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# Effectiveness of single-pill combination olmesartan/amlodipine/hydrochlorothiazide therapy in patients with apparent resistant hypertension

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This pioneering study investigated the real-life effectiveness of single-pill combination (SPC) antihypertensive therapy in patients with uncontrolled blood pressure (BP) and cardiovascular risk factors. After treatment with olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide for 24 weeks, adults with apparent resistant hypertension had significantly reduced systolic BP and approximately 80% achieved target BP. SPC therapy may improve adherence in patients with pseudo-resistant hypertension and is a potentially effective treatment for resistant hypertension.

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## TO THE EDITOR:

Hypertension is a leading cause of morbidity and mortality globally; resistant hypertension is a severe, challenging and increasingly prevalent form, that needs special treatment [1–3]. Effective management begins by distinguishing true resistant hypertension from pseudo-resistant hypertension, which is often due to non-adherence to antihypertensive medications [1, 2]. Based on evidence that single-pill combination (SPC) antihypertensives control blood pressure (BP) more effectively than multi-pill regimens due to better adherence [1, 4, 5], SPCs are recommended for treating resistant hypertension [1–6]. However, there is limited evidence supporting the real-world effectiveness of SPC therapy in Asians with resistant hypertension [7], especially among those with cardiovascular risk factors, which affect many patients [8–10]. To address this evidence gap and inform improved treatment strategies, we investigated the effectiveness of SPC in Korean patients with apparent resistant hypertension.

This was a post-hoc subgroup analysis of patients with unconfirmed resistant hypertension, who were identified from a prior observational study on the effectiveness of SPC therapy in Korean adults with hypertension and cardiovascular risk factors [5]. Patients were  $\geq 19$  years old with  $\geq 1$  cardiovascular risk factor as defined by Korean guidelines (male age  $\geq 45$ , female age  $\geq 55$ ; smoking; diabetes; dyslipidemia; chronic kidney disease; prior or

present cardiovascular disease) [6], and were naïve to and newly prescribed olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide SPC tablets (OLM/AML/HCT).

This post-hoc sub-analysis included patients who completed 24 weeks of OLM/AML/HCT, had baseline and follow-up BP data, and met additional inclusion criteria for uncontrolled hypertension based on a previously published operational definition [11]. Accordingly, we defined apparent resistant hypertension as having baseline systolic BP (SBP)  $\geq 140$  mmHg ( $\geq 135$  mmHg if diabetic) despite concurrent treatment with an angiotensin receptor blocker or angiotensin converting enzyme inhibitor, a calcium channel blocker, and a diuretic. Patients with baseline SBP above these thresholds but who were not using the specified antihypertensive drug combination, were deemed to have “non-resistant hypertension”, as defined by previous investigators [11].

Baseline data included age, sex, lifestyle-factors, medical history, and antihypertensive treatments. BP was measured in a clinic at each institution at baseline and 8, 16 and 24 weeks after starting OLM/AML/HCT, according to standard office BP measurement practices described in the 2018 Korea Society of Hypertension guidelines [6].

Groups with apparent resistant hypertension and “non-resistant hypertension” were compared using t-tests for continuous variables and Chi-square tests for categorical variables

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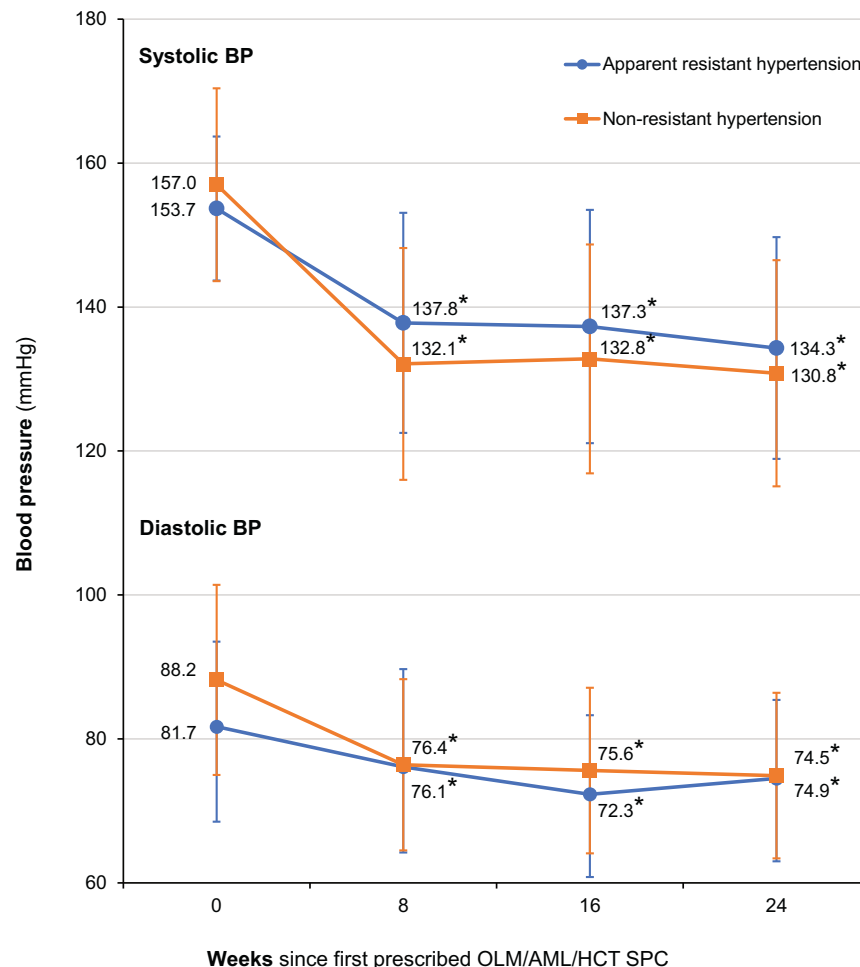
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(or Fisher's exact test if the expected frequency was  $\leq 5$  in  $>50\%$  of cells). The primary outcome was BP change from baseline at 24 weeks, with statistical significance assessed using a paired t-test (or Wilcoxon's signed-rank test for  $<30$  subjects); sub-analysis of the BP change by antihypertensive classes prescribed at 24 weeks used the same tests. Target SBP achievement after 24 weeks (secondary outcome) was compared using a Chi-square test. Residuals for normality and homoscedasticity were assessed to verify the model fit and appropriateness for statistical tests, as applicable. Two-sided  $p$ -values  $< 0.05$  were considered statistically significant. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Among 1538 patients with uncontrolled hypertension and baseline BP data who completed 24 weeks of OLM/AML/HCT, 120 had apparent resistant hypertension (Fig. S1), 51 (42.5%) of them despite using at least four antihypertensive medications (Table S1). Compared to patients with "non-resistant hypertension", those with apparent resistant hypertension were older (67.7 vs. 63.7 years,  $p = 0.044$ ), had lower baseline SBP (153.7 vs. 157.0 mmHg,  $p = 0.012$ ) but higher pulse pressure (72.0 vs. 68.8 mmHg,  $p = 0.033$ ), and were more frequently prescribed beta blockers (42.5 vs. 21.9%,  $p < 0.0001$ ) (Table S1). At 24 weeks,  $<10\%$  of patients were using other antihypertensive drugs concomitant with OLM/AML/HCT, with beta blockers (4%) the most common add-on (Table S2).

The mean SBP of both groups was significantly reduced from baseline at all timepoints after starting OLM/AML/HCT (Fig. 1). After 24 weeks, mean SBP had fallen by 19.5 mmHg from baseline in patients with apparent resistant hypertension and by 26.2 mmHg in those with "non-resistant hypertension" (both  $p < 0.0001$ ); consequently, 79.2% of patients with apparent resistant hypertension and 83.8% with "non-resistant hypertension" achieved their target SBP, with no significant between-group difference in the goal attainment rate ( $p = 0.192$ ) (Table S3). Uncontrolled BP despite OLM/AML/HCT for 24 weeks persisted in 255 patients (10.6%); 230 with "non-resistant hypertension" and 25 with apparent resistant hypertension (Fig. S1).

Resistant hypertension is a complex condition for which evidence on optimal treatment strategies is limited. This was the first real-world study of the effectiveness of SPC therapy to focus on patients with apparent resistant hypertension and cardiovascular risk factors. Patients with apparent resistant hypertension had a significant 19.5 mmHg reduction in SBP 24 weeks after starting OLM/AML/HCT SPC therapy, with 79% achieving target SBP, consistent with previous findings in the wider hypertensive population [5, 7]. Significantly reduced SBP in this group was especially noteworthy, given that 42% were previously using a beta blocker added to an angiotensin receptor blocker or angiotensin converting enzyme inhibitor, plus a calcium channel blocker and a diuretic. Effective BP control among patients who



**Fig. 1** Blood pressure changes from baseline in patients with apparent resistant hypertension and non-resistant hypertension over 24 weeks after starting OLM/AML/HCT. AML amlodipine besylate, BP blood pressure, HCT hydrochlorothiazide, OLM olmesartan medoxomil, SPC single-pill combination. \*  $P$  values were calculated using paired t tests:  $P < 0.0001$  vs baseline.

mostly used OLM/AML/HCT alone for 24 weeks (Table S2) is likely attributable to SPC therapy improving adherence compared with polypharmacy [1–6]. These observations implicate pseudo-resistant hypertension in many patients who met our criteria for apparent resistant hypertension, underscoring the importance of enhancing medication adherence in patients with suspected resistant hypertension [1–4, 6].

Diagnosing resistant hypertension requires confirmation of therapy adherence, out-of-office BP recordings and exclusion of secondary causes [1]. After 24 weeks of OLM/AML/HCT treatment, approximately 11% of patients (255/2401) still had uncontrolled BP, fulfilling criteria for resistant hypertension (uncontrolled BP despite  $\geq 3$  antihypertensive medications including a diuretic). This prevalence is consistent with the range of around 8–12% reported for true resistant hypertension in Korea [8–10, 12]. Hence, SPC therapy could potentially help to diagnose true resistant hypertension in unconfirmed cases.

Although guidelines recommend mineralocorticoid receptor antagonists as an add-on treatment for BP that remains uncontrolled by triple antihypertensive therapy [1, 4, 6], our patients were more likely to be prescribed beta blockers, consistent with frequent use of beta blockers globally and relative underuse of mineralocorticoid receptor antagonists [1, 3]. This gap between guidelines and practice may reflect concern about an association between mineralocorticoid receptor antagonists and hyperkalemia in patients with comorbid renal dysfunction [1, 2, 4], which is common in Korea.

Although both groups had generally similar baseline characteristics, patients with apparent resistant hypertension were comparatively older than those with “non-resistant hypertension”, highlighting that age is an important risk factor for apparent resistant hypertension [2, 3]. Pertinently, patients with apparent resistant hypertension, who were predominantly  $\geq 65$  years old, had higher mean pulse pressure, characteristic of isolated systolic hypertension.

This study gives valuable insights into the utility of SPC treatment in the real-world management of hypertension; nevertheless, we acknowledge limitations. Observational studies are subject to inherent biases and variable data quality that may affect the results. An observational design precludes evaluating causality, and the findings may not necessarily be generalizable or comparable with other studies due to differing population characteristics, settings, and definitions of apparent resistant hypertension. For example, selection bias due to enrolling patients from specific clinics may limit generalization to the entire hypertensive population in Korea. Information bias, arising from using office-based BP measurements rather than ambulatory monitoring, could potentially introduce white-coat hypertension effects and lead to misclassification of resistant hypertension. Selecting patients with high office BP values, which are known to have a large random error, may make BP changes partly attributable to “regression to the mean”. Defining “non-resistant hypertension” indirectly, based on not using a particular treatment combination, may not completely exclude patients with resistant hypertension, as shown by the presence of some cases (~10%) among the group with “non-resistant hypertension”. The subgroup analysis of BP changes according to antihypertensive classes prescribed at 24 weeks was exploratory and without prior power calculations, increasing the potential for type I error, and insufficient statistical power. The antihypertensive adherence rates before and during OLM/ALM/HCT SPC therapy were not determined. Consequently, our findings should be interpreted cautiously pending corroboration by further studies.

SPC therapy effectively treats resistant hypertension in real-world patients at high cardiovascular risk and may improve antihypertensive adherence in patients with pseudo-resistant hypertension.

## SUMMARY TABLE

What is known about this topic

- Resistant hypertension is increasingly prevalent due to population aging and causes substantial burdens of cardiovascular disease, kidney disease, and mortality, necessitating special treatment strategies.
- Single-pill combination (SPC) therapy, which improves antihypertensive adherence, is recommended; however, real-world data on SPC effectiveness are lacking.

What this study adds

- This is the first study of the effectiveness of SPC therapy in real-life patients with uncontrolled blood pressure and cardiovascular risk factors.
- Twenty-four weeks of treatment with olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide SPC significantly reduced systolic blood pressure in patients with apparent resistant hypertension and non-resistant hypertension; approximately 80% achieved BP targets.
- SPC therapy may improve antihypertensive adherence in patients with pseudo-resistant hypertension and effectively treats resistant hypertension in patients at high cardiovascular risk.

## DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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## AUTHOR CONTRIBUTIONS

Jaewon Oh, Wonho Kim, Gee-Hee Kim, Hack-Lyoung Kim, Sang-Don Park, Kyung Wan Min, Dongkeun Hyun, Jun Hwa Hong, Soo Lim, Ji-Hwan Bae, and Jinho Shin contributed to data acquisition and interpretation. Jaewon Oh and Ji-Hwan Bae contributed to conceiving the design and wrote and revised the first draft manuscript. Jinho Shin contributed to reviewing and critically revising the manuscript. All authors reviewed and approved the manuscript submitted for publication and agree to be accountable for all aspects of the work, and for ensuring the accuracy and integrity of the publication.

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## COMPETING INTERESTS

Jaewon Oh, Wonho Kim, Gee-Hee Kim, Hack-Lyoung, Sang-Don Park, Kyung Wan Min, Dongkeun Hyun, Jun Hwa Hong, and Soo Lim declare that they have no competing interests. Ji-Hwan Bae is a full-time employee of Daiichi Sankyo Korea Co., Ltd. Jinho Shin received honoraria from Daiichi Sankyo, Organon, Bristol Myers Squibb, Menarini, Sanofi, Hanmi, Boryung, Chong Kun Dang, and Daewoong, and grants from Sanofi and Hanmi.

## ETHICAL APPROVAL

This study was conducted according to ethical principles established by the Declaration of Helsinki. The Review Boards of participating institutions approved the protocol. All patients provided informed written consent.

## ADDITIONAL INFORMATION

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