



Original Research

Efficacy and Safety of Rosuvastatin/Amlodipine FDC in Patients With Hypertension and Dyslipidemia: A Multicenter, Prospective, Observational Study

Jae Hyoung Park, MD, PhD¹, Kyung Hoon Cho, MD, PhD², Seong-Il Woo, MD, PhD³, Seung-Woon Rha, MD, PhD⁴, Yun-Hyeong Cho, MD, PhD⁵, Kwang Soo Cha, MD, PhD⁶, Hong Euy Lim, MD, PhD⁷, Wonho Kim, MD, PhD⁸, Namho Lee, MD, PhD⁹, Seong Wook Cho, MD, PhD¹⁰, Sung Uk Kwon, MD, PhD¹¹, Shin-Jae Kim, MD, PhD¹², Se Hun Kang, MD, PhD¹³, Jin Oh Choi, MD, PhD¹⁴, Jung-Woo Son, MD, PhD¹⁵, Seongwoo Han, MD, PhD¹⁶, Yongwhi Park, MD, PhD¹⁷, Seo-Won Choi, MD, PhD¹⁸, Sangmin Lee, MD¹, Moo Hyun Kim, MD, PhD^{19,20,*}

¹ Department of Internal Medicine, Division of Cardiology, Korea University Anam Hospital, Seoul, Republic of Korea

² Department of Cardiology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea

³ Department of Cardiology, Inha University Hospital, Incheon, Korea

⁴ Department of Internal Medicine, Division of Cardiology, Korea University Guro Hospital, Seoul, Republic of Korea

⁵ Division of Cardiology, Cardiovascular Center, Internal Medicine, Myongji Hospital, Goyang, Korea,

⁶ Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan, Korea

⁷ Division of Cardiology, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong, Republic of Korea

⁸ Division of Cardiology, Eulji University Hospital, Eulji University School of Medicine, Daejeon, Korea

⁹ Division of Cardiology, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea

¹⁰ Division of Cardiology, Department of Internal Medicine, Bundang Jesaeng General Hospital, Daejin Medical Center, Seongnam, Republic of Korea

¹¹ Division of Cardiology, Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea

¹² Division of Cardiology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

¹³ Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Korea

¹⁴ Division of Cardiology, Department of Internal Medicine, Cardiovascular Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

¹⁵ Department Division of Cardiology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Seoul, Republic of Korea

¹⁶ Division of Cardiology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea

¹⁷ Department of Internal Medicine, Gyeongsang National University College of Medicine and Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, Korea

¹⁸ Department of Cardiology, Gwangju Veterans Hospital, Gwangju, Republic of Korea

¹⁹ Department of Cardiology, Dong-A University Hospital, Busan, Korea

²⁰ Donga Heart Clinic, Busan, Republic of Korea

ARTICLE INFO

Keywords:

Rosuvastatin/amlodipine
Fixed-dose combination therapy
Hypertension
Dyslipidemia
Major adverse cardiovascular and cerebrovascular events
Real-world data

ABSTRACT

Background: A fixed-dose combination of rosuvastatin and amlodipine (Ros/Aml) offers a simplified approach to simultaneously address hypertension and dyslipidemia. While pivotal trials have demonstrated the efficacy and safety of this regimen, real-world evidence on its clinical outcomes related to major adverse cardiovascular and cerebrovascular events (MACCE) had been limited.

Methods: This multicenter, prospective, non-interventional study was conducted across 39 sites in South Korea (2020–2024) to evaluate the 12-month effectiveness and safety of Ros/Aml in adults with coexisting hypertension and dyslipidemia. The primary endpoint was the incidence of MACCE. Secondary endpoints included changes in blood pressure, lipid profiles, and safety outcomes.

Results: A total of 5018 patients were enrolled, with 5009 (99.82%) included in the Safety and Efficacy Sets. The mean age was 66.80 years, and 60.39% were male. In the efficacy set, the 12-month MACCE incidence

* Address correspondence to: Moo Hyun Kim, MD, PhD, Donga Heart Clinic, 95, Gudeok-ro, Seo-gu, Busan, Republic of Korea.

E-mail address: kimmhjr@gmail.com (M.H. Kim).

was 0.54% [95% CI: 0.36–0.78], with no significant differences among four dose groups. Ros/Aml significantly reduced systolic and diastolic blood pressure at 6 and 12 months (both $P < 0.001$), and LDL-C levels ($P < 0.0001$). Adverse drug reactions were reported in 3.11% of patients; with only 0.06% experiencing serious ADRs and no ADR-related deaths occurred, suggesting a tolerable safety profile.

Conclusions: In this large real-world study, Ros/Aml demonstrated a favorable safety profile and was effective in reducing MACCE risk, blood pressure, and lipid levels over 12 months. These findings in patients with hypertension and dyslipidemia support its use as a viable strategy for integrated cardiovascular risk management in clinical practice.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide,^{1,2,3} accounting for approximately 17.9 million deaths in 2021.⁴ Beyond its clinical implications, CVD imposes a significant socioeconomic burden on healthcare systems, due to long-term treatment costs, productivity loss, and increased hospitalizations. Effective prevention and management of CVD risk factors are therefore critical for both public health and economic sustainability.⁵

Hypertension and dyslipidemia are among the most significant and modifiable risk factors for CVD. These conditions frequently coexist, with more than half of hypertensive patients also exhibiting dyslipidemia.^{6,7} Importantly, their coexistence is not merely additive but synergistic, contributing to accelerated atherosclerotic progression and elevated cardiovascular risk.^{8,9} Consequently, an integrated approach to managing both conditions may be important, and fixed-dose combination (FDC) therapies can present certain advantages in this context.^{10,11} By improving treatment convenience and adherence, FDCs may enhance overall clinical effectiveness.^{12,13}

In particular, a meta-analysis by Bangalore et al.¹⁴ found that FDCs reduced medication noncompliance by 26% compared with free-drug combinations across chronic diseases, and Du et al.¹⁵ confirmed improved adherence in patients with hypertension. These findings support the role of FDCs in enhancing adherence, particularly in those with both hypertension and dyslipidemia. An FDC of rosuvastatin and amlodipine (Ros/Aml; Rosuampin® tablet) which is available in four dosage regimens, has demonstrated favorable lipid-lowering and antihypertensive effects in pivotal trials¹⁶, and is currently marketed in South Korea. However, these trials^{6,16,17}, have predominantly been limited to controlled settings, small patient populations (typically < 200 subjects), short durations (≤14 weeks), thereby restricting the evaluation of the long-term efficacy and safety of the combination therapy.

Notably, previous studies have primarily relied on surrogate endpoints, such as blood pressure and LDL-C levels. In a phase III pivotal trial¹⁶, Ros/Aml 20/10 mg reduced mean sitting systolic blood pressure (SBP) by 22.82 mm Hg and Low-Density Lipoprotein Cholesterol (LDL-C) levels by 52.53% from baseline after 8 weeks, showing greater reductions over monotherapy. These markers are useful for assessing short-term treatment effects; however, they do not always translate into reduced rates of hard clinical outcomes, and some interventions that improve surrogate markers have failed to show corresponding reductions in cardiovascular events. Accordingly, recent research increasingly focuses on major adverse cardiovascular and cerebrovascular events (MACCE) as a clinically meaningful outcome to guide risk reduction approaches.¹⁸ Given that FDC of Ros/Aml has already demonstrated substantial improvements in key surrogate markers, evaluating its impact on MACCE—which require longer follow-up—provides a more direct assessment of clinically meaningful benefit.

However, to date, no domestic study has evaluated the impact of the Ros/Aml on MACCE outcomes, underscoring the need for real-world data to address this evidence gap. To provide robust real-world evidence, this study was designed to evaluate the 12-month incidence of MACCE as the primary endpoint, assessing the effectiveness and safety of Ros/Aml in patients with coexisting hypertension and dyslipidemia.

Method

Study Design and Participants

This multicenter, prospective, noninterventional observational study was conducted across 39 institutions in South Korea from 2020 to 2024 to evaluate the real-world effectiveness and safety of Ros/Aml (Yuhan Corporation, Seoul, Republic of Korea) in patients with concomitant hypertension and dyslipidemia. The study received institutional review board (IRB) approval at each participating site prior to initiation, in accordance with applicable ethical guidelines and regulations. Patients aged 19 years or older with both hypertension and dyslipidemia, who were either already receiving Ros/Aml or deemed eligible for its use based on the investigator's clinical judgment in accordance with the locally approved labeling in Korea were included. Exclusion criteria included known hypersensitivity to any component of Ros/Aml, severe hepatic or renal dysfunction, clinically significant myopathy, severe aortic stenosis, concomitant treatment with cyclosporine, and participation in other clinical trials. Pregnant or lactating women and women of child-bearing potential not using contraception were ineligible. Participants provided written informed consent before enrollment.

Ros/Aml was administered orally once daily at doses of 5/5 mg, 10/5 mg, 20/5 mg, or 10/10 mg, in accordance with the approved prescribing information. Treatment duration was up to 12 months, with dose adjustments permitted based on clinical needs. Patients were scheduled for follow-up visits at baseline, 6 months, and 12 months to monitor clinical outcomes and treatment response.

Study Endpoints and Measures

The primary efficacy endpoint was the incidence of MACCE over the 12-month study period following Ros/Aml administration. MACCE included cardiovascular death, myocardial infarction, stroke (ischemic or hemorrhagic), and any unscheduled coronary revascularization. Secondary efficacy endpoints included changes from baseline in seated SBP and diastolic blood pressure (DBP) at 6 and 12 months, as well as percentage changes in lipid profile parameters (total cholesterol (TC), LDL-C, High-Density Lipoprotein Cholesterol (HDL-C), and triglycerides (TG)). Additionally, changes in inflammatory markers (high-sensitivity C-reactive protein (hs-CRP)) and diabetes-related markers (fasting blood glucose (FBG) and HbA1c) were evaluated at 6 and 12 months.

Safety endpoints included the incidence of adverse events (AEs) throughout the 12-month period, the rate of treatment discontinuation due to AEs, and changes in physical measurements, vital signs, and laboratory parameters. Treatment-emergent adverse events (TEAEs) were monitored continuously until resolution or until further follow-up was deemed unnecessary. TEAEs were identified through spontaneous patient reports, responses to open-ended questions, clinical examinations, and laboratory tests. All reported events were reviewed and confirmed by investigators.

Primary outcome such as MACCE and safety assessments were continuously monitored and analyzed as cumulative data over the study period, whereas secondary efficacy parameters, including blood pressure and lipid profile, were assessed at baseline, 6 months, and 12 months.

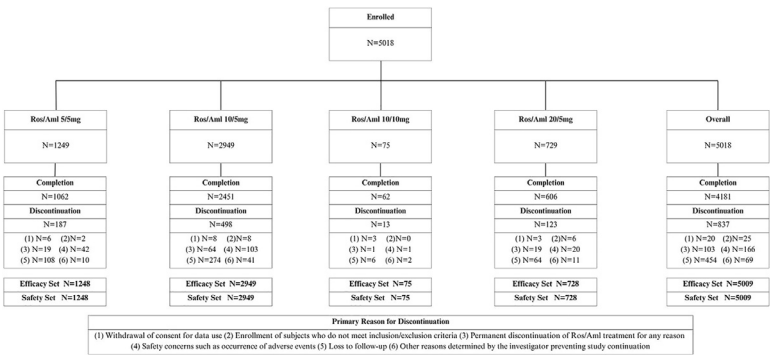


Figure 1. Patient disposition flowchart in study
Patient disposition is presented by Rosuvastatin/Amlodipine dose groups (5/5 mg, 10/5 mg, 10/10 mg, 20/5 mg) and overall. The figure illustrates the number of subjects who completed the study, those who discontinued, and the reasons for discontinuation. Details are also provided for the Efficacy Set and Safety Set populations. #: number of subjects.

All evaluations were conducted using validated, standardized methods to ensure reliability and consistency.

Additionally, subgroup analyses were conducted to assess the incidence of MACCE over 12 months following Ros/Aml administration based on sex, age, smoking status, cardiovascular risk category, baseline blood pressure, baseline lipid levels, and diabetes status classified according to the presence of a Diabetes Mellitus (DM) diagnosis in medical history or concurrent disease. Furthermore, changes in LDL-C levels were evaluated based on statin use history to provide a comprehensive evaluation of treatment effectiveness in routine clinical settings.

Statistical Analysis

This study aimed to evaluate the 12-month incidence of MACCE in patients with concomitant hypertension and dyslipidemia receiving Ros/Aml. The ACCORD-Lipid trial¹⁹ which enrolled patients with diabetes reported an annual cardiovascular event rate of 2.64%, while the JUPITER trial²⁰ estimated an annual MACCE incidence of 0.84% among patients treated with rosuvastatin. Given that this study population included both diabetic and nondiabetic patients, the event rate was expected to be lower than that of ACCORD-Lipid. Therefore, a conservative estimate of 0.84% annual incidence was adopted based on the JUPITER trial. Based on a two-sided significance level of 5%, a target 95% confidence interval (CI) width of 0.6%, and an anticipated dropout rate of 20%, the required sample size was determined to be 5,000 using the PASS 16 software.

The primary efficacy endpoint, the incidence of MACCE, was analyzed in the Efficacy Set. This set, defined in accordance with the intent-to-treat (ITT) principle, included patients who received at least one dose of Ros/Aml and had at least one assessment for primary endpoint (MACCE). For the analysis of MACCE, the number and proportion of participants who experienced at least one event were summarized for the overall cohort and by dose group, along with two-sided 95% CIs. In addition, the incidence rate per person-year was calculated for each group, and the cumulative incidence at 12 months was estimated using the Kaplan–Meier method, with corresponding 95% CIs. Each component of MACCE was analyzed using the same approach, with incidence proportions, 95% CIs, and person-year rates presented by dose group and overall.

Subgroup analyses were conducted by sex, age, smoking status, cardiovascular risk category, baseline blood pressure, baseline lipid levels, and diabetes status, with comparisons between groups made using chi-square or Fisher’s exact tests. Results were presented as percentages, exact 95% CIs, and event rates per person-year in each subgroup.

For continuous variables related to secondary endpoints, including LDL-C, SBP, DBP, TC, HDL-C, TG, hs-CRP, and glycemic markers (FBG and HbA1c), descriptive statistics were used to summarize values at each time point. Within-group changes from baseline were assessed using paired t-tests or Wilcoxon signed-rank tests. Between-group comparisons of changes from baseline at 6 and 12 months were conducted using analysis of covariance (ANCOVA), with corresponding baseline values

included as covariates. Least squares mean, standard errors, 95% CI, and p-values for between-group differences were reported.

Safety outcomes were evaluated in the Safety Set and included the incidence of TEAEs, serious adverse events (SAEs), and AEs leading to treatment discontinuation, with 95% CI. AEs were coded using MedDRA (version 27.0) and summarized by System Organ Class and Preferred Term. Laboratory parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), creatinine, and creatinine clearance [CLcr]) and vital signs (blood pressure and pulse rate) were assessed at each visit. The incidence of treatment discontinuation due to AEs was also analyzed by dose group with corresponding CI.

Analyses were performed using data from observed cases, and no imputation was performed for missing data. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), with statistical significance defined as a two-sided p-value <0.05.

Results

Subject Demographics and Baseline Characteristics

A total of 5,018 subjects were enrolled at 39 sites, of whom 5009 (99.82%) received at least one dose of Ros/Aml and were included in the Safety Set. All subjects in the Safety Set underwent at least one MACCE assessment and were included in the Efficacy Set. Of these, 4,181 subjects (83.3%) completed the study, while 837 (16.7%) discontinued due to various reasons such as loss to follow-up, adverse events, or withdrawal of consent. The study disposition of all subjects is summarized in (Figure 1).

Among the 5,009 subjects, the mean age was 66.80 ± 11.22 years, with 57.02% under 70 years. 60.39% of subjects were male (Table 1). Baseline data for variables other than sex and age included missing values; therefore, the number of analyzed subjects varied by parameter. Of 4,685 subjects assessed for smoking status, 63.33% were nonsmokers, 16.12% current smokers, and 20.55% former smokers. Alcohol consumption analysis (n = 4,661) showed 59.17% nondrinkers, 29.93% current drinkers, and 10.90% former drinkers. The mean duration of hypertension was 111.84 ± 100.91 months (n = 4,531), and dyslipidemia was 74.23 ± 75.98 months (n = 4,132).

Among the 5,009 subjects in the safety set, the mean daily dosing frequency (± SD) of Ros/Aml Tablet was 1.02 (± 0.15) times, and the mean total duration of treatment (± SD) was 343.39 (± 96.51) days. The majority (4455 subjects, 88.93%) had no treatment modifications. Regarding treatment modifications, discontinuation occurred most frequently, affecting 566 subjects (11.29%, 684 cases), followed by dose modification in 117 subjects (2.34%, 126 cases). The primary reasons for treatment discontinuation were classified as ‘other’ in 449 subjects (8.96%, 469 cases), adverse events in 241 subjects (4.81%, 252 cases), and lack of efficacy in 36 subjects (0.72%, 36 cases). Additionally, a considerable proportion of patients received concomitant cardiovascular medications during the study period. Specifically, 41.45% received agents acting on

Table 1
Demographic and baseline characteristics (Efficacy set).

Characteristic	Ros/Aml 5/5 mg (n = 1248)	Ros/Aml 10/5 mg (n = 2949)	Ros/Aml 10/10 mg (n = 75)	Ros/Aml 20/5 mg (n = 728)	Overall (n = 5009)
Age (years)					
Mean (SD)	67.22 (11.32)	67.09 (11.25)	65.53 (12.29)	65.10 (10.71)	66.80 (11.22)
Median	68.00	68.00	66.00	66.00	67.00
Min, Max	28.00, 94.00	19.00, 100.00	28.00, 85.00	25.00, 90.00	19.00, 100.00
Age Group, n (%)					
<70 years	691 (55.37)	1648 (55.88)	47 (62.67)	464 (63.74)	2856 (57.02)
≥70 years	557 (44.63)	1301 (44.12)	28 (37.33)	264 (36.26)	2153 (42.98)
Sex, n (%)					
Male	643 (51.52)	1818 (61.65)	53 (70.67)	505 (69.37)	3025 (60.39)
Female	605 (48.48)	1131 (38.35)	22 (29.33)	223 (30.63)	1984 (39.61)
Smoking Status, n (%)					
Non-smoker	839 (70.33)	1718 (63.42)	38 (52.05)	367 (52.35)	2967 (63.33)
Current smoker	150 (12.57)	447 (16.50)	14 (19.18)	142 (20.26)	755 (16.12)
Former smoker	204 (17.10)	544 (20.08)	21 (28.77)	192 (27.39)	963 (20.55)
Alcohol Consumption, n (%)					
Non-drinker	732 (61.46)	1623 (60.40)	37 (50.68)	360 (51.36)	2758 (59.17)
Current drinker	361 (30.31)	757 (28.17)	22 (30.14)	253 (36.09)	1395 (29.93)
Former drinker	98 (8.23)	307 (11.43)	14 (19.18)	88 (12.55)	508 (10.90)
Duration of Hypertension (months)					
Mean (SD)	118.20 (98.85)	110.40 (101.82)	115.92 (102.61)	105.79 (100.43)	111.84 (100.91)
Median	103.30	94.00	95.00	83.33	95.97
Min, Max	0.00, 660.00	0.00, 1336.20	0.03, 516.00	0.00, 912.00	0.00, 1336.20
Duration of Dyslipidemia (months)					
Mean (SD)	75.93 (76.89)	72.40 (74.47)	88.43 (90.19)	76.36 (78.66)	74.23 (75.98)
Median	48.80	48.33	73.00	56.33	51.87
Min, Max	0.00, 480.00	0.00, 504.00	0.03, 420.00	0.00, 912.00	0.00, 912.00
Height (cm)					
Mean (SD)	162.01 (9.30)	163.01 (9.07)	164.24 (9.16)	164.51 (8.56)	163.01 (9.08)
Median	162.00	163.90	165.00	165.00	164.00
Min, Max	135.00, 190.00	116.40, 186.00	140.10, 180.00	106.70, 183.40	106.70, 190.00
Weight (kg)					
Mean (SD)	66.25 (11.90)	68.14 (12.81)	68.80 (13.75)	69.02 (12.26)	67.80 (12.53)
Median	65.00	67.00	68.00	69.00	67.00
Min, Max	39.00, 145.00	34.80, 141.00	42.00, 101.00	30.20, 127.30	30.20, 145.00

SD = standard deviation, Min = minimum, Max = maximum.

Note: Percentages are calculated based on the number of subjects with non-missing values in each group.

Duration of hypertension (months) = (date of informed consent – date of hypertension diagnosis + 1)/30.

Duration of dyslipidemia (months) = (date of informed consent – date of dyslipidemia diagnosis + 1)/30.

the renin-angiotensin system, 28.63% were on beta-blockers, 15.41% on calcium channel blockers, 14.19% on lipid-modifying agents, and 10.82% on diuretics (Supplementary Table 1).

Primary Efficacy Outcome

In the Efficacy Set, the 12-month incidence of MACCE following Ros/Aml administration was 0.54% (27 of 5,009 subjects) [95% CI: 0.36, 0.78]. When analyzed by dosage group, the incidence was 0.32% in the 5/5 mg group (4 of 1,248 subjects), 0.54% in the 10/5 mg group (16 of 2,949 subjects), 0.00% in the 10/10 mg group (0 of 75 subjects), and 0.96% in the 20/5 mg group (7 of 728 subjects), with no statistically significant differences between dosage groups ($P = 0.2877$). The MACCE event rate per person-year was 0.0059 cases, with 0.0034 in the 5/5 mg group, 0.0061 in the 10/5 mg group, 0 in the 10/10 mg group, and 0.0103 in the 20/5 mg group (Table 2).

Cardiovascular-related mortality, myocardial infarction, stroke, and coronary revascularization rates were 0.02% (1 case of 5,009 subjects) [95% CI: 0.00, 0.11], 0.18% (9 cases of 5,009 subjects) [95% CI: 0.08, 0.34], 0.18% (9 cases of 5,009 subjects) [95% CI: 0.08, 0.34], and 0.20% (10 cases of 5,009 subjects) [95% CI: 0.10, 0.37], respectively.

Kaplan-Meier analysis estimated a 12-month cumulative MACCE risk of 0.58% [95% CI: 0.39, 0.85]. When analyzed by dose group, the cumulative risk was 0.36% [95% CI: 0.13, 0.96] in the 5/5 mg group, 0.60% [95% CI: 0.36, 0.97] in the 10/5 mg group, and 0.94% [95% CI: 0.42, 2.08] in the 20/5 mg group (Figure 2). No MACCE events were observed in the 10/10 mg group, and thus cumulative risk was not estimable. Me-

dian time to the first MACCE event and corresponding 95% CI could not be calculated, as event rates were below 1% across all dose groups.

Secondary Efficacy Outcomes

In the Efficacy Set, Ros/Aml treatment resulted in a statistically significant reduction in SBP and DBP at both 6 and 12 months compared to baseline. At 6 months, reductions in SBP and DBP were -3.25 ± 17.83 mmHg and -2.11 ± 11.89 mmHg, respectively (both $P < 0.001$). At 12 months, reductions in SBP and DBP were -3.95 ± 17.84 mmHg and -2.64 ± 11.99 mmHg, respectively (both $P < 0.001$).

Lipid profile analysis showed a statistically significant reduction in LDL-C and TC at 6 and 12 months. LDL-C decreased by -10.46 ± 34.70 mg/dL at 6 months and -13.47 ± 30.64 mg/dL at 12 months (both $P < 0.001$), while TC decreased by -6.59 ± 22.62 mg/dL at 6 months and -5.58 ± 20.30 mg/dL at 12 months (both $P < 0.001$). Although no statistically significant differences were observed between dose groups, within-group reductions were significant in most groups. The 10/10 mg group, with a relatively small sample size ($n = 75$), did not show statistically significant changes at either 6 or 12 month (Table 3).

The changes from baseline in SBP and DBP, and the percentage changes from baseline in TC, LDL-C, TG, and HDL-C at 6 and 12 months (LSM $\pm$ SE) were analyzed for each dose group. The results are presented as six separate graphs in the Supplementary Figure 1–6. Comparisons between each dose group and the 5/5 mg group revealed no statistically significant differences, except for reductions in DBP at 12 months

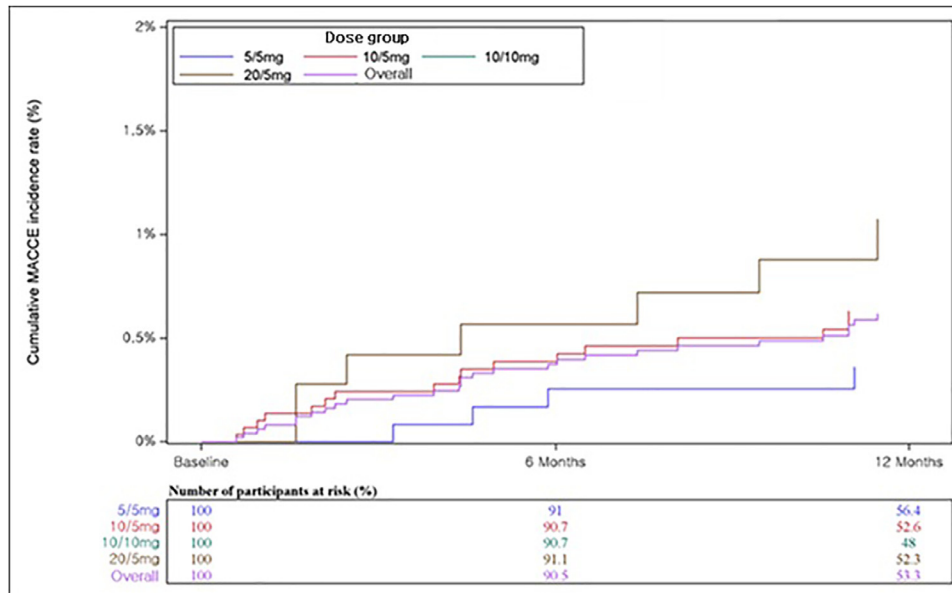


Figure 2. Cumulative MACCE Incidence Rate by Rosuvastatin/Amlodipine Dose Group Kaplan–Meier curves showing the CUMULATIVE incidence of MACCE over 12 months, stratified by Rosuvastatin/Amlodipine dose group (5/5 mg, 10/5 mg, 10/10 mg, 20/5 mg) and overall. The number and percentage of participants at risk at baseline, 6 months, and 12 months are presented for each dose group and the total population. MACCE: major adverse cardiovascular and cerebrovascular events.

Table 2

Incidence of MACCE over 12 months following administration of ros/aml (Efficacy set).

	Ros/Aml 5/5 mg (n = 1248)	Ros/Aml 10/5 mg (n = 2949)	Ros/Aml 10/10 mg (n = 75)	Ros/Aml 20/5 mg (n = 728)	Overall (n = 5009)
Patients with MACCE, n (%) [Events]	4 (0.32%) [4]	16 (0.54%) [17]	0 [0]	7 (0.96%) [7]	27 (0.54%) [28]
Exact 95% Confidence Interval	[0.09, 0.82]	[0.31, 0.88]	[0.00, 4.80]	[0.39, 1.97]	[0.36, 0.78]
P-value [1]					0.2877 (f)
MACCE incidence per person-year	0.0034	0.0061	0.0000	0.0103	0.0059

MACCE: Major Adverse Cardiovascular and Cerebrovascular Events, including cardiovascular death, myocardial infarction, stroke (ischemic or hemorrhagic), and unscheduled coronary revascularization.

[Events] indicates the total number of events including multiple events in the same patient if applicable.

[1] Testing for between-treatment group (chi-square test (c) or Fisher's exact test (f)).

Note: Denominator of percentage is the number of subjects in each group.

Person-year rate was calculated as: the total number of MACCE occurrences during the study period / the sum of person-years for all participants.

Person-years were calculated as: (Date of last administration of study drug – Date of first administration + 1) / 365.25.

MACCE occurrences are displayed as 'number of subjects (percentage of subjects) [number of events]'.

Table 3

Changes in blood pressure and lipid profile from baseline at 6 and 12 months following ros/aml administration (Efficacy set).

	Blood pressure		Lipid profile			
	SBP	DBP	TC	LDL-C	TG	HDL-C
Baseline						
n	4959	4959	2484	2017	2373	2239
Mean (SD)	133.98(16.47)	75.95(12.16)	160.83(43.02)	90.27(37.70)	140.21(88.66)	52.16(14.26)
6 Months						
n	4481	4481	1566	1247	1466	1408
Mean (SD)	130.64(13.80)	73.78(11.17)	143.97(30.82)	73.03(24.17)	132.53(78.27)	51.60(13.60)
Change from Baseline at 6 Months						
n	4448	4448	765	592	665	607
Mean (SD)	−3.25(17.83)	−2.11(11.89)	−6.59(22.62)	−10.46(34.70)	4.78(60.96)	1.36(19.61)
P-value [1]	<0.0001 (w)	<0.0001 (w)	<0.0001 (w)	<0.0001 (w)	0.0747 (w)	0.8928 (w)
12 Months						
n	4083	4083	1798	1252	1712	1674
Mean (SD)	130.01(13.52)	73.28(11.05)	143.45(28.82)	69.92(22.71)	132.56(95.08)	51.86(14.07)
Change from Baseline at 12 Months						
n	4057	4057	1131	717	1053	987
Mean (SD)	−3.95(17.84)	−2.64(11.99)	−5.58(20.30)	−13.47(30.64)	8.27(60.08)	1.76(21.49)
P-value [1]	<0.0001 (w)	<0.0001 (w)	<0.0001 (w)	<0.0001 (w)	0.2875 (w)	0.1432 (w)

DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; SBP = systolic blood pressure, TC=total cholesterol, TG=triglycerides.

[1] Testing for within-treatment group (Wilcoxon signed rank test (w)).

Table 4

Overall summary of TEAEs and ADR (Safety set).

Category	Ros/Aml 5/5 mg (n = 1248)	Ros/Aml 10/5 mg (n = 2949)	Ros/Aml 10/10 mg (n = 75)	Ros/Aml 20/5 mg (n = 728)	Overall (n = 5009)
Subjects with TEAEs	308(24.68) [470]	693(23.50) [1063]	10(13.33) [17]	156(21.43) [238]	1167(23.30) [1788]
Subjects with ADRs	38(3.04) [44]	100(3.39) [119]	1(1.33) [1]	17(2.34) [19]	156(3.11) [183]
Subjects with Serious TEAEs	45(3.61) [52]	119(4.04) [134]	1(1.33) [2]	35(4.81) [42]	200(3.99) [230]
Subjects with Serious ADRs	0	2(0.07) [3]	0	1(0.14) [1]	3(0.06) [4]
TEAEs Leading to Permanent Discontinuation	45(3.61) [53]	115(3.90) [128]	2(2.67) [2]	26(3.57) [27]	188(3.75) [210]
ADRs Leading to Permanent Discontinuation	30(2.40) [35]	67(2.27) [77]	1(1.33) [1]	10(1.37) [10]	108(2.16) [123]
TEAEs Leading to Death	4(0.32) [4]	5(0.17) [5]	0	2(0.27) [2]	11(0.22) [11]
ADRs Leading to Death	0	0	0	0	0

TEAEs = treatment-emergent adverse events; ADRs = Adverse drug reactions.

Note: Denominator of percentage is the number of subjects in each group.

Overall Summary of TEAEs are displayed as 'number of subjects (percentage of subjects) [number of events]' and others are displayed as "number of events."

(10/5 mg vs 5/5 mg, $P = 0.0123$), TC at 12 months (10/5 mg vs 5/5 mg, $P = 0.0257$), and LDL-C at 6 months (10/5 mg vs 5/5 mg, $P = 0.0160$).

No significant within-group changes or between-group differences were observed in HDL-C, TG, FBG, HbA1c, or hs-CRP levels at either 6 or 12 month.

Subgroup Analysis

During the 12-month follow-up period, the incidence of MACCE was significantly higher in patients with diabetes (0.95%, 95% CI: 0.44–1.46) compared to those without diabetes (0.38%, 95% CI: 0.18–0.59), with a statistically significant difference ($P = 0.0151$) (Supplementary Table 2). Similarly, MACCE incidence differed by sex, with males showing a higher incidence (0.79%, 95% CI: 0.48–1.11) than females (0.15%, 95% CI: 0.00–0.32) ($P = 0.0024$) (Supplementary Table 3).

Although the statin-treated group had a lower baseline LDL-C level (78.32 ± 37.18 mg/dL) compared to the statin-naïve group (99.77 ± 41.86 mg/dL, $P < 0.0001$), both groups showed a significant reduction in LDL-C levels. At 6 months, LDL-C levels were significantly reduced in both groups, with a mean change of -2.94 ± 34.86 mg/dL in the statin group and -16.68 ± 33.37 mg/dL in the nonstatin group ($P = 0.0011$ and $P < 0.0001$, respectively). By 12 months, reductions were -7.45 ± 39.63 mg/dL and -17.96 ± 30.66 mg/dL, respectively (both $P < 0.0001$) (Supplementary Table 4).

Additionally, subgroup analyses based on cardiovascular risk category, smoking status, age, baseline blood pressure, and lipid levels were conducted, but no significant differences in MACCE incidence were observed.

Safety Outcomes

The incidence of TEAEs was 23.30% (1,167/5,009, 95% CI: 22.13–24.49), with dizziness (2.02%), chest pain (1.74%), and increased blood pressure (1.20%) being the most frequently reported. Permanent treatment discontinuation due to TEAEs occurred in 3.75% (188/5,009, 95% CI: 3.24–4.32).

Adverse drug reactions (ADRs) were reported in 3.11% (156/5,009, 95% CI: 2.65, 3.63), with dizziness (0.50%), peripheral oedema (0.32%), and headache (0.30%) being the most common. Permanent treatment discontinuation due to ADRs occurred in 2.16% (108/5,009, 95% CI: 1.77, 2.60), dizziness (0.32%) and headache (0.32%) were the most frequently reported, followed by peripheral oedema (0.16%) and hypotension (0.16%) (Table 4).

ADRs commonly associated with calcium channel blockers (CCBs) and statins were also assessed. Among CCB-related events, Oedema peripheral (0.30%), Oedema (0.16%), face oedema (0.06%), flushing (0.04%), and orthostatic hypotension (0.06%) led to permanent drug discontinuation, while electrolyte imbalance did not. Additionally,

statin-related ADRs such as myalgia (0.12%) and hepatic function abnormal (0.02%) contributed to permanent drug discontinuation. These ADRs were consistent with those listed in the approved product information. In addition to these known reactions, several rare ADRs were identified that were neither listed in the approved labeling nor previously reported in postmarketing surveillance. These included the following events, each reported in one case (0.08%): blood potassium increased, low-density lipoprotein increased, deep vein thrombosis, labile blood pressure, eye pain, xerophthalmia, alcoholic liver disease, urinary tract infection, and epicondylitis (Supplementary Table 5).

Serious treatment-emergent adverse events (SAEs) were reported in 3.99% (200/5,009) of subjects. TEAEs leading to death occurred in 0.22% (11/5,009). Serious ADRs were rare, occurring in 0.06% (3/5,009), and no ADRs leading to death were reported in any group. No apparent dose-dependent trends were observed across groups for any of these events.

Time to first TEAE was analyzed in the safety set by dose group and overall at 3, 6, 9, and 12 months, using the earliest event date per subject. In most dose groups and in the overall population, the cumulative incidence of first TEAE increased through the first 6 months and rose more gradually thereafter; the 10/10 mg group, with a smaller sample size, showed greater variability over time (Supplementary Figure 7).

Discussion

In this study, the 12-month incidence of MACCE following administration of fixed-dose Ros/Aml was 0.54% with no significant differences among dosage groups. Kaplan–Meier analysis supported these results, showing a uniformly low cumulative incidence of MACCE (0.58%) across all treatment groups. Ros/Aml therapy was associated with meaningful reductions in both systolic and diastolic blood pressure, achieving target values recommended by hypertension guidelines. However, the modest BP-lowering effect may reflect the high proportion of patients already on antihypertensive therapy at baseline and the lack of a washout period. The absence of further reduction between 6 and 12 months likely indicates a plateau, suggesting sustained efficacy of the initial response. Additionally, TC and LDL-C levels showed significant improvements at both 6 and 12 months across all dosage groups, indicating a consistent lipid-lowering effect. The changes from baseline in these biomarkers were analyzed for each dose group, showing minimal variation across doses. As this was not a randomized controlled trial, the dose groups were not necessarily well balanced, and higher doses may have been prescribed to patients with greater comorbidity or higher baseline risk, potentially confounding between-group comparisons.

Although indirect comparisons should be interpreted with caution due to differences in study design, population characteristics, and end-point definitions, the observed 12-month MACCE incidence of 0.54% in

this study appears to fall within a range comparable to major cardiovascular outcome rates reported in prior large-scale studies.

For example, the JUPITER trial²⁰, which investigated rosuvastatin in individuals with elevated hs-CRP but no established cardiovascular disease, reported an annual incidence of major adverse cardiovascular events (MACE) of approximately 0.77% in the treatment group. Similarly, the HOPE-3 trial²¹, conducted in an intermediate-risk population, demonstrated a MACE incidence of about 1% per year among those receiving combination lipid-lowering and antihypertensive therapy. Furthermore, a recent real-world study in Asian patients with hypertension and dyslipidemia²² reported composite cardiovascular event rates ranging from 0.73% to 1.33% per year, depending on risk stratification.

Compared with the phase 3 trial, which employed rigorous inclusion criteria such as predefined LDL-C and blood pressure thresholds, washout requirements, and the exclusion of patients with specific comorbidities, our study adopted a more pragmatic design. Both patients who were already receiving the fixed-dose combination and those newly prescribed the treatment based on clinical judgment were included, without a washout period. The inclusion of individuals with diverse comorbidities allowed our study to capture a broader patient population, enhancing the reflection of real-world treatment patterns among those with both hypertension and dyslipidemia. Therefore, the low MACCE incidence observed in this study supports the cardiovascular protective potential of the FDC in real-world clinical practice. Given that MACCE represents a clinically meaningful outcome in this population, these findings highlight the value of this regimen as a useful treatment option in routine care.

Given the substantial public health burden of CVDs, FDC therapy has been increasingly recognized as a cost-effective and scalable strategy for prevention.^{23,24} Systematic reviews of economic evaluations indicate that FDCs can improve adherence and quality of life at equal or lower cost compared with multiple monotherapies.²⁵ These attributes make FDCs well suited for integration into broader public health initiatives and healthcare delivery systems aimed at reducing the societal and economic impact of CVDs.^{26,27}

Subgroup analysis revealed a significantly higher incidence of MACCE in males and in patients with diabetes, consistent with established associations between these risk factors and cardiovascular disease.^{28,29} These findings reinforce the need for tailored preventive strategies targeting these high-risk populations.

Cardiovascular risk stratification using the SCORE2 Asia-Pacific model (2019 ESC guideline) classified patients into low-to-moderate, high, and very high-risk categories. While no statistically significant difference in MACCE incidence was observed across groups, a trend toward increasing event rates with escalating risk level was noted (0.0000, 0.0024, and 0.0077 events/person-year, respectively) (Supplementary Table 6). The modest increase in the very high-risk group may reflect the positive impact of intensive risk factor control, including pharmacologic interventions.

Meanwhile, significant reductions in LDL-C levels were observed in both statin-naïve patients and those on prior statin therapy, indicating treatment efficacy across both groups. Given that further LDL-C lowering is generally limited when continuing the same statin regimen, the observed reduction in this group may suggest a potential benefit associated with switching to the FDC. One possible explanation is improved adherence resulting from regimen simplification³⁰, which has been associated with fixed-dose therapies. Although adherence was not directly measured in this study, the lipid-lowering effects observed even in previously treated patients may indirectly reflect favorable changes in medication-taking behavior. Although further studies are needed to understand the mechanisms behind these findings, our results suggest that FDC therapy with Ros/Aml may help reduce clinical inertia in routine practice.

The overall safety profile of fixed-dose rosuvastatin/amlodipine therapy was favorable. Although some studies have suggested a potential association between statin use and an increased risk of new-onset dia-

betes mellitus (NODM)³¹, no significant changes in FBG or HbA1c were observed across any dose group over the 12-month follow-up in this real-world study. Rare ADRs not listed in the approved product information were observed, interpretation requires caution due to the high rate of concomitant medication use (92.59% of all patients; 79.74% received cardiovascular system drugs).

This study has several limitations. Missing data for certain clinical parameters, such as blood pressure and lipid profiles, may have influenced the completeness of some analyses. However, this reflects the nature of real-world research, where data collection follows routine clinical care rather than a strict protocol. Despite these gaps, the large sample size allowed for sufficient statistical power to identify meaningful insights. Secondly, although the improvements observed in blood pressure and lipid levels may be partly attributable to better medication adherence, adherence was not directly measured in this study. This reflects a common limitation of real-world studies, where detailed adherence tracking is often unfeasible. As adherence is central to the rationale for FDCs, future studies could incorporate digital tools or claims-based proxies to better capture adherence. Thirdly, as the study population was limited to Korean patients, generalizability to other ethnic groups may be limited. However, the baseline demographics, including mean age (66.80 years) and sex distribution, were comparable to those reported in major global MACCE trials such as JUPITER²⁰ and HOPE-3²¹, supporting the external relevance of our findings to broader hypertensive and dyslipidemic populations. Fourth, due to the observational design of this study, there is limited ability to control for confounding variables and to establish causal relationships. Moreover, the large variation in patient numbers across dose groups limits the statistical reliability of between-group comparisons. Notably, efficacy outcomes such as MACCE did not demonstrate clear dose dependency. Finally, the 12-month follow-up period may be insufficient to capture longer-term cardiovascular outcomes, suggesting the need for further studies with longer follow-up.

Despite these limitations, this is the first real-world study in Korea to report 12-month follow-up clinical outcomes of Ros/Aml combination therapy in a large-scale study of more than 5,000 patients, offering practical insights into its use in routine care. In Korea, only the highest-dose regimen (Ros/Aml 20/10 mg) was evaluated in a phase 3 trial for regulatory approval, while lower-dose combinations were approved based on comparative dissolution test results. Their inclusion in this study reflects real-world prescribing patterns and addresses the need for evidence on their long-term effectiveness and safety.

Conclusion

In conclusion, these results indicate that Ros/Aml is a safe and effective strategy for the simultaneous management of hypertension and dyslipidemia. The relatively low MACCE incidence observed, even when compared to other large-scale clinical trials, highlights the potential clinical utility of this combination therapy in real-world cardiovascular risk reduction.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Moo Hyun Kim reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Jae Hyoung Park reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Kyung Hoon Cho reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Seong-Il Woo reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Seung-Woon Rha

reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Yun-Hyeong Cho reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Kwang Soo Cha reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Hong Euy Lim reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Wonho Kim reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Namho Lee reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Seong Wook Cho reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Sung Uk Kwon reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Shin-Jae Kim reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Se Hun Kang reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Jin Oh Choi reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Jung-Woo Son reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Seongwoo Han reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Yongwhi Park reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Seo-Won Choi reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. Sangmin Lee reports administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Yuhan Corporation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Jae Hyoung Park: Writing – review & editing, Writing – original draft, Investigation. **Kyung Hoon Cho:** Writing – review & editing, Investigation. **Seong-Il Woo:** Writing – review & editing, Investigation. **Seung-Woon Rha:** Writing – review & editing, Investigation. **Yun-Hyeong Cho:** Writing – review & editing, Investigation. **Kwang Soo Cha:** Writing – review & editing, Investigation. **Hong Euy Lim:** Writing – review & editing, Investigation. **Wonho Kim:** Writing – review & editing, Investigation. **Namho Lee:** Writing – review & editing, Investigation. **Seong Wook Cho:** Writing – review & editing, Investigation. **Sung Uk Kwon:** Writing – review & editing, Investigation. **Shin-Jae Kim:** Writing – review & editing, Investigation. **Se Hun Kang:** Writing – review & editing, Investigation. **Jin Oh Choi:** Writing – review & editing, Investigation, Conceptualization. **Jung-Woo Son:** Writing – review & editing, Investigation. **Seongwoo Han:** Writing – review & editing, Investigation. **Yongwhi Park:** Writing – review & editing, Investigation. **Seo-Won Choi:** Writing – review & editing, Investigation. **Sangmin Lee:** Writing – review & editing. **Moo Hyun Kim:** Writing –

review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Acknowledgments

The authors would like to thank the subjects for taking part in this study.

Funding

The study was funded by Yuhan Corporation, Seoul, Republic of Korea

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clinthera.2025.09.012](https://doi.org/10.1016/j.clinthera.2025.09.012).

References

- Zhao Y, Tu X. Editorial for the molecular genetics and genomics of metabolic disorders in cardiovascular and cerebrovascular diseases special issue: June 2023. *Genes (Basel)*. 2023;14(8):1568. Published 2023 Aug 1. doi:10.3390/genes14081568.
- Kahleova H, Levin S, Barnard ND. Vegetarian dietary patterns and cardiovascular disease. *Prog Cardiovasc Dis*. 2018;61(1):54–61. doi:10.1016/j.pcad.2018.05.002.
- Mangione CM, Barry MJ, et al. US Preventive Services Task Force Statin use for the primary prevention of cardiovascular disease in adults: us preventive services task force recommendation statement. *JAMA*. 2022;328(8):746–753. doi:10.1001/jama.2022.13044.
- World Health Organization. *news-room/fact-sheets detail cardiovascular-diseases* Updated June 11 Accessed April 18, 2025 <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-%28cvds%29>.
- Kazi DS, Elkind MSV, Deutsch A, et al. Forecasting the economic burden of cardiovascular disease and stroke in the United States through 2050: a presidential advisory from the American heart association. *Circulation*. 2024;150(4):e89–e101. doi:10.1161/CIR.0000000000001258.
- Kim MC, Ahn Y, Kim MH, et al. A randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of a quadruple combination of amlodipine, losartan, rosuvastatin, and ezetimibe in patients with concomitant essential hypertension and dyslipidemia. *Am J Cardiovasc Drugs*. 2023;23(4):441–454. doi:10.1007/s40256-023-00590-9.
- Lee HY, Kim SY, Choi KJ, et al. A randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and the tolerability of a triple combination of amlodipine/losartan/rosuvastatin in patients with comorbid essential hypertension and hyperlipidemia. *Clin Ther*. 2017;39(12):2366–2379. doi:10.1016/j.clinthera.2017.10.013.
- Jin X, Kim MH, Han KH, et al. Efficacy and safety of co-administered telmisartan/amlodipine and rosuvastatin in subjects with hypertension and dyslipidemia. *J Clin Hypertens (Greenwich)*. 2020;22(10):1835–1845. doi:10.1111/jch.13893.
- Zheng H, Li H, Wang Y, et al. Rosuvastatin Slows Progression of Carotid Intima-Media Thickness: the meteor-china randomized controlled study. *Stroke*. 2022;53(10):3004–3013. doi:10.1161/STROKEAHA.120.031877.
- Park JH, Lee YH, Ko SK, Cha BS. Cost-effectiveness analysis of low density lipoprotein cholesterol-lowering therapy in hypertensive patients with type 2 diabetes in Korea: single-pill regimen (amlodipine/atorvastatin) versus double-pill regimen (amlodipine+atorvastatin). *Epidemiol Health*. 2015;37:e2015010. doi:10.4178/epih/e2015010.
- Kim TK, Lee JE, Jeong K, et al. Strategic design and clinical evaluation of a fixed-dose combination tablet comprising valsartan, amlodipine, rosuvastatin and ezetimibe for patients with hypertension and dyslipidemia. *J Pharm Invest*. 2024;54(2):99–112. doi:10.1007/s40005-023-00651-w.
- Bramlage P, Schmidt S, Sims H. Fixed-dose vs free-dose combinations for the management of hypertension-An analysis of 81 958 patients. *J Clin Hypertens (Greenwich)*. 2018;20(4):705–715. doi:10.1111/jch.13240.
- Egan BM, Bandopadhyay D, Shaftman SR, et al. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension*. 2012;59(6):1124–1131. doi:10.1161/HYPERTENSIONAHA.112.194167.
- Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120(8):713–719. doi:10.1016/j.amjmed.2006.08.033.
- Du LP, Cheng ZW, Zhang YX, et al. The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: a meta-analysis. *J Clin Hypertens (Greenwich)*. 2018;20(5):902–907. doi:10.1111/jch.13272.
- Kim W, Chang K, Cho EJ, et al. A randomized, double-blind clinical trial to evaluate the efficacy and safety of a fixed-dose combination of amlodipine/rosuvastatin in patients with dyslipidemia and hypertension. *J Clin Hypertens (Greenwich)*. 2020;22(2):261–269. doi:10.1111/jch.13774.
- Hong SJ, Jeong HS, Cho JM, et al. Efficacy and Safety of Triple Therapy With Telmisartan, Amlodipine, and Rosuvastatin in Patients With Dyslipidemia and Hypertension: the Jeil Telmisartan, Amlodipine, and Rosuvastatin Randomized Clinical Trial. *Clin Ther*. 2019;41(2):233–248 e9. doi:10.1016/j.clinthera.2018.12.008.

18. Verdecchia P, Gentile G, Angeli F, Reboldi G. Beyond blood pressure: evidence for cardiovascular, cerebrovascular, and renal protective effects of renin-angiotensin system blockers. *Ther Adv Cardiovasc Dis.* 2012;6(2):81–91. doi:[10.1177/1753944712444866](https://doi.org/10.1177/1753944712444866).
19. Elam M, Lovato L, Ginsberg H. The ACCORD-Lipid study: implications for treatment of dyslipidemia in Type 2 diabetes mellitus. *Clin Lipidol.* 2011;6(1):9–20.
20. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195–2207.
21. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med.* 2016;374(21):2021–2031. doi:[10.1056/NEJMoa1600176](https://doi.org/10.1056/NEJMoa1600176).
22. Lin CP, Hsu TJ, Tung YC, et al. Clinical benefit of fixed-dose combination of amlodipine and potent atorvastatin in patients with concomitant hypertension and hypercholesterolemia. *J Am Heart Assoc.* 2024;13(9):e033780. doi:[10.1161/JAHA.123.033780](https://doi.org/10.1161/JAHA.123.033780).
23. Kazi DS, Elkind MSV, Deutsch A, et al. Forecasting the economic burden of cardiovascular disease and stroke in the united states through 2050: a presidential advisory from the American heart association. *Circulation.* 2024;150(4):e89–e101. doi:[10.1161/CIR.0000000000001258](https://doi.org/10.1161/CIR.0000000000001258).
24. Luengo-Fernandez R, Walli-Attaei M, Gray A, et al. Economic burden of cardiovascular diseases in the European Union: a population-based cost study. *Eur Heart J.* 2023;44(45):4752–4767. doi:[10.1093/eurheartj/ehad583](https://doi.org/10.1093/eurheartj/ehad583).
25. ahangiri R, Rezapour A, Malekzadeh R, et al. Cost-effectiveness of fixed-dose combination pill (Polypill) in primary and secondary prevention of cardiovascular disease: a systematic literature review. *PLoS One.* 2022;17(7):e0271908. doi:[10.1371/journal.pone.0271908](https://doi.org/10.1371/journal.pone.0271908).
26. Yusuf S, Pinto FJ. The polypill: from concept and evidence to implementation. *Lancet.* 2022;400(10364):1661–1663. doi:[10.1016/S0140-6736\(22\)01847-5](https://doi.org/10.1016/S0140-6736(22)01847-5).
27. Agarwal A, Mehta PM, Jacobson T, et al. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular disease. *Nat Med.* 2024;30(4):1199–1209. doi:[10.1038/s41591-024-02896-w](https://doi.org/10.1038/s41591-024-02896-w).
28. Joseph JJ, Deedwania P, Acharya T, et al. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American heart association. *Circulation.* 2022;145(9):e722–e759. doi:[10.1161/CIR.0000000000001040](https://doi.org/10.1161/CIR.0000000000001040).
29. Lehto HR, Lehto S, Havulinna AS, Salomaa V. Does the clinical spectrum of incident cardiovascular disease differ between men and women? *Eur J Prev Cardiol.* 2014;21(8):964–971. doi:[10.1177/2047487313482284](https://doi.org/10.1177/2047487313482284).
30. Du LP, Cheng ZW, Zhang YX, et al. The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: a meta-analysis. *J Clin Hypertens (Greenwich).* 2018;20(5):902–907. doi:[10.1111/jch.13272](https://doi.org/10.1111/jch.13272).
31. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA.* 2011;305(24):2556–2564. doi:[10.1001/jama.2011.860](https://doi.org/10.1001/jama.2011.860).