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Efficacy and safety of dual vs single renin–angiotensin–aldosterone system blockade in chronic kidney disease

An updated meta-analysis of randomized controlled trials

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Abstract

Background: To lower albuminuria and to achieve blood pressure (BP) goals, dual renin–angiotensin–aldosterone system (RAAS) inhibitors are sometimes used in clinical practice for the treatment of CKD. However, the efficacy and safety of dual RAAS blockade therapy remains controversial.

Methods: PubMed, EMBASE, and Cochrane Library were searched, and random effects model was used to calculate the effect sizes of eligible studies. Potential sources of heterogeneity were detected by meta-regression and subgroup analysis.

Results: The present meta-analysis of 72 randomized controlled trials with 10,296 patients demonstrated that dual RAAS blockade therapy was superior to monotherapy in reducing the urine albumin excretion, urine protein excretion, and BP. These beneficial effects were related to the decrease of glomerular filtration rate, the increase of serum potassium level, and higher rates of hyperkalemia and hypotension. Meanwhile, these effects did not lead to improvements in short-term or long-term outcomes, including doubling of serum creatinine, acute kidney injury, end-stage renal disease, mortality, and hospitalization. Compared with the single therapy, angiotensin-converting enzyme inhibitor (ACEI) in combination with angiotensin-receptor blocker (ARB) was a better dual therapy than ACEI or ARB in combination with renin inhibitor or aldosterone receptor antagonist in decreasing urine albumin excretion, urine protein excretion and BP, and the combination was not associated with a lower glomerular filtration rate.

Conclusion: Compared with the single therapy, ACEI in combination with ARB was a better dual therapy than ACEI or ARB in combination with renin inhibitor or aldosterone receptor antagonist. Although ACEI in combination with ARB was associated with higher incidences of hyperkalemia and hypotension, careful individualized management and potassium binders may further expand its application (PROSPERO number CRD42020179398).

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AKI = acute kidney injury, ARA = aldosterone receptor antagonist, ARB = angiotensin-receptor blocker, BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, ESRD = end-stage renal disease, GFR = glomerular filtration rate, RAAS = renin–angiotensin–aldosterone system, RCTs = randomized controlled trials, RI = renin inhibitor, RR = relative risk, SBP = systolic blood pressure, SMD = standard mean difference, WMD = weighted mean difference.

Keywords: blood pressure, chronic kidney disease, dual therapy, glomerular filtration rate, hyperkalemia, hypotension, proteinuria, renin–angiotensin–aldosterone system blockade

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Chronic kidney disease (CKD), defined as decreased kidney function shown by glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause, is an increasing public health issue due to its high prevalence and increased risk of end-stage renal disease (ESRD), cardiovascular disease, and premature death.[1,2] Prevalence of CKD is estimated to be 8% to 16% worldwide, 78% of which are concentrated in middle- and low-income countries.[3,4] Hypertension usually coexists with CKD, and its prevalence increases with the decline of renal function.[5,6] The complex interaction between hypertension and CKD increases the risk of adverse cardiovascular outcomes.[7]

CKD can be detected by routine laboratory tests. The treatment proposed in the guidelines can prevent and slow down the progress of CKD, reduce the complications of reduced GFR and the risk of cardiovascular diseases, and improve the rate of survival and quality of life.[8] For the CKD patients with proteinuria, the renin–angiotensin–aldosterone system (RAAS) has been an important therapeutic target. According to recent guidelines, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) should be the drugs of first choice.[9] A previous meta-analysis demonstrated that the combined RAAS blockade therapy was superior to single RAAS blocker in reducing proteinuria.[10] However, all recent guidelines against the use of dual RAAS blockade therapy based on less benefits for most patients and more adverse events, including renal dysfunction, hyperkalemia, and hypotension.[11] Among the latest published randomized controlled trials (RCTs), the efficacy and safety of dual RAAS blockade therapy remains controversial. Therefore, we conducted the meta-analysis of RCTs to reassess the efficacy and safety of dual RAAS blockade therapy in patients with CKD.

2. Methods

2.1. Data sources and searches

We searched PubMed, EMBASE, and Cochrane Library from inception to March 2020 to retrieved relevant articles. Two reviewers (Mingming Zhao and Rumeng Wang) screened the titles and abstracts and retrieved full-text articles respectively. The disagreements were resolved by consulting a third investigator (Yu Zhang). Medical subject headings terms and free-text terms used in each database were as follows: "diabetic nephropathy," "hypertensive nephropathy," "glomerular disease," "proteinuria," "renal insufficiency," "kidney disease," "chronic renal failure," "chronic kidney disease," "drug therapy, combination," "renin–angiotensin system," "angiotensin-converting enzyme inhibitor," "angiotensin-receptor blocker," "aldosterone blockade," "selective aldosterone blockade," "renin inhibitor," "direct renin inhibitor." (Item S1, Supplemental Digital Content, http://links.lww.com/MD2/A262)

2.2. Study selection

We included studies if they met the following inclusion criteria:

(1) patients with CKD;
(2) the intervention group received dual RAAS blockade (dual therapy), and the control group received single RAAS blockade (single therapy);
(3) the outcomes involved albuminuria, proteinuria, GFR, serum potassium, blood pressure (BP), or any adverse effect;
(4) randomized, controlled, crossover or parallel trials;
(5) the articles were published in English language.

2.3. Data extraction and quality assessment

Two reviewers (Mingming Zhao and Rumeng Wang) extracted data independently and resolved disagreements by consulting with a third investigator (Yu Zhang). The data extracted from each of the published studies included in our review were as follows: the first author's name, publication year, study design, intervention, sample size, percentage of men, mean age of subjects, duration of intervention, GFR, urine albumin excretion or urine protein excretion, BP, including systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure, serum potassium, etc. The methodological quality of included studies was assessed based on the Cochrane Handbook, including random sequence generation, assignment concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Marked 1 point when the risk was low.

2.4. Data synthesis and analysis

The random effects model was used to calculate the effect sizes of eligible studies. For continuous outcomes, we calculated a weighted mean difference (WMD) or standard mean difference (SMD) with a 95% confidence interval (CI). For dichotomous outcomes, we estimated the relative risk (RR) with a 95% CI.

Heterogeneity of included studies was described with the I^2 index and the chi-square test. $I^2 \geq 50\%$ and $P < .05$ indicated medium-to-high heterogeneity. Meta-regression and subgroup analysis were used to detect the potential sources of heterogeneity. Sensitivity analysis was performed to assess the robustness of the pooled results. Begg's test and Egger's test were used to evaluate the publication bias. Statistical analysis was performed by Stata (version 15.1). The methodological quality of eligible studies was performed by RevMan5.3. We have registered the protocol for the present systematic review and meta-analysis, and the registered number in PROSPERO is CRD42020179398.

3. Results

3.1. Characteristics and quality of the studies

A total of 25,089 studies (18,664 from PubMed, 4,047 from EMBASE, and 2,378 from the Cochrane Library) were identified, of which 72 studies met the inclusion criteria (Fig. 1).

The characteristics of the individual trials are displayed in Table 1. Seventy-two studies with 10,296 patients consisted of 22 crossover and 50 parallel-arm RCTs. These studies used various combinations of blockers: 95 study arms used ACEI in combination with ARB, 6 study arms used ACEI or ARB in combination with a renin inhibitor (RI), 16 study arms used ACEI or ARB in combination with an aldosterone receptor antagonist (ARA). The sample size varied from 10 to 1,448, and the mean age of the subjects of the trials ranged from 12 to 76 years, and the duration of intervention ranged from 1 to 60 months. Forty-one studies enrolled patients with GFR ≥ 60 mL/min or mL/min/1.73 m^2 and 10 studies enrolled patients with GFR < 60 mL/min or

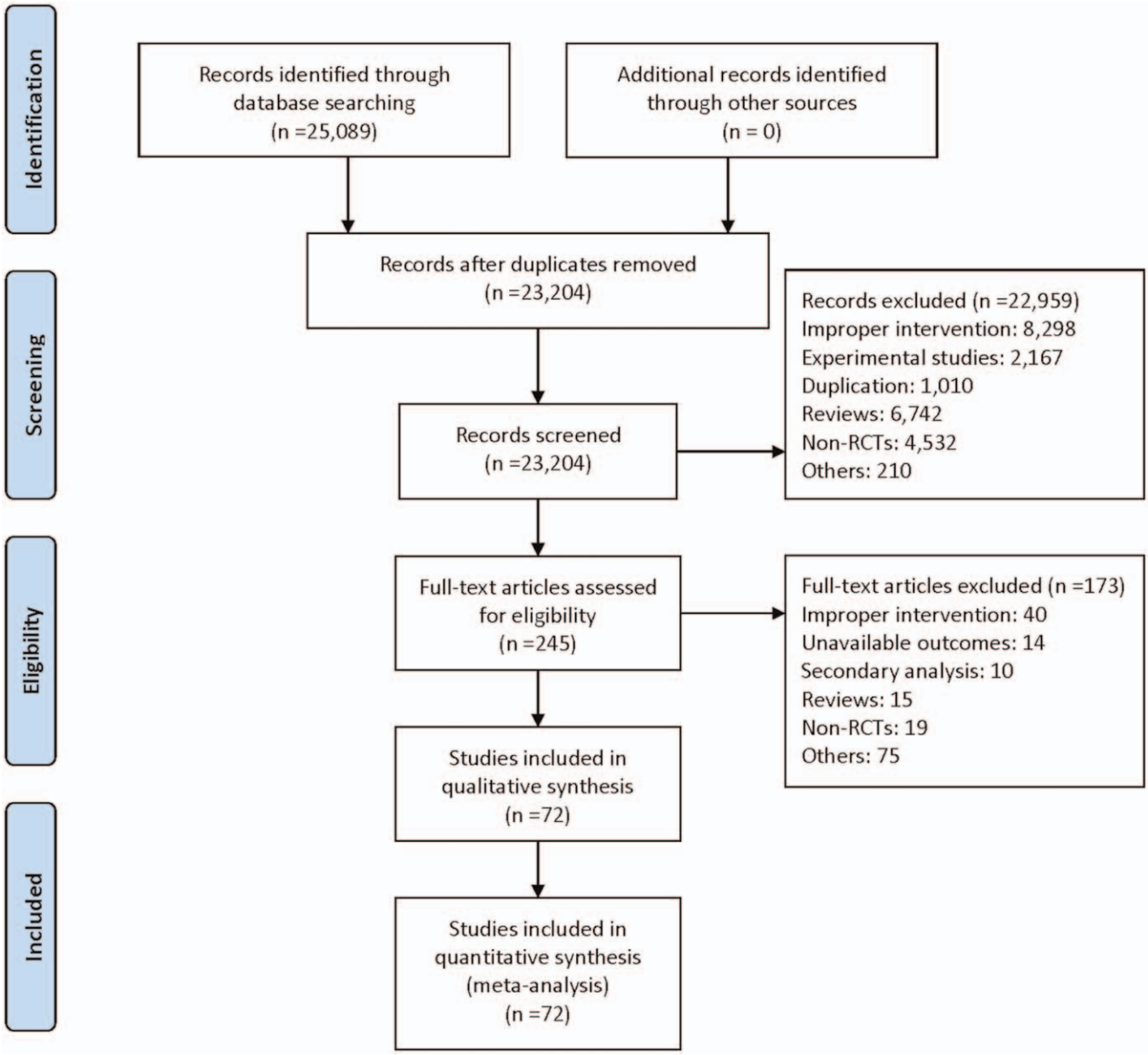

Figure 1. Flow diagram of searching for eligible studies.

mL/min/1.73 m^2. Twenty-one studies did not report the subjects' baseline of kidney function. At enrollment, the patients in 25 studies had albuminuria, and those in 36 studies had proteinuria. Eleven studies did not report the urine albumin or protein excretion at enrollment. The trials involved diabetics (32 studies), nondiabetics (22 studies). About 73.61% of the studies were of good quality (score 4–7), while the rest were of fair quality (score 1–3) (Fig. 2).

3.2. Effect of dual renin–angiotensin–aldosterone system blockade therapy on kidney-related endpoints

Twenty-two study arms reported changes in albuminuria and 50 study arms reported changes in proteinuria. Compared with the single therapy, dual therapy significantly reduced the urine albumin excretion (SMD, -0.53; 95% CI, -0.75 to -0.30; $P < .001$) (Fig. 3, Table 2) and urine protein excretion (SMD, -0.17; 95% CI, -0.27 to -0.07; $P = .001$) (Fig. 4, Table 2). However, dual therapy did not significantly increase the rate of return to normoalbuminuria (RR, 1.27; 95% CI, 0.95 to 1.71; $P = .11$) (Fig. 5, Table 3).

Sixty-one study arms reported changes in GFR. Meta-analysis showed that dual RAAS blockade therapy was associated with a decrease in GFR (SMD, -0.07; 95% CI, -0.13 to -0.01; $P = .02$) compared with monotherapy (Fig. 6, Table 2). No effects of dual RAAS blockade therapy as compared with single RAAS blockade therapy, was observed on doubling of serum creatinine (RR, 1.10; 95% CI, 0.66 to 1.83; $P = .73$), acute kidney injury (AKI: RR, 1.42; 95% CI, 0.98 to 2.06; $P = .07$) and ESRD (RR, 0.72; 95% CI, 0.51 to 1.03; $P = .07$) (Table 3).

Fifty-two study arms reported changes in serum potassium and 43 study arms reported the rate of hyperkalemia. By meta-

Table 1

Characteristics of randomized controlled trials included in this meta-analysis of trials of dual vs single therapy for blockade of the renin–angiotensin–aldosterone system.

		Renin–angiotensin–aldosterone system blockade			Male (%)		Age (Y)						
Studies	Design	Dual therapy (mg/day)	Single therapy (mg/d)	N (T/C)	T	C	T	C	Duration (months)	GFR (mL/min or mL/min/1.73 m^2)	Albuminuria or proteinuria (g/g or g/24 h)	SBP (mm Hg)	DBP (mm Hg)
Shima et al[30]	Parallel- arm	Lisinopril 20 mg + losartan 100 mg	Lisinopril 20 mg	31/31	58.06	51.61	12.00	11.90	24	120.70	0.60	109.05	63.00
Saglimbene et al[31]	Parallel- arm	ACEI + ARB	ACEI	416/413	27.52	28.75	63.40	62.20	32.4	67.85	0.16*	137.90	80.50
		ACEI + ARB	ARB	416/414	27.52	28.54	63.40	62.60	32.4	69.10	0.17*	138.10	80.30
Chen et al[32]	Parallel- arm	Irbesartan 150 mg + spironolactone 20 mg	Irbesartan 150 mg	52/53	48.08	52.83	67.00	68.00	18	79.20	NR	155.00	95.00
		Irbesartan 300 mg + spironolactone 20 mg	Irbesartan 150 mg	49/53	53.06	52.83	67.00	68.00	18	79.55	NR	155.00	94.50
		Irbesartan 150 mg + spironolactone 20 mg	Irbesartan 300 mg	52/52	48.08	51.92	67.00	67.00	18	79.00	NR	155.50	95.00
		Irbesartan 300 mg + spironolactone 20 mg	Irbesartan 300 mg	49/52	53.06	51.92	67.00	67.00	18	79.35	NR	155.50	94.50
Katayama et al[33]	Parallel- arm	ACEI or ARB+ finerenone	ACEI or ARB+ placebo	84/12	79.76	83.33	62.40	66.75	3	64.68	0.22*	137.04	76.19
Zinellu[18]	Parallel- arm	Ramipril 5 mg+ telmisartan 40 mg	Telmisartan 80 mg	12/12	33.33	33.33	62.00	58.00	6	48.72	1.22	133.00	80.00
Bakris[34]	Parallel- arm	ACEI or ARB+ finerenone	ACEI or ARB+ placebo	727/94	78.40	73.40	64.34	63.26	3	67.60	0.20*	138.18	77.15
Woo et al[35]	Parallel- arm	Aliskiren 150 mg+ losartan 100 mg	Losartan 100 mg	51/52	40.38	30.77	55.00	52.00	36	48.00	1.35	135.50	85.00
		Aliskiren 150 mg + losartan 100 mg	Aliskiren 150 mg	51/52	40.38	37.25	55.00	52.00	36	48.50	1.25	133.50	85.00
Schrier et al[36]	Parallel- arm	Lisinopril + telmisartan	Lisinopril + placebo	273/285	51.65	49.82	37.00	36.30	60	91.50	0.02*	NR	NR
Rajkumar[37]	Parallel- arm	Olmesartan 40 mg+ aliskiren 150 mg	Olmesartan 40 mg	25/25	72.00	64.00	54.28	51.04	2	NR	0.68	167.60	96.40
Makhlough et al[38]	Parallel- arm	Losartan 25 mg+ spironolactone 25 mg	Spironolactone 25 mg+ placebo	30/30	23.33	36.36	51.20	52.30	3	114.05	0.09*	134.18	81.42
Zwiech et al[39]	Parallel- arm	Ramipril 5 mg+ losartan 50 mg	Ramipril 10 mg	47/47	61.70	59.57	59.90	60.10	4	NR	NR	127.50	78.50
Ziaee et al[40]	Parallel- arm	Enalapril 50 mg+ spironolactone 25 mg	Enalapril 50 mg	29/31	58.62	64.52	53.10	53.03	3	81.20	0.12*	125.72	77.64
Nakamura et al[41]	Parallel- arm	Imidapril 5 mg + losartan 50 mg	Losartan 100 mg	14/14	71.43	64.29	61.70	61.40	12	87.75	0.25*	135.00	79.00
Lizakowski et al[42]	Crossover	Telmisartan 80 mg + aliskiren 300 mg	Telmisartan 160 mg	18/18	77.78	39.30	2	85.20	1.62	116.80	73.80		
		Telmisartan 80 mg + eplerenone 50 mg	Telmisartan 160 mg	18/18	77.78	39.30	2	85.20	1.62	116.80	73.80		
Fried et al[43]	Parallel- arm	Lisinopril 40 mg + losartan 100 mg	Losartan 100 mg+ placebo	724/724	98.76	99.59	64.50	64.70	26.4	53.65	1.04*	136.95	72.65
Fernandez Juarez et al[44]	Parallel- arm	Lisinopril 5 mg + irbesartan 75 mg	Lisinopril 10 mg	70/35	78.00	70.00	63.00	68.70	32	49.00	1.20	152.50	80.50
		Lisinopril 5 mg + irbesartan 75 mg	Irbesartan 150 mg	70/28	78.00	75.00	63.00	67.90	32	48.00	1.40	153.00	81.50
Bakris et al[45]	Parallel- arm	Valsartan 320 mg + aliskiren 300 mg	Valsartan 320 mg	574/565	59.41	56.81	55.00	55.20	2	95.40	NR	166.00	98.30
Titan et al[46]	Parallel- arm	Enalapril 40 mg + losartan 100 mg	Enalapril 40 mg+ placebo	28/28	71.43	53.57	58.10	58.00	4	49.87	3.22	148.65	80.45
Slagman et al[47]	**Crossover**	Lisinopril 40 mg + valsartan 320 mg+ low sodium	Lisinopril 40 mg + placebo + low sodium	52/52	82.69	51.50	1.5	70.50	1.63	131.00	76.25		
		Lisinopril 40 mg + valsartan 320 mg + regular sodium	Lisinopril 40 mg + placebo + regular sodium	52/52	82.69	51.50	1.5	70.50	1.63	131.00	76.25		
Meier et al[48]	Crossover	Losartan 100 mg+ lisinopril 20 mg	Losartan 100 mg	20/20	50.00	53.00	2	67.00	6.39	138.50	83.50		
		Losartan 100 mg+ lisinopril 20 mg	Losartan 200 mg	20/20	50.00	53.00	2	67.00	6.39	138.50	83.50		
Bilić et al[49]	Parallel- arm	Ramipril + valsartan	Ramipril	26/23	NR	46.10	46.30	12	74.05	5.20	143.60	89.20	
		Ramipril + valsartan	Valsartan	26/22	NR	46.10	47.40	12	76.25	4.60	147.10	89.60	
Ohishi et al[50]	Parallel- arm	Imidapril 10mg+ valsartan 160 mg	Olmesartan 40 mg	18/19	86.49	64.00	4	41.05	1.70	106.00	86.00		
Cice et al[51]	Parallel- arm	ACEI + telmisartan 80 mg	ACEI + placebo	165/167	53.33	54.49	62.70	62.80	36	NR	NR	125.40	81.00
Mehdi et al[52]	Parallel- arm	Lisinopril 80 mg+ losartan 100 mg	Lisinopril 80 mg + placebo	26/27	50.00	44.44	52.30	49.30	12	68.90	0.91*	134.00	73.00
		Lisinopril 80 mg + spironolactone 25 mg	Lisinopril 80 mg + placebo	27/27	48.15	44.44	51.70	49.30	12	62.20	1.01*	132.00	73.50
Masajtis-Zagajewska and Nowicki[53]	Crossover	ACEI+ losartan 50 mg	ACEI+ placebo	21/21	76.19	54.10	1	NR	NR	99.55†			
Krairittichai and Chaisuvannarat[54]	Parallel- arm	Enalapril 40 mg+ telmisartan 80 mg	Enalapril 40 mg	40/40	53.75	55.67	6	46.33	2.31	140.46	75.47		
Edwards et al[55]	Parallel- arm	ACEI or ARB+ spironolactone 25 mg	ACEI or ARB+ placebo	56/56	57.14	58.93	54.00	53.00	9	51.00	NR	130.00	77.00
Zhu et al[56]	Parallel- arm	Benazepril 10 mg + valsartan 80 mg	Benazepril 10 mg+ placebo	27/28	55.56	57.14	56.00	55.00	3	NR	0.33*	153.50	95.50
		Benazepril 10 mg + valsartan 80 mg	Valsartan 80 mg + placebo	27/27	55.56	59.26	56.00	57.00	3	NR	0.33*	152.50	94.50
Parving et al[57]	Parallel- arm	Losartan 100 mg + aliskiren 300 mg	Losartan 100 mg+ placebo	301/298	68.44	74.16	59.80	61.80	6	67.65	0.53*	134.50	77.50
Mori-Takeyama et al[58]	Parallel- arm	Benazepril 2.5–10 mg + candesartan 4 mg	Candesartan 4–12 mg	39/38	56.41	63.16	36.90	37.80	36	94.95	1.35	134.15	82.60
Menne et al[59]	Parallel- arm	Lisinopril 20 mg + valsartan 320 mg	Lisinopril 40 mg	40/47	77.50	70.21	59.20	59.70	7.5	113.05	NR	151.70	90.35

(*continued*)

Table 1
(continued).

Studies	Design	Renin–angiotensin–aldosterone system blockade		N (T/C)	Male (%)		Age (Y)		Duration (months)	GFR (mL/min or mL/min/1.73 m^2)	Albuminuria or proteinuria (g/g or g/24 h)	SBP (mm Hg)	DBP (mm Hg)
		Dual therapy (mg/day)	Single therapy (mg/d)		T	C	T	C					
		Lisinopril 20 mg + valsartan 320 mg	Valsartan 320 mg	40/42	77.50	66.67	59.20	57.00	7.5	119.75	NR	151.75	91.00
Knudsen et al[60]	Parallel- arm	Lisinopril 20 mg + candesartan 16 mg	Lisinopril 40 mg	25/26	72.00	80.77	56.00	57.00	12	117.50	NR	140.50	83.00
Ogawa et al[61]	Parallel- arm	Temocapril 2 mg + candesartan 4 mg	Temocapril 4 mg	37/34	48.65	47.06	61.80	60.90	24	NR	0.24*	154.00	91.15
		Temocapril 2 mg + candesartan 4 mg	Candesartan 8 mg	37/40	48.65	47.50	61.80	62.20	24	NR	0.24*	153.00	90.80
		Candesartan 4 mg + temocapril 2 mg	Temocapril 4 mg	35/34	48.57	47.06	62.50	60.90	24	NR	0.25*	151.50	90.20
		Candesartan 4 mg + temocapril 2 mg	Candesartan 8 mg	35/40	48.57	47.50	62.50	62.20	24	NR	0.25*	150.50	89.85
Nakamura et al[62]	Parallel- arm	Temocapril 2 mg + olmesartan 10 mg	Temocapril 2 mg	8/8	50.00	50.00	31.00	31.00	3	88.70	1.95	116.50	68.00
		Temocapril 2 mg + olmesartan 10 mg	Olmesartan 10 mg	8/8	50.00	62.50	31.00	34.00	3	88.50	1.95	117.50	69.00
Bakris et al[63]	Parallel- arm	Ramipril 10 mg + irbesartan 150–300 mg	Ramipril 10 mg + placebo	204/201	60.29	63.68	65.50	65.80	5	NR	NR	163.50	89.50
Abe et al[64]	Parallel- arm	ACEI + losartan 25 mg or 50 mg	ACEI	14/20	78.57	55.00	59.50	59.80	12	NR	1.35*	144.00	79.00
van den Meiracker et al[65]	Parallel- arm	ACEI or ARB + spironolactone 25–50	ACEI or ARB + placebo	24/29	69.57	58.62	55.20	55.20	12	75.50	0.89*	146.00	81.00
Song et al[66]	Crossover	Ramipril 5 mg + candesartan 8 mg	Ramipril 10 mg	21/21	52.38	49.00	4	40.60	4.10	133.00	81.00		
		Ramipril 5 mg + candesartan 8 mg	Candesartan 16 mg	21/21	52.38	49.00	4	40.60	4.10	133.00	81.00		
Sengul et al[67]	Parallel- arm	Lisinopril 20 mg + telmisartan 80 mg	Lisinopril 20 mg	47/48	38.30	35.42	57.00	57.20	7	95.15	0.16*	139.80	82.15
		Lisinopril 20 mg + telmisartan 80 mg	Telmisartan 80 mg	47/48	38.30	37.50	57.00	56.40	7	94.15	0.17*	139.95	83.30
		Telmisartan 80 mg + lisinopril 20 mg	Lisinopril 20 mg	49/48	40.82	35.42	56.90	57.20	7	94.70	0.17*	140.15	82.85
		Telmisartan 80 mg + lisinopril 20 mg	Telmisartan 80 mg	49/48	40.82	37.50	56.90	56.40	7	93.70	0.17*	140.30	84.00
Kanno et al[68]	Parallel- arm	ACEI + candesartan 2–12 mg	ACEI	45/45	40.00	40.00	60.30	59.50	36	NR	1.70	137.50	84.50
Igarashi et al[19]	Parallel- arm	Enalapril 5 mg + losartan 50 mg	Enalapril 10 mg	13/13	76.92	61.54	63.50	63.90	3	75.55	1.81	148.70	80.45
Horita et al[69]	Parallel- arm	Temocapril 1 mg + losartan 12.5 mg	Temocapril 1 mg	13/14	53.85	57.14	38.00	43.00	12	92.55	0.70	118.00	73.00
		Temocapril 1 mg + losartan 12.5 mg	Losartan 12.5 mg	13/16	53.85	56.25	38.00	42.00	12	91.65	0.82	123.50	78.00
Epstein et al[70]	Parallel- arm	Enalapril 20 mg + eplerenone 50 mg	Enalapril 20 mg + placebo	91/91	65.93	54.95	58.70	59.65	3	72.51	0.43*	143.35	85.32
		Enalapril 20 mg + eplerenone 100 mg	Enalapril 20 mg + placebo	86/91	65.12	54.95	59.06	59.65	3	73.34	0.35*	144.06	85.97
Chrysostomou et al[71]	Parallel- arm	Ramipril 5 mg + irbesartan 150 mg	Ramipril 5 mg + placebo	10/10	80.00	70.00	56.30	59.20	3	74.80	2.55	132.50	79.50
		Ramipril 5 mg + spironolactone 25 mg	Ramipril 5 mg + placebo	10/10	70.00	70.00	65.70	59.20	3	70.50	2.40	137.00	77.75
Atmaca and Gedik[72]	Parallel- arm	Lisinopril 10 mg + losartan 50 mg	Lisinopril 10 mg	8/9	37.50	44.44	55.10	55.10	12	NR	0.07*	120.00	78.30
		Lisinopril 10 mg + losartan 50 mg	Losartan 50 mg	8/9	37.50	44.44	55.10	55.10	12	NR	0.07*	120.00	78.85
Schjoedt et al[73]	Crossover	ACEI or ARB + spironolactone 25 mg	ACEI or ARB+ placebo	20/20	75.00	45.00	2	NR	>0.30*	NR	NR		
Scaglione et al[74]	Parallel- arm	Ramipril 5 mg + losartan 50 mg	Ramipril 5 mg + placebo	17/17	47.06	47.06	58.00	54.00	6	71.50	0.45*	160.50	95.50
		Ramipril 5 mg + losartan 50 mg	Losartan 50 mg + placebo	17/17	47.06	47.06	58.88	56.00	6	70.00	0.41*	162.50	93.00
Matos et al[75]	Crossover	Perindopril 8 mg + irbesartan 300 mg	Perindopril 8 mg	20/20	25.00	54.74	4	67.00	0.90	154.00	86.00		
		Perindopril 8 mg + irbesartan 300 mg	Irbesartan 300 mg	20/20	25.00	54.74	4	67.00	0.97	153.50	86.00		
Esnault et al[76]	Crossover	Ramipril 5 mg + valsartan 80 mg	Ramipril 10 mg	18/18	66.67	49.30	1	NR	3.71	149.06	83.00		
		Ramipril 5 mg + valsartan 80 mg	Valsartan 160 mg	18/18	66.67	49.30	1	NR	3.71	149.06	83.00		
Rutkowski et al[77]	Crossover	Benazepril 5 mg + losartan 25 mg	Benazepril 10 mg	24/24	50.00	35.46	4	85.72	2.13	139.52	90.73		
		Benazepril 5 mg + losartan 25 mg	Losartan 50 mg	24/24	50.00	35.46	4	85.72	2.13	139.52	90.73		
Renke et al[78]	Parallel- arm	Enalapril 10 mg + losartan 25 mg	Enalapril 10 mg	16/18	68.75	66.67	37.70	43.40	9	94.35	2.93	137.00	89.30
		Enalapril 10 mg + losartan 25 mg	Losartan 25 mg	16/18	68.75	38.89	37.70	40.40	9	93.65	2.71	138.55	89.50
Nakao et al[79]	Parallel- arm	Trandolapril 3 mg + losartan 100 mg	Trandolapril 3 mg	31/31	58.06	54.84	43.20	43.30	36	46.35	1.95	138.00	81.00
		Trandolapril 3 mg + losartan 100 mg	Losartan 100 mg	31/30	58.06	56.67	42.90	43.40	36	45.90	1.90	137.00	80.50
Morgan et al[80]	Crossover	Lisinopril 20 mg + candesartan 16 mg	Lisinopril 20 mg	23/23	95.65	75.60	1	77.00	NR	142.00	79.80		
		Lisinopril 20 mg + candesartan 16 mg	Lisinopril 40 mg	23/22	95.65	75.60	1	77.00	NR	142.00	79.80		

(*continued*)

Table 1

(continued).

Studies	Design	Renin–angiotensin–aldosterone system blockade		N (T/C)	Male (%)		Age (Y)		Duration (months)	GFR (mL/min or mL/min/1.73 m^2)	Albuminuria or proteinuria (g/g or g/24 h)	SBP (mm Hg)	DBP (mm Hg)
		Dual therapy (mg/day)	Single therapy (mg/d)		T	C	T	C					
		Lisinopril 20 mg + candesartan 16 mg	Candesartan 16 mg	23/23	95.65	75.60	1	77.00	NR	142.00	79.80		
		Lisinopril 20 mg + candesartan 16 mg	Candesartan 32 mg	23/23	95.65	75.60	1	77.00	NR	142.00	79.80		
Horita et al[81]	Parallel- arm	Temocapril 1 mg + losartan 12.5 mg	Temocapril 1 mg	11/10	45.45	40.00	39.60	39.60	6	92.00	0.74	121.00	75.50
		Temocapril 1 mg + losartan 12.5 mg	Losartan 12.5 mg	11/10	45.45	50.00	39.60	42.70	6	89.90	0.78	122.50	76.50
Song et al[82]	Crossover	Ramipril 5–7.5 mg + candesartan 4–8 mg	Ramipril 5–7.5 mg + placebo	14/14	42.86	31.00	4	60.30	4.00	91.20†			
		Ramipril 5–7.5 mg + candesartan 4–8 mg	Ramipril 5–7.5 mg + placebo	18/18	38.89	42.00	4	59.40	4.10	92.30†			
Segura et al[83]	Parallel- arm	Benazepril 10–20 mg + valsartan 160 mg	Benazepril10–20 mg	12/12	83.33	66.67	47.90	49.80	6	70.00	3.95	151.50	90.50
		Benazepril 10–20 mg + valsartan 160 mg	Valsartan 160 mg	12/12	83.33	66.67	47.90	49.70	6	71.00	4.35	150.50	88.00
Rossing et al[84]	Crossover	ACEI + candesartan 16 mg	ACEI + placebo	20/20	85.00	62.00	2	NR	>0.30*	NR	NR		
Kim et al[85]	Crossover	Ramipril + candesartan 4 mg	Ramipril + placebo	41/41	46.34	34.00	3	61.20	4.00	93.00†			
Jacobsen et al (E+I)[86]	Crossover	Enalapril 40 mg + irbesartan 300 mg	Enalapril 40 mg + placebo	24/24	70.83	42.00	2	NR	>0.30*	NR	NR		
Jacobsen et al (B+V)[87]	Crossover	Benazepril 20 mg + valsartan 80 mg	Benazepril 20 mg	18/18	72.22	43.00	2	NR	0.67*	141.00	81.00		
		Benazepril 20 mg + valsartan 80 mg	Valsartan 80 mg	18/18	72.22	43.00	2	NR	0.67*	141.00	81.00		
Campbell et al[88]	Crossover	Benazepril 10 mg + valsartan 80 mg	Benazepril 20 mg	24/24	95.83	48.90	2	69.14	3.28	140.00	91.00		
		Benazepril 10 mg + valsartan 80 mg	Valsartan 160 mg	24/24	95.83	48.90	2	69.14	3.28	140.00	91.00		
Tylicki et al[89]	Parallel- arm	Enalapril 10 mg + losartan 25 mg	Enalapril 10 mg	15/17	73.33	70.59	36.64	44.00	3	95.05	2.97	136.68	88.34
		Enalapril 10 mg + losartan 25 mg	Losartan 25 mg	15/17	73.33	41.18	36.64	41.23	3	93.35	2.71	138.71	89.00
Rossing et al[90]	Crossover	ACEI + candesartan 8 mg	ACEI + placebo	18/18	76.47	58.00	2	NR	1.78*	159.00	85.00		
Nakamura et al[91]	Parallel- arm	Trandolapril 2 mg + candesartan 8 mg	Trandolapril 2 mg	15/15	73.33	66.67	57.80	57.00	18	102.60	NR	123.00	75.00
		Trandolapril 2 mg + candesartan 8 mg	Candesartan 8 mg	15/15	73.33	60.00	57.80	56.50	18	103.70	NR	122.00	74.00
Luño et al[92]	Parallel- arm	Lisinopril 20 mg + candesartan 16 mg	Lisinopril 40 mg	16/14	56.25	85.71	42.00	50.00	6	90.00	3.70	135.00	82.00
		Lisinopril 20 mg + candesartan 16 mg	Candesartan 32 mg	16/15	56.25	66.67	42.00	45.00	6	100.00	3.90	134.00	82.00
Kincaid-Smith et al[93]	Crossover	ACEI + candesartan 8 mg	ACEI	60/60	NR	NR	NR	NR	3	NR	2.30	136.50	83.00
Jacobsen et al[94]	Crossover	ACEI + irbesartan 300 mg	ACEI + placebo	21/21	80.95	45.00	2	NR	1.87*	156.00	87.00		
Ferrari et al[95]	Crossover	Fosinopril 20 mg + irbesartan 150 mg	Fosinopril 20 mg	10/10	70.00	48.00	1.5	77.00	7.90	143.50	91.00		
		Fosinopril 20 mg + irbesartan 150 mg	Irbesartan 150 mg	10/10	70.00	48.00	1.5	77.00	7.90	143.50	91.00		
Berger et al[96]	Crossover	ACEI + candesartan 8 mg	ACEI + placebo	12/12	50.00	52.00	2	65.00	2.00	128.50	79.00		
Tütüncü et al[97]	Parallel- arm	Enalapril 5 mg + losartan 50 mg	Enalapril 5 mg	10/12	NR	57.70	51.40	12	NR	0.09*	117.50	75.00	
		Enalapril 5 mg + losartan 50 mg	Losartan 50 mg	10/12	NR	57.70	58.10	12	NR	0.10*	117.50	77.50	
Agarwal[98]	Crossover	Lisinopril 40 mg + losartan 50 mg	Lisinopril 40 mg + placebo	16/16	NR	53.00	1	66.00	3.58	156.00	88.00		
Ruilope et al[99]	Parallel- arm	Benazepril 5 or 10 mg + valsartan 80 mg	Valsartan 160 mg	42/22	70.00	73.00	56.90	57.30	1	NR	1.81	156.50	93.50
		Benazepril 5 or 10 mg + valsartan 160 mg	Valsartan 160 mg	44/22	29/25	66.00	57.60	57.30	1	NR	1.77	157.50	94.50

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, C = control group, DBP = diastolic blood pressure, GFR = glomerular filtration rate, N = Number of patients, NR = not reported, sCr = serum creatinine, SBP = systolic blood pressure, T = treatment group, Y = year.

* Value represents urinary albumin excretion.

† Mean arterial pressure.

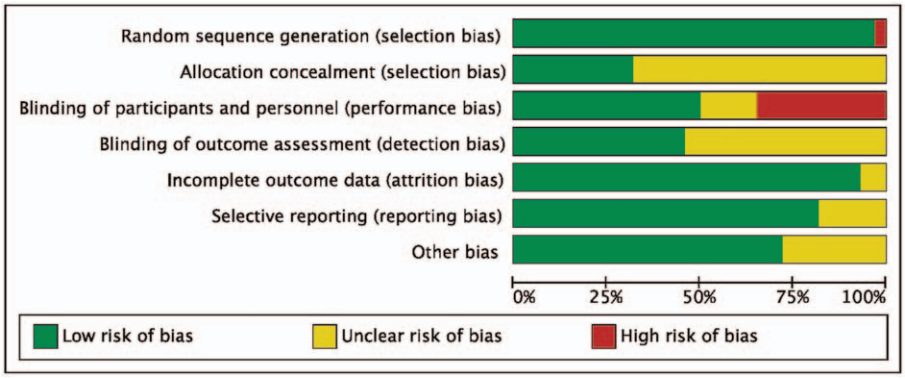

Figure 2. Risk of bias summary.

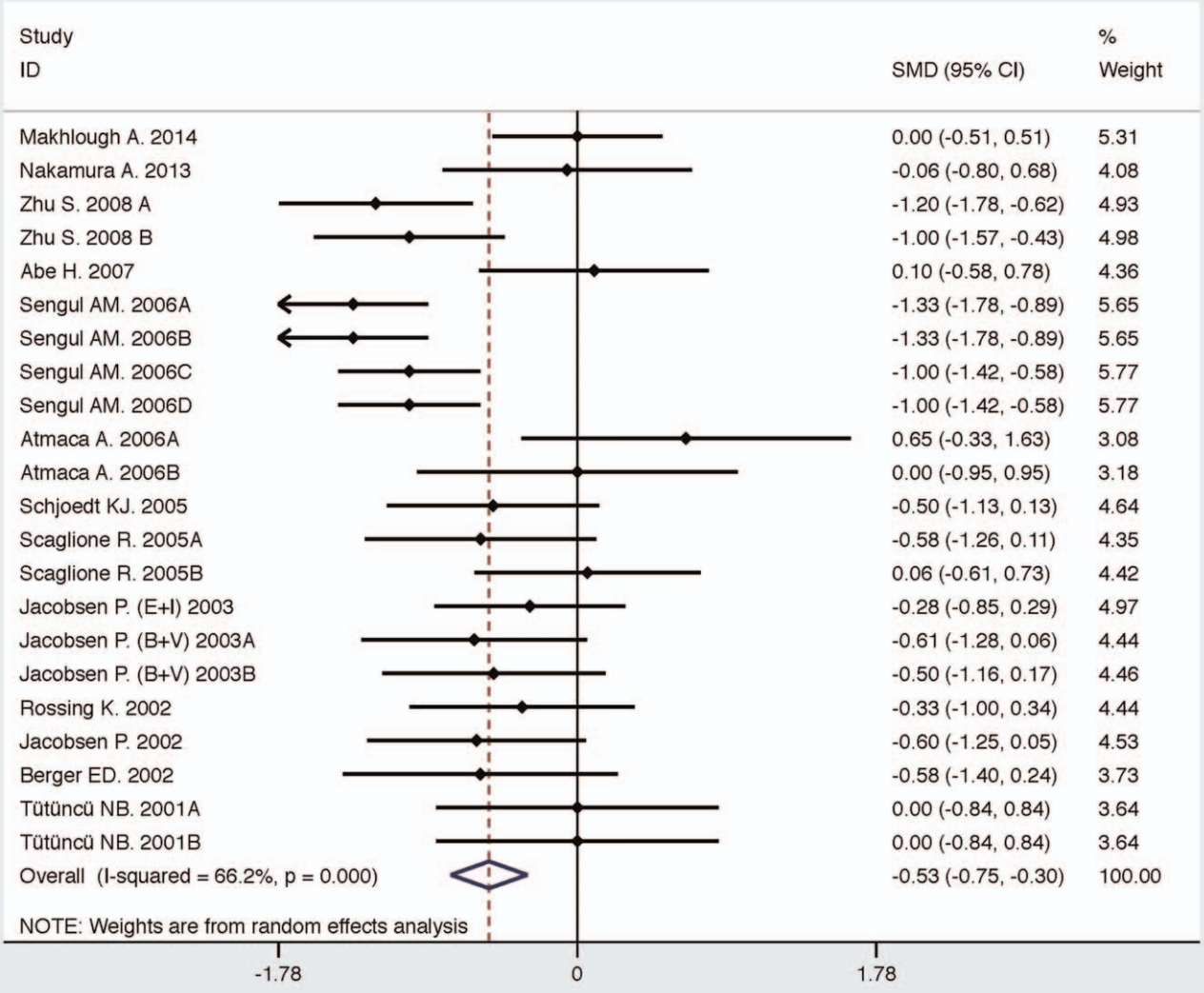

Figure 3. Comparison of dual RAAS blockade and single RAAS blockade for urine albumin excretion. RAAS = renin–angiotensin–aldosterone system.

Table 2

Summary effect of dual vs single RAAS blockade therapy on continuous outcomes.

Outcomes	No. study arms	No. participants	Random-effects model 95% CI	*P*-value	Assessment of heterogeneity I^2 (%)	*P*-value	Publication bias (*P*-value) Begg's Test	Egger's test
Urine albumin excretion (g/g of creatinine or g/24 h)	22	1,018	SMD: −0.53 (−0.75, -0.30)	<.001	66.2	<.001	.004	<.001
Urine protein excretion (g/g of creatinine or g/24 h)	50	2,586	SMD: −0.17 (−0.27, -0.07)	.001	33.5	.01	.12	.10
Glomerular filtration rate (mL/min or mL/min/1.73 m^2)	61	4,162	SMD: −0.07 (−0.13, −0.01)	.02	0.0	1.00	.39	.72
Serum potassium (mmol/L)	52	3,464	WMD: 0.10 (0.05, 0.15)	<.001	63.1	<.001	.67	.06
Systolic blood pressure (mm Hg)	76	3,730	WMD: −1.35 (−1.86, −0.84)	<.001	0.0	.53	.48	<.001
Diastolic blood pressure (mm Hg)	76	3,730	WMD: −2.03 (−2.97, −1.09)	<.001	78.1	<.001	.58	.007

CI = confidence interval.

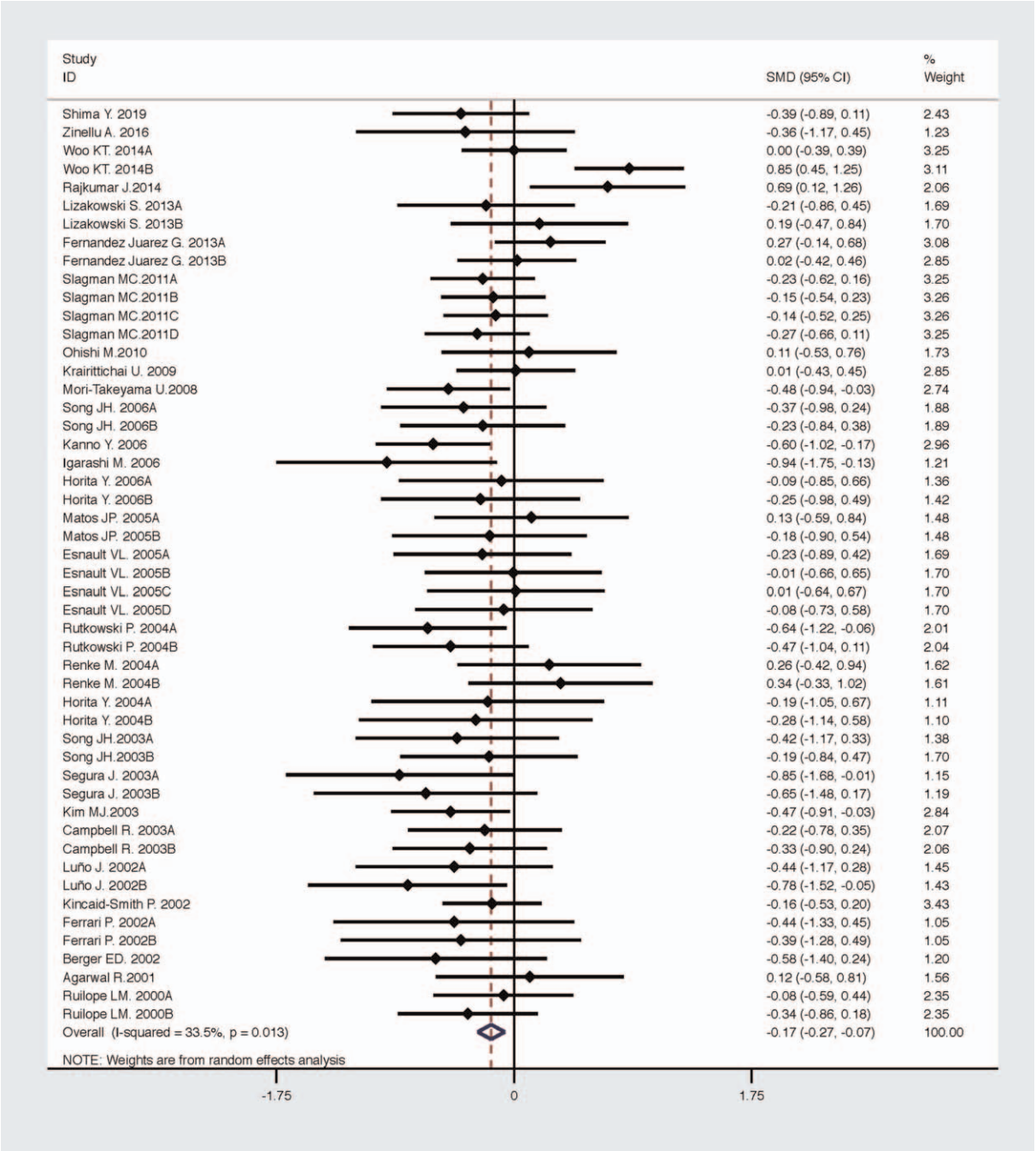

Figure 4. Comparison of dual RAAS blockade and single RAAS blockade for urine protein excretion. RAAS = renin–angiotensin–aldosterone system.

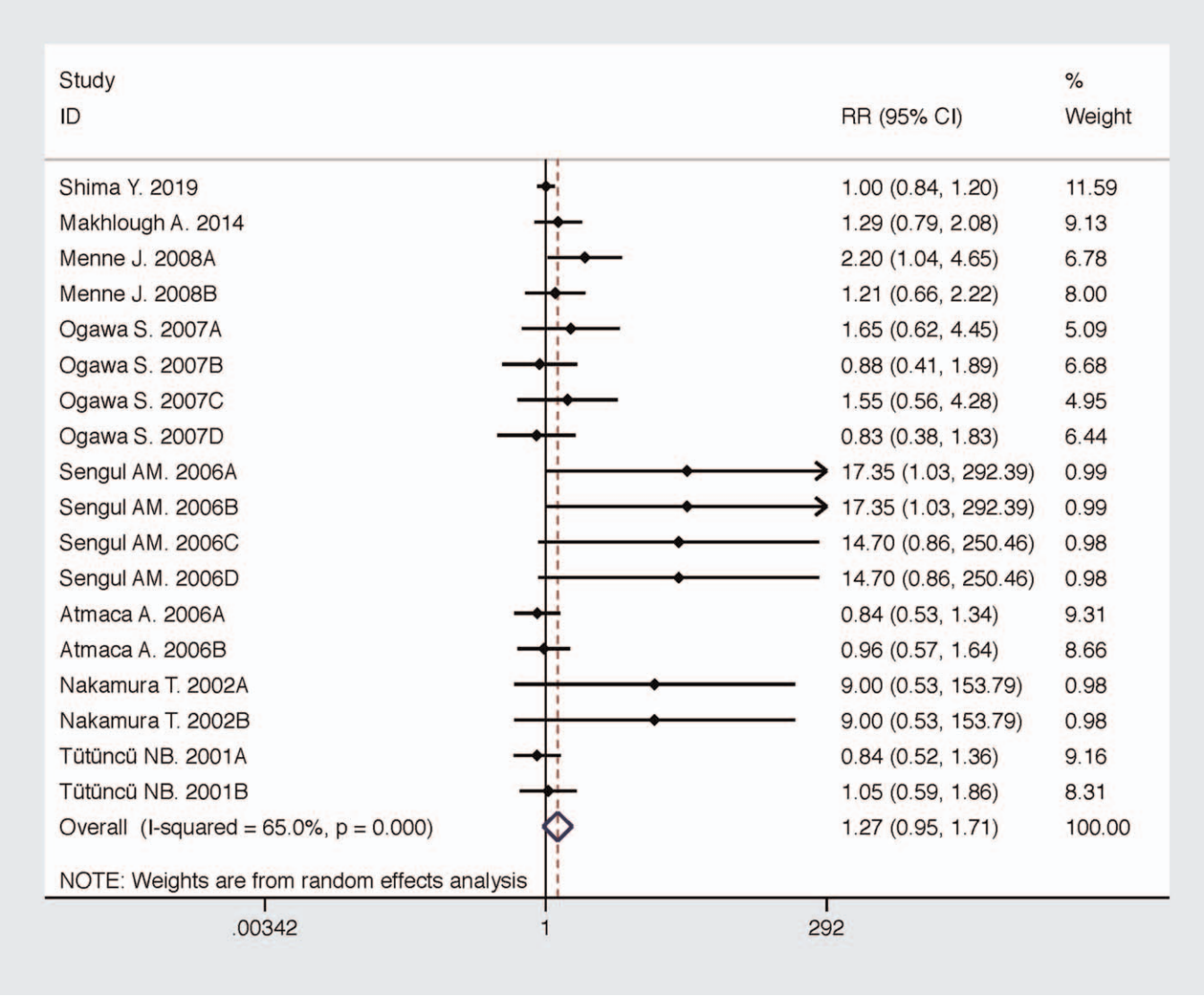

Figure 5. Comparison of dual RAAS blockade and single RAAS blockade for regression to normoalbuminuria. RAAS = renin–angiotensin–aldosterone system.

Table 3

Summary effect of dual vs single RAAS blockade therapy on dichotomous outcomes.

			Random-effects model		Assessment of heterogeneity		Publication bias (*P*-value)	
Outcomes	**No. study arms**	**No. participants**	**RR (95% CI)**	***P*-value**	**I^2 (%)**	***P*-value**	**Begg's test**	**Egger's test**
Any adverse effect	21	7,530	1.05 (1.00, 1.11)	.07	0.0	.67	.12	.23
Development of hyperkalemia	43	9,576	1.78 (1.41, 2.24)	<.001	15.9	.19	.22	.008
Development of hypotension	24	3,659	2.38 (1.58, 3.58)	<.001	0.0	.97	.59	.29
Doubling of serum creatinine	5	1,872	1.10 (0.66, 1.83)	.73	16.7	.31	.22	.76
Acute kidney injury	4	2,649	1.42 (0.98, 2.06)	.07	13.5	.33	1.00	0.80
End-stage renal disease	8	3,521	0.72 (0.51, 1.03)	.07	0.0	.80	.90	.34
Mortality	8	4,799	0.88 (0.67, 1.16)	.37	28.1	.20	0.54	0.35
Hospitalization	6	615	1.40 (0.52, 3.74)	.51	37.9	.15	.71	.02
Regression to normoalbuminuria	18	1,100	1.27 (0.95, 1.71)	.11	65.0	<.001	.004	<.001

CI = confidence interval.

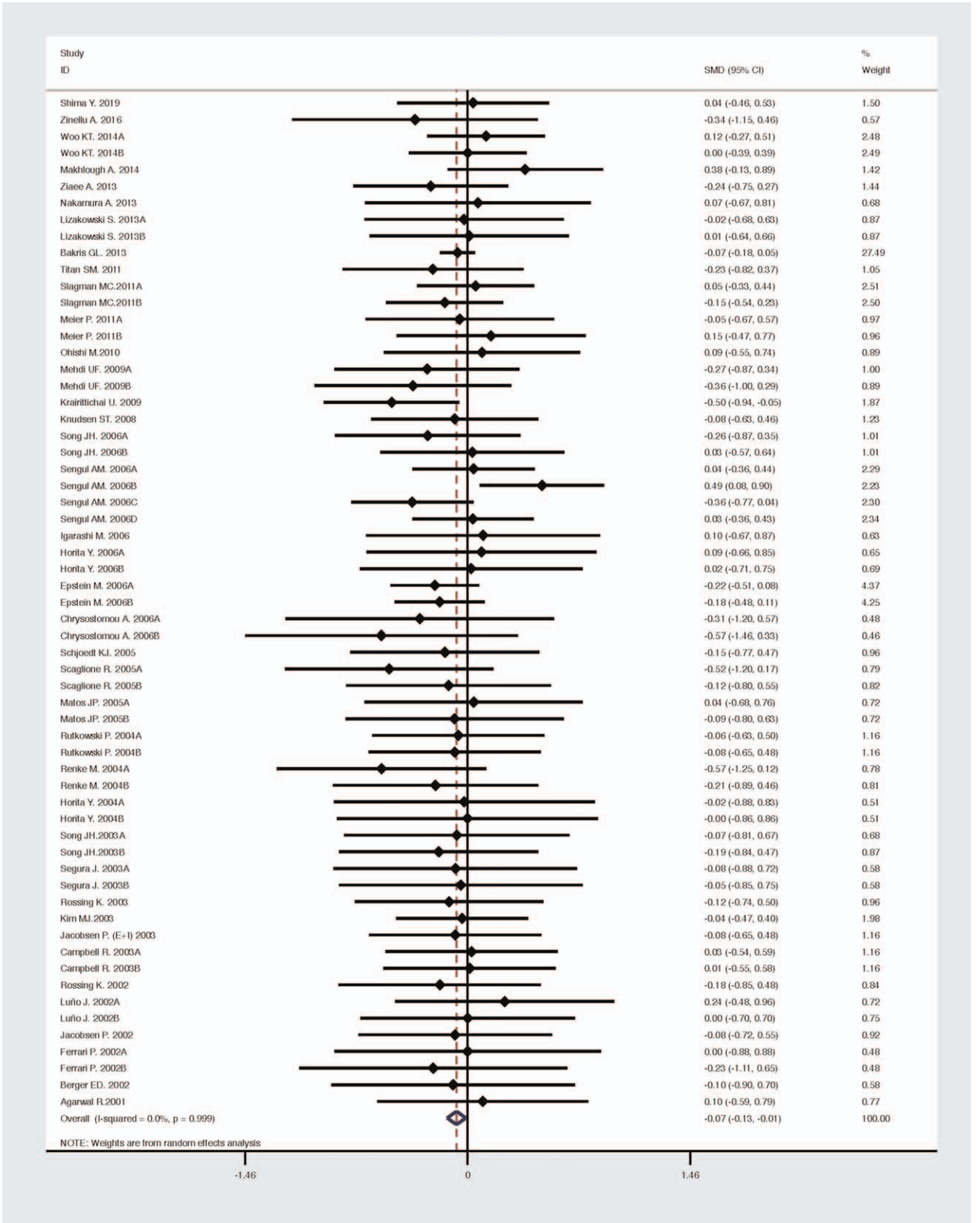

Figure 6. Comparison of dual RAAS blockade and single RAAS blockade for GFR. GFR = glomerular filtration rate, RAAS = renin–angiotensin–aldosterone system.

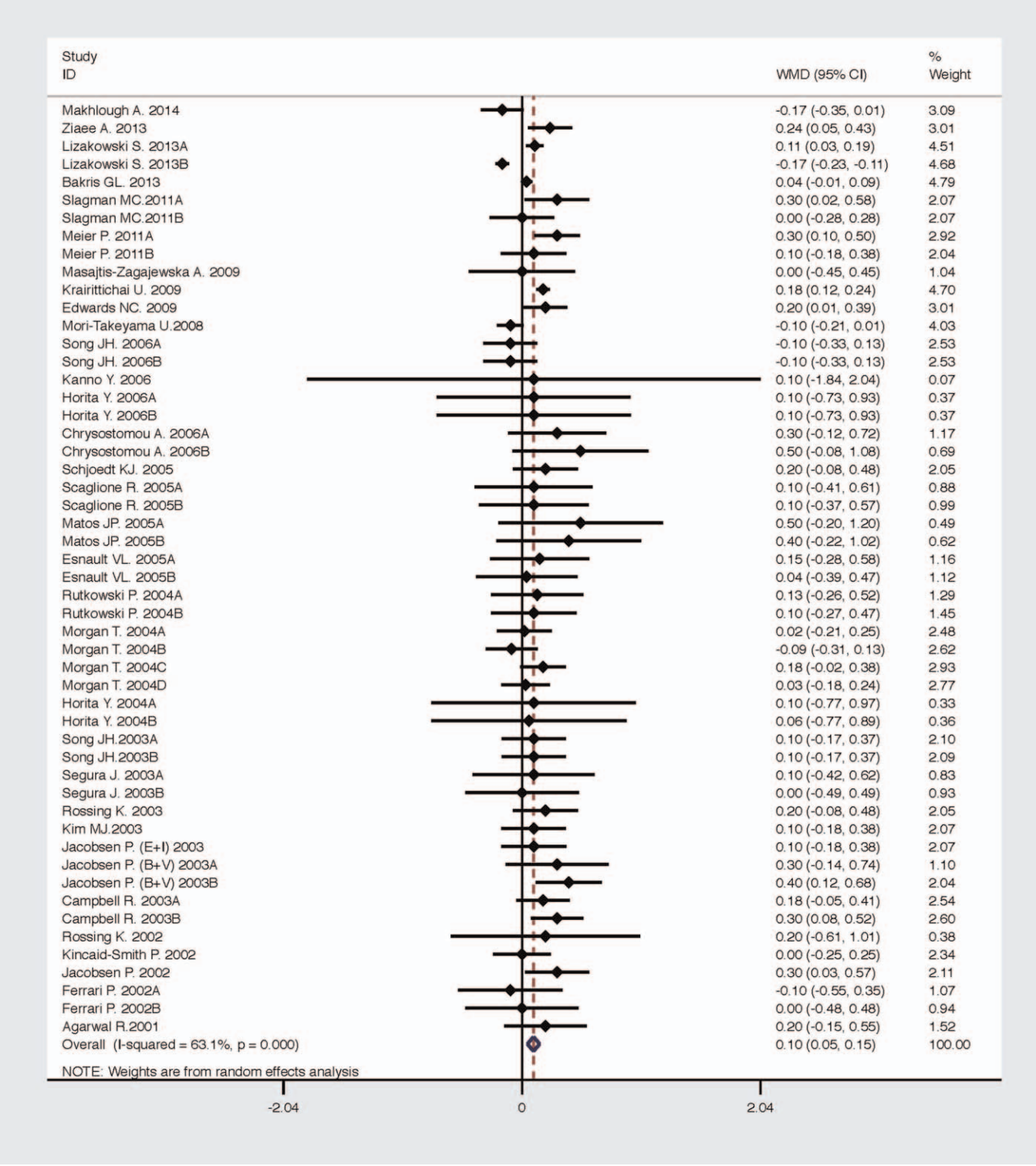

Figure 7. Comparison of dual RAAS blockade and single RAAS blockade for serum potassium. RAAS = renin–angiotensin–aldosterone system.

analysis, dual RAAS blockade therapy significantly increased the serum potassium (WMD, 0.10; 95% CI, 0.05 to 0.15; $P < .001$) (Fig. 7, Table 2). Meta-analysis showed that the rate of hyperkalemia (RR, 1.78; 95% CI, 1.41 to 2.24; $P < .001$) was higher with dual RAAS blockade therapy (Fig. 8, Table 3).

3.3. Effect of dual renin–angiotensin–aldosterone system blockade therapy on blood pressure

Seventy-six study arms reported on changes of SBP and DBP, and 24 study arms reported the rate of hypotension. Compared with the single therapy, dual RAAS blockade therapy significantly

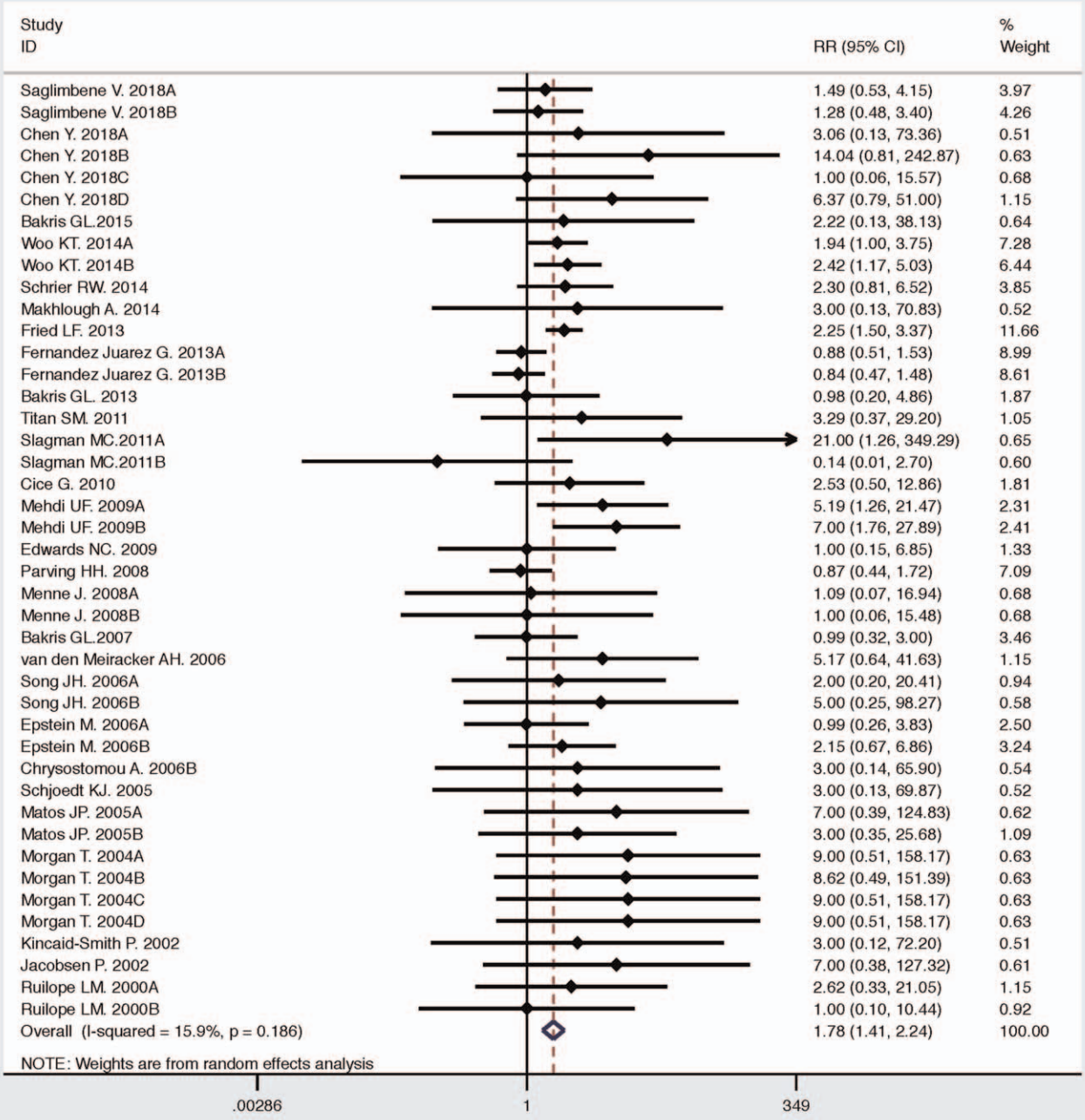

Figure 8. Comparison of dual RAAS blockade and single RAAS blockade for the development of hyperkalemia. RAAS = renin–angiotensin–aldosterone system.

decreased the SBP (WMD, -1.35; 95% CI, -1.86 to -0.84; $P < .001$) and DBP (WMD, -2.03; 95% CI, -2.97 to -1.09; $P < .001$) (Figs. 9 and 10, Table 2). Compared with the single therapy, the rate of hypotension was higher with dual RAAS blockade therapy (RR, 2.38; 95% CI, 1.58 to 3.58; $P < .001$) (Fig. 11, Table 3).

3.4. Effect of dual renin–angiotensin–aldosterone system blockade therapy on other endpoints

Twenty-one study arms reported on the incidence of any adverse effect (as defined in individual trials, such as hyperkalemia, hypotension, cough, dizziness, diarrhea, headache, and so on). Meta-analysis showed that dual RAAS

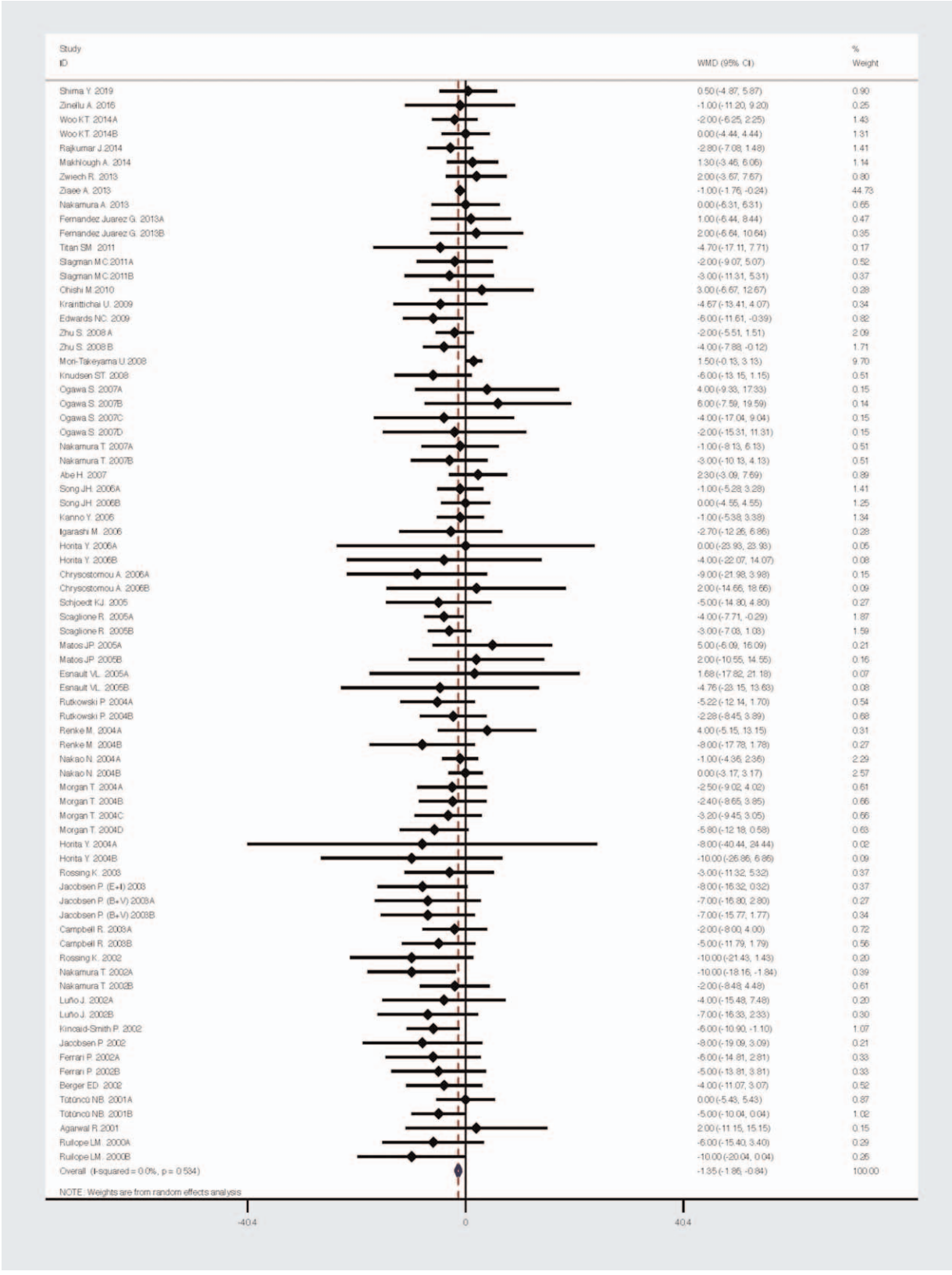

Figure 9. Comparison of dual RAAS blockade and single RAAS blockade for systolic blood pressure. RAAS = renin–angiotensin–aldosterone system.

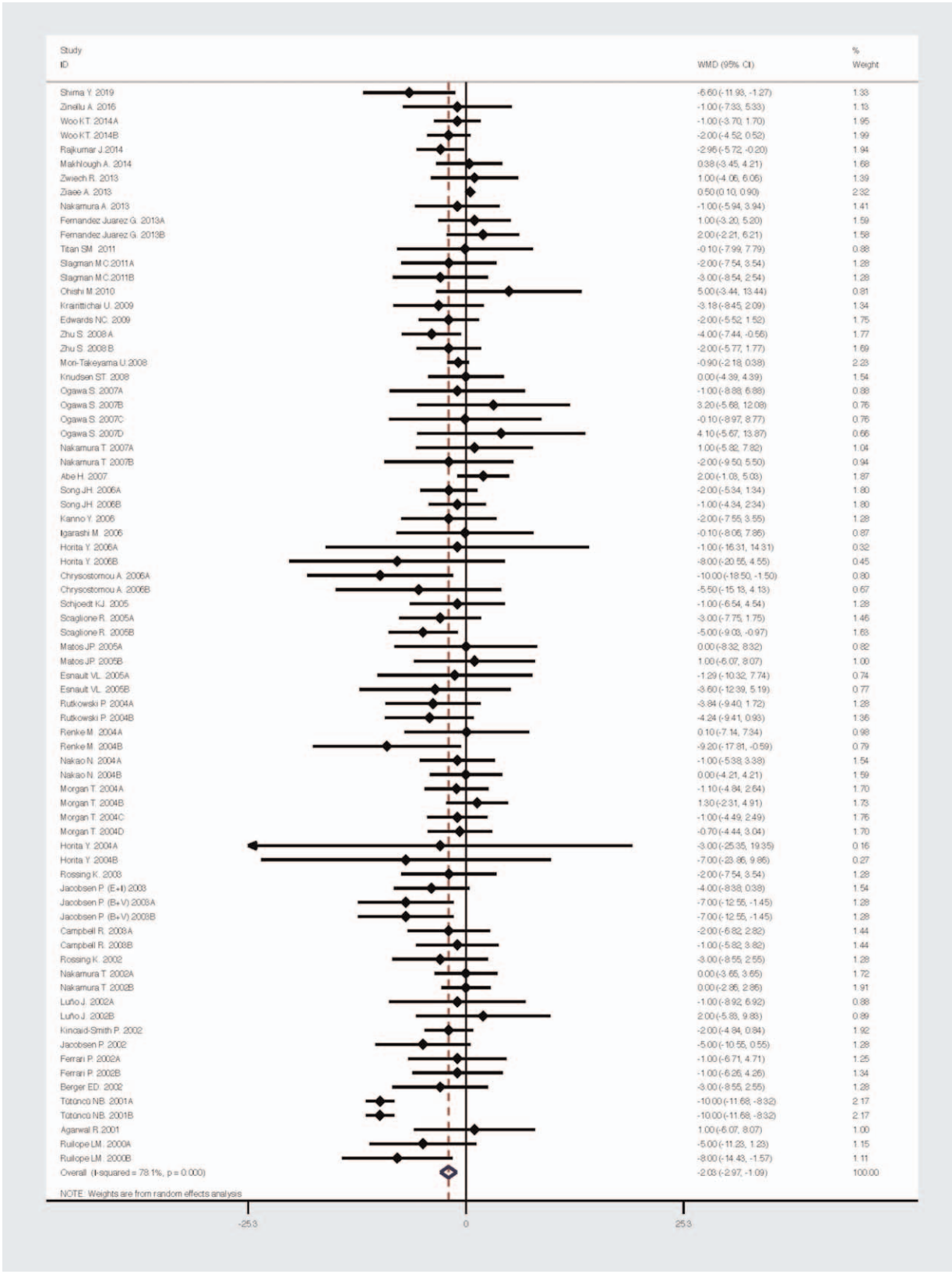

Figure 10. Comparison of dual RAAS blockade and single RAAS blockade for diastolic blood pressure. RAAS = renin–angiotensin–aldosterone system.

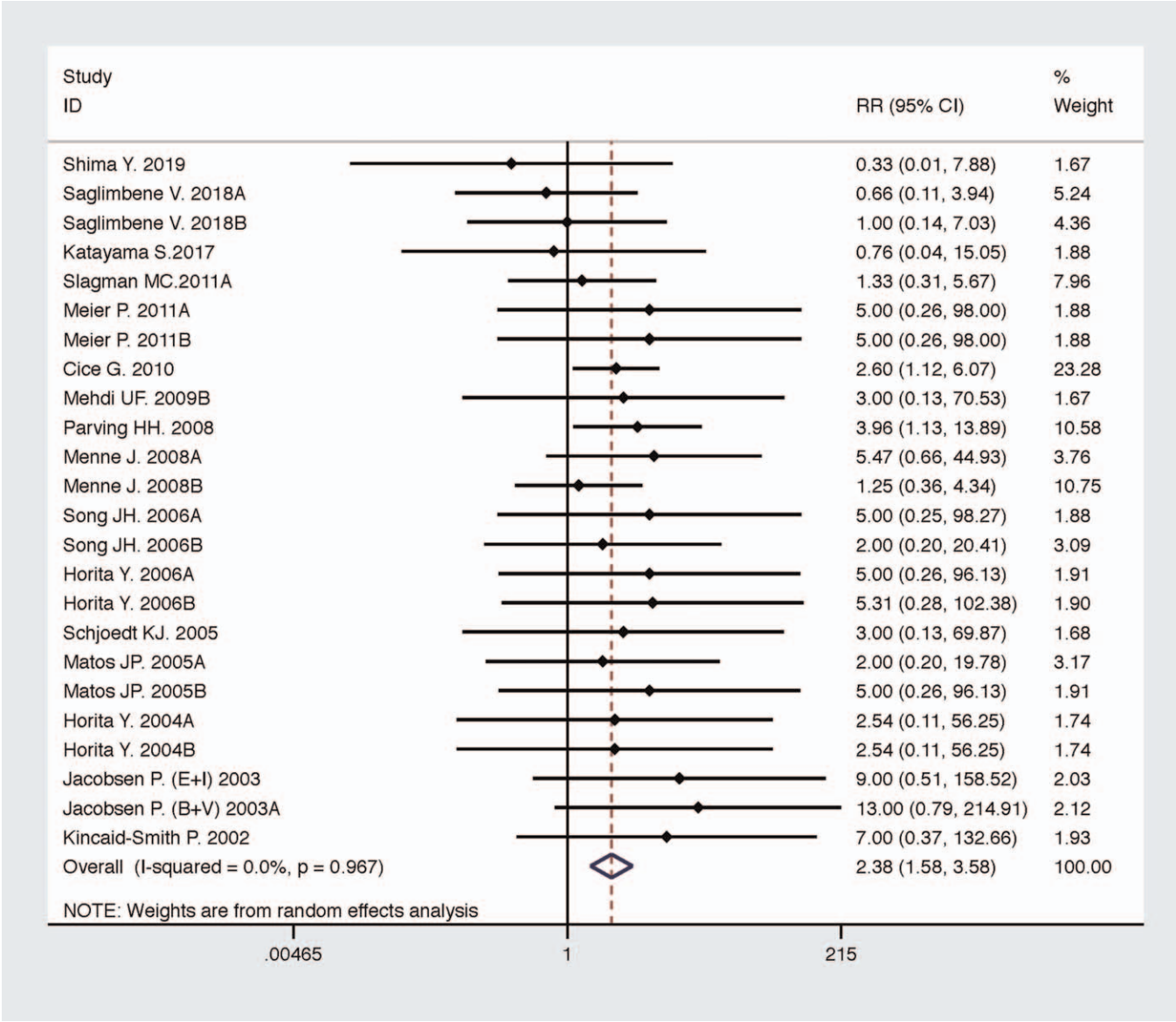

Figure 11. Comparison of dual RAAS blockade and single RAAS blockade for the development of hypotension. RAAS = renin–angiotensin–aldosterone system.

blockade therapy did not significantly increase the rate of any adverse effect (RR, 1.05; 95% CI, 1.00 to 1.11; $P=.07$) (Fig. 12, Table 3).

Eight study arms reported on the incidence of mortality and 6 study arms on the incidence of hospitalization. By meta-analysis, dual RAAS blockade therapy was not associated with any of these outcomes (Table 3).

3.5. Sensitivity analysis and meta-regression

To ensure the reliability of the present meta-analysis, we evaluated the robustness of the results (Tables 2 and 3) by sensitivity analysis, which indicated that the results of the meta-analysis were robust.

Significant heterogeneities for the continuous outcomes and dichotomous outcomes were observed (Tables 2 and 3). Based on a priori selected study characteristics, including the mean age of subjects, duration of intervention, baseline of GFR, and quality of included studies, we detected the potential sources of heterogeneity by meta-regression.

A significant heterogeneity for the outcome of urine protein excretion was observed ($I^2=33.5\%$, $P=.01$), which was dependent on the baseline of GFR (exp, 0.99; 95% CI, 0.99 to 1.00; adjusted $R^2=30.97\%$; $P=.04$). A significant heterogeneity for the outcome of serum potassium was observed ($I^2=63.1\%$, $P<.001$), which had obvious correlation with the baseline of GFR (exp, 1.00; 95% CI, 0.99 to 1.00; adjusted $R^2=26.86\%$; $P=.03$). A significant heterogeneity for the outcome of regression to normoalbuminuria was observed ($I^2=65.0\%$, $P<.001$), which had obvious correlation with baseline of GFR (exp, 0.91; 95% CI, 0.87 to 0.96; adjusted $R^2=100.00\%$; $P=.002$). By meta-regression, heterogeneities of urine albumin

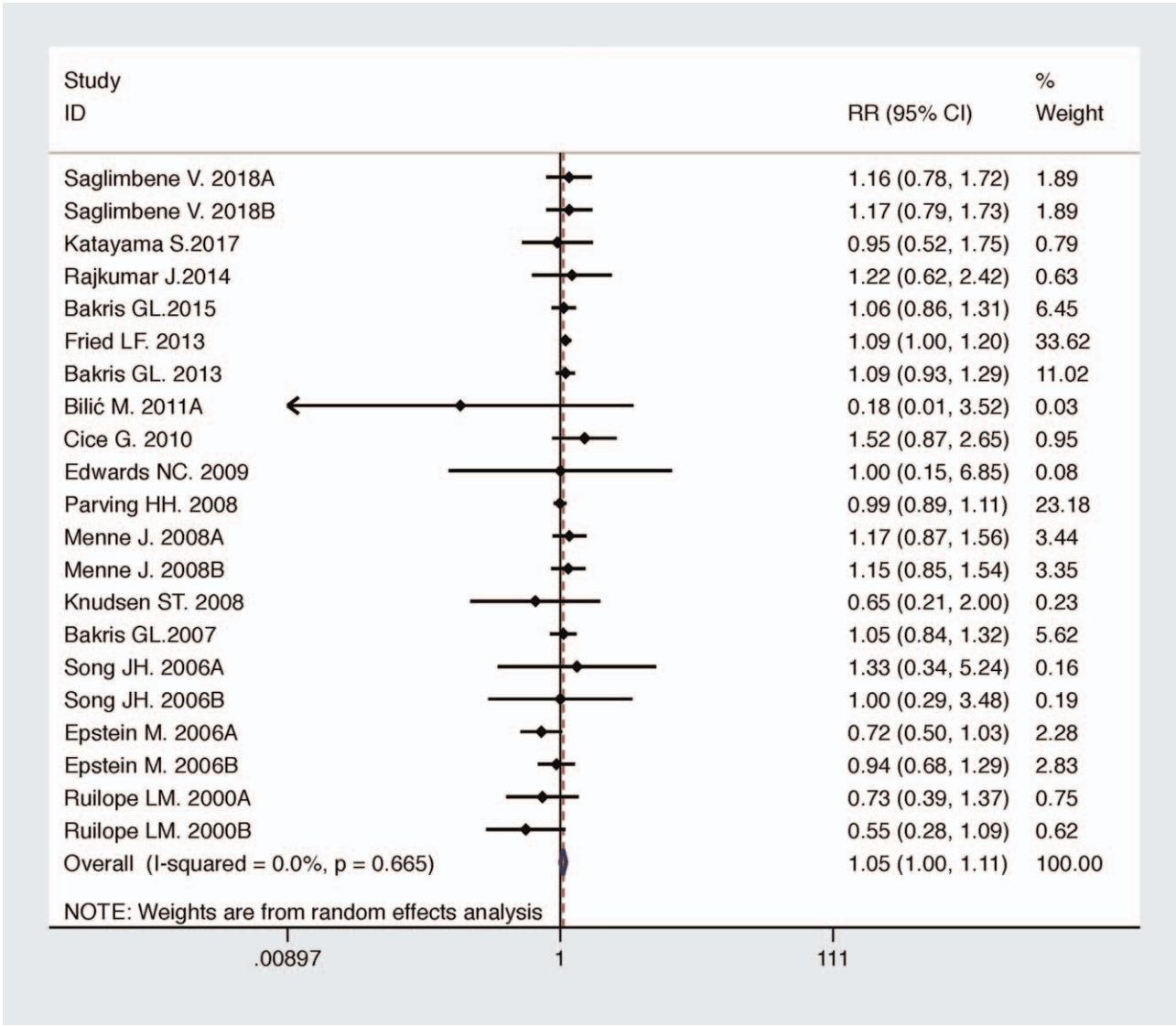

Figure 12. Comparison of dual RAAS blockade and single RAAS blockade for the incidence of any adverse effect. RAAS = renin–angiotensin–aldosterone system.

excretion and DBP were not associated with priori selected study characteristics.

3.6. Subgroup analysis

To detect the potential sources of heterogeneity, subgroup analysis was performed.

Only 1 study with ACEI or ARB in combination with RI reported on the development of hypotension and only 1 study with ACEI or ARB in combination with ARA reported on the urine protein excretion, which made these studies unable to compare with the corresponding effects of other combination therapies. Compared with the single therapy, ACEI or ARB in combination with RI or ARA did not decrease the urine albumin excretion (ACEI or ARB in combination with ARA: SMD, -0.21; 95% CI, -0.70 to 0.27; $P = .39$), urine protein excretion (ACEI or ARB in combination with RI: SMD, 0.35; 95% CI, -0.16 to 0.86; $P = .18$) and SBP (ACEI or ARB in combination with RI: WMD, -1.64; 95% CI, -4.14 to 0.86; $P = .20$; ACEI or ARB in combination with ARA: WMD, -1.28; 95% CI, -3.12 to 0.55; $P = .17$), and increased the incidence of hyperkalemia (ACEI or ARB in combination with RI: RR, 1.53; 95% CI, 1.04 to 2.25; $P = .03$; ACEI or ARB in combination with ARA: RR, 3.75; 95% CI, 1.86 to 7.55; $P < .001$). Compared with the single therapy, ACEI in combination with ARB was superior in the decrease of urine albumin excretion (SMD, -0.56; 95% CI, -0.80 to -0.32; $P < .001$), urine protein excretion (SMD, -0.23; 95% CI, -0.31 to -0.15; $P < .001$) and BP (SBP: WMD, -1.62; 95% CI, -2.35 to -0.89; $P < .001$; DBP: WMD, -2.13; 95% CI, -3.18 to -1.08; $P < .001$), and the combination was not associated with a lower GFR (SMD, -0.07; 95% CI, -0.15 to 0.02; $P = .11$) (Table 4).

3.7. Publication bias

Begg's test and Egger's test were used to evaluate publication bias based on the key outcomes of the meta-analysis. The result

Table 4

Subgroup analyses based on the type of dual therapy.

Outcomes	Types of dual therapy					
	ACEI + ARB		ACEI or ARB + RI		ACEI or ARB + ARA	
	95% CI	*P*-value	95% CI	*P*-value	95% CI	*P*-value
Urine albumin excretion (g/g of creatinine or g/24 h)	SMD: -0.56 (-0.80, -0.32)	<.001	Not reported	Not reported	SMD: -0.21 (-0.70, 0.27)	.39
Urine protein excretion (g/g of creatinine or g/24 h)	SMD: -0.23 (-0.31, -0.15)	<.001	SMD: 0.35 (-0.16, 0.86)	.18	Not available	Not available
Glomerular filtration rate (mL/min or mL/min/1.73 m^2)	SMD: -0.07 (-0.15, 0.02)	.11	SMD: -0.05 (-0.15, 0.06)	.39	SMD: -0.15 (-0.31, 0.01)	.06
Systolic blood pressure (mm Hg)	WMD: -1.62 (-2.35, -0.89)	<.001	WMD: -1.64 (-4.14, 0.86)	.20	WMD: -1.28 (-3.12, 0.55)	.17
Diastolic blood pressure (mm Hg)	WMD: -2.13 (-3.18, -1.08)	<.001	WMD: -1.97 (-3.51, -0.44)	.01	WMD: 0.45 (0.06, 0.84)	.02
Development of hyperkalemia	RR: 1.77 (1.27, 2.46)	0.001	RR: 1.53 (1.04, 2.25)	.03	RR: 3.75 (1.86, 7.55)	<.001
Development of hypotension	RR: 2.27 (1.45, 3.54)	<.001	Not available	Not available	RR: 1.84 (0.31, 10.95)	.50

ACEI = angiotensin-converting enzyme inhibitor, ARA = aldosterone receptor antagonist, ARB = angiotensin-receptor blocker, CI = confidence interval, RI = renin inhibitor.

suggested less susceptibility to publication bias, except for urine albumin excretion and regression to normoalbuminuria (Tables 2 and 3).

4. Discussion

The present meta-analysis of 72 RCTs demonstrated that dual RAAS blockade therapy was superior to single therapy in reducing urine albumin excretion, urine protein excretion and BP, including SBP and DBP. These beneficial effects were related to the decrease of GFR, the increase of serum potassium, and higher rates of hyperkalemia and hypotension. Meanwhile, these effects did not lead to improvements in short-term or long-term outcomes, including doubling of serum creatinine, AKI, ESRD, mortality, and hospitalization. The results of most subgroup analyses were consistent with the overall results, but some were different. Compared with the single therapy, ACEI in combination with ARB was a better dual therapy than ACEI or ARB in combination with RI or ARA in decreasing urine albumin excretion, urine protein excretion and BP, and the combination was not associated with a lower GFR.

Proteinuria and hypertension are risk factors of progression in CKD[12,13] Considering traditional cardiovascular risk factors, albuminuria and impaired kidney function may increase the risk of cardiovascular diseases by 2 to 4 times, as well as predict the development of cardiovascular events.[14,15] The crucial strategy to treat hypertension in renal diseases is to inhibit RAAS. Experimental and clinical studies have demonstrated that dual RAAS blockade therapy is superior to single RAAS blockade in reducing proteinuria and controlling BP.[10,16] The 2012 Kidney Disease: Improving Global Outcomes guideline suggests that patients with IgA nephropathy increase the dose of ACEI or ARB until proteinuria <1 g/d. It should be noted that in order to reduce albuminuria and achieve BP targets, moderate to high doses of RAAS blockers are usually required.[9] ACEI or ARB may reduce proteinuria by up to 40% to 50% in a dose-dependent manner, especially if the patient complies with dietary salt restriction.[17] Proteinuria is still present in some patients after treatment with ACEI or ARB.[18,19] Based on subgroup analyses, ACEI in combination with ARB was a superior dual therapy in reducing urine albumin excretion, urine protein excretion and BP compared with single therapy.

According to our meta-analysis, other RAAS blockers, RI and ARA are also being used in the treatment of CKD, but their efficacy is limited.[20] Considering the adverse effects, aliskiren in combination with ACEI or ARB is contraindicated in patients with diabetes mellitus or CKD stages 3 to 5.[11] Our results not only confirmed that ACEI or ARB in combination with RI increased the incidence of hyperkalemia, but also concluded that ACEI or ARB in combination with RI did not significantly decrease urine protein excretion and SBP in comparison with single RAAS blockade therapy.[21,22]

Despite treatment with agents such as ACEI or ARB, many studies have demonstrated that the RAAS is not completely blocked, showing persistent or elevated plasma aldosterone levels. This phenomenon is often referred to as "aldosterone escape" and is considered to be one of the main factors in the progression of CKD.[23] Increasing researches have shown that ARA, spironolactone, eplerenone and finerenone, can reduce proteinuria and BP in patients at all stages of CKD.[24,25] However, our meta-analysis demonstrated that ACEI or ARB in combination with ARA did not decrease urine albumin excretion and SBP compared with single RAAS blockade therapy, and increased the incidence of hyperkalemia.

The key safety issues associated with dual RASS block therapy are syncope due to hypotension and AKI and hyperkalemia due to impaired renal function.[26] In this meta-analysis, although overall analysis showed a decrease of GFR was more common in patients with dual RAAS blockade therapy, subgroup analysis revealed ACEI in combination with ARB did not reduce the GFR. On the premise of reducing urine albumin excretion, urine protein excretion and BP, ACEI in combination with ARB increased the incidence of hyperkalemia and hypotension. According to recent researches, the application of dual RAAS blockade therapy may be further expanded by careful individualized management and potassium binders.[20,27]

Potassium binders can optimize RAAS inhibitor therapy in CKD patients at risk of hyperkalemia, obtain the benefits of potassium-rich diet, and improve hemodialysis outcomes.[28,29] When diarrhea or vomiting occurs, it should be instructed to stop dual RAAS blockade therapy, and ambulatory BP monitoring can be used to avoid hypotension.[11]

In recent years, dual RAAS blockade therapy has caused a lot of controversy. In past 7 years, there was no systemic review and meta-analysis had analyzed the efficacy and safety of dual RAAS blockade therapy in patients with CKD. As far as we know, this is the largest systematic review and meta-analysis of patients with CKD to assess the effect of dual RAAS blockade therapy on

kidney-related endpoints, BP, and other clinically important endpoints based on the type of dual therapy. However, several limitations should be noted. ACEI in combination with ARB was used in most of the included studies, while ACEI or ARB in combination with RI or ARA was less; thus, researches on ACEI or ARB in combination with RI or ARA are not enough. The included studies were heterogeneous, and we performed sensitivity analysis, meta-regression and subgroup analysis to warrant the reliability.

5. Conclusion

In conclusion, compared with the single therapy, ACEI in combination with ARB is a better dual therapy than ACEI or ARB in combination with RI or ARA in decreasing urine albumin excretion, urine protein excretion and BP without decreased GFR. Although ACEI in combination with ARB is associated with higher incidences of hyperkalemia and hypotension, careful individualized management and potassium binders may further expand its application.

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