and after	¥125,300 (¥179,000)
Stroke treatment	
1st year	¥700,000 (¥1,000,000)
2nd year and after	¥125,300 (¥179,000)
3. A population projection for Japan [17] is used and sex and age structure is applied for the annual economic model	
4. The uptake of SHC is fixed at 41.3 % for 15 years [18]	

Results

Table 3 shows the model estimators of budget impact. Compared with do-nothing scenario, total additional expenditure of dipstick test only decrease from ¥79 million (US$0.79 million) in the first year (2012) to ¥−1,067 million (US$−10.67 million) in the fifteenth year (2026); those of serum Cr assay only increase from ¥2,505 million (US$25.05 million) to ¥9,235 million (US$92.35 million); those of both dipstick test and serum Cr assay increase from ¥2,517 million (US$25.17 million) to ¥9,251 million (US$92.51 million); and those of status quo increase from ¥1,542 million (US$15.42 million) to ¥5,122 million (US$51.22 million). These estimators are also shown in Fig. 2. The breakdown of additional expenditures for screening and curative care is also reported in Table 3. Additional expenditures for screening are almost constant: ¥16 million (US$0.16 million) for dipstick test only, ¥8 million (US$0.08 million) for serum Cr assay only, ¥20 million (US$0.2 million) for dipstick test and serum Cr assay, and ¥18 million (US$0.18 million) for status quo. Decreases or increases during the 15 years are attributable to the changes in additional expenditure for curative care.

Table 4 shows the results of budget impact analysis in the same way focusing on the two policy options. Compared with status quo, the budget impacts as total additional expenditure of Policy 1 which requires serum Cr assay increase from ¥975 million (US$9.75 million) in the first year (2012) to ¥4,129 million (US$41.29 million) in the fifteenth year (2026); and those of Policy 2 which requires serum Cr assay and abandons dipstick test increase from ¥963 million (US$9.63 million) to ¥4,113 million (US$41.13 million). These are drawn in Fig. 3 as well. Breakdowns of screening and curative care are also reported in Table 4. Additional expenditures for screening are almost constant: ¥2 million (US$0.02 million) for Policy 1, and ¥−10 million (US$−0.1 million) for Policy 2. Increases during the 15 years are attributable to the changes in additional expenditure for curative care.

Discussion

We estimate the budget impacts of CKD screening test in SHC, of which use has been found cost-effective elsewhere [12]. With regard to two reform policy options: mandate

Table 3 Model estimators of budget impact

Year	Budget impact: total additional expenditure (¥, million)				Additional expenditure for screening (¥, million)				Additional expenditure for curative care (¥, million)			
	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo
1st (2012)	79	2,505	2,517	1,542	16	8	20	18	64	2,497	2,497	1,524
2nd (2013)	−96	3,295	3,308	1,946	16	8	20	18	−112	3,287	3,288	1,928
3rd (2014)	−278	3,972	3,985	2,280	16	8	20	18	−294	3,964	3,965	2,262
4th (2015)	−454	4,561	4,574	2,563	16	8	20	18	−470	4,553	4,554	2,545
5th (2016)	−615	5,089	5,103	2,815	16	8	20	18	−631	5,081	5,083	2,797
6th (2017)	−755	5,572	5,586	3,049	16	8	20	18	−771	5,564	5,566	3,031
7th (2018)	−872	6,025	6,039	3,274	16	8	20	18	−887	6,017	6,019	3,256
8th (2019)	−964	6,453	6,467	3,494	16	8	20	18	−979	6,445	6,447	3,476
9th (2020)	−1,032	6,861	6,875	3,712	16	8	20	18	−1,048	6,853	6,855	3,693
10th (2021)	−1,079	7,261	7,275	3,933	16	8	20	18	−1,094	7,252	7,255	3,915
11th (2022)	−1,105	7,660	7,675	4,162	16	8	20	18	−1,120	7,652	7,655	4,144
12th (2023)	−1,114	8,060	8,076	4,399	16	8	20	18	−1,129	8,052	8,056	4,380
13th (2024)	−1,109	8,456	8,472	4,638	16	8	20	18	−1,124	8,448	8,452	4,620
14th (2025)	−1,092	8,845	8,861	4,878	16	8	20	18	−1,108	8,837	8,841	4,860
15th (2026)	−1,067	9,235	9,251	5,122	16	8	20	18	−1,083	9,227	9,231	5,104

Cr creatinine

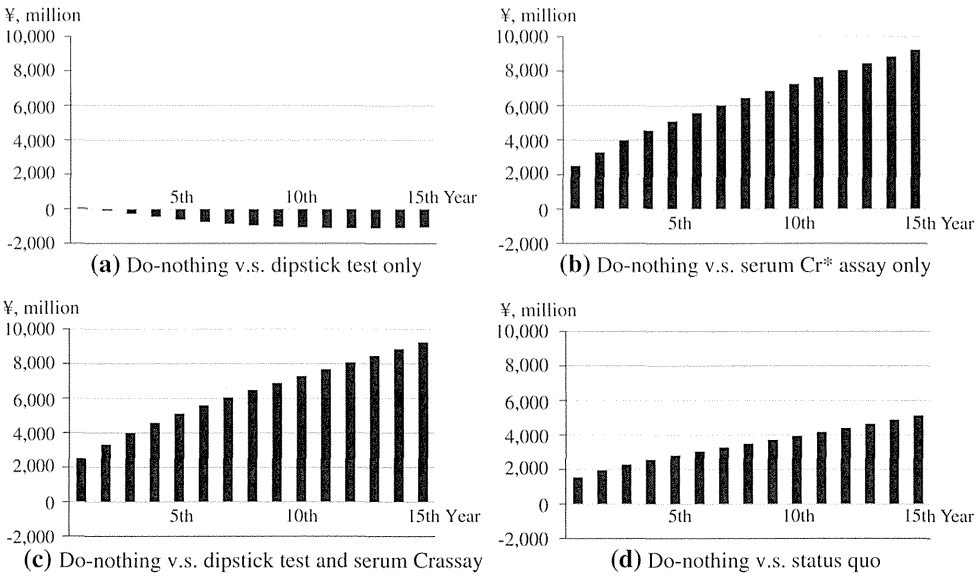


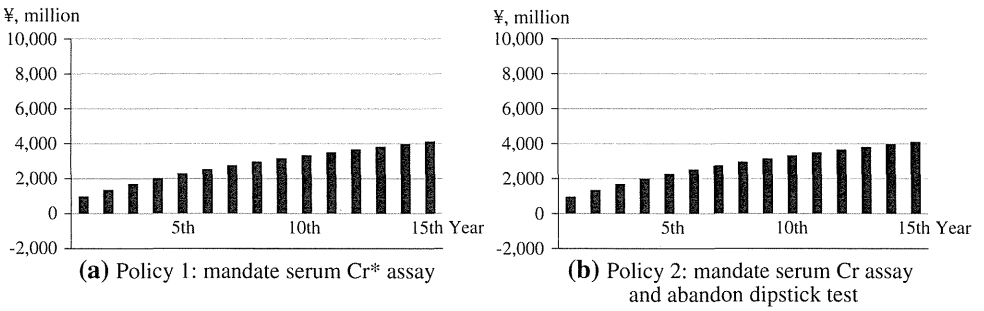
Fig. 2 *Black bars* depict annual budget impacts of mass screening compared with do-nothing scenario. Negative budget impacts on (**a**) imply that the continuation of current policy which mandates dipstick test only would contain medical care expenditure. **a** Do-nothing versus dipstick test only. **b** Do-nothing versus serum Cr assay only. **c** Do-nothing versus dipstick test and serum Cr assay. **d** Do-nothing versus status quo. *Cr* creatinine

serum Cr assay in addition to the dipstick test (Policy 1), and mandate serum Cr assay and abandon dipstick test (Policy 2), both positive and increasing budget impacts are found in the fifteen-year time frame. Although there is no established rule for interpreting the results of budget impact analysis, estimated values of ¥963 million (US$9.63 million) to ¥4,129 million (US$41.29 million) per year over fifteen years are considerable amounts of money of limited resources. These amount to 0.0026 to 0.011 % of national medical care expenditure in 2010 [22], and 0.068 and 0.29 % of the annual increase between 2009 and 2010, ¥1,413,500 million (US$14,135 million), respectively. Our case study exemplifies a situation where budgetary constraints, or affordability, matters to the use of

Table 4 Results of budget impact analysis

Year	Budget impact: total additional expenditure (¥, million)		Additional expenditure for screening (¥, million)		Additional expenditure for curative care (¥, million)	
	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test
1st (2012)	975	963	2	−10	973	973
2nd (2013)	1,362	1,349	2	−10	1,360	1,359
3rd (2014)	1,705	1,692	2	−10	1,704	1,702
4th (2015)	2,011	1,998	2	−10	2,010	2,008
5th (2016)	2,287	2,274	2	−10	2,285	2,284
6th (2017)	2,537	2,523	2	−10	2,535	2,533
7th (2018)	2,765	2,751	2	−10	2,763	2,761
8th (2019)	2,973	2,958	2	−10	2,971	2,969
9th (2020)	3,164	3,149	2	−10	3,162	3,159
10th (2021)	3,342	3,328	2	−10	3,341	3,338
11th (2022)	3,513	3,498	2	−10	3,511	3,508
12th (2023)	3,677	3,662	2	−10	3,675	3,672
13th (2024)	3,833	3,818	2	−10	3,832	3,828
14th (2025)	3,983	3,967	2	−10	3,981	3,977
15th (2026)	4,129	4,113	2	−10	4,127	4,123

Cr creatinine



(a) Policy 1: mandate serum Cr* assay

(b) Policy 2: mandate serum Cr assay and abandon dipstick test

Fig. 3 *Black bars* depict annual budget impacts associated with suggested mass screening policy reforms which mandate the use of serum Cr assay. Positive budget impacts on both panels imply that the reforms would result in the increase of medical care expenditure. **a** *Policy 1* mandate serum Cr assay. **b** *Policy 2* mandate serum Cr assay and abandon dipstick test. *Cr* creatinine

cost-effective interventions which have been judged as worth using according to social willingness to pay for new intervention.

The most impressive finding of this study, however, is the decreasing additional expenditures of dipstick test only scenario, which become negative in just its second year. This suggests that the mandatory dipstick test under current practice would contain medical care expenditure, i.e. 'decreasing annual national medical costs'. In other words, this is a valuable evidence that prevention saves life as well as money. And requiring dipstick test instead of serum Cr assay as a mandatory test item in SHC in 2008 may have been a sensible choice.

Due caution is needed to interpret the results of our budget impact analysis, since they depend on crucial assumptions. Positive budget impacts are found to be attributable to additional expenditure for curative care; however, for example, the analysis does not take medical advancement or health system development into account. In the coming 15 years, innovative therapeutic agents to prevent progression to ESRD are expected [23–26], and community-based CKD control intervention under collaboration between general practitioners and nephrologists is under study [27]. More prevention of ESRD should bring significant reduction in budget impact, since treatment of ESRD is most costly. With regard to the mass screening test, other

tests such as microalbuminuria or cystatin C could be an option in the middle to long run [24], which would fundamentally change the background of this analysis.

In the policy arena, the revision of SHC after its first five-year period was made in 2012, in which the continuation of current policy was chosen. And our study is in accord with keeping dipstick test in the mandatory test list. Further economic evaluation incorporating medical advancement or health system development is necessary for the future development of SHC and the next revision of CKD mass screening.

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Conflict of interest The authors have declared that no conflict of interest exists.

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ACE insertion/deletion polymorphism (rs1799752) modifies the renoprotective effect of renin-angiotensin system blockade in patients with IgA nephropathy

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Abstract

Introduction: Little is known about genetic predictors that modify the renoprotective effect of renin-angiotensin system (RAS) blockade in IgA nephropathy (IgAN).

Materials and methods: The present multicenter retrospective observational study examined effect modification between RAS blockade and three RAS-related gene polymorphisms in 237 IgAN patients, including *ACE* I/D (rs1799752), *AT1R* A1166C (rs5186) and *AGT* T704C (rs699).

Results: During 9.9 ± 4.2 years of observation, 63 patients progressed to a 50% increase in serum creatinine level. Only *ACE* I/D predicted the outcome (*ACE* DD vs ID/II, hazard ratio 1.86 (95% confidence interval 1.03, 3.33)) and modified the renoprotective effect of RAS blockade (p for interaction between *ACE* DD and RAS blockade = 0.087). RAS blockade suppressed progression in *ACE* DD patients but not in ID/II patients (*ACE* ID/II with RAS blockade as a reference; ID/II without RAS blockade 1.45 (0.72, 2.92); DD without RAS blockade 3.06 (1.39, 6.73); DD with RAS blockade 1.51 (0.54, 4.19)), which was ascertained in a model with the outcome of slope of estimated glomerular filtration rate (p = 0.045 for interaction).

Conclusion: *ACE* I/D predicted the IgAN progression and the renoprotective effect of RAS blockade in IgAN patients whereas neither *AT1R* A1166C nor *AGT* T704C did.

Keywords

Candidate gene approach, *ACE* I/D, *AT1R* A1166C, *AGT* T704C, renal prognosis, interaction, PREDICT-IgAN

Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common glomerulonephritis worldwide,[1–4] progressing to end-stage renal disease (ESRD) within 10 years of diagnosis in approximately 15%–25% patients.[5] A series of randomized controlled trials demonstrated that renin-angiotensin system (RAS) blockade using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) decreased urinary protein[6–10] and suppressed progression of IgAN.[6,7] RAS blockade is regarded as a major treatment strategy to prevent the progression of IgAN.[11,12]

Recent studies reported that intrarenal expression of angiotensinogen, a key regulator of RAS activity, is enhanced in IgAN patients[13,14] and is correlated with urinary angiotensinogen level, a surrogate marker of intrarenal RAS activity.[14] Urinary angiotensinogen level predicts renal prognosis in patients with chronic kidney disease,[15] including IgAN.[16] RAS blockade is likely to suppress

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intrarenal RAS activity and therefore improve renal prognosis of IgAN patients. Accordingly, the patients with higher intrarenal RAS activity potentially reap the greater benefit of RAS blockade. Strong candidates affecting intrarenal RAS activity are RAS-related gene polymorphisms, including angiotensin-converting enzyme *ACE* insertion/deletion (I/D) polymorphism (rs1799752). Compared with *ACE* II/ID subjects, *ACE* DD subjects have higher circulating and tissue *ACE* level,[17–19] suggesting that they may be amenable to treatment with RAS blockade.

The objective of the present multicenter retrospective observational study was to examine whether three major RAS-related gene polymorphisms modify the renoprotective effects of RAS blockade in IgAN patients. This study is one of the largest genetic studies of IgAN ($n = 237$) and involved the longest observational period (9.9 ± 4.2 years), thus providing pivotal information for establishing a therapeutic strategy of RAS blockade in IgAN patients.

Materials and methods

Participants

Genetic and clinical data of 237 IgAN patients included in the present study were derived from our previous study, Polymorphism REsearch to DIstinguish genetic factors Contributing To progression of IgA Nephropathy (PREDICT-IgAN).[20–22] Briefly, between January 1990 and December 2005, 1132 patients aged ≥15 years were diagnosed with IgAN by kidney biopsy at the Osaka University Hospital, Osaka General Medical Center and Osaka Rosai Hospital in the Osaka prefecture, Japan. Among 482 patients who visited these hospitals between April 2006 and March 2008, 429 patients participated in PREDICT-IgAN. Of 281 patients aged ≥18 years with ≥0.3 g/day of urinary protein and ≥15 ml/min/1.73 m^2 of estimated glomerular filtration rate (eGFR), 40 patients with RAS blockade (ACEIs ($n = 31$) and ARBs (n = 10)) at kidney biopsy were excluded, because RAS blockade at kidney biopsy might influence baseline prognostic confounders and potentially lead to the biased estimates of associations between RAS blockade and IgAN progression (prevalent user bias).[23] After excluding one patient with malignant hypertension at kidney biopsy and six patients with missing baseline data, a final 237 IgAN patients were enrolled in the present study. The study protocol was approved by the ethical committee of Osaka University, Osaka General Medical Center and Osaka Rosai Hospital.

Measurements

Based on previous genetic studies of RAS-related gene polymorphisms, we selected three major RAS-related gene polymorphisms as possible predictors of the renoprotective effect of RAS blockade: *ACE* I/D (rs1799752),[17] angiotensin II type 1 receptor *AT1R* A1166C (rs5186)[24] and angiotensinogen *AGT* T704C (rs699).[25] Clinical characteristics collected at kidney biopsy included age, gender, smoking status, mean arterial pressure (diastolic blood pressure + [systolic blood pressure − diastolic blood pressure]/3), hypertension (defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg or use of antihypertensive agents including calcium channel blockers, β-blockers, α-blockers and thiazides), serum creatinine level, eGFR based on the Japanese equation (eGFR (ml/min/1.73m^2) = 194 × serum creatinine [mg/dl]$^{-1.094}$ × age [year]$^{-0.287}$ (× 0.739 if female))[26] and urinary protein level and urinary occult blood. The values of eGFR and urinary protein were stratified into four categories (<45, 45–59, 60–89, and ≥90 ml/min/1.73 m^2) and three categories (<0.50, 0.50–0.99 and ≥1.00 g/day), respectively. The values of urinary occult blood were measured using dipstick and were stratified into three categories (negative or trace, 1+ or 2+ and 3+ or more). Smoking status was based on a questionnaire completed at admission for kidney biopsy.[27] Nonsmokers and past smokers were combined into a single category (non- or past smokers) because the number of past smokers was very small ($n = 7$). Therapeutic interventions assessed were RAS blockade, including use of ACEIs and/or ARBs, and use of immunosuppressants, including corticosteroids and other immunosuppressive agents. As long-term survivors might have more opportunities to receive therapeutic interventions in an observational study, thus potentially biasing their effectiveness (survivor treatment selection bias),[28,29] we confined the therapeutic interventions to those initiated within one year of kidney biopsy.

The observational period was defined as the time from kidney biopsy to incidence of ESRD or the last measurement of the serum creatinine level before September 2009, whichever came first. The study outcomes were an irreversible 50% increase in the serum creatinine level at kidney biopsy and the slope of eGFR (ml/min/1.73 m^2 per year), which was calculated based on serum creatinine levels at kidney biopsy and the end of the observational period. To clarify the clinical course of blood pressure and urinary protein after initiating RAS blockade, we assessed blood pressure and dipstick urinary protein at one and two years after kidney biopsy. Measurements closest to year 1 and 2 within a caliper width of 60 days were collected.

Statistics

Clinical characteristics of patients with and without RAS blockade within one year of kidney biopsy and clinical courses of blood pressure and dipstick urinary protein within two years of kidney biopsy were compared using the Student's t test, Wilcoxon's rank sum test and χ^2 test as appropriate. Genotype frequencies of three polymorphisms in the Hardy-Weinberg equilibrium were compared

between the patients with and without RAS blockade, by using the χ^2 test. Each gene polymorphism had three genotypes: major homozygote, heterozygote and minor homozygote. The associations between each polymorphism and the outcomes were examined using dominant models (homozygote of nonrisk allele vs heterozygote/homozygote of risk allele) and recessive models (homozygote of risk allele vs heterozygote/homozygote of nonrisk allele). Based on previous studies, we classified the following as risk alleles: *ACE* D allele of *ACE* I/D,[30–32] C allele of *AT1R* A1166C[24] and C allele of *AGT* T704C.[25] We did not analyze dominant or recessive models with <10% frequencies of minor homozygotes because a small sample size would hinder any meaningful statistical analysis.

Genetic predictor of IgAN progression were identified using facility-adjusted Cox proportional-hazards (CPH) models and multivariate CPH models adjusting for facility and clinically relevant factors. To identify genetic predictors of the renoprotective effectiveness of RAS blockade, we examined the effect modification between each RAS-related gene polymorphism and RAS blockade in a multivariate CPH model. Because a test for interaction is generally conservative, p for interaction <0.1 was regarded as statistically significant.[33] To clarify the effect modification, patients were classified into four categories based on gene polymorphisms, and RAS blockade and their hazard ratios were calculated in multivariate CPH models. As a sensitivity analysis, the effect modifications of each gene polymorphism and RAS blockade were examined using multivariate linear regression model with the slope of eGFR as the outcome.

Normally distributed continuous variables were expressed as mean ± SD, and non-normally distributed continuous variables were expressed as median (interquartile range). Categorical variables were expressed as number (proportion). Statistical significance was defined as $p < 0.05$, if not specified. All statistical analyses were performed using STATA version 11 (STATA Corp., College Station, TX, USA).

Results

The baseline characteristics of 237 IgAN patients are presented in Table 1. Within one year of kidney biopsy, 124 patients (52.3%) received RAS blockade, including ACEIs ($n = 95$ (76.6%)) and/or ARBs ($n = 43$ (34.7%)). Compared to those without RAS blockade, patients with RAS blockade were significantly male predominant (57.3% vs 33.6%, $p < 0.001$), hypertensive (58.1% vs 45.1%, $p = 0.047$) and had a higher serum creatinine level (median 0.9 (interquartile range 0.7, 1.1) vs 0.8 (0.6, 1.0) mg/dl, $p = 0.002$). Genotype frequencies of the RAS-related polymorphisms were not significantly different between patients with and without RAS blockade. Because of the small sample size (<10%) of minor homozygotes, a recessive model of *AT1R* A1166C (CC; $n = 1$ (0.4%)) and a dominant model of *AGT* T704C (TT; $n = 6$ (2.5%)) were not assessed in subsequent analyses.

The predictors of a 50% increase in serum creatinine level were assessed using facility-adjusted and multivariate CPH models (Table 2). During 9.9 ± 4.2 years of the observational period, 31 (25.0%) patients with RAS blockade experienced a 50% increase in serum creatinine level and 12 (9.7%) progressed to ESRD. In comparison, 32 (28.3%) patients without RAS blockade experienced a 50% increase in serum creatinine level and 13 (11.5%) developed ESRD. In facility-adjusted CPH models, *ACE* DD was significantly associated with a 50% increase in serum creatinine level (vs ID/II, hazard ratio 1.97 (95% confidence interval 1.15, 3.40), $p = 0.014$), along with older age, male gender, current smokers, lower eGFR level and higher urinary protein level (Table 2). After adjusting for clinically relevant factors, *ACE* DD (vs ID/II; 1.86 (1.03, 3.33), $p = 0.038$), current smokers (vs non-/past smokers; 2.41 (1.38, 4.20), $p = 0.002$) and lower eGFR (vs eGFR ≥90 ml/min/1.73 m^2; 60–89 ml/min/1.73 m^2 1.02 (0.46, 2.23), $p = 0.969$; 45–59 ml/min/1.73 m^2, 1.32 (0.51, 3.41), $p = 0.562$; <45 ml/min/1.73 m^2, 5.02 (1.94, 12.9), $p = 0.001$) were identified as significant predictors of a 50% increase of serum creatinine level. No other genotype was associated with a 50% increase of serum creatinine level (Table 3).

To identify genetic predictors that modify the renoprotective effectiveness of RAS blockade, effect modifications between each RAS-related gene polymorphism and RAS blockade were examined in multivariate CPH models. A significant interaction was observed in a recessive model of *ACE* I/D polymorphism (p for *ACE* DD * RAS blockade = 0.087) but not in other models (Table 3). To clarify the effect modification between *ACE* I/D and RAS blockade, patients were categorized into four groups based on *ACE* I/D and RAS blockade (Figure 1). The hazard ratio of *ACE* DD patients with RAS blockade was remarkably lower than that of ACE *DD* patients without RAS blockade; however, this trend was not observed in *ACE* ID/II patients (*ACE* ID/II without RAS blockade as a reference; ID/II patients with RAS blockade, 1.45 (0.72, 2.92), $p = 0.292$; DD patients without RAS blockade, 3.06 (1.39, 6.73), $p = 0.006$; DD patients with RAS blockade, 1.51 (0.54, 4.19), $p = 0.432$). RAS blockade approximately halved the risk of a 50% increase in serum creatinine level in *ACE* DD patients, whereas it did not in *ACE* ID/II patients.

A sensitivity analysis effect modification between *ACE* I/D and RAS blockade was also ascertained, with the slope of eGFR as the outcome. The slopes of eGFR of *ACE* ID/II patients without RAS blockade, ID/II patients with RAS blockade, DD patients without RAS blockade and DD patients with RAS blockade were –1.2 (interquartile range –2.6, –0.2), –1.4 (–2.9, 0.0), –2.3 (–4.8, –0.6), and –1.7

Table 1. Clinical characteristics of 237 IgAN patients.

	RAS blockade[a] (n = 124)	No RAS blockade[a] (n = 113)	p
Clinical characteristics at kidney biopsy			
Age (year)	40 (28, 50)	38 (25, 50)	0.478
Male (n (%))	71 (57.3)	38 (33.6)	<0.001
Current smokers	34 (27.4)	30 (26.5)	0.880
Mean arterial pressure (mmHg)	95 ± 14	92 ± 12	0.080
Hypertension (n (%))[b]	72 (58.1)	51 (45.1)	0.047
Serum creatinine (mg/dl)	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	0.002
eGFR (ml/min/1.73 m^2)	72 ± 23	77 ± 24	0.068
≥90 ml/min/1.73 m^2 (n (%))	22 (17.8)	37 (32.7)	0.041
60–89 ml/min/1.73 m^2 (n (%))	64 (51.6)	47 (41.6)	
45–59 ml/min/1.73 m^2 (n (%))	27 (21.8)	17 (15.0)	
<45 ml/min/1.73 m^2 (n (%))	11 (8.9)	12 (10.6)	
Urinary protein (g/day)	0.88 (0.49, 1.55)	0.68 (0.42, 1.19)	0.137
< 0.50 g/day (n (%))	33 (26.6)	36 (31.9)	0.358
0.50–0.99 g/day (n (%))	37 (29.8)	38 (33.6)	
≥1.00 g/day (n (%))	54 (43.6)	39 (34.5)	
Urinary occult blood negative or trace (n (%))	11 (8.9)	8 (7.1)	0.430
1+ or 2+ (n (%))	42 (33.9)	31 (27.4)	
3+ or more (n (%))	71 (57.3)	74 (65.5)	
Genotype frequency			
ACE I/D DD (n (%))	18 (14.5)	23 (20.4)	0.495
ID (n (%))	53 (42.7)	45 (39.8)	
II (n (%))	53 (42.7)	45 (39.8)	
AT1R A1166C AA (n (%))	108 (87.1)	102 (90.3)	0.528
AC (n (%))	15 (12.1)	11 (9.7)	
CC (n (%))	1 (0.8)	0 (0.0)	
AGT T704C CC (n (%))	82 (66.1)	73 (64.6)	0.968
CT (n (%))	39 (31.5)	37 (32.7)	
TT (n (%))	3 (2.4)	3 (2.7)	
Use of immunosuppressants, observational period and outcomes			
Use of immunosuppressants[a] (n (%))	54 (43.5)	44 (39.0)	0.518
Observational period (year)	8.6 (5.9, 12.0)	11.5 (7.8, 14.0)	0.002
50% increase in serum creatinine (n (%))	31 (25.0)	32 (28.3)	0.564
Slope of eGFR (ml/min/1.73 m^2 per year)	−1.4 (−2.9, 0.0)	−1.5 (−2.8, −0.3)	0.724

IgAN: IgA nephropathy; RAS: renin-angiotensin system; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme; I: insertion; D: deletion. Mean ± standard deviation (SD) or median (25%, 75%). [a]RAS blockade and use of immunosuppressants within one year of kidney biopsy. [b]Defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg or use of antihypertensive agents including calcium channel blockers, β-blockers, α-blockers and thiazides.

(−2.8, −0.2) ml/min/1.73 m^2 per year, respectively. A multivariate linear regression model adjusting for the clinically relevant factors determined a significant effect modification between *ACE* I/D and RAS blockade (p for *ACE* DD * RAS blockade = 0.045). A similar effect modification was observed in the multivariate linear regression model (Figure 1(b)).

Similar effect modification between *ACE* I/D polymorphism and RAS blockade was observed in dipstick urinary protein within two years of kidney biopsy (Figure 2). At one year after kidney biopsy, the proportion of negative or trace urinary protein of *ACE* DD patients with RAS blockade was significantly higher than that of *ACE* DD patients without RAS blockade (56.2% vs 15.8%, p = 0.012). At two years after kidney biopsy, proportions of negative or trace urinary protein and also ≤1+ of urinary protein were significantly different between *ACE* DD patients with RAS blockade and those without RAS blockade (negative or trace urinary protein, 60.0% vs 22.8%, p = 0.027; ≤1+ of urinary protein 86.7% vs 50.0%, p = 0.026), even though six (33.3%) patients without RAS blockade within one year of kidney biopsy received RAS blockade two years after kidney biopsy. In contrast, proportions of dipstick urinary protein were not significantly different at one and two years after kidney biopsy between *ACE* II/ID patients with RAS blockade and those without RAS blockade, except a small difference in ≤1+ of urinary protein one year after kidney biopsy (76.0% vs 59.7%, p = 0.021). The