The Efficacy and Safety of Triple vs Dual Combination of Angiotensin II Receptor Blocker and Calcium Channel Blocker and Diuretic: A Systematic Review and Meta-Analysis

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[Correction added after online publication 14-Dec-2012: the author Mehmet Berktas has been added. Affiliations have been added to relfect this change.]

Many hypertensive patients require ≥2 drugs to achieve blood pressure targets. This study aims to review and analyze the clinical studies conducted with dual or triple combination of angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics. Medical literature between January 1990 and April 2012 was reviewed systematically and data from eligible studies were abstracted. Data were analyzed using random-effects models. Of the 224 studies screened, 7563 eligible patients from 11 studies were included. Triple combinations of ARBs (olmesartan or valsartan), CCBs (amlodipine), and diuretics (hydrochlorothiazide) at any dose provided more blood pressure reduction in office and 24-hour ambulatory measurements than any dual combination of these molecules ($P<.0001$ for both). Significantly more patients achieved blood pressure targets with triple combinations (odds ratio, 2.16; $P<.0001$). Triple combinations did not increase adverse event risk (odds ratio, 0.96; $P=.426$). Triple combinations at any dose seem to decrease blood pressure more effectively than dual combination of the same molecules without any remarkable risk elevation for adverse events. Further prospective studies evaluating the efficacy and safety of triple combinations, especially in the form of single pills, are required. *J Clin Hypertens (Greenwich).* 2013; 15:193–200. ©2012 Wiley Periodicals, Inc.

Hypertension is a major global health problem associated with significant morbidity and mortality. The prevalence rates of hypertension in adults ranges from 20% to 50% in developed countries whereas rates up to 70% have been reported in some developing countries.[1] In 2008, hypertension and its complications were estimated to cost $69 billion in the United States alone.[2] Even though the importance of successful treatment for hypertension has been known for a long time, many patients with hypertension still have poor control of blood pressure (BP).[2]

Early and effective treatment of hypertension to reduce cardiovascular morbidity and mortality is recommended by all guidelines.[3,4] Most patients with hypertension need ≥2 drugs to achieve targets for BP.[5,6] In the Strategies in Treatment of Hypertension Study, a significantly higher percentage of patients treated with a low-dose combination achieved BP targets compared with those taking high-dose monotherapy.[7] A relatively new meta-analysis showed that using drugs from 2 different classes decreases BP approximately 5 times greater than doubling the dose of a single drug.[8] Moreover, in several clinical studies including the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the United Kingdom Prospective Diabetes Study (UKPDS), and the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH), patients required at least 2 different antihypertensive drugs to achieve BP targets.[9]

Today, triple combinations are available as antihypertensive therapy and are frequently used in many countries. In a few studies, efficacy and safety of angiotensin II receptor blocker (ARB), calcium channel blocker (CCB), and diuretic combination have been shown. However, an extensive clinical study or a meta-analysis comparing efficacy and safety of dual or triple combinations of ARBs, CCBs, and diuretics are not currently available. The aim of this meta-analysis paper is to systematically review and analyze the clinical studies conducted with dual or triple combination of ARBs, CCBs, and diuretics.

METHODS

Study Selection

Study selection was performed in 3 phases: identification, selection, and full-text assessment. In the identification phase, medical literature was reviewed systematically by searching PubMED, EMBASE,

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Cochrane, and BIOSIS databases between January 1990 and April 2012 with the terms "ARB$ or angiotensin II receptor blocker$ or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan" and "CCB$ or calcium channel blocker$ or amlodipine" and "diuretic$ or HCTZ or hydrochlorothiazide." In the screening phase, among papers retrieved during identification phase, those investigating the use of ARB, CCB, and diuretic as dual or triple combination in patients with high BP were reviewed for eligibility.

Clinical studies with randomized parallel groups or single-arm design, which had been published in English, were included to full-text assessment period. Maximum antihypertensive treatment duration was selected to be 24 weeks, and studies with longer follow-up were excluded. Observational studies were also excluded. No criterion was established for blinding methodology or characteristics of the patients in the studies or definition of hypertension. After full-text assessment, the studies with suitable design and sufficient data were included in the analysis.

Study Procedures

Two independent reviewers performed identification and screening phases. Both results were reviewed by another investigator. Inconsistencies detected between the lists were discussed by two reviewers, and a semifinal list was prepared. Two independent reviewers have reviewed the full texts of the studies in the semifinal list and the details given below. Two reports have been evaluated by two reviewers and then studies for analysis were selected.

During the full-text assessment, the details of study design, basic patient characteristics (sex, age), inclusion criteria for BP, antihypertensive treatment (type and dosage of molecules used, treatment duration), changes in BP (office and 24-hour ambulatory measurements), BP control rates, and adverse event (observed due to any reason during study) incidence were abstracted.

Statistical Analyses

The reported eligible results, not individual patient data, in the studies were used in this analysis, otherwise calculated manually based on the results given. Changes in BP were summarized by using mean (95% confidence interval [CI]), while BP control rates and adverse events were summarized by using percentage.

The mean and standard error (95% CI) of difference between BP changes of dual and triple combination were calculated. Odds ratios (ORs) (95% CI) for BP control rates and adverse events were also calculated.

Although the studies included in the analyses had been performed both independently and in different populations, it is unlikely that the studies were functionally equivalent. Therefore, the random-effects model is superior to the fixed-effects model to extrapolate our results to the entire population.[10] Additionally, heterogeneity was tested by using Q value and I^2 statistics to evaluate inconsistency in the results of the studies. Publication bias was assessed using funnel graphics and Egger's method and the "trim and fill" method was used to calculate best estimate of the unbiased effect size.[11,12] Sensitivity analyses were performed to investigate the robustness of studies and to detect the outliners.

All analyses were performed with Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ). The results were reported using the PRISMA statement and its explanation and elaboration document.[13,14]

RESULTS

Characteristics of Studies and Patients

Of the 224 studies screened, full-text of 42 had been assessed and 11 were included in the analyses (Figure 1). Most of the studies analyzed[9] were randomized, double-blind,[8] and parallel-group design.[9] In these studies, the CCB amlodipine, the ARBs olmesartan and valsartan, and the diuretic hydrochlorothiazide (HCTZ) was used (Table I). The data of 9737 patients were available from 11 studies, but 7563 (77.7%) eligible ones were included to the analyses. Treatment durations differed between 8 and 20 weeks. Patients enrolled in the studies were older than 18 years and almost all studies included an elderly population. Patients primarily had stage 1 or 2 hypertension at baseline, but, in some studies, more severe hypertensive patients were also enrolled (Table I). The efficacy and safety results abstracted from studies were summarized in Table II.

BP-Lowering Efficacy

The results of 10 studies showed that triple combination of ARB and CCB and HCTZ at any dose decreased BP more than any dual combination of these agents (5.8/3.5 mm Hg in systolic BP/diastolic BP [SBP/DBP]; for both, $P<.0001$, Table III). Based on the results of 7 studies, adding HCTZ to ARB and

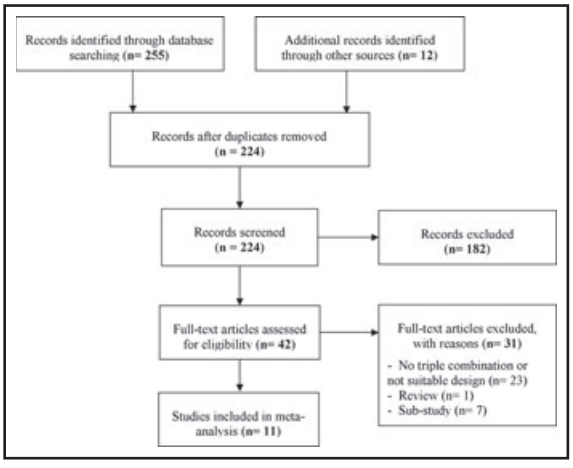

FIGURE 1. Study selection flow diagram.

TABLE I. Design and Patients Characteristics of the Studies Included in the Meta-Analysis

Study	Molecules	Design	Randomization	Blinding	No.	Duration, wk	Patient Age, y	Baseline BP, mm Hg
BP-CRUSH study[21]	Aml, Olm, HCTZ	SA	NA	OL	999	20	18–80	SBP ≥140, ≤180
Calhoun and colleagues[16,22,23]	Aml, Val, HCTZ	PG	Yes	DB	2271	8	18–85	≥145/100
EXALT study[24,25]	Aml, Val, HCTZ	PG	Yes	DB	488	12	>18	SBP ≥160, <200
EX-EFFECTS study[26,27]	Aml, Val, HCTZ	PG	Yes	DB	646	8	≥18	SBP ≥160, <200
EX-FAST study[28,29]	Aml, Val, HCTZ	PG	Yes	DB	894	16	>18	≥140/90, ≤110/180
EX-STAND study[30]	Aml, Val, HCTZ	PG	Yes	DB	572	12	>18	SBP ≥160, <200
EXTRA study[31–33]	Aml, Val, HCTZ	PG	Yes	DB	728	12	>18	SBP ≥150, <200
Fogari and colleagues[34]	Aml, Olm, Val, HCTZ	PG	Yes	OL	149	8	35–75	DBP ≥99, <110
Ram and colleagues[35]	Aml, Olm, HCTZ	SA	NA	OL	207	18	18–80	>130/80
TRINITY study[17,36]	Aml, Olm, HCTZ	PG	Yes	DB	2492	12	≥18	≥140/100 or ≥ 160/100 (off treatment)
Val-DICTATE study[37]	Aml, Val, HCTZ	PG	Yes	DB with OL ext.	291	20	≥18	>150/95, <180/110

Abbreviations: Aml, amlodipine; DB, double-blind; Ext, extension; HCTZ, hydrochlorothiazide; OL, open-label; Olm, olmesartan; PG, parallel groups; SA, single arm; Val, valsartan; BP CRUSH, Blood Pressure Control In All Subgroups With Hypertension; EXALT, the Exforge as Compared to Losartan Treatment in Stage 2 Systolic Hypertension; EX-EFFECTS, Exforge Efficacy and Control in Treatment of Stage 2 Hypertension; EX-FAST, The Exforge in Failure After Single Therapy; EX-STAND, Efficacy and Safety of Initial Combination Therapy With Amlodipine/Valsartan Compared With Amlodipine Monotherapy in Black Patients With Stage 2 Hypertension; EXTRA, Moderate vs Intensive Treatment of Hypertension With Amlodipine/Valsartan for Patients Uncontrolled on Angiotensin Receptor Blocker Monotherapy; TRINITY, Triple Therapy With Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study; Val-DICTATE, The Valsartan Hydrochlorothiazide Diuretic for Initial Control and Titration to Achieve Optimal Therapeutic Effect.

amlodipine combination provided a mean 5.2/3.2 mm Hg additional decrease in SBP/DBP whereas adding amlodipine to ARB and HCTZ combination (results from two studies) decreased BP 7.6/5.0 mm Hg and adding ARB to amlodipine and HCTZ combination (results from 5 studies) provided 7.5/4.9 mm Hg decrease (P for all <.0001). In further analyses, no evidence for heterogeneity was detected for SBP and DBP results (Q=17.0 and 22.4, respectively, all P>.05). Signs for publication bias were detected in funnel graphs of SBP and DBP (Egger's tests P<.001). Although the adjusted estimates suggested lower reductions than the original analyses, they were fairly close to the original estimates (Figure 2). Sensitivity analyses revealed that the estimate difference in means of SBP varied between 5.7 mm Hg and 6.1 mm Hg while it varied between 3.5 mm Hg and 3.7 mm Hg when one study was removed, suggesting no robustness.

Similarly, based on the results of 4 studies, triple combinations decreased 24-hour ambulatory SBP/DBP 7.1/4.5 mm Hg more than dual combinations (for both, P<.0001). In subanalyses, adding HCTZ (3 studies), amlodipine (2 studies), and ARB (3 studies) to dual combination provided 6.4/4.2 mm Hg, 6.4/3.9 mm Hg, and 10.5/8.0 mm Hg additional reduction in 24-hour ambulatory SBP/DBP, respectively (P for all <.0001, Table III). In further analyses, no evidence for heterogeneity was detected for 24-hour ambulatory SBP/DBP results (Q=5.5 and 8.9, respectively, all P>.05). The signs for publication bias were detected in funnel graphs of SBP and DBP (Egger's tests P<.05).

Based on the evaluable results of the 7 studies, all triple combinations provided more BP control than dual combinations (OR, 2.16; P<.0001). Maximum BP target achievement was seen with adding ARB (4 studies), then amlodipine (2 studies), and HCTZ (5 studies, OR, 3.03, P<.0001; OR, 2.29, P<.0001; OR, 1.86, P<.0001, respectively, Figure 3). There was no evidence of publication bias in these analyses (Egger's test P=.909). Although no heterogeneity was detected in subgroup analyses (P for Q value >.05), a sign for heterogeneity was found in overall analysis (Q=42.6, P<.05). In sensitivity analyses, no sign for an outliner was detected.

Safety

In 6 studies, adverse event incidences were reported separately for dual and triple combinations. Overall, triple combinations did not increase adverse event risk (OR, 0.96; P=.426). In subanalyses, adding HCTZ (5 studies), amlodipine (2 studies), and ARB (3 studies) to dual combinations did not affect the risk of adverse events (OR, 1.03, P=.095; OR, 0.94, P=.425; and OR, 1.06, P=.434, respectively, Figure 4). No sign for publication bias was detected (Egger's test P=.315). Heterogeneity was detected in HCTZ added group subanalysis, which probably led heterogeneity in overall analysis (Q=27.3 and 32.6, P for both <.05, Figure 4). In sensitivity analyses, no sign for an outliner was detected.

DISCUSSION

This systematic review and meta-analysis evaluated triple vs dual antihypertensive combinations for the

TABLE II. Efficacy and Safety Results of Analyzed Studies

	Efficacy								
	Office				ABPM (24 Hour)			Safety	
	No.	SBP	DBP	Control Rate[a]	No.	SBP	DBP	No.	Any AE (%)
BP-CRUSH study[21]									
A/O/H 10/40/0	776	−20.3	−11.3	65.7	229	−14.8	−9.4	795	23.6
A/O/H 10/40/12.5	671	−23.8	−13.3	74.2		NR		699	25.8
A/O/H 10/40/25	484	−25.1	−13.7	76.0	199	−21.0	−13.3	496	20.0
Calhoun and colleagues[16,22,23]									
A/V/H 0/320/25	553	−32.0	−19.7	48.3	69	−23.9	−15.5	559	45.3
A/V/H 10/320/0	558	−33.5	−21.5	54.1	71	−24.1	−14.9	566	44.9
A/V/H 10/0/25	554	−31.5	−19.5	44.8	76	−18.8	−11.7	561	48.3
A/V/H 10/320/25	571	−39.7	−24.7	70.8	67	−30.3	−19.7	582	45.2
EXALT study[24,25]									
A/V/H 5/160/0	241	−24.0	−9.8	NR		NR		NR	
A/V/H 5/160/25	229	−31.8	−13.7	56.8	36	−22.0	−13.3	NR	
EX-EFFECTS study[26,27]									
A/V/H 10/0/12.5	206	−24.3	−8.3	15.4[b]		NR		208	33.2
A/V/H 10/160/12.5	133	−30.5	−13.8	37.7[b]		NR		136	33.8
EX-FAST study[28,29]									
A/V/H 5/160/0	59	−11.7	−4.6	NR		NR		NR	
A/V/H 5/160/12.5	59	−18.9	−10.7	NR		NR		NR	
A/V/H 5/160/0	51	−6.8	−5.7	NR		NR		NR	
A/V/H 5/160/25	51	−15.7	−10.4	NR		NR		NR	
A/V/H 10/160/0	57	−17.8	−10.1	NR		NR		NR	
A/V/H 10/160/12.5	57	−22.7	−13.8	NR		NR		NR	
A/V/H 10/160/0	29	−9.1	−7.6	NR		NR		NR	
A/V/H 10/160/25	29	−16.3	−10.1	NR		NR		NR	
EX-STAND study[30]									
A/V/H 10/0/12.5	251	−30.0	−12.8	35.9		NR		NR	
A/V/H 10/320/12.5	250	−37.0	−16.1	57.2		NR		NR	
EXTRA study[31–33]									
A/V/H 5/160/0	357	−19.2	−8.7	31.3		NR		170	22.4
A/V/H 5/160/12.5	357	−23.2	−11.5	46.2		NR		170	28.8
A/V/H 5/160/25	170	−25.3	−12.3	50.7	36	−16.3	−10.2	170	37.6
A/V/H 10/320/0	366	−23.0	−10.4	43.7		NR		127	23.6
A/V/H 10/320/12.5	366	−27.9	−14.3	61.7		NR		127	33.1
A/V/H 10/320/25	127	−29.0	−14.8	59.8	44	−21.5	−13.7	127	40.2
Fogari and colleagues[34]									
A/O/H 5/0/12.5	75	−24.5	−14.3	NR	74	−21.1	−14.1	NR	
A/O/H 5/20/12.5	75	−36.7	−24.0	NR	74	−28.5	−23.0	75	8.0
A/V/H 5/0/12.5	74	−24.4	−14.4	NR	75	−20.9	−13.9	NR	
A/V/H 5/160/12.5	74	−40.8	−26.1	NR	75	−31.5	−25.4	74	9.0
Ram and colleagues[35]									
A/O/H 10/40/0	163	−22.6	−10.4	71.0	165	−19.9	−11.2	167	19.8
A/O/H 10/40/12.5	144	−27.6	−14.0	78.0		NR		146	17.8
A/O/H 10/40/25	100	−28.0	−13.7	83.0		NR		101	11.9
TRINITY study[17,36]									
A/O/H 10/40/0	624	−30.0	−18.0	52.9	112	−23.5	−13.9	596	51.7
A/O/H 0/40/25	627	−29.7	−16.9	53.4	116	−23.9	−14.5	580	55.0
A/O/H 10/0/25	593	−27.5	−15.1	41.1	95	−18.5	−10.7	552	58.9
A/O/H 10/40/25	614	−37.1	−21.8	69.9	117	−30.3	−18.0	574	58.4
Val-DICTATE study[37]									
A/V/H 0/320/25		NR		36.0		NR		NR	
A/V/H 5/320/25		NR		43.0		NR		NR	
A/V/H 10/320/25		NR		58.0		NR		NR	

Abbreviations: A, amlodipine; AE, adverse event; ABPM, ambulatory blood pressure measurement; H, hydrochlorothiazide; NR, not reported in evaluable format; O, olmesartan; SBP/DBP, systolic/diastolic blood pressure; V, valsartan. [a]Ratio of patients achieving blood pressure target <140/90 mm Hg. [b]Additional blood pressure control rate after hydrochlorothiazide was added.

TABLE III. Blood Pressure Reductions With Dual and Triple Combinations

	Systolic/Diastolic Blood Pressure (mm Hg)				
	Reduction[a]	Difference±SE (95% CI)[b]		P[c]	Q[d]
Office blood pressure					
ARB/CCB	−23.3/−12.5	SBP	5.2±0.4 (4.3–6.1)	<.0001	7.7, P=.9, I^2=0.0%
ARB/CCB/diuretic	−29.2/−16.2	DBP	3.2±0.3 (2.6–3.7)	<.0001	8.9, P=.84, I^2=0.0%
ARB/diuretic	−30.8/−18.2	SBP	7.6±1.5 (4.7–10.4)	<.0001	0.0 P=.92, I^2=0.0%
ARB/CCB/diuretic	−38.4/−23.2	DBP	5.0±1.0 (3.1–6.8)	<.0001	0.0, P=.96, I^2=0.0%
CCB/diuretic	−28.5/−15.3	SBP	7.5±1.0 (5.6–9.5)	<.0001	3.1, P=.68, I^2=0.0%
ARB/CCB/diuretic	−37.6/−21.6	DBP	4.9±0.7 (3.5–6.4)	<.0001	5.9, P=.32, I^2=15.2%
Dual combination	−25.5/−14.0	SBP	5.8±0.4 (5.0–6.5)	<.0001	17.0, P=.76, I^2=0.0%
Triple combination	−32.9/−18.7	DBP	3.5±0.2 (3.0–4.0)	<.0001	22.4, P=.44, I^2=1.7%
24-hour ambulatory blood pressure					
ARB/CCB	−18.8/−11.8	SBP	6.4±1.1 (4.2–8.5)	<.0001	0.1, P=.97, I^2=0.0%
ARB/CCB/diuretic	−25.5/−15.9	DBP	4.2±0.7 (2.8–5.6)	<.0001	0.5, P=.76, I^2=0.0%
ARB/diuretic	−23.9/−14.9	SBP	6.4±1.2 (4.0–8.8)	<.0001	0.0, P=1.00 I^2=0.0%
ARB/CCB/diuretic	−30.3/−18.6	DBP	3.9±0.7 (2.4–5.3)	<.0001	0.2, P=.63, I^2=0.0%
CCB/diuretic	−19.7/−12.5	SBP	10.5±1.8 (7.0–14.1)	<.0001	0.9, P=.81, I^2=0.0%
ARB/CCB/diuretic	−30.2/−21.1	DBP	8.0±1.4 (5.3–10.7)	<.0001	0.5, P=.92, I^2=0.0%
Dual combination	−20.1/−12.7	SBP	7.1±0.7 (5.6–8.5)	<.0001	5.5, P=.71, I^2=0.0%
Triple combination	−28.2/−18.4	DBP	4.5±0.5 (3.6–5.5)	<.0001	8.9, P=.35, I^2=10.3%

Abbreviations: ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SE, standard error. [a]Weighted mean of original results. [b]Unstandardized difference in means of blood pressure reduction of dual and triple combinations, all results favor triple combinations. [c]P value for comparison of dual vs triple combinations. [d]Q value for heterogeneity, P value of Q and I^2 statistics results.

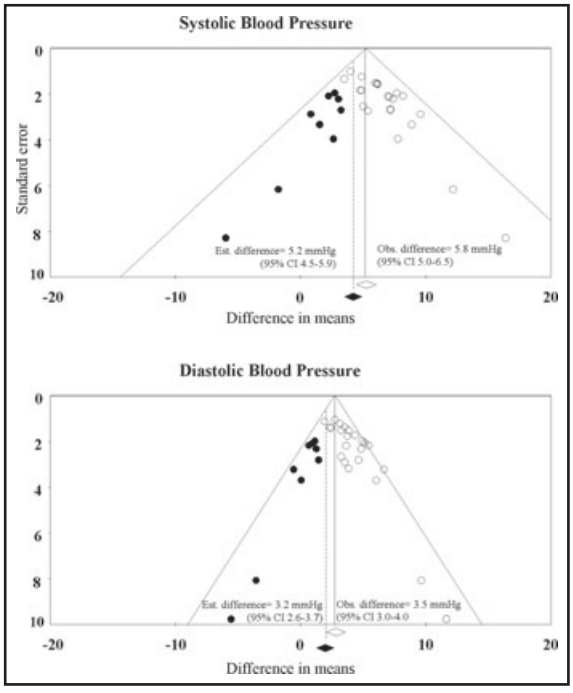

FIGURE 2. Funnel plots for systolic and diastolic blood pressure analyses. The observed studies are shown as open circles, and the observed point estimate of difference in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of triple and dual combinations is shown as an open diamond. The 9 imputed studies are shown as filled circles, and the imputed point estimate of difference in mean SBP and DBP of triple and dual combinations is shown as a filled diamond.

efficacy and safety in the management of high BP. The analyses made with the eligible 11 studies revealed that any triple combination of ARB (olmesartan or valsartan), amlodipine, and HCTZ at any dose provides more BP reduction than any dual combination of these molecules. Moreover, the ratio of patients achieving target BP also increased by using triple antihypertensive combination and triple combinations did not increase adverse event risk in the overall analysis. Heterogeneity was detected for achievement of target BP and adverse events analyses. Sensitivity analyses showed no sign for robustness.

Bakris summarized the results of several clinical trials of hypertension and showed that patients with moderate or severe hypertension or with concomitant disease (eg, diabetes mellitus, renal failure) require ≥2 antihypertensive drugs with complementary mode of action to achieve BP targets.[9] Due to multifactorial etiology of hypertension, combination therapy provides more BP reduction.[6] Concomitant use of ≥2 molecules may also result in better tolerability. A good example for such an effect is the combination of CCB and ARB. CCBs cause arterial vasodilatation, which would result in decreased total peripheral resistance. This effect could lead to BP reduction and an increase in capillary hydrostatic pressure, with consequent transcapillary fluid loss. On the other hand, ARBs dilate veins as well as arteries. This venous vasodilatation might normalize the capillary hydrostatic pressure elevated by CCB, which, in turn, could decrease exuda-

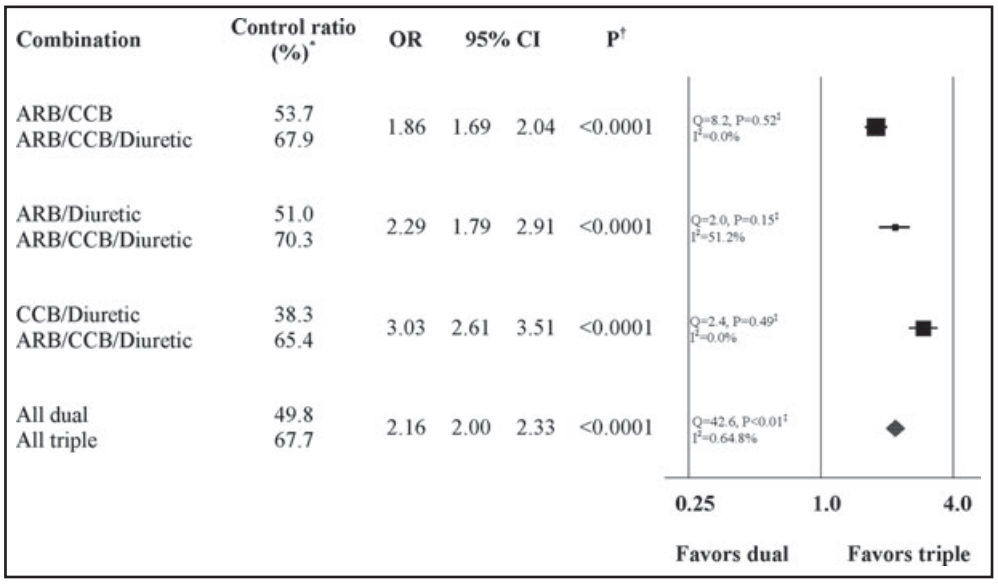

FIGURE 3. Odds ratios for blood pressure control rate in dual and triple combination groups. ARB indicates angiotensin II receptor blocker (valsartan or olmesartan); CCB, calcium channel blocker (amlodipine); CI, confidence interval, odds ratio >1.0 favors triple combinations in terms of blood pressure target achieving. *Ratio of patients achieving blood pressure target <140/90 mm Hg. †*P* value for odds ratio, *P*<.05 means significant odds difference between dual and triple combination. ‡The parameters for heterogeneity, *P* value for *Q*.

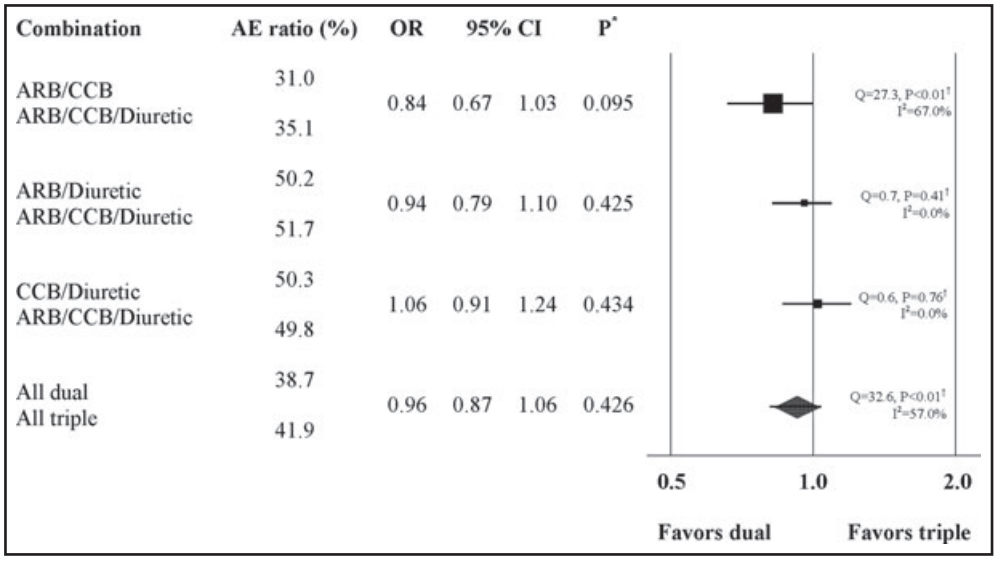

FIGURE 4. Odds ratios for adverse events in dual and triple combination groups. AE, adverse event; ARB, angiotensin II receptor blocker (valsartan or olmesartan); CCB, calcium channel blocker (amlodipine); CI, confidence interval, odds ratio<1.0 favors dual combinations in terms of adverse event ratio. **P* values for odds ratio, *P*<.05 means significant odds difference between dual and triple combination. †The parameters for heterogeneity, *P* value for *Q*.

tion to interstitial tissue.[15] The results of the current meta-analysis are in line with previously available data for combination therapies in terms of efficacy and tolerability.

The efficacy and safety of two different single-pill triple combinations of ARB, CCB, and HCTZ available on the market has been evaluated in two randomized, double-blind studies.[16,17] These two studies formed the basis of our analyses. With the results of the other 9 studies, we were able to evaluate similar treatment modalities in different patient populations and showed that adding a new molecule to a dual combination or using a triple combination from the beginning provide more BP reduction and control

rates. Adding ARBs to a dual combination provides more dramatic BP control rates than adding amlodipine or HCTZ, which may support the fact that renin-angiotensin system blockage is required in most of the hypertensive patients.

For combination therapy, free and single pill forms are available. Single-pill antihypertensive combinations have been shown to be associated with better compliance, and less adverse events compared with free combinations.[5,18] In the ACCOMPLISH study, single pill combinations were used from the beginning of the study, which resulted in a high compliance to study drugs. Three fourths of the patients achieved BP targets and almost 20% relative risk reduction was observed in primary cardiovascular endpoint at the end of the study. Investigators of the ACCOMPLISH study suggested that using single-pill combination has a significant effect on compliance, thereby on efficacy.[19] In the current meta-analysis, we were not able to retrieve sufficient data regarding type of combination used in the studies analyzed. Therefore, the effect of single-pill or free combination was not evaluated.

LIMITATIONS

One of the major limitations of our study was its methodology. We combined the results of the several studies, which have different designs, treatment duration, and patient population. Although every possible effort was made to select similar studies, there are still major differences among the studies included. Moreover, the number of the studies and patients evaluated in our analysis was relatively low; therefore, we analyzed olmesartan and valsartan studies together. In some analyses, we detected publication bias, which may prevent our results from being extrapolated to the entire population. It has been reported that the only effective method to eliminate publication bias is conducting more prospective studies with similar design; thereby, no action was taken to correct publication bias detected in our analyses.[20] The heterogeneity we detected in some analyses would likely decrease when more data become available from further prospective studies.

CONCLUSIONS

Triple combinations of olmesartan or valsartan and amlodipine and HCTZ at any dose seem to decrease BP more effectively than dual combinations of the same agents without any remarkable increase in the risk of adverse events. Further prospective studies evaluating efficacy and safety of triple combinations are needed.

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