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Fixed-dose combination of amlodipine and atorvastatin improves clinical outcomes in patients with concomitant hypertension and dyslipidemia

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Abstract

Hypertension and dyslipidemia are important risk factors for cardiovascular disease. However, the clinical outcomes of fixed-dose combination (FDC) versus free-equivalent combination (FEC) of amlodipine and atorvastatin in the treatment of concurrent hypertension and dyslipidemia remain unknown. In this study, we included patients with newly diagnosed hypertension and dyslipidemia, without previously established cardiovascular disease, and treated with either FDC or FEC of amlodipine and atorvastatin were identified from the National Health Insurance Research Database of Taiwan and follow-up for 5 years. By using 1:1 propensity score matching, a total of 1756 patients were enrolled in this study. The composite of major adverse cardiovascular events, including all-cause mortality, myocardial infarction (MI), stroke, and coronary revascularization, occurred more frequently in the FEC group than in the FDC group (hazard ratio, 1.88; 95% confidence interval [CI], 1.42 to 2.5). Although the all-cause mortality did not differ (hazard ratio, 0.46; 95% CI, 0.36 to 1.59), the FEC group developed increased MI, stroke, and coronary revascularization (hazard ratio, 2.87; 95% CI, 1.07 to 7.68; hazard ratio, 1.97; 95% CI, 1.41 to 2.74; and hazard ratio, 2.44; 95% CI, 1.26 to 4.69, respectively). Furthermore, as an unexpected result, a higher risk to develop new-onset diabetes mellitus was observed with FEC regimens (hazard ratio, 2.19; 95% CI, 1.6 to 3.0). In conclusion, although the all-cause mortality did not differ between the two groups, the FDC regimen of amlodipine and atorvastatin improved clinical outcomes when compared to FEC in patients with newly diagnosed hypertension and dyslipidemia.

1 | INTRODUCTION

Cardiovascular disease (CVD) is caused by several factors and its risk factors rarely occur alone.[1-3] The combination of certain risk factors such as hypertension and dyslipidemia can act multiplicatively or synergistically to increase the risk of CVD events.[4,5] Additionally, the relationship between these two risk factors is an important modifiable element for CVD. Therefore, this synergistic relationship is recognized by most major clinical guidelines used to aid the management of

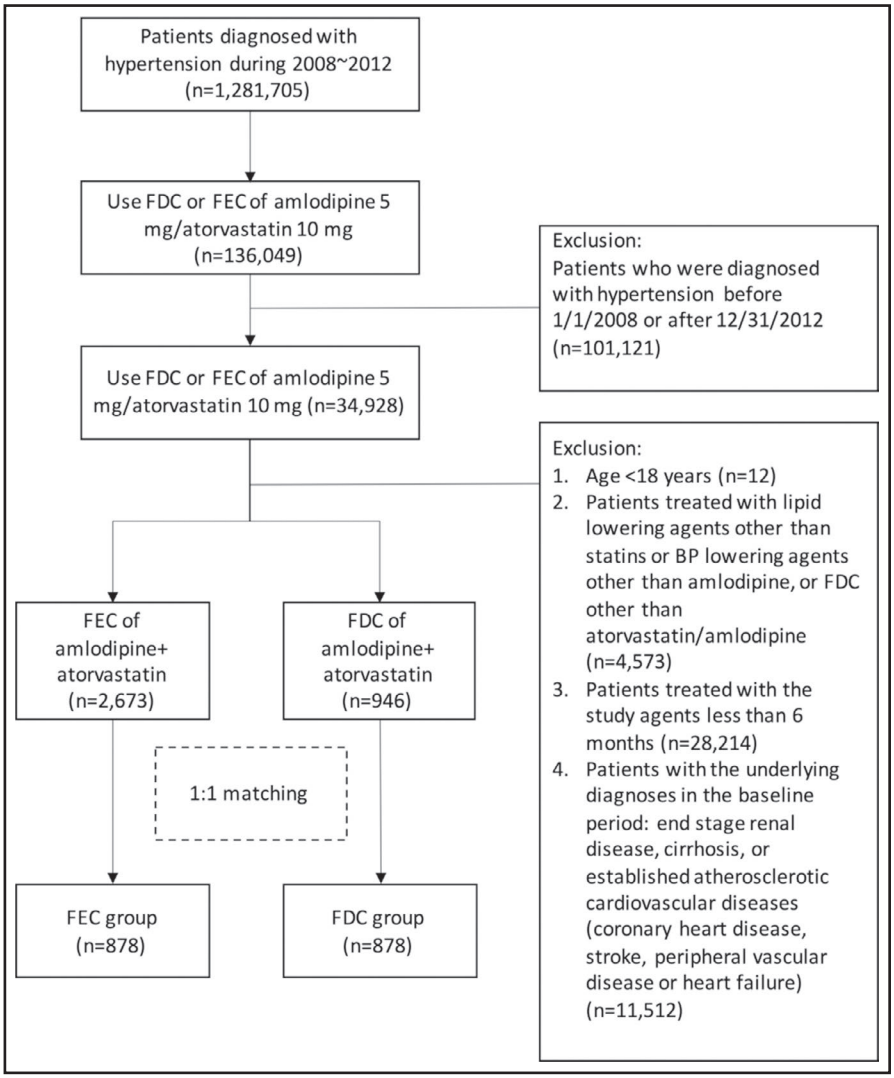

FIGURE 1 Patient enrollment. FDC, fixed-dose combination; FEC, free-equivalent combination

symptomatic patients or those at risk for CVD since they recommend a strategy of treating these risk factors simultaneously rather than in isolation.[6-8]

Previously, several studies have suggested that, in hypertensive patients, fixed-dose combination (FDC) is more effective to control blood pressure than free-equivalent combination (FEC) or monotherapy.[9-11] Better medication compliance with FDC regimens may significantly reduce the major adverse cardiovascular events (MACE) and health care costs,[12,13] which was also recommended by the current major guidelines.[14,15] However, studies comparing the efficacy and interaction between FDC and FEC in two different diseases, such as hypertension and dyslipidemia, are rare.[16-18] Furthermore, in these studies, only drug adherence or laboratory efficacy was compared, with clinical outcomes remaining unassessed between these two treatment strategies in patients with concomitant hypertension and dyslipidemia.

In the present study, we aimed to analyze the clinical outcomes of FDC versus FEC regimes of amlodipine and atorvastatin in the primary prevention of cardiovascular events in patients with concurrent hypertension and dyslipidemia. Simultaneously, drug adherence was also evaluated in these two different strategies.

2 | METHOD

2.1 | Data source

The data included in this study were obtained from the National Health Insurance Research Database (NHIRD) of Taiwan. The National Health Insurance (NHI) program, a state-operated universal health insurance program, implemented from 1995, covering over 99% of the entire Taiwanese population. The NHIRD contains both inpatient and outpatient registries from all medical facilities contracted with the NHI Administration and provides comprehensive medication, procedure, and the established diagnoses of patients, classified into one principal and four secondary International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes. The Bureau of NHI encrypted all personal identifiers before the release of information to the researchers. Confidentiality was addressed by following the data processing regulations set by the Bureau of NHI. The Institutional Review Board of the Chang Gung Memorial Hospital in Linkou approved this study (approval number: 201701147B0).

2.2 | Study cohort and design

Two study cohorts of patients with newly diagnosed hypertension (ICD-9-CM, 401.×) from January 2008 to December 2012 were generated from the NHIRD. The first cohort consisted of patients receiving the FDC regimen of amlodipine and atorvastatin, while the second cohort received the FEC with the same medications (Figure 1). The date of the first prescription of the studied medications was defined as the index date, and 6 months preceding the index date was defined as the baseline period. Hypertensive patients who received any FDC regimen other than amlodipine/atorvastatin or FEC regimens other than these two drugs during the baseline period were excluded from this study. To avoid the clinical effects of different durations of hypertension, we only enrolled newly diagnosed hypertension during this study period. In this study, the only available daily dosage of the FDC regimen was amlodipine 5 mg plus atorvastatin 10 mg. In the FEC group, nonequivalent dosages of both drugs were also excluded. To estimate the frequency of newly onset MACE in this population without established cardiovascular diseases, we excluded patients with a previous diagnosis of coronary artery disease (CAD), myocardial infarction (MI), stroke, end-stage renal disease, cirrhosis, peripheral artery disease, or heart failure before or during the baseline period. Other exclusion criteria were age <18 years, previously diagnosed hypertension, or study agents prescribed less than 6 months. Additionally, we performed propensity score matching to avoid selection biases resulting from the nonrandom assignment. The variables used in the matching process were sex, age, diabetes mellitus (DM) (ICD-9-CM, 250), chronic kidney disease (CKD) (ICD-9-CM, 585), Charlson Comorbidity Index (CCI), and baseline concomitant medications including antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), beta-blockers, diuretics, oral hypoglycemic agents, insulin, and other anti-hypertensive drugs. The FDC group was matched at a 1:1 ratio to the FEC group. Medication adherence was assessed by using the proportion of days covered (PDC) according to the insurance claims for the medications, which is defined as the total number of days covered by the study drugs divided by the total number of days in the study period.[12] All patients were followed up for 5 years or until the development of end points, whichever was first.

2.3 | Study end points

The primary end point was the composition of MACE, including all-cause mortality, MI (ICD-9-CM, 410-410.9), stroke (ICD-9-CM, 430-437), percutaneous coronary intervention (PCI) (ICD-9-CM, 36.0-36.03 and 36.05-36.09), or coronary artery bypass grafting surgery (CABG) (ICD-9-CM, 36.1-36.99 and V45.81). Mortality was identified by using death certificate data files. The secondary end points included the components of the primary end point, new-onset diabetes mellitus (NODM), hospitalization for CAD, and newly initiated hemodialysis. All these end points were based on the morbidity-driven ICD-9-CM coding.

2.4 | Statistics

Continuous variables were compared by using Student's *t* test, and categorical variables were analyzed by the chi-square test. Data are presented as means and standard deviations or medians and percentages. A Cox proportional hazard model was used for a time to event analysis. Univariable and multivariable logistic regression analyses were used to identify independent predictors for primary end point. All analyses were conducted by using SAS Statistical Software, version 9.3 (SAS Institute Inc.) and R: A language and environment for statistical computing, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). *P* values <.05 were considered statistically significant.

2.5 | Privacy and confidentiality

The NHIRD deleted all identifiable information, and we further protected all patient information. Only the researchers and the authorized research participants had access to the dataset. All the database information was saved and locked in a safe place.

3 | RESULTS

A total of 1 281 705 patients diagnosed with hypertension were identified in NHIRD from January 2008 to December 2012, but only 136 049 participants were treated daily with either FDC or FEC regimens composed of amlodipine 5 mg and atorvastatin 10 mg. After exclusion, 3619 newly diagnosed hypertensive patients were included for further propensity score matching, including 2673 patients in the FEC group and 946 patients in the FDC group (Figure 1). After matching, 1756 patients were enrolled in the present study, including 878 in each group. No significant inter-group differences were observed in sex, age, type 2 DM, CKD, CCI, and baseline concomitant medications (Table 1).

Medication adherence as assessed by PDC was better in the FDC group than in the FEC group (0.49 ± 0.26 vs 0.32 ± 0.3, $P < .001$). The Cox proportional hazards model revealed significantly enhanced MACE in the FEC group than in the FDC group (hazard ratio, 1.88; 95% confidence interval [CI], 1.42 to 2.5; $P < .001$) within 5 years (Figure 2). A difference in favor of the FDC group was seen early in this analysis. Regarding each component of MACE, a higher incidence of MI, stroke, and revascularization (PCI or CABG) were observed in the FEC group than in the FDC group (hazard ratio, 2.87; 95% CI, 1.07 to 7.68; $P = .04$; hazard ratio, 1.97; 95% CI, 1.41 to 2.74; $P < .001$; and hazard ratio, 2.44; 95% CI, 1.26 to 4.69; $P = .008$, respectively) (Figure 3). However, all-cause mortality was not different between the two groups (hazard ratio, 0.76; 95% CI, 0.36

TABLE 1 Patient demographic characteristics

	Before match			After match		
	FEC	FDC	*P*-value	FEC	FDC	*P*-value
N	2673	946		878	878	
Male (%)	1269 (47.5)	482 (51.0)	.07	428 (48.7)	453 (51.6)	.25
Age (mean [sd])	58.05 (11.74)	58.60 (11.48)	.21	58.01 (11.66)	58.36 (11.48)	.53
Type 2 diabetes mellitus (%)	929 (34.8)	481 (50.8)	<.001	405 (46.1)	423 (48.2)	.42
Chronic kidney disease (%)	65 (2.4)	17 (1.8)	.32	16 (1.8)	14 (1.6)	.85
Charlson comorbidity index (mean [sd])	0.66 (1.16)	1.28 (1.30)	<.001	1.12 (1.42)	1.15 (1.21)	.56
Baseline concomitant medications						
Antiplatelet agents (%)	280 (10.5)	189 (20.0)	<.001	151 (17.2)	155 (17.7)	.85
ACE inhibitors (%)	408 (15.3)	210 (22.2)	<.001	185 (21.1)	188 (21.4)	.91
ARBs (%)	596 (22.3)	453 (47.9)	<.001	404 (46.0)	391 (44.5)	.57
Beta-blockers (%)	646 (24.2)	347 (36.7)	<.001	306 (34.9)	304 (34.6)	.96
Diuretics (%)	334 (12.5)	174 (18.4)	<.001	144 (16.4)	152 (17.3)	.66
Oral hypoglycemic agents (%)	799 (29.9)	433 (45.8)	<.001	364 (41.5)	377 (42.9)	.56
Insulin (%)	147 (5.5)	102 (10.8)	<.001	84 (9.6)	82 (9.3)	.94
Other anti-HTN agents (%)	65 (2.4)	43 (4.5)	.002	34 (3.9)	38 (4.3)	.72

Note: Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; FDC, fixed-dose combination; FEC, free-equivalent combination; HTN, hypertension.

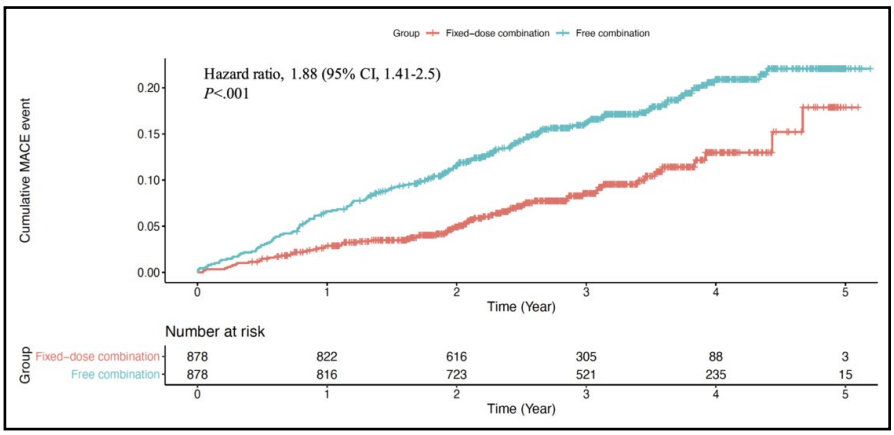

FIGURE 2 Cumulative events of MACE (primary end point) in FDC (red line) and FEC (blue line) groups of amlodipine 5 mg/atorvastatin 10 mg. FDC, fixed-dose combination; FEC, free-equivalent combination; MACE, major adverse cardiovascular event

to 1.59; $P = .46$). Compared with the FDC group, a greater number of patients developed NODM in the FEC group (hazard ratio, 2.19; 95% CI, 1.6 to 3.0; $P < .001$) during the follow-up period (Figure 4). Similarly, more patients in the FEC groups experienced CAD hospitalization and newly initiated hemodialysis (hazard ratio, 2.0; 95% CI, 1.56 to 2.57; $P < .001$ and hazard ratio, 3.34; 95% CI, 1.67 to 6.66; $P = .001$, respectively).

In univariable and multivariable analyses, FEC group, male gender, age, concomitant use of antiplatelet agents, beta-blockers, and diuretics were positive predictors for primary end points, while concomitant use of ARBs negatively predicted MACE (Table 2).

4 | DISCUSSION

This nationwide population-based cohort study is the first study to compare the clinical outcomes of FDC versus FEC of amlodipine and atorvastatin in patients with concomitant hypertension and dyslipidemia without previous established cardiovascular diseases. During 5 years of follow-up, we observed that the FDC treatment strategy was more effective in reducing the risk of MACE than the FEC strategy. Meanwhile, compared to FDC, FEC group was also an independent predictor for MACE by multivariable analysis. Additionally, FDC was also superior to FEC in reducing the incidence of MI, stroke, NODM, CAD hospitalization, and newly initiated hemodialysis. The

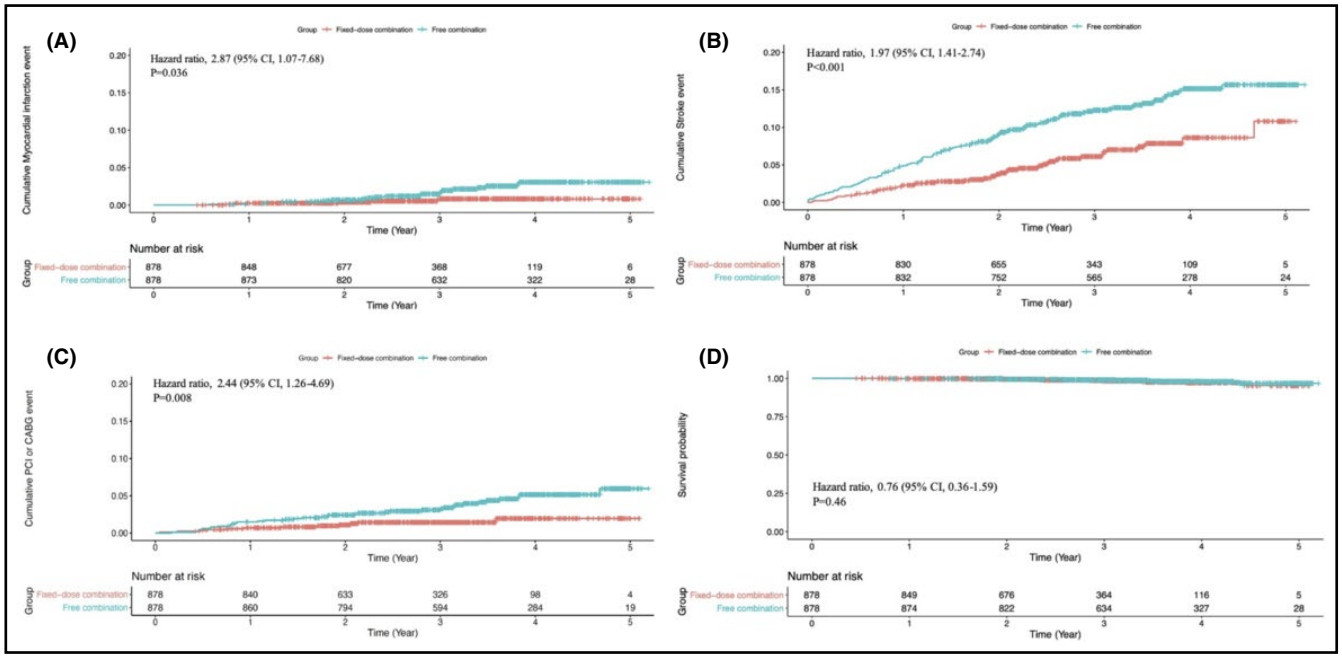

FIGURE 3 Comparison of the components of the primary end point in FDC (red line) versus FEC (blue line) of amlodipine/atorvastatin: A, myocardial infarction; B, stroke; C, coronary revascularization; and D, survival probability. FDC, fixed-dose combination; FEC, free-equivalent combination

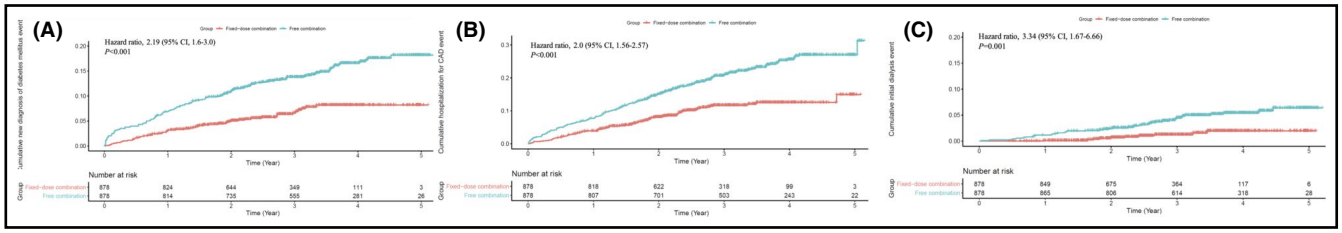

FIGURE 4 Comparison of secondary end points of FDC (red line) versus FEC (blue line) of amlodipine/atorvastatin: A, newly onset diabetes mellitus; B, hospitalization for coronary artery disease; and C, newly initiated hemodialysis. FDC, fixed-dose combination; FEC, free-equivalent combination

benefit of the FDC treatment strategy, which was apparent early in these outcomes except in MI, was observed in newly diagnosed hypertensive patients with a higher proportional incidence of DM and receiving ACEI, ARB, beta-blockers, and oral hypoglycemic agents.

Previous studies have evaluated the efficacy and compliance of combination regimens of anti-hypertension/lipid-lowering.[16-18] In a randomized, multi-center, double-blind, placebo-controlled study comparing the efficacy and tolerability of triple combination of amlodipine/losartan/rosuvastatin (A/L/R) to either losartan/rosuvastatin (L/R) or amlodipine/losartan (A/L) double combination in patients with hypertension and dyslipidemia,[16] the low-density lipoprotein cholesterol (LDL-C) level was reportedly lower in the A/L/R group than in the A/L group after 8 weeks of treatment. In addition, the mean reduction in sitting diastolic blood pressure was significantly greater in the A/L/R group than in the L/R group, with no clinically significant tolerability issue reported throughout the study. Two other studies both demonstrated that the FDC of amlodipine/atorvastatin can help to improve drug adherence versus the two-pill calcium channel blocker (CCB) + statin regimen.[17,18] Furthermore, such an FDC of amlodipine/atorvastatin for LDL-C reduction was also cost-effective compared with the two-pill regimen.[13] However, none of the above studies demonstrated the beneficial clinical outcomes of FDC regimens.

Adherence is a substantial factor governing the outcome of medical treatment, especially in chronic diseases.[19] Furthermore, nonadherence was also confirmed as an important contributor to the higher hospitalization rate and health care cost.[20] Currently, FDC is widely used in several chronic diseases such as hypertension, DM, and pulmonary tuberculosis to simplify treatment regimens, improving medication adherence and clinical outcomes.[10,12,21-24] In our previous study, compared to the free combination of CCB/ARB, the FDC of amlodipine/valsartan improves MACE-free survival, medication compliance, hospitalization rates, and also decreases total health care costs.[12] The effect of FDC in the treatment of type 2 DM has been addressed in a systemic review including 10 studies, 2 of which were prospective, 1 was observational, and 7 were randomized, double-blinded, parallel studies.[21] The authors concluded that the FDCs of various oral hypoglycemic agents significantly reduce

TABLE 2 Univariable and multivariable logistic analyses to predict major adverse cardiovascular events

	Univariable analysis		Multivariable analysis	
Risk factor	**HR (95% CI)**	***P*-value**	**aHR (95% CI)**	***P*-value**
FEC Group	1.883 (1.418, 2.501)	<.0001	2.048 (1.596, 2.627)	<.0001
Male	1.411 (1.085, 1.836)	.0102	1.606 (1.355, 1.903)	<.0001
Age	1.029 (1.018, 1.041)	<.0001	1.041 (1.034, 1.049)	<.0001
Type2 DM[a]	1.235 (0.952, 1.604)	.1121		
CKD	1.920 (0.853, 4.321)	.1151		
CCI Score	1.013 (0.918, 1.119)	.7949		
Antiplatelet agents	1.595 (1.182, 2.154)	.0023	1.372 (1.100, 1.711)	.005
ACE inhibitors	1.033 (0.749, 1.425)	.841		
ARBs	0.971 (0.747, 1.262)	.8251	0.817 (0.668, 0.998)	.048
Beta-blockers	0.998 (0.758, 1.314)	.9883	1.342 (1.116, 1.614)	.0018
Diuretics	1.644 (1.214, 2.228)	.0013	1.307 (1.047, 1.633)	.0181
Other anti-HTN agents	1.162 (0.616, 2.191)	.6426		

Abbreviations: ACE, angiotensin-converting enzyme; aHR, adjusted hazard ratio; ARBs, angiotensin-receptor blockers; CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; FEC, free-equivalent combination; HR, hazard ratio; HTN, hypertension.

[a]Glucose-lowering agents were not included in this analysis because of collinearity with DM.

glycated hemoglobin and fasting plasma glucose values, improve adherence, and reduce serious adverse drug reactions in diabetic patients. On the other hand, two previous meta-analyses on anti-tuberculosis treatments have shown no clinical benefit of FDC in terms of acquired drug resistance, culture conversion, treatment failure, or relapse when compared with separate drug formulations.[22,24] The authors explained that these results could be generated due to infrequent outcomes.

Although the all-cause mortality rate did not differ between the FDC and FEC groups in the current study, similar results have been reported in previous studies.[25,26] A population-based, retrospective cohort study demonstrated that the FDC of blood pressure-lowering medications among hypertensive patients was not associated with lower mortality when compared with the multi-pill group by on-treatment analysis, despite the superior adherence recorded.[25] In another comprehensive review of randomized controlled trials regarding the FDC of blood pressure-lowering and lipid-lowering for the prevention of atherosclerotic CVD, compared with the comparator groups such as placebo, usual care, or active drug treatment, the effects of the FDC treatment on mortality did not differ from these groups (RR, 1.1; 95% CI, 0.64 to 1.89).[26] However, superior drug adherence may have the potential to reduce mortality in some specific populations. In patients with documented CVD, the lower adherence to statin therapy has been associated with a greater mortality risk.[27] In another health care database study from Sweden, lower refill adherence to lipid-lowering medications resulted in higher CVD mortality among patients with type 2 DM.[28] Similarly, in newly diagnosed type 2 DM patients, lower anti-diabetic medication adherence has been associated with higher long-term all-cause mortality.[29] In the current study, the difference in mortality was insignificant between the FDC and FEC groups may be explained by the low event rates in both groups, which could be attributed to the limited sample size, limited 4-year follow-up period, and the primary preventive nature of the intervention.

In a previous collaborative meta-analysis assessing randomized statin trials, statin use was associated with a 9% increased risk of developing NODM,[30] which was positively correlated with the strength of the statin[31]; however, the risk was reportedly low in absolute terms and when compared with the reduction in coronary events. Furthermore, the underlying mechanisms of statin-induced NODM are not precisely known, and several possibilities have been proposed.[32] Notably, the beneficial effects of statins on CVD outweigh its risk of NODM development, with no neutralizing factor for such a risk documented in the literature. In the current study, we demonstrated the unexpected finding that in the FEC group of atorvastatin and amlodipine, the risk of NODM was more than twice when compared with the FDC group. The risk of NODM in anti-hypertensive drug therapy, including CCBs, has been evaluated in previous meta-analyses.[33-35] Compared to diuretics and beta-blockers, CCBs are associated with reduced odds of developing NODM among hypertensive patients.[33-35] In contrast, treatment with CCBs is associated with a higher risk of developing NODM when compared with both ACEI and ARB treatment.[33,34] However, the use of ARB or ACEI in addition to CCB has demonstrated comparable incidences of NODM when compared to CCB monotherapy.[36] The drug-drug interaction between CCBs and statins on the development of NODM remains unclear and is yet to be evaluated. In a previous study, combined treatment with amlodipine and atorvastatin improved endothelial function and inflammation as reflected by lower circulating levels of intercellular adhesion molecule-1 and tumor necrosis factor-α.[37]

Similarly, oral administration of atorvastatin combined with amlodipine effectively prevents both endothelial dysfunction and elevated blood pressure in insulin-resistant rats.[38] Furthermore, combination therapy with amlodipine and atorvastatin, but not individual monotherapy, suppresses angiotensin II-induced abdominal aortic aneurysm formation in mice in vivo, by involving the inhibition of Rho-kinase.[39] In the current study, medication adherence was superior in the FDC group than in the FEC group. One possibility was that the higher risk of developing NODM due to higher atorvastatin treatment in the FDC group could be counterbalanced by higher amlodipine administration. However, some confounding factors which may affect the development of NODM were not included in our database and could not be corrected by the matching such as body mass index, metabolic profiles, and socioeconomic status. The underlying molecular mechanism of such a phenomenon remains unclear and further interventional studies are needed to elucidate whether amlodipine could attenuate or neutralize the NODM risk of atorvastatin.

4.1 | Study limitation

This study was based on a large administrative database and carried several limitations. First, we had no personal data such as family history, lifestyle, smoking, laboratory data, body weight, or blood pressure records. Therefore, the efficacy of blood pressure- or cholesterol-lowering, as well as the critical link between medication compliance and patient outcomes, could not be estimated in this study. Second, although PDC has been widely used in studies of pharmacy claims datasets,[12] this surrogate marker of medication compliance does not ensure that the patients consumed the medications accordingly. Thus, medication compliance could be overestimated. Third, we used propensity score matching to balance the potential differences between two study groups; however, some parameters were not considered and may have confounded the study results, which is an inherent limitation of retrospective studies. Finally, we only enrolled hypertensive patients without established CVD so that these results could not be extrapolated to patients with documented atherosclerotic CVD as secondary prevention.

5 | CONCLUSION

In this retrospective claims database study, although the all-cause mortality did not differ, the FDC regimen of amlodipine and atorvastatin improved compliance and clinical outcomes, including MACE, MI, stroke, revascularization (PCI/CABG), hospitalization for CAD, NODM, and newly initiated hemodialysis when compared to an FEC regimen with the same medications in patients with newly diagnosed hypertension and dyslipidemia, with no previous CVD.

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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