Beneficial Effects of Fixed-Dose Combination of Amlodipine and Atorvastatin in Patients with Concomitant Hypertension and Hypercholesterolemia: A Multi-Institutional Cohort Study

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Research Article

Keywords: hypercholesterolemia, hypertension, fixed-dose combination, glycated hemoglobin, clinical outcomes

Posted Date: December 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1101983/v1

Abstract

Background

Blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) are important risk factors for cardiovascular (CV) diseases and treating these factors simultaneously is recommended by current guidelines but only short-term clinical results were available. The objective of this study was to examine the longer-term efficacy and safety of fixed-dose combination (FDC) versus free combination of amlodipine and atorvastatin in patients with concomitant hypertension and hypercholesterolemia.

Methods

Patients with hypertension and hypercholesterolemia were stratified into three groups (FDC of amlodipine 5 mg/atorvastatin 10 mg [Fixed 5/10], FDC of amlodipine 5 mg/atorvastatin 20 mg [Fixed 5/20], and free combination of amlodipine 5 mg/atorvastatin 10 mg [Free 5/10]). After inverse probability of treatment weighting, the composite CV outcome, liver function, BP, LDL-C and glycated hemoglobin (HbA1c) changes were compared.

Results

A total of 1,788 patients were eligible for analysis and the mean follow-up period was 1.7 year. There was no significant difference in the composite CV outcome among the three groups during the 30-month follow-up period (Fixed 5/10 6.1%, Fixed 5/20 6.3% and Free 5/10 6.0%). The LDL-C level was significantly reduced in the Fixed 5/20 group (-35.7 mg/dL) compared to the Fixed 5/10 (-23.6 mg/dL) and Free 5/10 (-10.3 mg/dL) groups (P=0.001 and <0.001, respectively). The changes in HbA1c were similar among the three groups.

Conclusions

FDC of amlodipine and atorvastatin, especially the regimen with higher dosage of statin, significantly reduced the mid-term LDL-C level compared to free combination in patients with concomitant hypertension and hypercholesterolemia. Blood sugar level during the follow-up period was not significantly changed by this aggressive treatment strategy.

Introduction

Hypertension and hypercholesterolemia are two important modifiable risk factors for cardiovascular disease (CVD). They have been reported to coexist in up to 30% of patients with CVD [1, 2], and their synergistic effect on cardiovascular mortality is greater than each condition alone [3]. Therefore, current clinical guidelines recommended treating these risk factors simultaneously rather than in isolation [4, 5].

However, the increased pill burden when prescribing antihypertensive and lipid-lowering therapy concomitantly may have a negative impact on drug adherence [6], which may then attenuate the beneficial effects of the simultaneous treatment strategy.

Fixed-dose combination (FDC) is widely used in several chronic diseases including hypertension, diabetes mellitus and pulmonary tuberculosis. Compared to free combination, FDC simplifies the treatment regimen, reduces healthcare costs, and improves both drug compliance and clinical outcomes [7–12]. Relatively few studies have compared the efficacy, adherence and interaction between FDC and free combination strategies in patients with two different diseases, such as hypertension and hypercholesterolemia. Among these studies, the follow-up periods ranged from only 6 weeks to 6 months [13–22]. In our previous work, we demonstrated improved clinical outcomes with the use of FDC of amlodipine and atorvastatin in patients with concomitant hypertension and dyslipidemia compared to a free-equivalent combination (FEC), including major adverse cardiovascular events, hospitalization for coronary artery disease and newly initiating hemodialysis [23]. However, these results were generated from the National Health Insurance Research Database (NHIRD) of Taiwan, which is a large administrative database that does not contain personal data such as smoking, body weight, blood pressure (BP) records or laboratory data. Therefore, the efficacy of lowering BP and cholesterol, and the safety profiles such as blood sugar, renal and liver function could not be estimated.

In the present study, we aimed to analyze the longer-term efficacy and safety of FDC versus free combination of amlodipine and atorvastatin in patients with concomitant hypertension and hypercholesterolemia registered in a real-world, multi-institutional, electronic medical record (EMR) database.

Methods

Data source

The data used in this study were retrospectively obtained from the Chang Gung Research Database (CGRD), which is a multi-institutional, de-identified standardized EMR database maintained by the Chang Gung Memorial Hospital (CGMH) organization, and also the largest such database in Taiwan [24, 25]. The CGMH organization is currently the largest medical system in Taiwan, comprising two medical centers, two regional hospitals and three district hospitals, with a total of 10,070 beds, more than 280,000 admissions, 8,500,000 outpatient visits and 500,000 emergency department visits a year [25].

The CGRD contains more clinical details than administrative claims databases, including pathological reports, laboratory results, procedure reports, smoking habit, vital sign records and body mass index (BMI). Diseases were recorded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes before 2016, and ICD-10-CM codes thereafter. The research was performed in accordance with the Declaration of Helsinki in 1964. It was approved and the need for informed consent was waived by the ethics committee of Institutional Review Board of CGMH, Linkou,

Taiwan (committee's approval number: 202100864B0) because of the retrospective design of the study and anonymized clinical data.

Study cohort and design

We identified patients diagnosed with hypertension in the CGRD from September 1st, 2016 to September 30th, 2019 who had prescriptions of FDC or free combinations of amlodipine with atorvastatin (Figure 1). The only available dosages of amlodipine/atorvastatin FDC in Taiwan are amlodipine 5 mg with atorvastatin 10 or 20 mg, and both dosages of FDC were available at CGMH from September 2016. To avoid the potential confounding of previously prescribed medications, we only included patients with a first prescription of either FDC or free combination of amlodipine and atorvastatin. The date of the first prescription of the studied medication was defined as the index date.

Patients who received any form of dihydropyridine calcium-channel blockers (DCCB) or statins before the index date were excluded from this study. To evaluate the long-term efficacy, we excluded patients who developed cardiovascular (CV) outcomes within 3 months after the index date or whose follow-up period was less than 90 days. To ascertain the long-term use of the studied drugs, we also excluded patients who switched drugs or received the treatment medication for less than 60 days within 3 months after the index date. Other exclusion criteria were an age less than 18 years, a diagnosis of liver cirrhosis, those undergoing dialysis and those with heart failure before the index date. After exclusion, three study cohorts were generated. The first cohort consisted of patients who received FDC of amlodipine 5 mg and atorvastatin 10 mg (Fixed 5/10 group), the second received FDC of amlodipine 5 mg and atorvastatin 20 mg (Fixed 5/20 group), and the third received free combination of amlodipine 5 mg plus atorvastatin 10 mg (Free 5/10 group). The baseline characteristics and clinical outcomes of these three cohorts were compared.

Covariates

Covariates were obtained from the CGRD including age, sex, BMI, smoking status, CVD (including coronary artery disease, peripheral artery disease, acute coronary syndrome or stroke), comorbidities, Charlson's Comorbidity Index (CCI) score, concomitant medications, vital signs (office BP and heart rate) and laboratory data. Comorbidities included diabetes mellitus, chronic kidney disease, atrial fibrillation, malignancy and chronic obstructive pulmonary disease. The presence of CVD and comorbidities was confirmed if the patients had at least one inpatient or two outpatient diagnoses before the index date. Concomitant medications included antiplatelet agents, anti-hypertensive agents other than DCCBs (angiotensin converting enzyme inhibitors, angiotensin receptor blockers [ARBs], beta-blockers, diuretics and other anti-hypertensive agents such as nitrates and vasodilators) and anti-diabetic drugs (glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors [SGLT2i], insulin and other oral anti-diabetic drugs). Laboratory data included low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, triglycerides, glycated hemoglobin (HbA1C), fasting glucose, serum creatinine, estimated glomerular filtration rate (eGFR), serum uric acid, urine albumin/creatinine ratio, alanine amino transferase (ALT) and aspartate transaminase (AST).

Concomitant medications, BMI, vital signs and laboratory data were extracted from the EMRs within 3 months before or after the index date.

Outcomes

The primary outcome was composite CV outcome, including all-cause death, coronary intervention, acute myocardial infarction (MI) and stroke. Coronary interventions were identified by inpatient procedure codes of percutaneous coronary intervention or coronary arterial bypass grafting. Acute MI was defined as having a principal inpatient diagnosis of MI with an elevated cardiac troponin level above the 99th percentile upper reference limit during hospitalization. Stroke was defined as having a principal inpatient diagnosis and an image (computed tomography or magnetic resonance imaging) showing stroke. Information on deaths was obtained from the sub-database of death certificates in the CGRD.

The secondary outcomes were renal, safety and laboratory/BP outcomes. The renal outcomes included a decline in eGFR of more than 40%, newly initiating dialysis, the composite of both outcomes, and all-cause death. The safety outcomes included new-onset diabetes mellitus (NODM) and abnormal liver function. NODM was identified as having newly diagnosed diabetes mellitus and an HbA1c level greater than 6.5% during follow-up. Abnormal liver function was defined as an elevation in ALT level of more than three times the upper reference limit, namely greater than 105 U/L. Laboratory outcomes were long-term LDL-C and HbA1c levels during follow-up.

Medication adherence was assessed by using the proportion of days covered (PDC) according to the EMRs, which was defined as the total number of days covered by the study drugs divided by the total number of follow-up days [7, 9, 13, 23, 26]. The follow-up period started from the index date of the first prescription of the study drug until the date of an outcome, death, the date of switching among the studies drugs, the last visit date in the CGRD, or the end of the study period (September 30th, 2019), whichever occurred first.

Statistical analyses

The distribution of baseline characteristics among the three study groups (Fixed 5/10 vs. Fixed 5/20 vs. Free 5/10) was balanced by using generalized boosted modeling-inverse probability of treatment weighting (GBM-IPTW) based on propensity scores with 10,000 trees [27]. The propensity scores were calculated based on all of the baseline characteristics, except that the follow-up year was replaced with the index date. Baseline characteristic data that were missing were imputed using a single expectation-maximization algorithm before conducting GBM-IPTW. The balance among the three study groups before and after GBM-IPTW was assessed by using the maximum absolute standardized difference (MASD), and an MASD less than 0.2 was considered to indicate good balance among the groups [27].

The risk of fatal outcomes (i.e., all-cause death, composite CV outcome) among the three study groups was compared by using a Cox proportional hazard model. The incidence of non-fatal outcomes (i.e., decline in renal function) among the three study groups was compared using a Fine and Gray sub-distribution hazards model, which considered all-cause death during follow-up as a competing risk. The

study groups were the only explanatory variables in the aforementioned survival analyses. A subgroup analysis of primary CV outcomes was further stratified by prior CVD. Changes in laboratory data and BP from baseline to long-term follow-up among the three study groups were compared by using a generalized estimating equation which contained the intercept, main effects of the study groups and time (treated as a continuous variable) and an interaction effect of the study groups by time. Changes between groups were considered to be significantly different when the interaction was statistically significant.

A two-sided *P* value less than 0.05 was considered to be statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), including the “PHREG” procedure for conducting the survival analysis and the “TWANG” macro for estimating GBM-IPTW [27].

Results

Baseline characteristics

A total of 16,156 hypertensive patients with prescriptions of the studied drugs were identified in the CGRD during the study period. After exclusion, 1,788 patients were eligible for further analyses, including 787 patients in the Fixed 5/10 group, 458 patients in the Fixed 5/20 group, and 543 patients in the Free 5/10 group (Fig. 1). The mean age of all patients was 60 ± 12.2 years, and 53.9% were male.

Medication adherence rates assessed by PDC after IPTW were 58 ± 35% in the Fixed 5/10 group, 62.6 ± 39.4% in the Fixed 5/20 group and 58.8 ± 45.9% in the Free 5/10 group, which were not significantly different (MASD 0.087; **data not shown**). Compared to the patients in the other two groups, those in the Free 5/10 group were older, had lower BMI, higher prevalence of stroke and higher CCI score (MASD >0.2; Table 1). Regarding the baseline concomitant medications, patients in the Free 5/10 group received more anti-platelet agents but fewer SGLT2is (MASD 0.272 and 0.238, respectively) than those in the other two groups, whereas the Fixed 5/20 group received more ARBs (43.9%, MASD 0.277). Both baseline systolic and diastolic BP were significantly higher in the Fixed 5/20 group than in the other groups. The Fixed 5/20 group also had higher LDL-C, non-HDL-C, total cholesterol and ALT levels.

Table 1
Baseline characteristics of the study patients

Variable	Available numbers	All (n = 1,788)	Fixed 5/10 (n = 787)	Fixed 5/20 (n = 458)	Free 5/10 (n = 543)	MASD
Age, years	1,788	64.0 ± 12.2	63.4 ± 11.9	62.3 ± 12.4	66.4 ± 12.0	0.232
Male	1,788	963 (53.9)	424 (53.9)	249 (54.4)	290 (53.4)	0.037
Body mass index, kg/m^2	1,375	26.5 ± 3.8	26.6 ± 3.8	27.1 ± 4.1	26.0 ± 3.5	0.248
Smoking	1,788	251 (14.0)	99 (12.6)	68 (14.8)	84 (15.5)	0.078
Cardiovascular disease						
Coronary artery disease	1,788	274 (15.3)	115 (14.6)	87 (19.0)	72 (13.3)	0.136
Peripheral artery disease	1,788	80 (4.5)	39 (5.0)	10 (2.2)	31 (5.7)	0.147
Acute coronary syndrome	1,788	35 (2.0)	7 (0.89)	12 (2.6)	16 (2.9)	0.107
Stroke	1,788	400 (22.4)	142 (18.0)	65 (14.2)	193 (35.5)	0.490
Any cardiovascular disease	1,788	674 (37.7)	264 (33.5)	147 (32.1)	263 (48.4)	0.318
Comorbidity						
Diabetes mellitus	1,788	700 (39.1)	323 (41.0)	168 (36.7)	209 (38.5)	0.101
Chronic kidney disease	1,788	350 (19.6)	158 (20.1)	81 (17.7)	111 (20.4)	0.074
Atrial fibrillation	1,788	75 (4.2)	28 (3.6)	22 (4.8)	25 (4.6)	0.114
Malignancy	1,788	388 (21.7)	186 (23.6)	100 (21.8)	102 (18.8)	0.079

Abbreviations: MASD, maximum absolute standardized difference; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HTN, hypertension; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; Non-HDL, non-high density lipoprotein cholesterol; HbA1C, glycated hemoglobin; eGFR, estimated Glomerular filtration rate; ACR, albumin/creatinine ratio; ALT, alanine amino transferase; AST, aspartate transaminase;

Data were presented as frequency (percentage), median [25th, 75th percentile] or mean ± standard deviation.

Variable	Available numbers	All (n = 1,788)	Fixed 5/10 (n = 787)	Fixed 5/20 (n = 458)	Free 5/10 (n = 543)	MASD
Chronic obstructive pulmonary disease	1,788	118 (6.6)	55 (7.0)	28 (6.1)	35 (6.4)	0.022
Charlson's Comorbidity Index score	1,788	2.1 ± 2.1	2.1 ± 2.1	1.8 ± 2.0	2.5 ± 2.2	0.308
Medication						
Antiplatelet agents	1,788	741 (41.4)	295 (37.5)	163 (35.6)	283 (52.1)	0.272
ACEi	1,788	64 (3.6)	28 (3.6)	19 (4.1)	17 (3.1)	0.039
ARBs	1,788	624 (34.9)	235 (29.9)	201 (43.9)	188 (34.6)	0.277
Beta-blockers	1,788	541 (30.3)	232 (29.5)	154 (33.6)	155 (28.5)	0.117
Diuretics	1,788	152 (8.5)	61 (7.8)	40 (8.7)	51 (9.4)	0.098
Other anti-hypertensive agents	1,788	182 (10.2)	65 (8.3)	54 (11.8)	63 (11.6)	0.113
GLP-1 RA	1,788	8 (0.45)	2 (0.25)	3 (0.66)	3 (0.55)	0.051
SGLT2i	1,788	77 (4.3)	31 (3.9)	36 (7.9)	10 (1.8)	0.238
Other oral hypoglycemic agents	1,788	275 (15.4)	119 (15.1)	60 (13.1)	96 (17.7)	0.166
Insulin	1,788	83 (4.6)	33 (4.2)	19 (4.1)	31 (5.7)	0.111
Vital signs at baseline						
Systolic blood pressure, mmHg	1,717	145.8 ± 21.4	146.2 ± 21.6	149.0 ± 22.4	142.5 ± 19.6	0.286
Diastolic blood pressure, mmHg	1,717	82.2 ± 13.2	82.8 ± 13.4	83.7 ± 13.2	79.9 ± 12.5	0.223

Abbreviations: MASD, maximum absolute standardized difference; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HTN, hypertension; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; Non-HDL, non-high density lipoprotein cholesterol; HbA1C, glycated hemoglobin; eGFR, estimated Glomerular filtration rate; ACR, albumin/creatinine ratio; ALT, alanine amino transferase; AST, aspartate transaminase;

Data were presented as frequency (percentage), median [25th, 75th percentile] or mean ± standard deviation.

Variable	Available numbers	All (n = 1,788)	Fixed 5/10 (n = 787)	Fixed 5/20 (n = 458)	Free 5/10 (n = 543)	MASD
Heart rate, beat/min	1,707	80.3 ± 13.3	79.8 ± 13.3	81.0 ± 13.9	80.5 ± 12.7	0.051
Laboratory data at baseline						
LDL, mg/dL	1,737	118.6 ± 49.0	115.1 ± 46.8	128.2 ± 52.9	115.6 ± 47.7	0.235
HDL, mg/dL	1,716	47.7 ± 13.3	48.0 ± 12.9	47.8 ± 13.5	47.2 ± 13.5	0.034
Non-HDL, mg/dL	1,634	142.4 ± 50.0	138.5 ± 41.7	151.7 ± 66.9	140.2 ± 43.0	0.213
Total cholesterol, mg/dL	1,741	191.3 ± 51.4	187.3 ± 43.1	202.4 ± 67.7	187.8 ± 44.9	0.236
Triglyceride, mg/dL	1,734	127 [89, 176]	128 [85, 174]	138 [97, 190]	120 [88, 166]	0.168
HbA1C, %	1,625	6.7 ± 1.5	6.7 ± 1.5	6.7 ± 1.5	6.7 ± 1.6	0.019
Fasting glucose, mg/dL	1,612	116.9 ± 40.9	118.4 ± 41.5	118.7 ± 45.6	113.3 ± 35.3	0.090
Creatinine, mg/dL	1,778	1.0 ± 1.0	1.0 ± 0.9	1.0 ± 0.7	1.1 ± 1.4	0.103
eGFR, ml/min/1.73m^2	1,778	81.2 ± 30.8	83.0 ± 30.5	79.5 ± 27.6	79.8 ± 33.5	0.096
Serum uric acid, mg/dL	1,587	6.0 ± 1.6	5.9 ± 1.6	6.1 ± 1.6	5.9 ± 1.7	0.075
Urine ACR	724	64 [6, 331]	42 [6, 289]	80 [7, 388]	87 [3, 348]	0.053
ALT, U/L	1,744	22 [16, 32]	22 [16, 31]	24 [17, 37]	21 [16, 29]	0.201
AST, U/L	1,426	25 [21, 32]	26 [21, 32]	25 [20, 31]	25 [21, 31]	0.066

Abbreviations: MASD, maximum absolute standardized difference; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HTN, hypertension; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; Non-HDL, non-high density lipoprotein cholesterol; HbA1C, glycated hemoglobin; eGFR, estimated Glomerular filtration rate; ACR, albumin/creatinine ratio; ALT, alanine amino transferase; AST, aspartate transaminase;

Data were presented as frequency (percentage), median [25th, 75th percentile] or mean ± standard deviation.

Variable	Available numbers	All (n = 1,788)	Fixed 5/10 (n = 787)	Fixed 5/20 (n = 458)	Free 5/10 (n = 543)	MASD
Follow up year	1,788	1.7 ± 0.9	1.7 ± 0.9	1.6 ± 0.8	1.6 ± 0.9	0.232

Abbreviations: MASD, maximum absolute standardized difference; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HTN, hypertension; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; Non-HDL, non-high density lipoprotein cholesterol; HbA1C, glycated hemoglobin; eGFR, estimated Glomerular filtration rate; ACR, albumin/creatinine ratio; ALT, alanine amino transferase; AST, aspartate transaminase;

Data were presented as frequency (percentage), median [25th, 75th percentile] or mean ± standard deviation.

After imputation and GBM-IPTW, all covariates at baseline were well-balanced with no significant differences among the three study groups (all MASD values <0.2; **Supplemental Table S1**). The maximum follow-up period in this study was 30 months, and the mean follow-up periods were 1.7 ± 0.9 years in the Fixed 5/10 group, 1.6 ± 0.8 years in the Fixed 5/20 group, and 1.7 ± 0.9 years in the Free 5/10 group, respectively (MASD 0.133).

Clinical outcomes

The number of events in each study group in the original cohort before GBM-IPTW is listed in **Supplemental Table S2**. After imputation and GBM-IPTW, the risk of clinical outcomes was compared among three study groups. The risk of composite CV outcome was not significantly different among the three groups (6.1% in the Fixed 5/10 group, 6.3% in the Fixed 5/20 group and 6.0% in the Free 5/10 group) as shown in Table 2 and Fig. 2. The results showed that the risks of each component of the composite CV outcome did not differ among groups. The incidence of composite renal outcome was also comparable among the groups, including eGFR decline >40%, newly initiating dialysis or all-cause mortality (10.4% in the Fixed 5/10 group, 11.1% in the Fixed 5/20 group and 11.5% in the Free 5/10 group). We further analyzed the composite CV outcome among the three study groups in patients with or without previously established CVD as primary and secondary prevention, which disclosed comparable results (*P* for interaction = 0.332) (Fig. 3).

Table 2
Follow-up outcomes of study cohort after imputation and GBM-IPTW

	Event rate (%)			HR or SHR (95% CI)		
Outcome	Fixed 5/10	Fixed 5/20	Free 5/10	Fixed 5/20 vs. Fixed 5/10	Free 5/10 vs. Fixed 5/10	Free 5/10 vs. Fixed 5/20
Cardiovascular outcome						
Coronary intervention	0.80	1.2	0.90	1.51 (0.75–3.04)	1.15 (0.53–2.50)	0.76 (0.36–1.59)
Acute myocardial infarction	0.00	1.8	0.12	NA	NA	NA
Stroke	3.8	3.6	3.6	0.99 (0.69–1.41)	0.96 (0.66–1.40)	0.97 (0.66–1.45)
All-cause death	1.8	1.0	1.9	0.56 (0.16–1.97)	1.06 (0.49–2.32)	1.91 (0.54–6.80)
Composite cardiovascular outcome*	6.1	6.3	6.0	1.10 (0.66–1.85)	1.01 (0.64–1.60)	0.92 (0.53–1.59)
Renal outcome						
eGFR decline >40%	9.2	10.6	10.9	1.23 (0.99–1.53)	1.23 (0.98–1.54)	1.00 (0.79–1.25)
Dialysis	1.3	1.3	1.8	1.03 (0.56–1.91)	1.49 (0.83–2.66)	1.44 (0.78–2.66)
Composite outcome of eGFR decline >40% or dialysis	9.5	10.8	11.2	1.22 (0.99–1.52)	1.23 (0.98–1.53)	1.00 (0.80–1.26)
Composite outcome of eGFR decline >40% or dialysis or all-cause death	10.4	11.1	11.5	1.14 (0.78–1.65)	1.14 (0.82–1.58)	1.01 (0.68–1.49)
Safety outcome						

Abbreviation: GBM-IPTW, generalized boosted modeling-inverse probability of treatment weighting; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval; NA, not applicable; CV, cardiovascular; eGFR, estimated Glomerular filtration rate; ALT, alanine amino transferase;

* Anyone of coronary intervention, acute myocardial infarction, stroke or all-cause death.

	Event rate (%)			HR or SHR (95% CI)		
New-diagnosed diabetes mellitus	11.3	13.2	8.5	1.43 (1.11–1.85)*	0.82 (0.61–1.10)	0.57 (0.42–0.77)*
ALT >105 U/L	3.9	3.8	2.1	1.02 (0.72–1.46)	0.53 (0.34–0.83)*	0.52 (0.33–0.82)*

Abbreviation: GBM-IPTW, generalized boosted modeling-inverse probability of treatment weighting; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval; NA, not applicable; CV, cardiovascular; eGFR, estimated Glomerular filtration rate; ALT, alanine amino transferase;

* Anyone of coronary intervention, acute myocardial infarction, stroke or all-cause death.

The risk of NODM was significantly higher in the Fixed 5/20 group compared to the other two groups (Fixed 5/20 versus Fixed 5/10, sub-distribution hazard ratio [SHR], 1.43; 95% confidence interval [CI], 1.11 to 1.85; Free 5/10 versus Fixed 5/20, SHR, 0.57; 95% CI, 0.42 to 0.77). The incidence of abnormal liver function was significantly lower in the Free 5/10 group than in the Fixed 5/20 group (SHR, 0.52; 95% CI, 0.33 to 0.82) and the Fixed 5/10 group (SHR, 0.53; 95% CI, 0.34 to 0.83; Table 2).

Laboratories and BP changes

We further evaluated the longitudinal changes of LDL-C, HbA1c and BP among the three groups. The mean levels and changes from baseline in the laboratory data and BP at different time points are provided in **Supplemental Table S3**.

During the follow-up period, the decreases in LDL-C level were 23.6, 35.7 and 10.3 mg/dL in the Fixed 5/10, Fixed 5/20 and Free 5/10 groups, respectively. The generalized estimating equation model showed that the Fixed 5/20 group had a greater reduction in LDL-C than the Fixed 5/10 (regression coefficient [B], -2.7; 95% CI, -4.3 to -1.2; $P < 0.001$) and Free 5/10 (B, -4.2; 95% CI -5.8 to -2.5; $P < 0.001$) groups. However, there was no significant difference between the Free 5/10 and Fixed 5/10 groups (B, 1.5; 95% CI, -0.1 to 3.0; $P = 0.072$) (Fig. 4a).

The reductions in systolic BP were 4.5, 9.5 and 3.3 in the Fixed 5/10, Fixed 5/20 and Free 5/10 groups, respectively, and the Fixed 5/20 group had a significantly greater reduction than the Fixed 5/10 (B, 0.9; 95% CI, 0.3 to 1.6; $P = 0.007$) and Free 5/10 (B, 0.8; 95% CI 0.1 to 1.5; $P = 0.037$) groups (Fig. 4b). The reductions in diastolic BP were 4.7, 5.6 and 1.4 in the Fixed 5/10, Fixed 5/20 and Free 5/10 groups, respectively. The Fixed 5/20 group had a borderline significantly greater reduction than the Fixed 5/10 group (B, 0.4; 95% CI -0.03 to 0.78; $P = 0.067$). In addition, there was a significant difference between the Free 5/10 and Fixed 5/20 groups (B, 0.5; 95% CI, 0.07 to 0.96; $P = 0.023$) (Fig. 4c).

We also evaluated HbA1c changes among the three groups and no significant effects were observed (Fig. 4d).

Discussion

This multi-institutional retrospective study is the first study to evaluate the mid-term efficacy and safety of FDC versus free combination of amlodipine and atorvastatin in patients with concomitant hypertension and hypercholesterolemia. During the 30-month follow-up period, we found no significant difference in the composite CV outcome among the three study groups. FDC of amlodipine 5 mg and atorvastatin 20 mg resulted in a greater reduction in LDL-C than the other two regimens but the HbA1c level was not significantly different.

In our previous study, we demonstrated that FDC regimen of amlodipine and atorvastatin improved composite CV outcomes compared to FEC of the same medications in patients with newly diagnosed hypertension and dyslipidemia during a 5-year follow-up period [23]. In that study, the medication adherence as assessed by PDC was better in the FDC than in the FEC group (0.49 ± 0.26 versus 0.32 ± 0.3, $P < 0.001$), and this may explain the results. However, based on the nature of the large administrative NHIRD, the major limitations of the study were a lack of possible confounding variables and efficacy parameters including BP and LDL-C changes. In the current study, we analyzed the efficacy and safety of FDC of amlodipine and atorvastatin by using data from the CGRD, a real-world, multi-institutional, standardized EMR database. In all previous studies, drug compliance with FDC is always better than free combination, which is the main explanation for the beneficial clinical effects of FDC [7, 9–11, 13, 14, 23]. However, the medication adherence as assessed by PDC in the current study was not significantly different among the three study groups, which may be related to the stricter study criteria compared to previous studies that we excluded patients who switched drugs or received the study medications for less than 2 months within 3 months after the index date. Subsequently, the remaining patients, especially those in the free combination group, may have had better drug compliance and tolerability which may explain the comparable medication adherence between the FDC and free combination groups in the present study. Moreover, the follow-up period and patient number were relatively limited that may have further resulted in the similar composite CV outcome among the three study groups.

In previous studies, different dosages of FDC amlodipine/atorvastatin have been administered and titrated to improve BP and lipid control [16, 20–22]. The JEWEL program, which included JEWEL 1 conducted in the United Kingdom and Canada and JEWEL 2 conducted in European countries, was an international open-label study which assessed the efficacy and safety of FDC amlodipine/atorvastatin in attaining BP and lipid targets recommended by country-specific guidelines [16]. Eight dosages of amlodipine/atorvastatin (5/10 to 10/80 mg) were titrated, and 62.9% of the patients in JEWEL 1 and 50.6% of the patients in JEWEL 2 achieved both country-specific BP and LDL-C goals. At the end of the study, the average dosages were 7.3/26.8 mg in JEWEL 1 and 6.7/24.1 mg in JEWEL 2 during a 16-week follow-up period. Similarly, the Gemini and Gemini-AALA studies were also open-label studies conducted in the United States and internationally (Australia, Asia, Latin America, Africa/Middle East), respectively, to evaluate the achievement of BP and lipid goals by titrating different dosages of amlodipine/atorvastatin FDC [20, 21]. After 14 weeks, 57.7% of the patients in Gemini and 55.2% of the patients in Gemini-AALA had achieved both their BP and LDL-C goals. The mean dosages at the end point

were 7.1/26.2 mg and 7.1/19.7 mg, respectively. In African Americans, Flack et al reported that different dosages of amlodipine/atorvastatin FDC in addition to lifestyle modification improved the attainment of BP and cholesterol goals [22]. After a 20-week follow-up period, 48.3% of the patients reached both their BP and LDL-C goals, and the mean received dose of amlodipine/atorvastatin was 8.2/26.4 mg at the final visit. In the current study, the patients in the Fixed 5/20 group had a significantly lower LDL-C level than those in the lower dose Fixed 5/10 and Free 5/10 groups, and the amlodipine/atorvastatin 5/20 dosage was closer to the mean dosages of the aforementioned studies, which may explain the better attainment of both BP and lipid goals in our patients. Interestingly, even under the titration design of the aforementioned studies, approximately half of the patients were started on the lowest amlodipine 5 mg/atorvastatin 10 mg FDC dosage, and about 30-60% of these patients were not up-titrated. Current guidelines recommend that the initial dosage of statins should be of moderate intensity [28–30], and it is thus reasonable to first prescribe or early up-titrate to Fixed 5/20 rather than Fixed 5/10 or Free 5/10 in order to achieve better BP and LDL-C control concomitantly.

The risk of NODM with statin therapy has been shown to be positively correlated with the strength of the statins [31], with a reported overall risk of 9% [32]. In the current study, we also found that the risk of reported NODM was highest in the Fixed 5/20 group and lowest in the Free 5/10 group, and this may be explained by the different strengths of the statins. However, there were no significant differences among the three study groups with regards to HbA1c level during follow-up. The reason for this discrepancy may be multifactorial, such as the different diagnostic criteria for diabetes among physicians, not routinely checking HbA1c level in all patients or by chance. On the other hand, statin-associated liver toxicity is well established, however there are very few reports of liver failure directly attributed to statins [33, 34]. In the current study, we also found an increased risk of ALT elevation in the higher strength statin (Fixed 5/20) group. However, it should be emphasized that the beneficial effects of statins on CVD outweigh the risk of NODM development or mild liver function abnormalities, and therefore adequate dosages of statin should be prescribed if indicated to improve CV outcomes. Myopathy, myalgia and fatigue are also possible adverse effects of statin but it was not routinely examined or reported in our database.

Adequate BP and LDL-C control are recommended by clinical guidelines both in primary and secondary CVD prevention [29, 35, 36]. In our previous study, we only demonstrated the beneficial effect of reducing major adverse cardiovascular events with FDC of amlodipine/atorvastatin in the primary prevention setting [23]. In the present study, we further analyzed the differences in efficacy among three study groups with regards to primary and secondary CVD prevention, and the results were comparable in composite CV outcome. The major adverse cardiovascular event rates were not significantly different among the three study groups both in primary and secondary prevention, which may be due to relatively homogenous drug compliance among the groups, shorter follow-up period, different population and study design.

Study limitations

This study was based on a multi-institutional standardized EMR database and has several limitations. First, although the CGRD is the largest EMR database in Taiwan and covers almost 10% of the entire population, we could not collect the clinical events that developed in hospitals that were not involved in the CGRD, which may have led to underestimation of the actual event rates. Meanwhile, we used IPTW to balance the confounding medications but any additional drugs from other institutes could not be obtained. However, this should be balanced among the three study groups, and the between-group comparisons should still be reasonable. Second, the BP values used in the present analysis were based on office BP records, which may not represented home BP and ambulatory BP monitoring. Therefore, we could not rule out the possibility of white-coat or masked hypertension. Third, we used PDC as a surrogate marker of medication adherence but we could not ensure that the patients consumed the medications accordingly, and therefore drug compliance may have been overestimated. Finally, this is a retrospective, non-randomized study, and the results may be confounded by other unmeasured factors. Therefore, the results should be interpreted with caution.

Conclusions

In this retrospective, EMR-based study, FDC of amlodipine and atorvastatin, especially the regimen with a higher dosage of statins, significantly reduced the mid-term LDL-C level compared to free combination in patients with concomitant hypertension and hypercholesterolemia. HbA1c control during the follow-up period was not compromised by this aggressive treatment strategy.

Abbreviations

BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; CV: cardiovascular; FDC: fixed-dose combination; HbA1c: glycated hemoglobin; CVD: cardiovascular disease; FEC: free-equivalent combination; NHIRD: National Health Insurance Research Database; EMR: electronic medical record; CGRD: Chang Gung Research Database; CGMH: Chang Gung Memorial Hospital; BMI: body mass index; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; DCCB: dihydropyridine calcium-channel blockers; CCI: Charlson's Comorbidity Index; ARB: angiotensin receptor blocker; SGLT2i: sodium-glucose co-transporter 2 inhibitor; HDL-C: high density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; ALT: alanine amino transferase; AST: aspartate transaminase; MI: myocardial infarction; NODM: new-onset diabetes mellitus; PDC: proportion of days covered; GBM-IPTW: generalized boosted modeling-inverse probability of treatment weighting; MASD: maximum absolute standardized difference.

Declarations

Ethics approval and consent to participate

This study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of CGMH, Linkou (approval number: 202100864B0). The need for informed consent was waived because

of the retrospective design of the study and anonymized clinical data.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors have no competing interests to declare

Funding

This research was supported by grants 109-2314-B-182A-155 from the Ministry of Science and Technology, Taiwan

Authors' contribution

CPL, FCH, and PHC contributed to the conception and design of the study. CPL, CTW, and YSL contributed to data acquisition and collection. CPL and SWC contributed to the statistical analyses. CPL and PHC wrote the draft of the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

We would like to thank Alfred Hsing-Fen Lin for his statistical analysis during the completion of this article.

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Figures

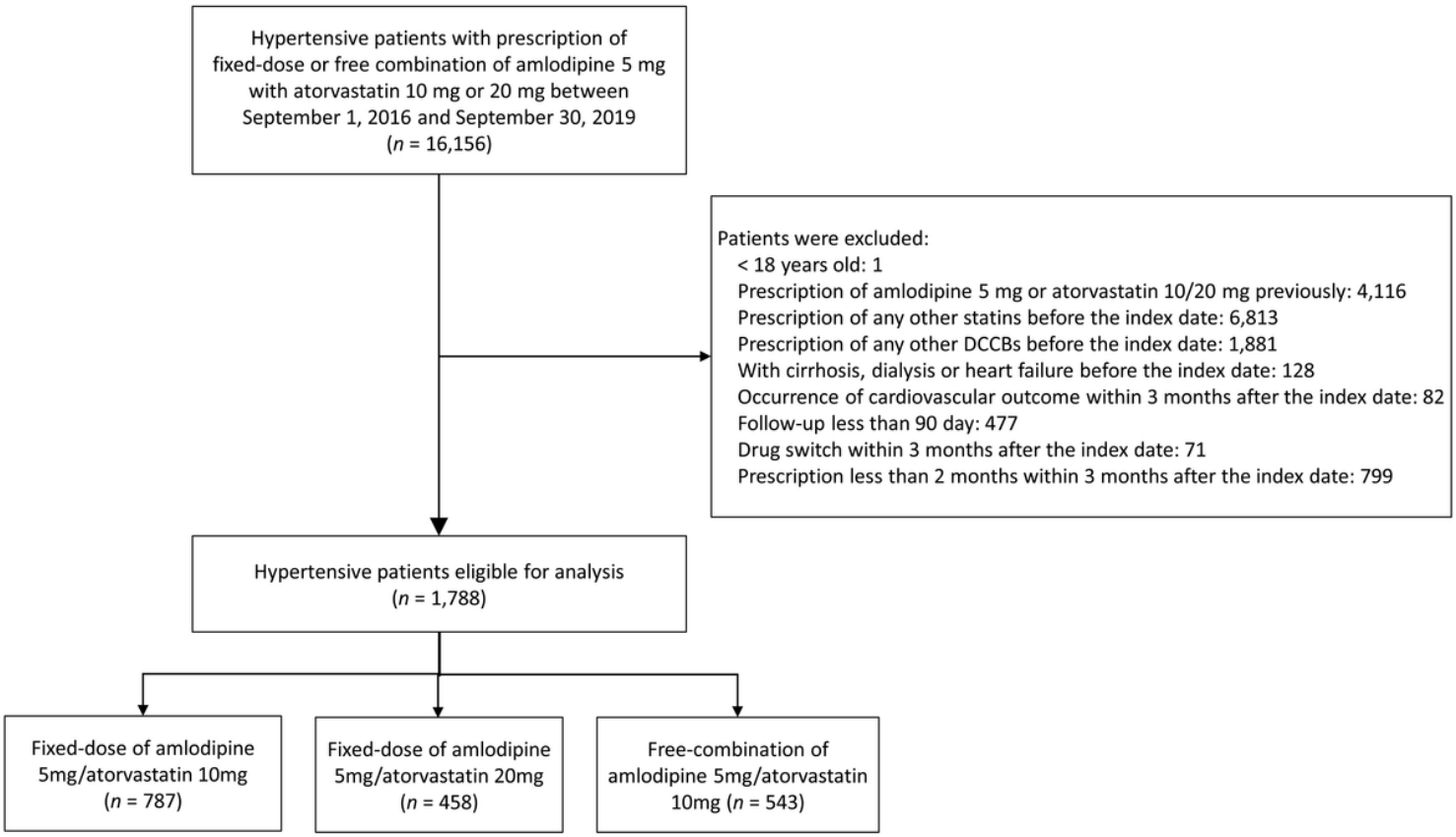
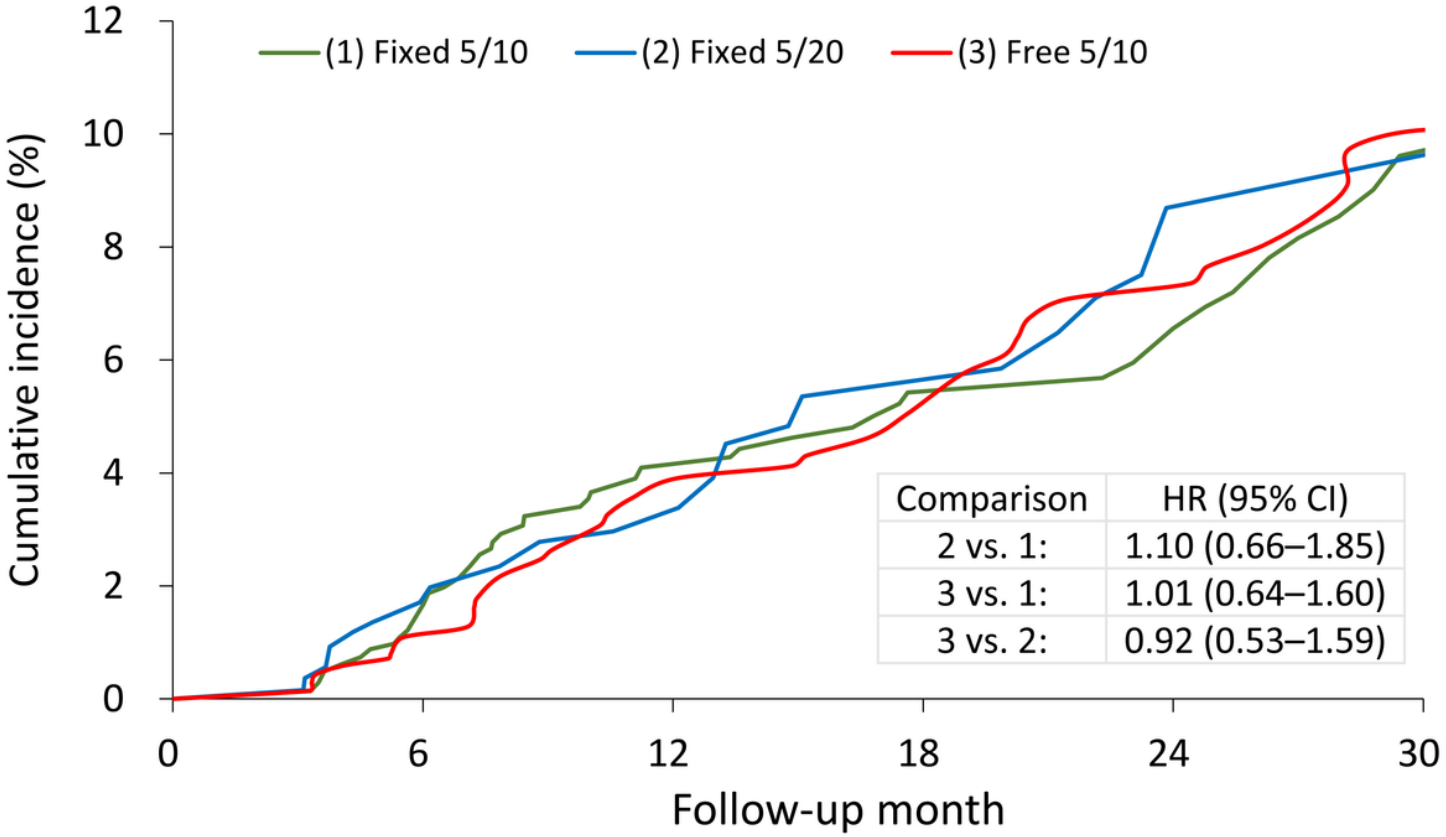


Figure 1

Study design and flow chart of the inclusion and exclusion of the patients. DCCBs, dihydropyridine calcium-channel blockers.



Patient at risk (%):

Fixed 5/10	100	89.5	70.7	54.4	38.5	24.0
Fixed 5/20	100	87.8	70.4	51.3	32.3	19.6
Free 5/10	100	87.8	68.7	53.7	38.3	23.2

Figure 2

The IPTW-adjusted cumulative incidence of composite cardiovascular outcomes in the FDC of amlodipine 5 mg/atorvastatin 10 mg (green line), FDC of amlodipine 5 mg/atorvastatin 20 mg (blue line), and free combination of amlodipine 5 mg/atorvastatin 10 mg (red line) groups. The cumulative incidence was derived from Kaplan-Meier estimate. IPTW, inverse probability of treatment weighting; FDC, fixed-dose combination; HR, hazard ratio; CI, confidence interval.

	Event rate (%)						*P* for interation
Subgroup	Fixed 5/10	Fixed 5/20	Free 5/10	Fixed 5/20 vs. Fixed 5/10	Free 5/10 vs. Fixed 5/10	Free 5/10 vs. Fixed 5/20	
Total	6.1	6.3	6.0				
Any cardiovascular disease							0.332
No	3.7	2.6	4.5				
Yes	10.4	12.9	8.3				

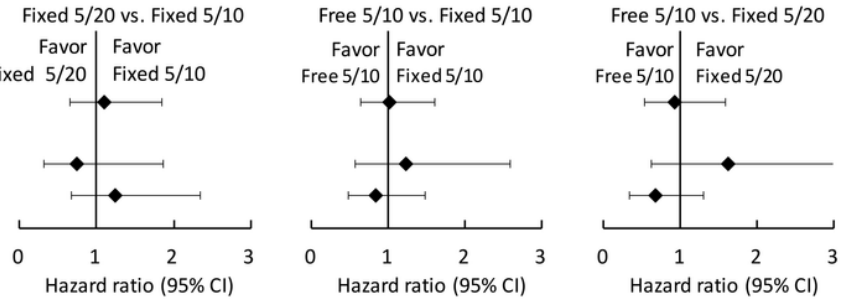


Figure 3

Forest plot of the subgroup analysis according to the presence of preexisting cardiovascular disease in the IPTW-adjusted cohort. CI, confidence interval; IPTW, inverse probability of treatment weighting.

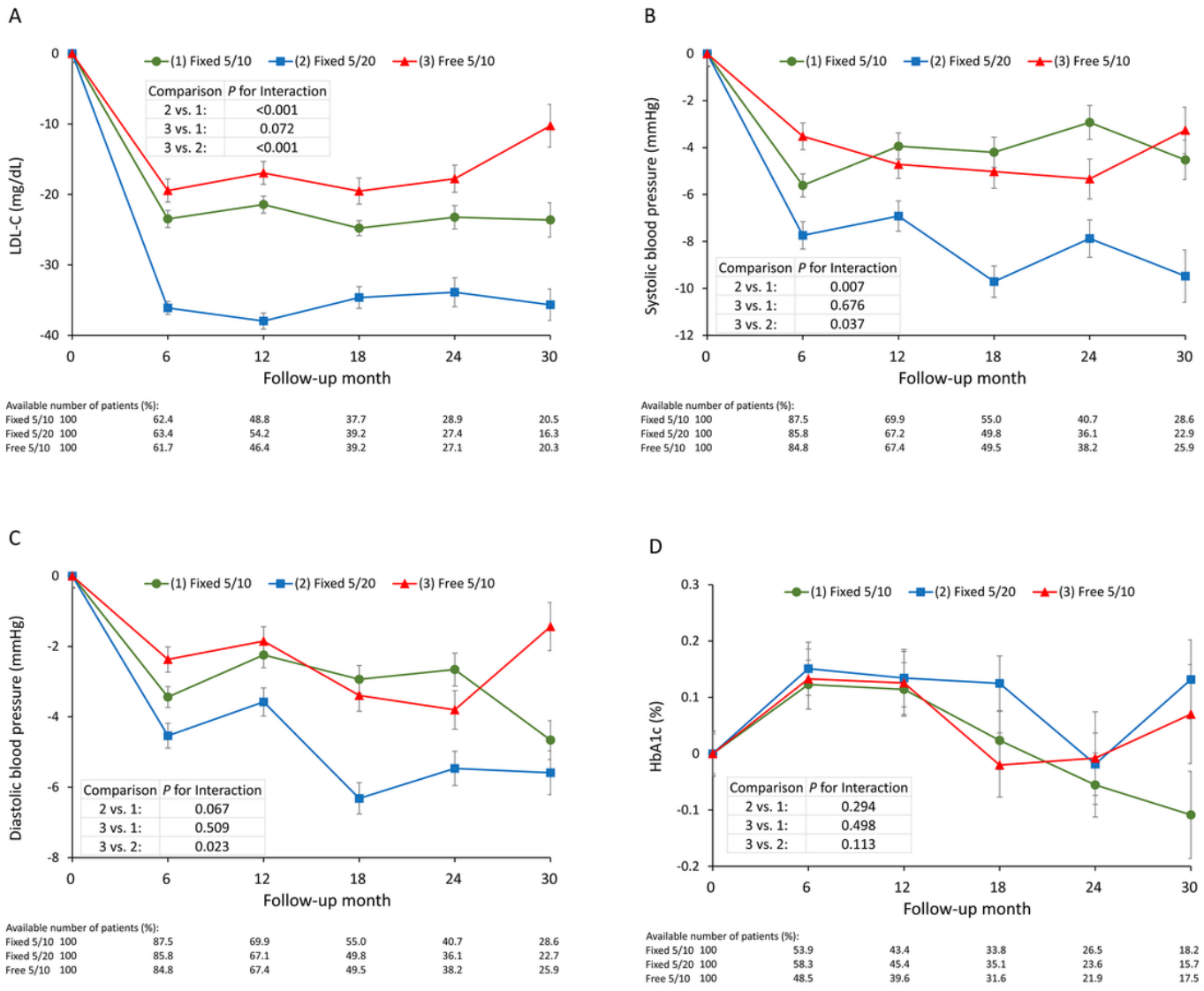


Figure 4

The longitudinal changes in LDL-C (a), systolic blood pressure (b), diastolic blood pressure (c) and HbA1c (d) in the FDC of amlodipine 5 mg/atorvastatin 10 mg (green line), FDC of amlodipine 5 mg/atorvastatin 20 mg (blue line), and free combination of amlodipine 5 mg/atorvastatin 10 mg (red line) groups. FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.

Supplementary Files

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