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Original Article

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Response surface analyses of antihypertensive effects of angiotensin receptor blockers and amlodipine or hydrochlorothiazide combination therapy in patients with essential hypertension

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ABSTRACT

While previous studies have examined the dose-response characteristics of certain antihypertensive drugs alone or in combination, response surface analysis for combination therapies involving angiotensin receptor blockers (ARBs) and either amlodipine (AML) or hydrochlorothiazide (HCT) has not been explored, particularly in the context of low-dose combinations. The objectives of present study were to generate useful dose-response information for the combination of ARB/AML or ARB/HCT and to predict the blood pressure lowering effects of combination therapies compared to monotherapies. We reviewed the New Drug Application data of combination drugs of ARB/AML and ARB/HCT. Data on systolic blood pressure (SBP), from studies conducted using a factorial dose-response design over a period of 8–12 weeks, were used. The placebo-subtracted SBP change was used for analysis. Response surface analyses of the collected data were conducted using a polynomial regression model. For ARB/AML combination, the quadratic polynomial regression model containing two linear terms, two quadratic terms, and one interaction term was best fitted to the naïve pooled data. Meanwhile, for ARB/HCT combination, the best-fitted model was a quadratic model that included two linear terms and two quadratic terms. The 1/2-dose combination of these medications, compared to each monotherapy, resulted in predicted SBP reductions that were 8–30% greater. The ratio of the estimated antihypertensive effects of the combination to the expected additive effects of each component ranged from 82% to 100% of the expected effect. These results can provide a rationale for developing lower-dose combinations of ARB/AML or ARB/HCT and assist in designing clinical trials.

Keywords: Angiotensin Receptor Blocker; Amlodipine; Hydrochlorothiazide; Drug Combinations; Drug Development

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INTRODUCTION

Hypertension is a leading modifiable risk factor for premature cardiovascular death, ischemic heart disease, and stroke-related death. The Global Burden of Diseases, Injuries, and Risk Factors (GBD) study reported 10.8 million cardiovascular deaths globally in 2022 [1]. In 2021, an estimated 1.28 billion people worldwide have hypertension, of which approximately 42% were diagnosed and treated. Despite the availability of several antihypertensive drugs, only 21% of adults with hypertension have it under control [2].

Previously, initial combination therapy was not recommended as a first-line treatment for hypertension; it was reserved for the patients who did not achieve target blood pressure (BP) levels with monotherapy. However, recent guidelines are more supportive of initial combination therapy in certain patient populations, such as those with high cardiovascular risk (with BP ≥ 140 or ≥ 90 mmHg) [3,4]. However, few patients receive such therapy mainly due to treatment inertia. One of the main factors for treatment inertia is the physicians' resistance to initial combination therapy, owing to concerns about potential adverse events and medication interactions, uncertainty about which combination of drugs to use, and a preference for a stepwise approach to treatment that begins with lifestyle changes and monotherapy [5]. Additionally, some physicians may feel that they lack the experience and knowledge necessary to effectively manage the complexities of combination therapies. This factor has increased an overall interest in the use of combination therapy as the initial treatment, especially regarding low-dose combination therapy [4]. Low-dose combination therapy provides greater efficacy, better response rates, and fewer adverse events than standard-dose monotherapy, and thus, may provide solutions to many problems contributing to poor BP control rates, especially when used as an initial therapy [4,5]. However, there is still insufficient information about low-dose combination therapy, its efficacy compared to standard monotherapy, or the sum of two monotherapies (expected additive effect), for it to be used adequately in clinical practice or to guide treatment decisions [6]. Moreover, to develop new fixed-dose combination (FDC) drugs, dose-response data are required to determine the minimum effective and/or standard dosages.

Clinical guidelines recommend a combination of angiotensin receptor blockers (ARBs) with either calcium channel blockers (CCBs) or diuretics for the treatment of hypertension, considering their complementary mechanisms of action [6,7]. CCBs and diuretics stimulate the renin-angiotensin-aldosterone system (RAAS) to compensate for the reduced pressure in the glomerular afferent arteriolar and loss of sodium, respectively. On the other hand, ARBs inhibit the RAAS with different mechanisms [8]. The most commonly marketed FDC drugs combine ARBs with amlodipine (AML) or hydrochlorothiazide (HCT). The dose-response characteristics of each of component (AML, HCT, and each class of ARB (such as candesartan, irbesartan, olmesartan, telmisartan, and valsartan)) as monotherapy have been investigated in previous studies [9-15]. Similarly, the dose-response information of the combinations of ARB with AML or HCT have been explored through factorial design trials conducted as part of FDC drug development programs [16-23]. Response surface methodology (RSM) is a statistical technique that allows the exploration of relationships between multiple variables and response outcomes [24,25]. It is based on fitting a polynomial equation to experimental or observed data [24,26]. Using RSM, investigators can optimize drug combinations and doses to achieve the desired therapeutic effect. Since Hung et al. [24] reported on the purpose and usefulness of factorial design and response surface analysis in determining the optimal combination for developing FDCs of antihypertensive drugs,

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response surface analysis has been performed to identify dose-response relationships and determine optimal doses for several antihypertensive combination drugs, such as fosinopril/HCT, diltiazem/HCT, and metoprolol/HCT [27-29].

However, the dose-response characteristics of the combination therapies of ARB with AML or HCT using response surface analysis remain unexplored, particularly in the context of low-dose combinations.

This study aimed to provide a comprehensive understanding of dose-response characteristics for combination drugs of ARB/AML and ARB/HCT, particularly low-dose combinations and using response surface analysis. The information may be valuable for regulatory agencies and pharmaceutical companies involved in the development of FDC products. Furthermore, the results of this study can assist healthcare professionals and patients in making informed decisions regarding the most effective combination therapy for managing BP.

METHODS

Data search and collection (Dataset to be re-analyzed)

We obtained public domain data from the Food and Drug Administration (FDA) to identify the antihypertensive combination drugs approved for marketing in the United States [30]. We utilized the generic and trade names of all drugs within three classes (ARBs, thiazides/diuretics, and CCBs) as keywords. These drug names were sourced from the reference pharmacopoeias [31,32]. Subsequently, we specifically reviewed the New Drug Application data included in FDA reviews to extract information of the BP lowering effects of combination drugs, which is highly reliable and valid due to its review by regulatory authorities for drug approvals. Lastly, our selection process focused on randomized controlled studies with a factorial dose-response design, which included lower doses than the standard dose. Two reviewers extracted and reviewed the data, and any discrepancy was resolved through discussions and referrals to original reports/FDA reviews.

Mean systolic blood pressure (SBP) reductions

For analysis, we used the data on SBP (sitting SBP from 13 studies and supine SBP from one study) obtained from studies that employed a factorial dose-response design and had a duration of 8–12 weeks. We used SBP rather than diastolic blood pressure (DBP) for the analysis, since SBP is an independent and strong predictor of cardiovascular risk and has a larger hazard ratio per unit increase than DBP [33]. The mean reduction in SBP was calculated as the change over 8 or 12 weeks in the treated group minus that in the placebo group for each drug taken separately (monotherapy) or for both drugs taken together (combination therapy).

Recommended starting dose (RSD) and relative doses

Relative doses of different drugs were determined by identifying the starting dose of each drug [31,32]. Patients usually begin each new treatment at the RSD on the FDA-approved label, based on the results of clinical trials. The dose of each drug in each trial is expressed as a multiple of the RSD. The relative doses of each drug are presented in **Table 1** based on their RSD. Since our interest was more focused on the low-dose combination therapy, we only included relative dose ranges between 0.25 and 2 in the analysis.

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Table 1. Relative doses of each antihypertensive drug

Relative doses	Actual dose (mg)						
	AML	HCT	CAN	IRB	OLM	TEL	VAL
RSD = 1	5	25	8	150	20	40	80
Half dose of RSD = 0.5	2.5	12.5	4	NA	10	20	40
Quarter dose of RSD = 0.25	NA	6.25	2	37.5	NA	NA	NA
Double dose of RSD = 2	10	NA	16	300	40	80	160

AML, amlodipine; HCT, hydrochlorothiazide; CAN, candesartan; IRB, irbesartan; OLM, olmesartan; TEL, telmisartan; VAL, valsartan; RSD, recommended starting dose; NA, not available.

Data analysis and dose-response surface model

Data were analyzed using R software version 4.1.3. First, a response surface model was constructed using data collected from the factorial design trials. Data on ARB class, relative doses of ARB, AML, or HCT, and placebo-subtracted SBP changes were used in the analysis. The ARB class was only used to display the overall distribution of data by class. Since there was insufficient data for each ARB class, naive pooling was performed without considering it as a covariate. A polynomial regression model was used to determine the shape of each ARB class. Subsequently, all ARB class data were pooled and a response surface model was developed. The data were fitted to linear (first-order), quadratic (second-order), and cubic (third-order) polynomial models with interaction terms using the 'lm' and 'poly' functions of R. To compare the models, the adjusted R^2, Akaike information criteria (AIC), Bayesian information criteria (BIC), and likelihood ratio test (LRT) were used. Since the LRT is a formal hypothesis testing method used to compare two nested models, the LRT results were checked first. Then AIC, BIC, and adjusted R^2 were used as supplementary tools for model comparison [34,35]. For the model diagnostic plots, overlay plots of the lower and upper 95% prediction surfaces and observed data are illustrated. Additionally, the combination dose-response relationship was illustrated for doses ranging from 0.25 to twice RSD with the mean prediction surface and predicted SBP reduction according to each relative dose.

RESULTS

The drug response data set

The dataset used in this study consisted of SBP measurements from 14 studies on 7 FDA-approved products, as listed in **Table 2**. Two groups of two-drug combination products were identified for the analysis, namely angiotensin receptor blocker plus amlodipine (ARB/AML) and angiotensin receptor blocker plus hydrochlorothiazide (ARB/HCT).

The data for these combination drugs were obtained from Drugs@FDA (US FDA), which is accessible at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

The drugs used in the analysis were as follows:

- ARB/AML: Twynsta (telmisartan/AML), Exforge (valsartan/AML), and Azor (olmesartan/AML)
- ARB/HCT: Micardis HCT (telmisartan/HCT), Diovan HCT (valsartan/HCT), Benicar HCT (olmesartan/HCT), Avalide (irbesartan/HCT), and Atacand HCT (candesartan/HCT).

Model comparison

After fitting the regression models to the pooled data for ARB/AML, we found the quadratic polynomial model, which included two linear terms, two quadratic terms, and

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Table 2. List of FDA-approved two-drug combination products

Class	Active ingredients	Drug name	NDA No.	Dosage form/route	Company	Studies included	No of patients	Criteria for eligibility in the studies	Treatment period	Body position to measure BP
ARB with AML										
ARB/AML	Olmesartan medoxomil; Amlodipine besylate	AZOR	#022100	TABLET; ORAL	DAIICHI SANKYO	One study: CS8663-A-U301	1,940	DBP 95–120 mmHg	8 wk	Sitting
ARB/AML	Telmisartan; Amlodipine besylate	TWYNSTA	#022401	TABLET; ORAL	BOEHRINGER INGELHEIM	One study: 1,235.1	1,461	DBP 95–119 mmHg	8 wk	Sitting
ARB/AML	Valsartan; Amlodipine besylate	EXFORGE	#021990	TABLET; ORAL	NOVARTIS	Two studies:			8 wk	Sitting
						A2201E1	1,911	DBP 95–109 mmHg		
						A2307E1	1,250	DBP 95–109 mmHg		
ARB with HCT										
ARB/HCT	Candesartan cilexetil; Hydrochlorothiazide	ATACAND HCT	#021093	TABLET; ORAL	ANI PHARMS	Five studies:				Sitting
						SH-AHK-004	371	DBP 95–114 mmHg	12 wk	
						EC408	693	DBP 95–110 mmHg	12 wk	
						AM153	275	DBP 95–114 mmHg	8 wk	
						AM124	602	DBP 95–114 mmHg	12 wk	
						EC403	1,096	DBP 95–110 mmHg	8 wk	
ARB/HCT	Irbesartan; Hydrochlorothiazide	AVALIDE	#020758	TABLET; ORAL	SANOFI AVENTIS US	Two studies:				Sitting
						CV131-037	683	DBP 95–110 mmHg	8 wk	
						CV131-038	815	DBP 95–110 mmHg	12 wk	
ARB/HCT	Olmesartan medoxomil; Hydrochlorothiazide	BENICAR HCT	#021532	TABLET; ORAL	DAIICHI SANKYO	One study: CS-866-318	502	DBP 111–114 mmHg	8 wk	Sitting
ARB/HCT	Telmisartan; Hydrochlorothiazide	MICARDIS HCT	#021162	TABLET; ORAL	BOEHRINGER INGELHEIM	One study: 502.204	818	DBP 95–114 mmHg	8 wk	Supine
ARB/HCT	Valsartan; Hydrochlorothiazide	DIOVAN HCT	#020818	TABLET; ORAL	NOVARTIS	One study: 301	871	DBP 95–115 mmHg	8 wk	Sitting

NDA, new drug application; BP, blood pressure; ARB, angiotensin receptor blocker; AML, amlodipine; DBP, diastolic blood pressure; HCT, hydrochlorothiazide.

one interaction term, to provide the best fit. Meanwhile, for ARB/HCT combination, the quadratic polynomial regression model containing two linear terms and two quadratic terms was best fitted to the naïve pooled data (**Table 3**). **Fig. 1** shows the goodness-of-fit of the predicted versus observed SBP reductions and plots of standardized residuals versus fitted values. **Fig. 2** shows a visual comparison of the predicted and observed SBP reductions.

Dose-response surface patterns

The estimated coefficients for each model are listed in **Table 4**. Response surface analysis of SBP reduction for all ARB/AML and ARB/HCT combinations within the range of doses studied indicated a statistically significant linear dose response for ARB ($p < 0.001$), AML ($p < 0.001$), and HCT ($p < 0.001$) in first-order terms. Regarding second-order terms, ARB^2 was statistically significant ($p < 0.001$), indicating a curvilinear dose-response of or flattening

Table 3. Model comparison

Response: SBP reduction	df	Adjusted R^2	AIC	BIC	*p*-value	
					Model 1 vs. Model 2 (LRT)	Model 2 vs. Model 3 (LRT)
ARB/AML						
Model 1 (degree = 1, linear)	2	0.92	255.31	260.66		
Model 2 (degree = 2, quadratic)	5	0.97	222.91	233.62	< 0.001	
Model 3 (degree = 3, cubic)	9	0.97	225.07	242.91		0.2115
ARB/HCT						
Model 1 (degree = 1, linear)	2	0.91	443.39	450.54		
Model 2 (degree = 2, quadratic)	5	0.95	403.75	418.05	< 0.001	
Model 3 (degree = 3, cubic)	9	0.95	409.34	433.16		0.6596

SBP, systolic blood pressure; df, degrees of freedom; AIC, Akaike information criteria; BIC, Bayesian information criteria; LRT, likelihood ratio test; ARB, angiotensin receptor blocker; AML, amlodipine; HCT, hydrochlorothiazide.

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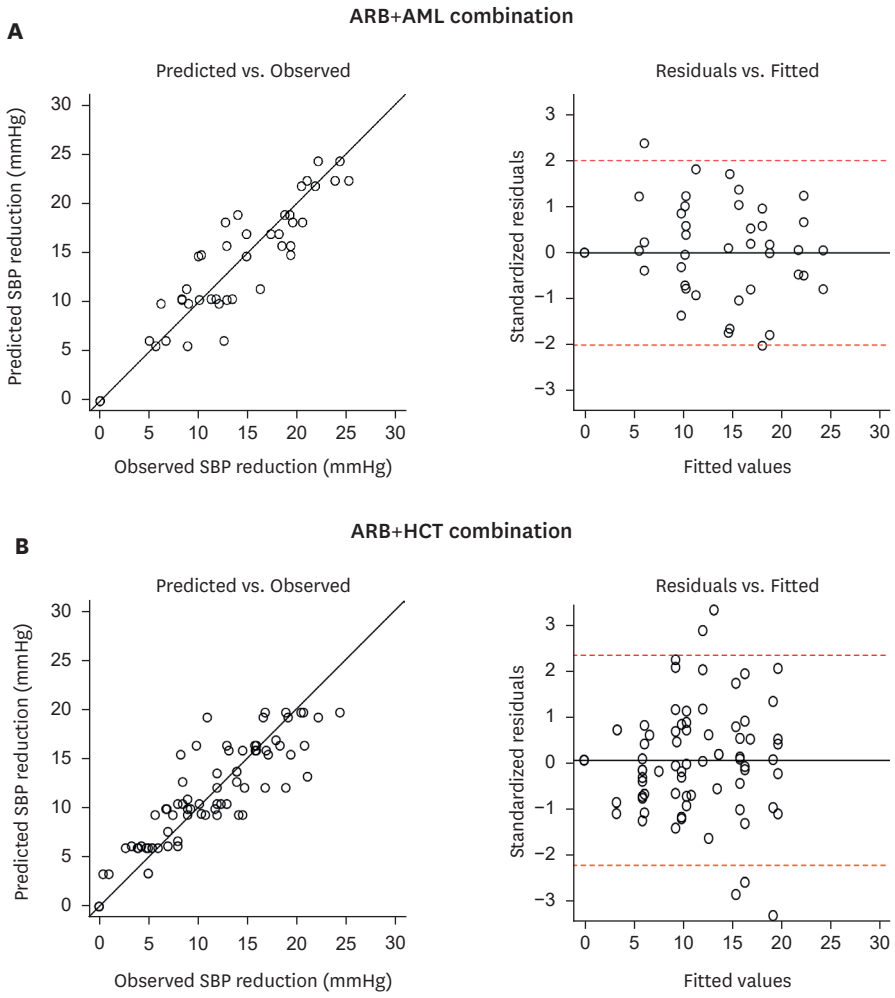

Figure 1. Goodness of fit plots of (A) ARB+AML combination and (B) ARB+HCT combination.
ARB, angiotensin receptor blocker; AML, amlodipine; SBP, systolic blood pressure; HCT, hydrochlorothiazide.

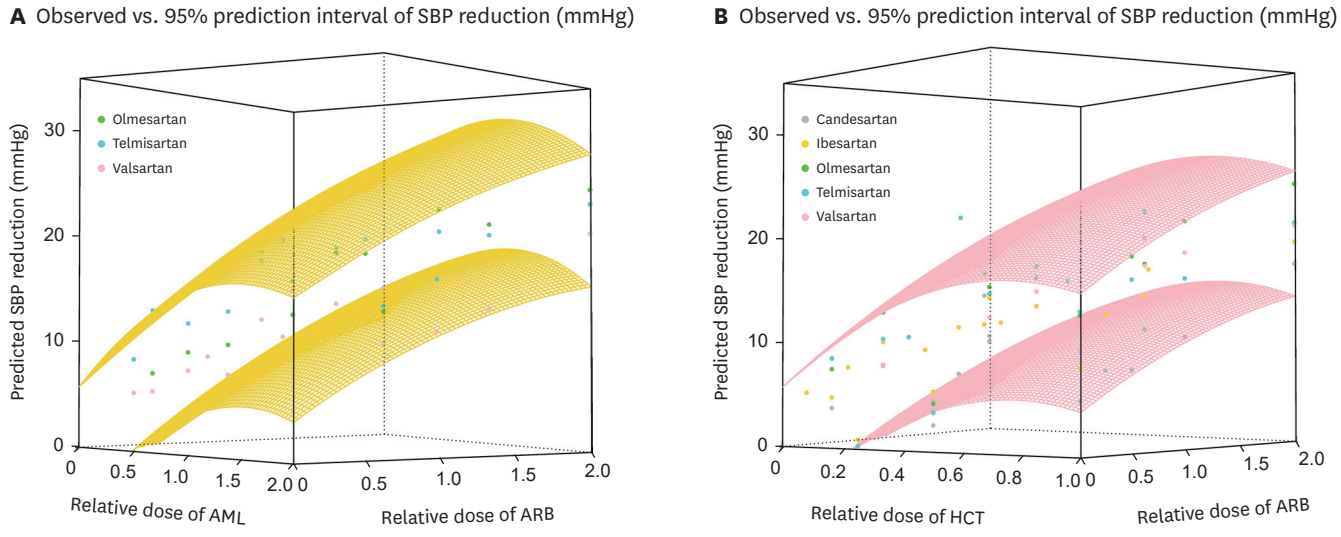

Figure 2. Visual comparison of observed versus 95% predicted response intervals of (A) ARB+AML combination and (B) ARB+HCT combination.
SBP, systolic blood pressure; AML, amlodipine; ARB, angiotensin receptor blocker; HCT, hydrochlorothiazide.

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Table 4. Estimated effects and coefficients for each model

Combination group	Coefficients	Standard error	*t*-value	*p*-value
ARB/AML				
ARB	14.51	1.74	8.36	< 0.001
AML	12.00	1.72	6.99	< 0.001
ARB*AML	−1.23	0.63	−1.94	0.0593
ARB^2	−4.68	0.90	−5.22	< 0.001
AML^2	−1.78	0.89	−1.99	0.0536
Response surface regression equation	$SBP\ Reduction\ (ARB/AML) = 0 + 14.51xARB + 12.00xAML - 1.23xARBxAML - 4.68xARB^2 - 1.78xAML^2$			
ARB/HCT				
ARB	14.61	1.35	10.84	< 0.001
HCT	14.43	2.44	5.91	< 0.001
ARB^2	−4.70	0.68	−6.89	< 0.001
HCT^2	−5.14	2.53	−2.03	0.046
Response surface regression equation	$SBP\ Reduction\ (ARB/HCT) = 0 + 14.61xARB + 14.43xHCT - 4.70xARB^2 - 5.14xHCT^2$			

ARB, angiotensin receptor blocker; AML, amlodipine; SBP, systolic blood pressure; HCT, hydrochlorothiazide.
The equation excluding the ARB*HCT interaction term is also provided for reference.

out of the ARB effect over the dose range studied, whereas AML^2 ($p = 0.0536$) and HCT^2 ($p = 0.046$) indicated an approximate curvilinear dose-response of these two drugs over the dose rage studied. The interaction term of ARB/HCT was not statistically significant and was dropped from the final model, suggesting a full additive effect when the two drugs were used together. However, the marginally significant *p*-value ($p = 0.0593$) of the ARB/AML interaction term could indicate a negative interaction, implying that the effect of the combination drug was less than the sum of the component effects. The equations for both the ARB/AML and ARB/HCT combinations are presented in **Table 4**. We employed a *p*-value threshold of 0.10 to determine whether to add terms to the model, and all the terms presented in **Table 4** were included in the model. Additionally, the mean predicted response surface versus the observed SBP reduction is depicted in **Fig. 3** for visual comparison.

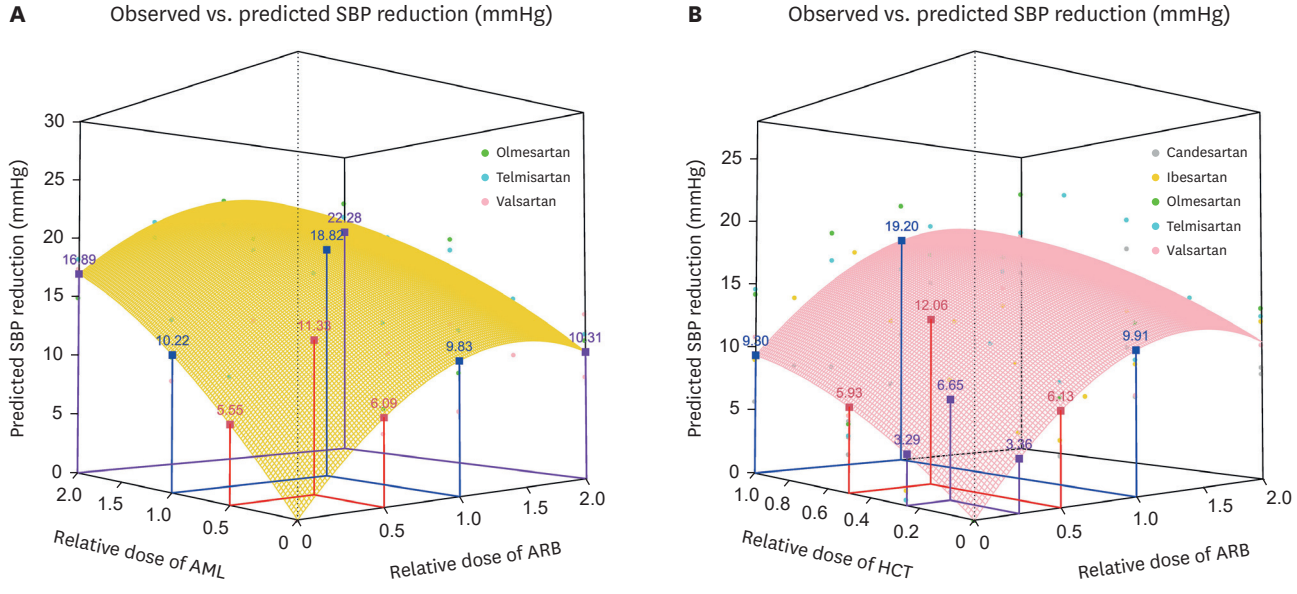

Figure 3. Response surface and estimates: predicted mean SBP reduction (mmHg) of (A) ARB+AML combination and (B) ARB+HCT combination.
SBP, systolic blood pressure; AML, amlodipine; ARB, angiotensin receptor blocker; HCT, hydrochlorothiazide.

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Table 5. Ratio of predicted values of combination and additive effects

Combination group	Relative dose	Predicted SBP reduction				Ratio†
		ARB	AML or HCT	Combination effect	Additive effect*	
ARB/AML	0.5	6.09	5.55	11.33	11.64	0.97
	1	9.83	10.22	18.82	20.05	0.94
	2	10.31	16.89	22.28	27.20	0.82
ARB/HCT	0.25	3.36	3.29	6.65	6.65	1.00
	0.5	6.13	5.93	12.06	12.06	1.00
	1	9.91	9.30	19.20	19.21	1.00

SBP, systolic blood pressure; ARB, angiotensin receptor blocker; AML, amlodipine; HCT, hydrochlorothiazide.
*Additive effect = the sum of the effects of two individual drugs (ARB plus AML or HCT).
†Ratio = combination effect/additive effect.

Dose-response in model prediction

As shown in **Fig. 3**, the predicted reduction in SBP increased as the doses of ARB, AML, or HCT increased, and the combined treatment showed an additive relationship. The predicted SBP reductions with RSD treatments were similar, ranging from 9.30 to 10.22 mmHg for monotherapies at RSD, and from 18.82 to 19.20 mmHg for combination therapies at RSD. The predicted SBP reduction with the lower-dose combination was greater than that with the higher-dose monotherapy. The predicted SBP reduction with the half-dose combination was 11.33 mmHg for ARB/AML and 12.06 mmHg for ARB/HCT, which were approximately 11–30% greater than the efficacies of each monotherapy at RSD. In case of the quarter-dose ARB/HCT combination, the predicted SBP reduction was 6.65 mmHg, which was 8–12% greater than in each of half-dose monotherapy, where the predicted SBP reductions were 6.13 mmHg for ARB and 5.93 mmHg for HCT (**Table 5**).

Combination versus sum of each monotherapy (expected additive effect)

For all dose combinations, the SBP-lowering effect was between 82 and 100% of the expected effect. It was 82–97% for ARB/AML combinations and 100% for ARB/HCT combinations. **Table 5** shows the ratio of estimated antihypertensive effects of the combination to the expected additive effects of each component when ARB/AML and ARB/HCT were used together.

DISCUSSION

Hypertension is a complex disease with remarkable variability in patients' BP responses. Achieving sufficient BP control in patients with hypertension remains a challenge. Interest in the use of combination therapy as an initial treatment has been increasing, especially for low-dose combination therapy [36]. The latter is known to provide greater efficacy, better response rate, and fewer side effects than monotherapy at RSD or higher-dose, and thus may provide solutions to many of the problems contributing to poor BP control rates, especially when it is used as an initial therapy [7].

Given the increasing interest in low-dose combination therapy as an optimal treatment option, reliable methods are required to predict its efficacy. In this study, we used RSM to explore the dose-response characteristics of combination therapy involving ARB with either AML or HCT particularly at low-doses. The RSM is a set of statistical techniques used for empirical model building [24]. It is useful for identifying the optimal dose for combination therapy, as well as the interactions between drugs and other variables [24,25,27-29]. Despite

its usefulness, RSM has limitations. Estimates from the model can only be interpreted within the analyzed dose range, and it relies on empirical model fitting, primarily using a quadratic model. Since confirming the information on a fitted dose-response relationship through a large factorial trial is difficult, the dose-response relationship based on RSM should primarily be interpreted for descriptive purposes [24,25]. Originally, the primary purposes of RSM in combination drug clinical trials are 1) to find the stationary points or the optimal doses of two drugs in combination, 2) to estimate response at specific doses and 3) to test whether specific combination dose means were greater than the corresponding monotherapy means [28]. However, since our interest was to predict antihypertensive effect (SBP reduction) of low-dose combination therapy involving ARB with AML or HCT, we focused on the doses ranging from 0.25 to 2 times the RSD of these combination drugs.

As a result of response surface analysis, we visualized the dose-response surface alongside the observed data from the factorial design trials. The findings revealed that the efficacy of low-dose combination therapy surpass that of RSD monotherapy for each individual component, with up to 30% greater reduction in SBP.

This implies that the initial combination therapy at half-dose has a meaningful BP lowering effect, at least equivalent to that of RSD monotherapy, providing a rationale for the use of initial low-dose combination therapy. For patients requiring substantial SBP reduction, half-dose combination therapy can offer significant BP control, equal to or even greater than monotherapy at RSD. Furthermore, we observed that the majority of the observed values fall within 95% of the predicted response intervals, indicating the reliability and predictiveness of our model. In this study, ratio of the combination effect to the expected additive effect ranged from 0.82 to 0.97, with a slightly higher ratio observed at lower doses than at higher doses for ARB/AML combination. The ratio is associated with the interaction term in a polynomial regression model. The interaction term in a polynomial regression model is related to the additivity of each monotherapy effects of the two drugs when used in combination. A positive (synergistic) interaction indicates that the BP reduction effect was greater than the sum of the effects of the two individual drugs, while a negative (infra-additive) interaction indicates an effect that is less than additive [37]. The ARB/AML combination exhibited a negative (infra-additive) interaction with a marginal significance ($p = 0.0593$) in present study. Therefore, the concurrent administration of AML with ARB exerts a greater antihypertensive effect than either drug given alone, but the combined effect is less than the sum of the effects of the two drugs when used individually. Furthermore, the relatively lower ratio at higher doses indicates that the negative interaction is more substantial at higher doses.

Our result is consistent with a previous meta-analysis, which reported a ratio of 0.89 observed to expected incremental BP lowering effects of adding a drug with CCBs [38]. Notably, in an FDA review of telmisartan and AML combination product, the reviewer observed the DBP reduction effect of the combination drug to be between 60 and 70% of the expected additive effect, which was within the range observed for other combination drugs [39]. These findings suggest that our approach of using RSM to predict the efficacy of low-dose combination therapy is promising and can help in optimizing the treatment of patients with hypertension. Interestingly, Heo et al. [40] reported a quantified negative interaction (infra-additivity) between valsartan and AML using a quantitative model to study the BP-lowering effect of the combination of these two drugs. Although it may vary depending on the BP level before treatment, it can be inferred that BP cannot continue to fall indefinitely after administering

antihypertensive drugs. Therefore, the magnitude of the interaction appears to be more significant in the development of a combination drug than the negative interaction itself. This is because it is related to estimating the effect size between combination therapy and monotherapy, as well as calculating the sample size for a clinical trial.

Furthermore, in terms of the mechanism of action of combination drugs, CCBs and diuretics stimulate the plasma renin and overall RAAS activity to compensate for the reduced pressure in the glomerular afferent arteriolar and loss of sodium, respectively. ARBs inhibit the RAAS and act through different and complementary mechanisms with CCBs or diuretics [8,41-43]. This impact may differ depending on the drug class or dosage and the extent to which they influence RAAS or other pathophysiological pathways. For example, HCT could increase activity of the circulating RAAS while simultaneously decreasing activity of the tissue RAAS [44]. Further investigation or additional data might be needed to clarify the true nature of the interaction effect.

Nevertheless, the overall lack of significant interaction between ARB/AML or ARB/HCT in this study suggests an additive effect of the two drugs when used in lower dose combination.

In the present study, we did not review safety data because our focus was on the dose-response for BP lowering effect. However, since the adverse events of CCBs and diuretics occur in a dose-dependent manner, administering these two drugs at lower doses is theoretically expected to reduce adverse events rather than increasing the dosage of each drug [31]. Moreover, there are no reports indicating that low-dose combination drugs increase the risk of adverse effects [45-47]. Addressing potential adverse effects or safety concerns of combination therapy is necessary for further study.

One limitation of this analysis was the small number of studies and data included, being limited to clinical trials that supported the FDA approval of new drugs. Another limitation was that the data used for the analysis and modeling were mean values from the FDA review and not raw data. Although the analysis was done using mean values, there are no major concerns expected when interpreting the clinical significance compared to the analysis using raw data. This is because the interpretation of research results from raw data is primarily based on average findings as well. Nevertheless, since the analysis outcome is based on the naïve pooling of SBP reductions from all ARB classes for each dose, it is expected that there will be slight differences among each ARB class. The ARB class was considered as a covariate. However, due to the limited amount of data available for each class of ARBs, it was deemed inappropriate to estimate the effect of each specific class. The modeling power is not expected to be high due to the limited amount of data. Therefore, the results are expected to be exploratory and can only serve as a reference for clinical decision-making.

Overall, our results demonstrated the potential of RSM as a valuable tool for predicting the efficacy of combination therapy, particularly for low-dose combinations. Compared to monotherapy, combination drug therapy has been shown to not only provide enhanced effectiveness but also the added benefit of allowing for the administration of a lower-dose combination therapy instead of resorting to a higher-dose monotherapy regimen. This finding is of significant clinical relevance, since it has the potential to improve patient outcomes by reducing the risk of adverse events associated with higher doses of medication while maintaining optimal BP control.

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