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Original Research

A Phase III Randomized, Double-Blind, Active-Controlled, Multicenter Study on the Efficacy and Safety of Ezetimibe/Atorvastatin/Amlodipine Combination in Patients With Comorbid Primary Hypercholesterolemia and Essential Hypertension

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ABSTRACT

Purpose: This study aimed to evaluate the efficacy and safety of triple combination of ezetimibe (Eze)/atorvastatin (Ato) 10/40 mg + amlodipine (Aml) 10 mg therapy for lowering the low-density lipoprotein cholesterol (LDL-C) and blood pressure compared with either Eze/Ato 10/40 mg or Aml 10 mg therapies in patients with comorbid primary hypercholesterolemia and essential hypertension.

Methods: This was a randomized, multicenter, double-blind, active-controlled, Phase III clinical trial. Participants underwent a wash-out period (2 weeks for nonfibrate medications, 6 weeks for fibrates) followed by 4 weeks of therapeutic lifestyle changes. Subsequently, 109 participants were randomly assigned to 3 groups: (1) Eze/Ato 10/40 mg + Aml 10 mg, (2) Eze/Ato 10/40 mg, and (3) Aml 10 mg. The coprimary end points were percentage change in LDL-C and change in mean sitting systolic blood pressure (SBP) compared with baseline at week 8.

Findings: A total of 109 participants were enrolled in the study, and there were no statistically significant differences in the baseline characteristics of participants across the 3 groups. After 8 weeks of treatment, the least-square (LS) mean (SE) of percent change from baseline in LDL-C was −57.95% (3.52%) for the Eze/Ato 10/40 mg + Aml 10 mg group and 8.93% (3.54%) for the Aml 10 mg group. The LS mean difference (SE) between these 2 groups was statistically significant at −66.88 (4.95) (95% CI, −76.77% to −56.99%) ($P < 0.0001$). Furthermore, at week 8, the LS mean (SE) change in mean sitting SBP between the Eze/Ato 10/40 mg + Aml 10 mg group and the Eze/Ato 10/40 mg group was −19.24 (2.42) mm Hg and −4.43 (2.56) mm Hg, respectively. The LS mean difference (SE) between the 2 groups was statistically significant −14.81 (3.53) (95% CI, −21.87 to −7.74) mm Hg ($P < 0.0001$). No serious adverse drug reactions occurred in any of the study groups.

Implications: Triple combination therapy with Eze/Ato + Aml has effectively reduced the LDL-C and SBP independently, compared with either Eze/Ato or Aml therapies over 8 weeks of treatment period. In terms of safety, there

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were no significant differences among the 3 treatment groups. This research lays the groundwork for the development of a triple fixed-dose combination in the future, which could improve patient convenience and adherence by reducing pill burden. Clinical Research Information Service (CRIS), Republic of Korea: KCT0006283.

Introduction

Cardiovascular (CV) diseases (CVDs) are the leading cause of mortality and morbidity globally, with their burden steadily increasing over decades.[1] Hypertension and hypercholesterolemia are the 2 most significant modifiable risk factors of CVDs[2] which often coexist and contribute synergistically to enhance the mortality and morbidity related to CVDs.[3,4] As per 2022 Global Burden of Disease Study, hypertension ranks first and dyslipidemia ranks third among the risk factors contributing to the CVD burden.[5] In the Republic of Korea, more than 50% of hypertensive patients have dyslipidemia,[5] and approximately 60% of dyslipidemic population have hypertenstion.[6] Individuals with comorbid dyslipidemia and hypertension are at a significantly higher risk for CVDs,[7] with their risk being 1.57 times higher than that of those with only 1 of these conditions.[8] Therefore, treating both conditions concurrently significantly reduces CVD risk,[9,10] highlighting the need for a multifactorial therapeutic approach that targets dyslipidemia and hypertension simultaneously.

Atorvastatin (Ato), a hydroxymethylglutaryl-coenzyme A reductase inhibitor, is one of the most commonly prescribed statins for preventing CV events by lowering the low-density lipoprotein cholesterol (LDL-C).[11] Nevertheless, a substantial number of patients do not achieve target lipid levels with statins alone, necessitating additional cholesterol-lowering therapies for further CV risk reduction.[12,13] Ezetimibe (Eze), a cholesterol absorption inhibitor, is recommended to use in combination with statins by recent guidelines to achieve more intensive LDL-C reduction in patients who do not reach target LDL-C levels with statins monotherapy.[14–16] Amlodipine (Aml), a long-acting dihydropyridine calcium channel blocker (CCBs), is one of the most widely prescribed antihypertensive medications[17] due to its minimal drug-drug interactions (DDIs) with other CVD regimens.[18] Therefore, a triple combination of statins, cholesterol absorption inhibitors, and CCBs could be an effective regimen for treating comorbid hypercholesterolemia and hypertension.

However, this triple therapy approach for managing the CV risk in patients with both chronic conditions might increase the pill burden. Given the chronic nature of these diseases, medication adherence is crucial for long-term management; increasing the number of pills may lead to nonadherence.[7] Thus, a fixed-dose combination (FDC) of these medications could increase adherence by reducing the pill burden,[5,19,20] while effectively improving the blood pressure (BP) and LDL-C levels over the long term. However, evaluating the safety and effectiveness of combination therapy is necessary before developing an FDC to avoid potential safety issues while maintaining the efficacy of each individual medication.

For a promising future triple FDC, this Phase III study was designed to evaluate the efficacy and safety of Eze/Ato + Aml, Eze/Ato, and Aml in South Korean patients with comorbid primary hypercholesterolemia and essential hypertension. This study investigated the efficacy of these 3 regimens over 8 weeks in lowering lipid levels and controlling BP, while also assessing their individual safety profiles.

Participants and Methods

Study Design

This Phase III (CRIS identifier: KCT0006283, cris.nih.go.kr/cris), randomized, multicenter, double-blind, active-controlled, parallel-design study was conducted at 13 sites across South Korea between October 2020 and November 2021. All essential study documents, including protocol and informed consent form, were reviewed and approved by the Ministry of Food and Drug Safety in July 2020. Subsequently, these documents were reviewed and approved by the institutional review board at each clinical site prior to the study commencement. The study was conducted in compliance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all relevant local laws and regulations. All participants provided written informed consent before participating in the study or undergoing any study-related procedures.

The study period consisted of a screening period (including 2 weeks of wash-out period (6 weeks for fibrates) and 4 weeks of therapeutic lifestyle changes [TLCs]) and 8 weeks of treatment period (Supplemental Figure 1 in the online version at doi:10.1016/j.clinthera.2025.03.001). Following written informed consent, participants underwent screening and those meeting all the eligibility criteria were required to comply with TLCs and discontinue all lipid-modifying and antihypertensive medications (2 weeks minimum, 6 weeks for fibrates) prior to randomization. At randomization, the participants underwent reevaluation of eligibility criteria, primarily through BP and lipid profile assessments. Participants who remained eligible were randomly assigned to one of the 3 groups: a test group receiving Eze/Ato 10/40 mg + Aml 10 mg, control group 1 receiving Eze/Ato 10/40 mg, and a control group 2 receiving Aml 10 mg, each at a ratio of 1:1:1, stratified by groups based on CV risk factors using block randomization method (block size of 6) performed by an independent statistician, SHK (Soo Hwan Kim).

All study-related personnel were blinded to the treatment groups. To maintain blinding, all participants were provided with 2 tablets at a fixed time once daily for 8 weeks. The Eze/Ato 10/40 + Aml 10 mg group received 2 active drugs, whereas the Eze/Ato 10/40 mg group and the Aml 10 mg group received 1 active drug, with a matching placebo for each group.

Participants were instructed to strictly adhere to the TLCs throughout the study duration. Safety and efficacy assessments, including physical examinations, vital signs monitoring, laboratory tests, ECGs, and evaluation of adverse events, were conducted at baseline (randomization) and during follow-up visits scheduled at week 4 and week 8 of the double-blind treatment period.

Study Population

At screening, participants with comorbid hypercholesterolemia and hypertension, aged 19 years or older, who consented to discontinue their current medications 2 weeks prior to study entry, and had a mean sitting systolic BP (MSSBP) <180 mm Hg and a mean sitting diastolic BP (MSDBP) <110 mm Hg, as well as LDL-C levels ≤250 g/dL and triglyceride (TG) levels <400 g/dL, were considered eligible. A full list of inclusion and exclusion criteria is provided in Supplemental Table I (in the online version at doi:10.1016/j.clinthera.2025.03.001).

The participants' eligibility was reassessed before randomization on the criteria of MSSBP between 140 and 180 mm Hg (130–180 mm Hg for patients with diabetes or chronic kidney disease), MSDBP <110 mm Hg, and specific lipid levels according to CV risk groups as defined by the 2016 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines.[21] These guidelines recommend different thresholds for initiating lipid-lowering medications based on CV risk group. Aligning with guidelines, we assessed each participant's CV risk group while determining enrollment eligibility prior to randomization. Participants who met the criteria based on the following LDL-C and TG levels corresponding to their respective risk groups were enrolled: (1) low-risk (190 ≤ LDL-C ≤ 250 mg/dL), (2) moderate-risk (100 ≤ LDL-C

≤ 250 mg/dL), (3) high-risk (70 ≤ LDL-C ≤ 250 mg/dL), and (4) very high–risk (70 ≤ LDL-C ≤ 250 mg/dL) groups, whereas the TG levels in all the groups were <400 mg/dL (Supplemental Table II in the online version at doi:10.1016/j.clinthera.2025.03.001). Participants meeting eligibility criteria at both screening and randomization were assigned to treatment.

Key exclusion criteria included a current and/or past medical conditions affecting study results, abnormal laboratory findings, a history of allergies and hypersensitivities, drug or alcohol abuse within 1 year of screening visit, pregnancy, genetic metabolic disorders, breastfeeding, participation in another clinical trial within 3 months prior to first dose of study treatments (except for noninterventional trial), participants with difference of MSSBP ≥20 mm Hg and MSDBP ≥10 mm Hg between both arms, or any individual deemed ineligible for the study by the investigator.

Efficacy and Safety End Points

The primary outcomes were the percent change in LDL-C between the Eze/Ato 10/40 + Aml 10 mg and the Aml 10 mg groups, and the change in MSSBP in the Eze/Ato 10/40 + Aml 10 mg and the Eze/Ato 10/40 mg groups compared with baseline at week 8. The secondary outcomes included (1) percent change in LDL-C from baseline to week 4; (2) change in MSSBP from baseline to week 4; (3) changes in MSDBP from baseline to week 4 and week 8; (4) proportion of participants achieving target MSSBP of <140/90 mm Hg, or <130/80 mm Hg for participants with diabetes or chronic kidney disease at week 4 and week 8 compared with baseline; (5) proportion of participants meeting the LDL-C targets according to the 2016 ESC/EAS guidelines[21] (low risk <115 mg/dL, moderate risk <100 mg/dL, high risk/very high risk <70 mg/dL) at week 4 and week 8 compared with baseline; and (6) percent changes from baseline in total cholesterol (TC), TG, and high-density lipoprotein cholesterol (HDL-C) at week 4 and week 8 from baseline.

Blood pressure was measured at screening, baseline, and follow-up visits (week 4 and week 8), without taking antihypertensive medication on the day of the visit and participants avoided caffeine, exercise, and smoking at least 30 minutes before BP measurement. At screening, participants with no anatomic arm abnormalities had their BP measured after resting for 5 minutes, with 3 measurements taken on both arms and the arm with higher MSSBP was selected as the reference arm, and if both arms have similar MSSBP, then the arm with the higher MSDBP was selected as the reference arm. At subsequent visits, BP was measured on the reference arm for 3 times with an interval of 2 minutes and the average of the last 2 readings was recorded. Remeasurements were allowed only once if valid reasons were identified. Blood lipid profiles were assessed at baseline and follow-up visits (week 4 and week 8) in a central lab for efficacy assessments, with local lab results used for safety evaluations.

Safety evaluations included treatment-emergent adverse events (TEAEs), serious adverse events, adverse drug reactions (ADRs), serious ADRs (SADRs), and unexpected ADRs. Other safety assessments included physical examinations, vital signs, laboratory tests, and 12-lead ECG. Treatment-emergent adverse events were categorized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities version 24.1.

Sample Size Calculation

This study aimed to simultaneously demonstrate the superiority of the Eze/Ato 10/40 + Aml 10 mg group over the Eze/Ato 10/40 mg group in MSSBP reduction and over the Aml 10 mg group in LDL-C reduction as coprimary end points. Since both coprimary end points should meet superiority hypothesis concurrently, no multiplicity adjustment was made, and a significance level of 5% with 90% was set for each end point, achieving an overall power of 80%.

In a study by Preston et al,[22] the treatment difference (least-square [LS] mean) in SBP change after 8 weeks of treatment between the Aml 10 mg + Ato 40 mg group and the Ato 40 mg group was −10.3 mm Hg (95% CI, −13.3 to −7.2 mm Hg). Considering both groups did not include the Eze, the treatment difference was assumed to be −10 mm Hg. The SD was assumed to be 12 mm Hg by rounding the calculated SD of 11.78 mm Hg which was derived from the LS mean (−10.3 mm Hg) and its upper limit of 95% CI (−7.2 mm Hg). Based on these assumptions, a sample size of 31 participants per treatment group was calculated, and considering a 10% dropout rate, 35 participants were needed per treatment group. In the same study, the LS mean in LDL-C level after 8 weeks of treatment between Aml 10 mg + Ato 40 mg and Aml 10 mg was −40.6% (95% CI, −44.6% to −36.7%). Since the Eze was not taken into account by the reference study, the treatment difference was assumed to be −40%. The SD was assumed to be 15% by rounding the calculated SD of 14.82% which was derived from the LS mean (−40.6%) and its upper limit of 95% CI (−36.7%). Based on these assumptions, 3 participants per treatment group were calculated and considering a 10% dropout rate, 4 participants were needed per treatment group. Finally, to secure enough number of participants to confirm 2 hypotheses simultaneously, a total of 105 participants were deemed sufficient for this study considering 35 participants per treatment group. Sample size calculations were made using PASS 15 (2017) (NCSS, LLC, Kaysville, Utah, ncss.com/software/pass).

Statistical Analysis

The full analysis set (FAS) comprised all randomized participants receiving at least 1 dose of the study treatment and assessed at least once for primary efficacy variables after administration. The per-protocol set (PPS) was a subset of FAS, including participants completing the study without major protocol deviations affecting efficacy assessment. The safety set included all randomized participants who received at least 1 dose of the study treatments.

The coprimary efficacy end points and continuous variables among secondary end points were analyzed using a mixed effect models for repeated measures with treatment group (LDL-C change rate and MSSBP change), visit (week 4, week 8), grouping of participants based on CV risk groups (2016 ESC/EAS guidelines), baseline values, and interaction between visit and treatment as fixed effects, with an assumed unstructured covariance structure. Between-group comparisons of the efficacy end points were evaluated based on the difference in LS mean difference at week 8. LS means, SE for each group was provided as well as *P* value and relative 95% CI on LS mean difference between groups. If the test group showed statistically significant superiority in both primary end points over each control group, combination therapy was deemed superior to monotherapy. Categorical secondary end points were compared using logistic regression.

For the efficacy assessments using mixed effect models for repeated measures analysis, missing values were not imputed, and the original data were analyzed without correction of missing values. For the FAS analysis of continuous variables (MSSBP and MSDBP), missing values were handled using the last observation carried forward method using the most recent values measured including data from and unplanned visit after administration of study treatment. Additionally, for the analysis of BP normalization rates and LDL-C target rates, if data were still missing or unavailable after applying last observation carried forward, then those participants were classified as nonresponders (nonresponse imputation). For PPS analysis, raw data without correction of missing values were used.

Data were summarized using descriptive statistics for continuous variables and counts and proportions for categorical variables. For between-group comparison, continuous variables were assessed using ANOVA or Kruskal-Wallis tests, and for categorical variables, χ^2 or Fisher exact tests were used. For within-group comparison, Paired *t* tests (1-sample *t* tests in case of change rate) or Wilcoxon signed-rank tests

were used for continuous variables, and for categorical variables, McNemar's test was used. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc, Cary, North Carolina), with statistical significance defined as a 2-tailed *P* value of <0.05.

Results

Demographics and Baseline Characteristics

Of the 216 screened participants, 109 participants were randomly assigned to the 8 weeks of double-blind treatment with either Eze/Ato 10/40 mg + Aml 10 mg (n = 37), Eze/Ato 10/40 mg (n = 36), and Aml 10 mg (n = 36). Three participants discontinued from the Eze/Ato 10/40 mg + Aml 10 mg group, 5 from the Eze/Ato 10/40 mg group, and 5 from the Aml 10 mg group. A total of 104 (95.4%) participants were included in the FAS and 86 (78.9%) in the PPS (Figure 1). A higher proportion of participants (n = 13) were excluded from the PPS in the Eze/Ato group due to visit window violations (n = 4), dropout from the study (n = 3), randomization errors (n = 2), and errors in efficacy measurements (n = 2).

The demographics and baseline characteristics of the participants are summarized in Table I. At screening, the mean age of participants was 60.14 years, with a higher proportion of males. At randomization, the average MSSBP and LDL-C levels were 151.44 mm Hg and 139.73 mg/dL, respectively. There were no statistically significant differences in baseline characteristics between the 3 treatment groups, including age, sex, weight, medical history, coronary heart disease, and CVD risk distribution, BP and lipid profiles.

Efficacy Outcomes

Primary Outcomes (FAS Analysis)

As per FAS, the LS means (SE) for percent change in LDL-C between the Eze/Ato 10/40 + Aml 10 mg group and the Aml 10 mg group were −57.95% (3.52%) and 8.93% (3.54%) at week 8. A significant LS mean difference (SE) of −66.88% (4.95%) (95% CI, −76.77% to −56.99%) was observed between the 2 groups ($P < 0.0001$). The change in LS means for LDL-C between the Eze/Ato 10/40 mg + Aml 10 mg and the Eze/Ato 10/40 mg groups at week 8 was −58.35% (2.18%) and −56.71% (2.26%), respectively, with LS mean difference (SE) of −1.64 (3.12), which was not statistically significant ($P = 0.6011$) (Table II, Figure 2).

The LS means (SE) for MSSBP changes were −19.24 (2.42) mm Hg for the Eze/Ato 10/40 mg + Aml 10 mg group and −4.43 (2.56) mm Hg for the Eze/Ato 10/40 mg group at week 8. There was a significant LS mean difference (SE) of −14.81 (3.53) (95% CI, −21.87 to −7.74) mm Hg between the 2 groups ($P < 0.0001$) at week 8. A comparable change in MSSBP was seen in the Eze/Ato 10/40 + Aml 10 mg group compared with the Aml monotherapy group −19.01 (1.83) mm Hg and −19.56 (1.89) mm Hg, respectively, at week 8, and this difference was not statistically significant ($P = 0.8335$) (Table III, Figure 3). Results from the PPS analysis were consistent with those observed in the FAS analysis.

These results indicate that the combination therapy of Eze/Ato 10/40 mg + Aml 10 mg is effective in terms of reducing the LDL-C and MSSBP compared with the Eze/Ato 10/40 mg and Aml 10 mg therapies.

Secondary Outcomes (FAS Analysis)

A statistically significant higher proportion of participants achieved the target LDL-C level with Eze/Ato 10/40 mg + Aml 10 mg (82.35% at week 4 and 91.18% at week 8) compared with the Aml 10 mg group (5.88% at week 4 and 8.82% at week 8), with both time points showing $P < 0.0001$(Figure 4A). The proportion of participants achieving the target LDL-C level in the Eze/Ato 10/40 mg + Aml 10 mg group at week 4 and at week 8 was not significantly different between the groups (week 4 $P = 0.3844$, week 8 $P = 0.8178$).

A significant difference from baseline in TC levels was observed between the Eze/Ato 10/40 mg + Aml 10 mg and the Aml 10 mg groups ($P < 0.0001$). However, no significant differences were observed from baseline in TC levels between the Eze/Ato 10/40 mg + Aml 10 mg and the Eze/Ato 10/40 mg groups (week 4 $P = 0.7184$, week 8 $P = 0.6199$) (Figure 4B). HDL-C levels did not change significantly at any point in the study, in any treatment group (Figure 4C). TG levels did not change significantly at week 4 ($P = 0.7285$) and week 8 ($P = 0.1570$) between the Eze/Ato 10/40 mg + Aml 10 mg group and the Eze/Ato 10/40 mg group, but the change between the Eze/Ato 10/40 mg + Aml 10 mg group and the Aml 10 mg group was significant at both week 4 and week 8 ($P = 0.0001$) (Figure 4D). The combination therapy with Eze/Ato 10/40 mg + Aml 10 mg significantly reduced the apolipoprotein B and non-HDL-C levels compared with Aml 10 mg alone at both week 4 and week 8 ($P < 0.0001$) (Figure 4E and F).

The proportion of participants achieving the target BP in the Eze/Ato 10/40 mg + Aml 10 mg group was 67.65% at both week 4 and week 8. In

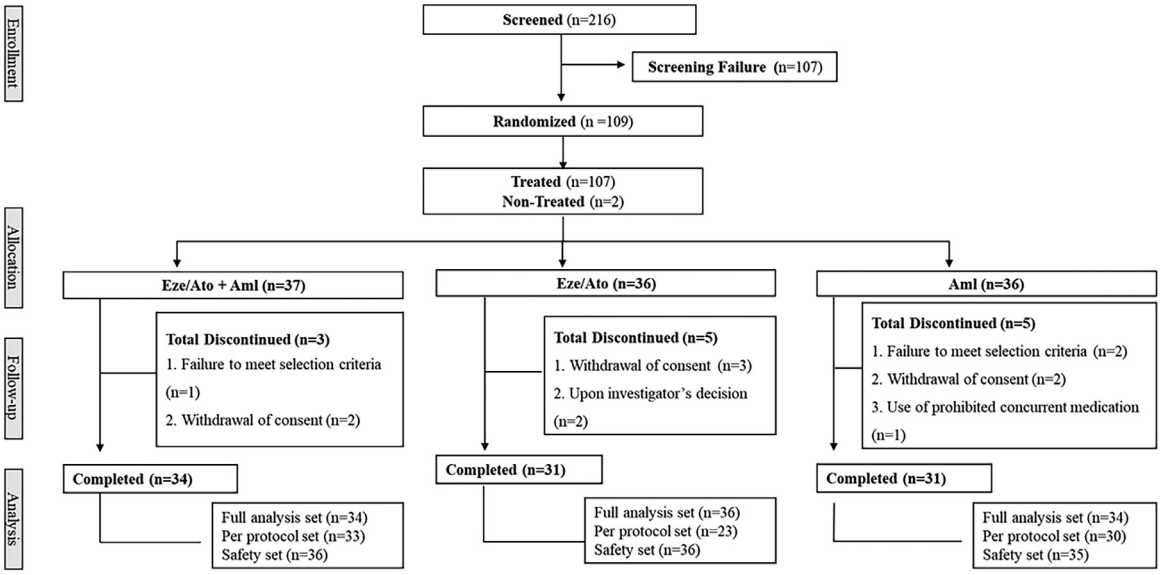

Figure 1. Participant disposition throughout the study. Aml = amlodipine; Ato = atorvastatin; Eze = ezetimibe; n = number of participants.

Table I
Demographics and baseline characteristics of the study participants.

Characteristics	Eze/Ato + Aml (n = 34)	Eze/Ato (n = 36)	Aml (n = 34)	Total (N = 104)	*P* Value
Age (y)	59.79 (11.31)	60.39 (11.09)	60.24 (9.04)	60.14 (10.44)	0.9707
Sex, male	25 (73.53)	25 (69.44)	27 (79.41)	77 (74.04)	0.6343
Height (cm)	166.42 (8.11)	164.95 (8.83)	166.75 (7.97)	166.02 (8.28)	0.6285
Weight (kg)	74.54 (12.99)	72.91 (15.70)	76.01 (13.61)	74.46 (14.11)	0.4499
BMI (kg/m^2)	26.77 (3.21)	26.64 (4.41)	27.25 (3.84)	26.88 (3.84)	0.533
HbA_{1c} (%)	6.08 (0.73)	6.04 (0.72)	6.23 (0.90)	6.12 (0.78)	0.7409
Current smoker	14 (41.18)	11 (30.56)	12 (35.29)	37 (35.58)	0.6445
Diabetes mellitus	10 (29.41)	11 (30.56)	13 (38.24)	34 (32.69)	0.6992
Coronary arterial disease	2 (5.88)	6 (16.67)	2 (5.88)	10 (9.62)	0.3353
Duration of hypertension (month)	128.14 (120.58)	110.37 (77.11)	118.10 (76.36)	118.71 (92.74)	0.8693
Lipids and BP at baseline					
MSSBP (mm Hg)	148.72 (9.54)	153.24 (12.20)	152.26 (10.69)	151.44 (10.96)	0.1932
MSDBP (mm Hg)	94.84 (8.13)	93.91 (10.45)	94.00 (7.73)	94.24 (8.81)	0.8962
Total cholesterol (mg/dL)	213.32 (31.41)	210.83 (32.81)	205.91 (35.03)	210.04 (32.93)	0.6441
Triglyceride (mg/dL)	183.94 (90.79)	191.25 (97.43)	177.53 (75.94)	184.38 (88.01)	0.9360
HDL-C (mg/dL)	48.68 (11.97)	48.86 (12.49)	48.41 (10.47)	48.65 (11.58)	0.9866
LDL-C (mg/dL)	143.62 (31.65)	138.28 (30.26)	137.38 (31.93)	139.73 (31.08)	0.6731
Non-HDL-C (mg/dL)	164.65 (29.97)	161.97 (34.36)	157.50 (34.28)	161.38 (32.77)	0.6658
Apolipoprotein B (mg/dL)	127.59 (23.32)	126.03 (25.91)	125.56 (27.08)	126.38 (25.26)	0.9425
Cardiovascular risk category*					
Low risk	0	0	0	0	0.9413
Moderate risk	14 (41.18)	13 (36.11)	12 (35.29)	39 (37.50)	
High risk	14 (41.18)	13 (36.11)	12 (35.29)	39 (37.50)	
Very high risk	12 (35.29)	16 (44.44)	15 (44.12)	43 (41.35)	

Continuous variables and categorical variables are presented as mean (SD) and n (%), respectively.
Aml = amlodipine; Ato = atorvastatin; Eze = ezetimibe; BMI = body mass index; BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure.
* 2016 European Society of Cardiology/European Atherosclerosis Society guideline.

Table II
Percent change from baseline in low-density lipoprotein cholesterol levels at week 8.

Assessment	Eze/Ato + Aml (n = 34)	Eze/Ato (n = 36)	Aml (n = 34)
Baseline			
Mean (SD)	143.62 (31.65)	138.28 (30.26)	137.38 (31.93)
Week 8			
Mean (SD)	58.79 (21.16)	58.89 (22.59)	146.26 (34.27)
MMRM result at week 8			
LS mean (SE)	−57.95 (3.52)		8.93 (3.54)
LS mean difference (SE)			−66.88 (4.95)
95% CI			−76.77 to −56.99
P value			<0.0001
MMRM result at week 8			
LS mean (SE)	−58.35 (2.18)	−56.71 (2.26)	
LS mean difference (SE)		−1.64 (3.12)	
95% CI		−7.86 to 4.59	
P value		0.6011	

Aml = amlodipine; Ato = atorvastatin; Eze = ezetimibe; LS = least-square; MMRM = mixed-effects model for repeated measures; n = number of participants.

the Eze/Ato 10/40 mg group, the proportion of participants was 25.00% at both week 4 and week 8. The Eze/Ato 10/40 mg + Aml 10 mg group had significantly higher proportion of participants achieving the target BP compared with the Eze/Ato 10/40 mg group at both week 4 and week 8 ($P = 0.0005$). The proportion of participants achieving the target BP was not significantly different between the Eze/Ato 10/40 mg + Aml 10 mg group and the Aml 10 mg group at any time point (week 4 $P = 0.3628$, week 8 $P = 0.9515$) (Figure 4G). The Eze/Ato + Aml triple combination therapy resulted in a more pronounced reduction in MSDBP than Eze/Ato and Aml therapies after 4 weeks and 8 weeks of treatment (data not shown).

Results from the PPS analysis were consistent with the finding from FAS analysis.

Safety Outcomes

A summary of the overall safety outcomes is presented in Table IV. Safety analysis included all participants who received at least 1 dose of

Table III
Changes in mean sitting systolic blood pressure from baseline.

Assessment	Eze/Ato + Aml (n = 34)	Eze/Ato (n = 36)	Aml (n = 34)
Baseline			
Mean (SD)	148.72 (9.54)	153.24 (12.20)	152.26 (10.69)
Week 8			
Mean (SD)	129.74 (11.32)	148.18 (15.54)	131.89 (12.73)
MMRM result at week 8			
LS mean (SE)	−19.24 (2.42)	−4.43 (2.56)	
LS mean difference (SE)		−14.81 (3.53)	
95% CI		−21.87 to −7.74	
P value		<0.0001	
MMRM result at week 8			
LS means (SE)	−19.01 (1.83)		−19.56 (1.89)
LS mean difference (SE)			0.55 (2.63)
95% CI			−4.70 to 5.81
P value			0.8335

Aml = amlodipine; Ato = atorvastatin; Eze = ezetimibe; LS = least-square; MMRM = mixed-effects model for repeated measures; n = number of participants.

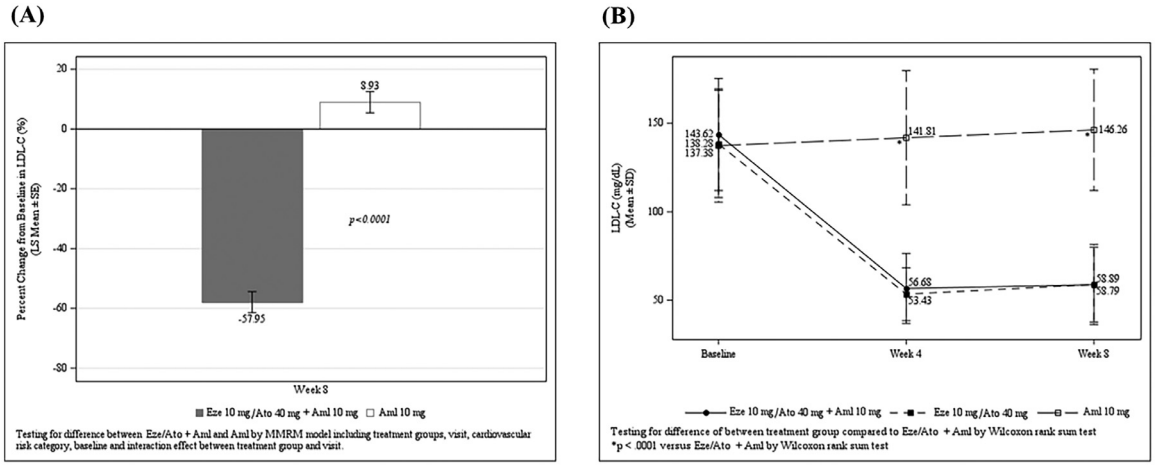

Figure 2. Percent change from baseline in low-density lipoprotein cholesterol (LDL-C) levels after 8 weeks of treatment with a combination therapy of ezetimibe (Eze)/atorvastatin (Ato) + amlodipine (Aml) compared with treatment with Aml therapy. (A) The bars represent the percent change in LDL-C from baseline to week 4 and week 8 in comparison to baseline. *P* values were calculated using mixed-effects model for repeated measures (MMRM) model to determine the differences in least-square (LS) mean. (B) The line graph represents mean LDL-C change (milligrams per deciliter) and *P* values are presented using Wilcoxon rank sum test.

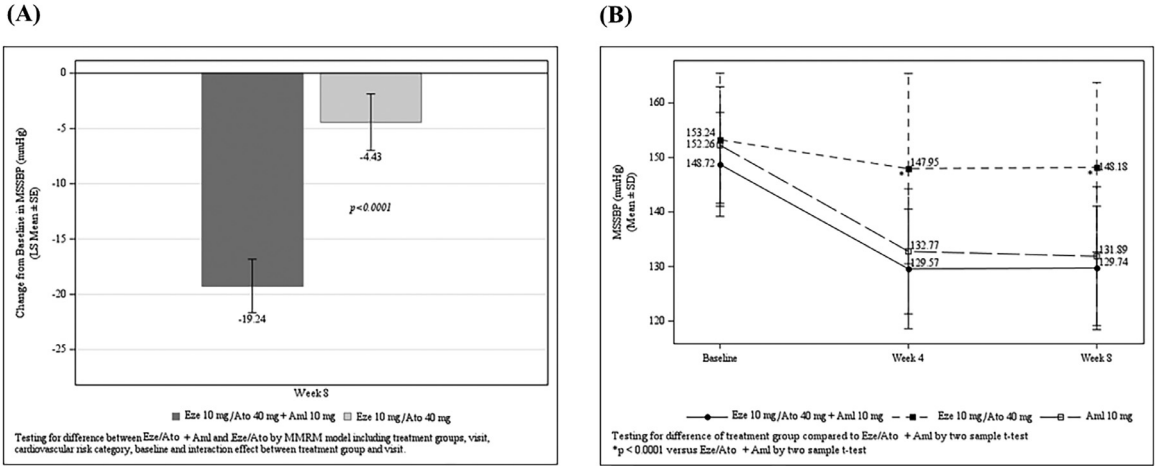

Figure 3. Changes in mean sitting systolic blood pressure (MSSBP) after 8 weeks of treatment with a combination therapy of ezetimibe (Eze)/atorvastatin (Ato) + amlodipine (Aml) compared with treatment with Eze/Ato therapy. (A) The bars represent the change in MSSBP (millimeters of mercury) from baseline to week 8 in comparison to baseline. *P* values were calculated using mixed-effects model for repeated measures (MMRM) model including treatment groups, visit, cardiovascular risk category, baseline and interaction effect between treatment group and visit to determine the treatment differences, presented as least-square (LS) mean. (B) The line graph represents mean MSSBP (millimeters of mercury) change from baseline to week 4 and week 8 and *P* values are presented using 2 sample *t* test.

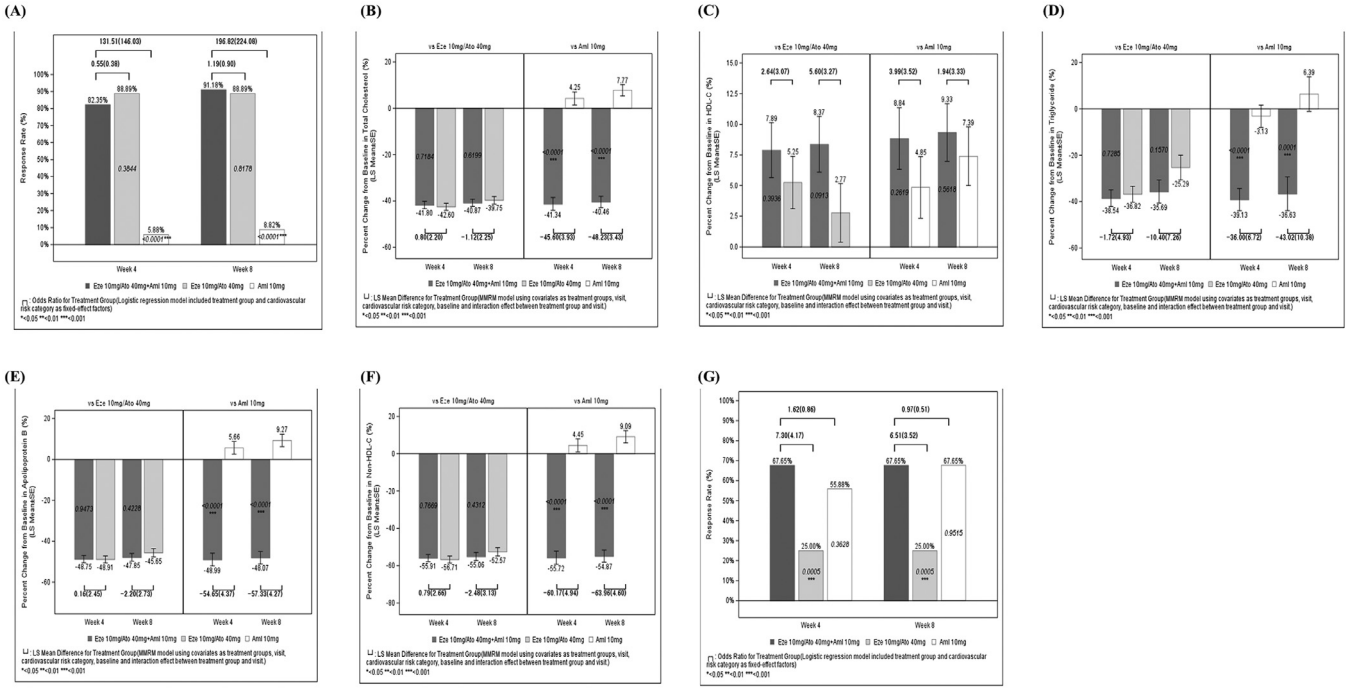

Figure 4. Assessment of secondary end points at week 4 and week 8 of treatment with combination therapy of ezetimibe (Eze)/atorvastatin (Ato) + amlodipine (Aml) compared with Eze/Ato, and amlodipine therapies. HDL-C = high-density lipoprotein cholesterol; LS = least squares; MMRM = mixed-effects model for repeated measures.

Table IV
Summary of treatment-emergent adverse events.

Adverse events	Eze/Ato + Aml (n = 36)	Eze/Ato (n = 36)	Aml (n = 35)	Total (N = 107)
TEAEs	9 (25.00) [16]	8 (22.22) [10]	5 (14.29) [6]	22 (20.56) [32]
ADRs	7 (19.44) [8]	5 (13.89) [7]	4 (11.43) [4]	16 (14.95) [19]
Blood pressure increased	0	4 (11.11) [4]	0	4 (3.74) [4]
Alanine aminotransferase increased	1 (2.78) [1]	0	0	1 (0.93) [1]
Hepatic enzyme increased	1 (2.78) [1]	0	0	1 (0.93) [1]
Constipation	2 (5.56) [2]	1 (2.78) [1]	1 (2.86) [1]	4 (3.74) [4]
Dyspepsia	1 (2.78) [1]		0	1 (0.93) [1]
Chest discomfort	1 (2.78) [1]	0	0	1 (0.93) [1]
Chest pain	0	0	1 (2.86) [1]	1 (0.93) [1]
Fatigue	0	1 (2.78) [1]	0	1 (0.93) [1]
Headache	1 (2.78) [1]	0	1 (2.86) [1]	2 (1.87) [2]
Hypoesthesia	0	0	1 (2.86) [1]	1 (0.93) [1]
Dry eye	1 (2.78) [1]	1 (2.78) [1]	0	2 (1.87) [2]
SAEs	1 (2.78) [1]	0	0	1 (0.93) [1]
Serious ADRs	0	0	0	0
TEAEs leading to drug interruption	0	0	0	0
TEAEs leading to drug withdrawal	0	2 (5.56) [2]	0	2 (1.87) [2]
TEAEs leading to death	0	0	0	0
ADRs leading to drug interruption	0	0	0	0
ADRs leading to drug withdrawn	0	2 (5.56) [2]	0	2 (1.87) [2]
ADRs leading to death	0	0	0	0

TEAEs are shown as number of participants (percentage of participants) [number of cases].
ADR = adverse drug reaction; Aml = amlodipine; Ato = atorvastatin; Eze = ezetimibe; n = number of participants; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

any of the study treatments. Among the 107 participants in the safety analysis set, 22 (20.56%) experienced 32 TEAEs with 9 (25.00%) participants in the Eze/Ato 10/40 mg + Aml 10 mg group, 8 (22.22%) participants in the Eze/Ato 10/40 mg group, and 5 (14.29%) participants in the Aml 10 mg group experienced TEAEs. Overall, 16 participants (14.95%) experienced ADRs, distributed as follows: 7 participants (19.44%) in the Eze/Ato 10/40 mg + Aml 10 mg group, 5 participants (13.89%) in the Eze/Ato 10/40 mg group, and 4 participants (11.43%) in the Aml group and none of them was regarded as SADRs. There were no statistically significant differences in the occurrence of ADRs among all the treatment groups ($P = 0.6234$).

Discussion

In this randomized, multicenter, double-blind, active-controlled Phase III trial, we sought to evaluate the efficacy and safety of Eze/Ato + Aml combination therapy versus Eze/Ato and Aml therapies for lowering the LDL-C and MSSBP in the South Korean popula-

tion with comorbid hypercholesterolemia and hypertension. We found that the triple combination therapy with Eze/Ato + Aml for 8 weeks was efficacious in lowering the LDL-C with comparable BP-lowering effect compared with Aml monotherapy, as expected. Additionally, the triple combination of Eze/Ato + Aml had achieved the target MSSBP as expected, with an equivalent LDL-C lowering effect, compared with Eze/Ato therapy. The safety profiles of the 2 groups were comparable. However, as this study was primarily designed to compare efficacy between the groups, the sample size may lack sufficient power for a robust comparison of safety, which can be considered a limitation of this study.

Statins are considered the first-line treatment for lowering lipid levels.[23] The Anglo-Scandinavian Cardiac Outcomes Trial, which included hypertensive patients with elevated TC levels (>250 mg/dL), has shown that the treatment with a statin (lipid-lowering arm) and Aml (BP-lowering arm) significantly reduced CV mortality and CV events associated with elevated blood lipids and high BP.[24] However, the proportion of patients reaching their target lipid levels with statin monotherapy remains suboptimal, necessitating additional lipid-lowering therapies.[25] To address this unmet need, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) and the randomized comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease (RACING) trials explored the synergistic effect of Eze combined with statins.[26,27] These studies demonstrated significantly greater LDL-C reduction with the Eze-statin combination compared to statin alone. The compelling results from these trials suggest that the combination of Eze with statins is appropriate for achieving the more intense LDL-C reduction[28,29] and outcomes from IMPROVE-IT have prompted the modification of the lipid-lowering guidelines to include more aggressive reduction in goal LDL-C levels.[30] Nevertheless, managing lipids or BP individually might not overcome the total CV risk; therefore, a triple combination of Eze/Ato + Aml could be a therapeutic strategy for comprehensively managing CV risk by simultaneously addressing elevated LDL-C and BP.

However, prior to developing a future FDC, the safety of these coadministered medications needs to be considered. The safety of coadministration of Eze + Ato has already been studied, and it is reported that this combination has a synergistic lipid-lowering effect, without any significant safety issues.[16,31] And the combination of Ato + Aml has shown comparable safety to each of its components individually.[32] In consistent with these findings, no SADRs were observed in the Eze/Ato + Aml treatment group, and none of the TEAEs led to the treatment discontinuation. These findings support the potential safety of Eze/Ato + Aml as a triple combination therapy.

Even though the individual medications are effective, in some cases, the combination therapy may increase the risk for DDIs, which may limit the use of FDC therapies.[12] This is the reason why pharmacokinetic (PK) and pharmacodynamic DDIs need to be considered while developing the FDC regimen. Previous studies have reported that the combination of fimasartan, an angiotensin-receptor blocker, and Ato (statin) may pose slight DDI risk[33]; however, coadministration of Aml/Ato does not have a clinically meaningful impact on the PK properties of each medication.[18] In addition, the combined use of Ato/Eze exhibited a PK and safety profile comparable to that observed with each medication administered individually.[34] Therefore, the FDC of Eze/Ato + Aml is expected to be safe, without additional DDI risks, and potentially effective for patients with comorbid hypercholesterolemia and hypertension.

A limitation of this study is that the population was confined to individuals of South Korean descent and given the potential variances in pharmacodynamics and PK properties across different ethnicities, it may be essential to evaluate this combination in more diverse populations. Although this study did not involve an FDC, the results obtained from this study could lay the groundwork for future FDC development. Future studies incorporating a triple FDC and larger, more diverse populations may provide a broader understanding of safety and efficacy outcomes. Despite these limitations, to our best knowledge, this is the first study to assess the effect of a triple combination of CCB (Aml), statin (Ato), and a cholesterol absorption inhibitor (Eze) in patients with comorbid hypertension and hypercholesterolemia. The Eze/Ato + Aml combination was as effective as the individual regimens of Eze/Ato or Aml in lowering LDL-C and BP. These results lay a groundwork for the development of Eze/Ato + Aml FDC, potentially improving real-world treatment adherence by reducing pill burden and ultimately lowering the CVD risks.

Conclusion

The triple combination of Eze/Ato + Aml in patients with hypercholesterolemia and essential hypertension effectively controls BP and improves lipid metabolism compared with Eze/Ato combination or Aml monotherapy, with comparable safety and tolerability profiles. These findings will serve as the rationale for the development of a future FDC of Eze/Ato + Aml.

Declaration of competing interest

None.

CRediT authorship contribution statement

Chan Joo Lee: Data curation, Resources, Investigation, Writing – original draft, Writing – review & editing. **Ji Yong Choi:** Data curation, Resources, Investigation, Writing – review & editing. **Seung Hwan Han:** Data curation, Resources, Investigation, Writing – review & editing. **Jinho Shin:** Data curation, Resources, Investigation, Writing – review & editing. **Jung Hyun Choi:** Data curation, Resources, Investigation, Writing – review & editing. **Eung Ju Kim:** Data curation, Resources, Investigation, Writing – review & editing. **Jin-Oh Choi:** Data curation, Resources, Investigation, Writing – review & editing. **Jung-Hoon Sung:** Data curation, Resources, Investigation, Writing – review & editing. **Kye Hun Kim:** Data curation, Resources, Investigation, Writing – review & editing. **Pil Hyung Lee:** Data curation, Resources, Investigation, Writing – review & editing. **Byung-Hee Hwang:** Data curation, Resources, Investigation, Writing – review & editing. **Young Won Yoon:** Data curation, Resources, Investigation, Writing – review & editing. **Seok-Min Kang:** Conceptualization, Investigation, Methodology, Data curation, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2025.03.001.

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