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Review

SYSTEMATIC REVIEW OF THE EFFICACY/ EFFECTIVENESS AND SAFETY OF FENOFIBRATE–STATIN COMBINATION THERAPY IN THE TREATMENT OF DYSLIPIDEMIA

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ABSTRACT: Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease. In patients with persistent hypertriglyceridemia or mixed dyslipidemia despite statin therapy, fenofibrate–statin combination therapy, including the fixed-dose combination (FDC) of fenofibrate/pravastatin 160/40 mg, may be considered to further improve control of non-LDL-C lipid parameters. This systematic review was conducted according to Cochrane guidance and the PRISMA 2020 checklist to evaluate the efficacy/effectiveness and safety of fenofibrate–statin combination therapy in the treatment of dyslipidemia. PubMed and Ovid EMBASE were searched up to July 2026; risk of bias was assessed using RoB 2 for randomized controlled trials and ROBINS-I for non-randomized studies. From 3,660 screened records and 203 full-text assessments, 10 studies (3 RCTs and 7 non-randomized studies) were included. FDC fenofibrate/pravastatin further reduced non-HDL-C by 12.9–16.3% and triglycerides by 22.6–31.6%, and increased dual lipid target attainment versus statin monotherapy, with effects sustained over 3 years in the POSE study. Large cohort studies reported that fenofibrate–statin combinations were associated with a 9.9–20.0% reduction in selected cardiovascular events and a 27.0–28.4% reduction in all-cause mortality among patients with type 2 diabetes. The combination was generally well tolerated, with no myopathy or rhabdomyolysis reported in RCTs, although some observational studies signaled increased risks of acute kidney injury, myositis, or liver injury, which require monitoring during treatment.

Keywords: fenofibrate, pravastatin, fixed-dose combination, systematic review, dyslipidemia

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1. INTRODUCTION

Dyslipidemia is an abnormality in the concentration and composition of plasma lipids, manifested by elevated total cholesterol, LDL-C, and triglycerides and/or reduced HDL-C. It is also an important risk factor for atherosclerotic cardiovascular disease (1,2). According to World Health Organization (WHO) statistics for 2019, atherosclerotic cardiovascular disease is one of the leading causes of death worldwide, accounting for more than 27% of deaths, of which 16% are due to myocardial infarction and 11% to stroke (3). In Vietnam, the prevalence of dyslipidemia has increased fastest in people aged 35–44 years, and the disease is tending to occur at younger ages (4).

According to the current 2019 European Society of Cardiology (ESC) guidelines and the 2015 guidelines on the diagnosis and treatment of dyslipidemia of the Vietnam National Heart Association, lifestyle modification is the foundation of treatment, and statins are the first-line drugs for lowering LDL-C and cardiovascular risk. In high-risk patients with persistent hypertriglyceridemia despite optimized lifestyle and statin therapy, fibrates may be considered, particularly in the atherogenic dyslipidemia phenotype with elevated triglycerides and low HDL-C. However, evidence that adding a fibrate to statin therapy reduces cardiovascular events is inconsistent, so statin–fibrate combination therapy is not routinely recommended for this purpose alone; the guidelines also stress monitoring for adverse muscle, liver, and kidney events when the drugs are combined (5–8).

In patients with persistent hypertriglyceridemia or mixed dyslipidemia despite statin therapy, fenofibrate–statin combination therapy is a strategy that may improve control of lipid components other than LDL-C, given either as separate drugs or as the fixed-dose combination of fenofibrate/pravastatin (FDC). FDC fenofibrate/pravastatin has been approved in Europe and Vietnam; it simplifies the regimen and may improve treatment adherence.

The available evidence on fenofibrate–statin combination therapy includes both studies of FDC fenofibrate/pravastatin itself and studies of fenofibrate or fenofibric acid combined with a statin as separate drugs. We therefore conducted this study to systematically review the evidence on the efficacy/effectiveness and safety of fenofibrate–statin combination therapy in the treatment of dyslipidemia, as a scientific basis for rational drug use in clinical practice.

2. SUBJECTS AND METHODS

2.1. Study design

This systematic review was conducted according to the Cochrane guidance for systematic reviews of interventions and followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

2.2. Study subjects

The study subjects were studies evaluating the efficacy/effectiveness and safety of fenofibrate–statin combination therapy in the treatment of dyslipidemia, including the fixed-dose combination of fenofibrate/pravastatin (FDC) and fenofibrate or fenofibric acid combined with a statin as separate drugs. The research question was formulated using the PICO framework (Table 1).

Table 1. Research question according to the PICO framework

Component	Content
P – Population	Patients with dyslipidemia, including mixed dyslipidemia; patients at cardiovascular risk or receiving primary/secondary cardiovascular prevention; patients with type 2 diabetes and dyslipidemia.
I – Intervention	Fenofibrate–statin combination therapy, including FDC fenofibrate/pravastatin and fenofibrate or fenofibric acid combined with a statin as separate drugs.

Component	Content
C – Comparator	All comparator drugs identified in the literature.
O – Outcome	Changes in non-HDL-C, LDL-C, HDL-C, triglycerides, and other lipid parameters; lipid target attainment; treatment adherence; cardiovascular events, including myocardial infarction, stroke, hospitalization for heart failure, and death; adverse events, serious adverse events, and discontinuation due to adverse events.

2.3. Methods

(i) Search strategy: PubMed and Ovid EMBASE were searched up to July 2026, with no restriction on publication date and limited to English-language publications. The search strategy was based on terms for the study population and intervention (dyslipidemia, fenofibrate, fenofibric acid, statin, pravastatin, combination therapy), combined with the Boolean operators AND/OR.

(ii) Screening and study selection: Search results were pooled and deduplicated in Excel, then screened in two independent rounds by two researchers on the Rayyan platform: round 1 screened titles/abstracts, and round 2 assessed full texts for final eligibility. Disagreements were resolved by discussion or by a third researcher.

- Inclusion criteria: Studies were included if they (1) evaluated fenofibrate–statin combination therapy, either FDC fenofibrate/pravastatin or fenofibrate/fenofibric acid combined with a statin as separate drugs; (2) were conducted in patients with dyslipidemia or in populations with dyslipidemia relevant to the research question; (3) reported at least one efficacy/effectiveness or safety outcome; (4) were randomized controlled trials, cohort studies, or pooled/subgroup analyses of clinical trials; and (5) were published in full text in English.

- Exclusion criteria: Studies were excluded if they were duplicate reports from the same dataset without additional relevant results, case reports or case series, unavailable in full text, or published in a language other than English.

(iii) Data extraction: Data from eligible studies were extracted into five groups: (1) publication characteristics, including authors, year of publication, and country; (2) methodological characteristics, including study design and sample size; (3) characteristics of the population, intervention, and comparator, distinguishing FDC fenofibrate/pravastatin from fenofibrate–statin combinations given as separate drugs; (4) treatment efficacy/effectiveness results; and (5) safety and adverse event results.

(iv) Study quality assessment: Risk of bias was assessed independently by two researchers using RoB 2 for randomized controlled trials and ROBINS-I for eligible non-randomized intervention/observational studies. Disagreements were resolved by discussion or by a third researcher.

3. RESULTS

3.1. Literature search results and study characteristics

The search identified 4,025 records from PubMed (n=804) and Ovid EMBASE (n=3,221). After 365 duplicates were removed, 3,660 records were screened by title/abstract; 3,457 did not meet the criteria, and 203 articles were assessed in full text. After full-text assessment, 193 articles were excluded, and 10 studies meeting the criteria were included in the systematic review.

The studies were classified into three intervention groups: (1) 5 studies directly evaluating FDC fenofibrate/pravastatin 160/40 mg, including 3 RCTs, 1 pooled analysis of phase III data, and 1 real-world observational study (POSE) (9–13); (2) 3 studies evaluating fenofibrate/fenofibric acid–statin combinations given as separate drugs, including 1 pooled analysis and 2 nationwide retrospective cohorts in Korea (14–16); and (3) 2 large retrospective cohort studies evaluating statin–fibrate combinations in general in the United States and Japan (17,18). Detailed characteristics of the 10 studies are presented

in Table 2.

Table 2. Characteristics of the included studies

No.	Author (year)	Location	Study design	Follow-up	Sample size (N)	Intervention (n)	Comparator (n)
Group 1. FDC fenofibrate/pravastatin							
1	Michel Farnier et al. (2010) (9)	France, Poland, Belgium	Double-blind, parallel, double-dummy RCT	12 weeks	248	FDC 160/40 mg (n=123)	Pravastatin 40 mg monotherapy (n=125)
2	Michel Farnier et al. (01/2011) (10)	France, Germany, Hungary, Norway, Poland, Romania	Double-blind, parallel RCT	12 weeks	291	FDC 160/40 mg (n=145)	Simvastatin 20 mg monotherapy (n=146)
3	Michel Farnier et al. (09/2011) (11)	France, Poland, Belgium	Open-label extension study	64 weeks (12 weeks double-blind + 52 weeks open-label)	224	FDC; continued FDC (n=108), switched to FDC after week 12 (n=115)	No control group in the extension phase
4	Michel Farnier et al. (2012) (12)	France, Belgium, Germany, Norway, Poland, Hungary	Pooled analysis of 5 phase III clinical trials	12–64 weeks	1,566	FDC 160/40 mg (n=1,566)	Statin monotherapy (n=519) or fenofibrate monotherapy (n=122) in the double-blind phase
5	Nikolaos Papadopoulos et al. (2024) (13)	Spain, Greece, Portugal	Real-world observational cohort (POSE), multicenter, open-label	3 years	3,075	FDC 160/40 mg (n=1,546)	Moderate-intensity statin monotherapy (n=1,529)
Group 2. Fenofibrate/fenofibric acid–statin combination as separate drugs							
6	Peter H. Jones et al. (2010) (14)	United States, Canada	Pooled subgroup analysis of 3 phase III RCTs	12 weeks	586	Fenofibric acid–statin combination (n=216)	Statin monotherapy (n=212) or fenofibric acid monotherapy (n=105)
7	Sangmo Hong et al. (2024) (15)	Korea	Retrospective cohort, 1:1 propensity score matching	Mean 4.03 years	221,446	Fenofibrate–statin combination as separate drugs (n=110,723)	Statin monotherapy (n=110,723)

No.	Author (year)	Location	Study design	Follow-up	Sample size (N)	Intervention (n)	Comparator (n)
8	Ji Yoon Kim et al. (2025) (16)	Korea	Retrospective cohort, 1:1 propensity score matching	Median 50.4 months	23,444	Fenofibrate–statin combination as separate drugs (n=11,722)	Statin monotherapy (n=11,722)
Group 3. Statin–fibrate combination in general							
9	David L. McClure et al. (2007) (17)	United States	Retrospective cohort	5 years (1999–2003)	15,033	Statin–fibrate combination (n=1,648)	Statin monotherapy (n=7,228) or no lipid-lowering drug (n=6,157)
10	Yohei Sobukawa et al. (2024) (18)	Japan	Retrospective cohort from an insurance database (SKDB)	1 year	285,508 before matching	Statin added to fibrate (n=498) or fibrate added to statin (n=1,183)	Fibrate monotherapy (n=2,988) or statin monotherapy (n=11,830)

3.2. Efficacy/effectiveness and safety results

Efficacy/effectiveness results are presented in Table 3. For FDC fenofibrate/pravastatin, the RCTs showed additional reductions of 12.9–16.3% in non-HDL-C and 22.6–31.6% in triglycerides and an increase in HDL-C compared with statin monotherapy, together with a 1.5- to 2.5-fold higher rate of dual lipid target attainment (9–11); the long-term observational POSE study found that lipid control was maintained for up to 3 years without an increase in cardiovascular events (13). For fenofibrate/fenofibric acid–statin combinations given as separate drugs, the pooled analysis by Jones showed a 5- to 7-fold higher rate of simultaneous attainment of 5 lipid targets compared with monotherapy (14), while two large Korean cohorts reported clear real-world clinical benefits, with 9.9–20.0% lower risks of selected major cardiovascular events (myocardial infarction, stroke, hospitalization for heart failure) and 27.0–28.4% lower risk of all-cause mortality in patients with type 2 diabetes (15,16).

Table 3. Efficacy/effectiveness results

Study	Intervention	Comparator	Main results	p-value
Group 1. FDC fenofibrate/pravastatin				
Michel Farnier et al. (2010) (9)	FDC 160/40 mg	Pravastatin 40 mg	non-HDL-C −14.1% vs −6.1%; TG −22.6% vs −2.0%; HDL-C +6.5% vs +2.3%; LDL-C −11.7% vs −5.9%; dual lipid target attainment 19.2% vs 7.6%.	0.002; 0.001; 0.009; 0.019; <0.01
Michel Farnier et al. (01/2011) (10)	FDC 160/40 mg	Simvastatin 20 mg	non-HDL-C −12.9% vs −6.8%; TG −28.6% vs +5.0%; HDL-C +6.3% vs +1.8%; LDL-C no difference; dual lipid target 28.5% vs 17.9%.	0.008; <0.001; 0.008; LDL-C 0.29; dual target <0.05

Study	Intervention	Comparator	Main results	p-value
Michel Farnier et al. (09/2011) (11)	FDC 160/40 mg	Vs. baseline/ switch	Week 64: non-HDL-C −16.3%, LDL-C −12.2%, TG −31.6%, HDL-C +4.8%; switch group reached dual target in 24.3%.	<0.0001 for main changes
Nikolaos Papadopoulos et al. (2024) (13)	FDC 160/40 mg	Moderate-intensity statin	After 3 years: TG −49.3% vs −16.4%; HDL-C +9.1% vs +2.6%; LDL-C −28.1% vs −32.5%; CV events 1.6% vs 1.2%.	Lipids <0.001; CV events >0.05
Group 2. Fenofibrate/fenofibric acid–statin combination as separate drugs				
Peter H. Jones et al. (2010) (14)	Fenofibric acid + statin	Statin/fenofibric acid monotherapy	TG −43.4 to −43.9%; HDL-C +16.3 to +16.8%; attainment of all 5 lipid targets 20.8–21.6% vs 3.0–4.1%.	<0.001
Sangmo Hong et al. (2024) (15)	Fenofibrate + statin	Statin monotherapy	MI reduced by 12.2% (HR=0.878); stroke 9.9% (HR=0.901); composite CV events 10.3% (HR=0.897); all-cause death 28.4% (HR=0.716).	<0.001
Ji Yoon Kim et al. (2025) (16)	Fenofibrate + statin	Statin monotherapy	HHF reduced by 20% (HR=0.80); HHF/CV death 21% (HR=0.79); all-cause death 27% (HR=0.73); TG −48.4 vs −28.9 mg/dL.	0.036; 0.016; <0.001; <0.001

Safety results are presented in Table 4. For FDC fenofibrate/pravastatin, adverse event rates did not differ significantly between groups, and no myopathy or rhabdomyolysis was reported, although there were slight changes in renal function (9–13). For combinations given as separate drugs, Kim reported an increased risk of acute kidney injury (aHR=1.32; p=0.004) but no increased risk of end-stage kidney disease (16). For statin–fibrate combinations in general, McClure reported an increased risk of myositis (RR=9.06; p<0.01) (17), and Sobukawa showed that adding a statin to a fibrate significantly increased the risk of liver injury and acute kidney injury (18).

Table 4. Safety results

Study	Intervention	Comparator	Main safety results	p-value
Group 1. FDC fenofibrate/pravastatin				
Michel Farnier et al. (2010) (9)	FDC 160/40 mg	Pravastatin 40 mg	Any AE 36.6% vs 32.0%; drug-related AE 10.6% vs 9.6%; SAE 4.1% vs 1.6%; myalgia 6.5% vs 6.4%; myopathy 0% vs 0.8%; no ALT/AST ≥3 ULN. Slight rise in creatinine and fall in CrCl from baseline.	AE/SAE: P>0.05; SAE: P=0.28; creatinine/CrCl: P<0.05
Michel Farnier et al. (01/2011) (10)	FDC 160/40 mg	Simvastatin 20 mg	Any AE 17.2% vs 15.1%; no myopathy/rhabdomyolysis. AST increase 9.6% vs 1.5%; creatinine increase 13.7% vs 6.8%; CrCl decrease 10.8% vs 4.3%.	AST: P=0.03; creatinine: P=0.002; CrCl: P<0.001; other AEs: P>0.05
Michel Farnier et al. (09/2011) (11)	FDC 160/40 mg	Vs. baseline	Any AE 59.4%; drug-related AE 10.7%; SAE 5.4%; discontinuation 2.2%; myopathy/rhabdomyolysis 0%; ALT ≥3 ULN 1.3%; CPK 5–10 ULN 0.4%; CrCl decreased from 96.1 to 91.4 mL/min.	Creatinine/CrCl: P<0.05; clinical AEs: P>0.05

Study	Intervention	Comparator	Main safety results	p-value
Michel Farnier et al. (2012) (12)	FDC 160/40 mg	Statin or fenofibrate monotherapy	Double-blind phase: drug-related AE 12.3% vs 8.9% vs 21.3%; discontinuation due to AE 5.1% vs 2.7% vs 4.9%; myopathy/rhabdomyolysis 0%. Long term: pancreatitis 0.3%, CrCl <60 mL/min 13.8%.	Clinical AEs: P>0.05; CrCl decrease: P<0.05
Nikolaos Papadopoulos et al. (2024) (13)	FDC 160/40 mg	Moderate-intensity statin	Composite safety events 6.8% vs 5.1%; musculoskeletal 3.0% vs 2.4%; renal–urinary 1.9% vs 1.6%; rhabdomyolysis 0% vs 0.07%; discontinuation due to AE 1.2% vs 0.4%.	P>0.05 for safety events
Group 2. Fenofibrate/fenofibric acid–statin combination as separate drugs				
Peter H. Jones et al. (2010) (14)	Fenofibric acid + statin	Statin/fenofibric acid monotherapy	TEAE 75.5–77.4%; myalgia 1.9–2.7%; ALT >3 ULN 0.9–1.9%; creatinine increase >1.5 times baseline 3.7–3.8%; no rhabdomyolysis.	P>0.05 for muscle and liver events
Sangmo Hong et al. (2024) (15)	Fenofibrate + statin	Statin monotherapy	No clinically significant differences in AST, ALT, or creatinine after treatment.	P>0.05
Ji Yoon Kim et al. (2025) (16)	Fenofibrate + statin	Statin monotherapy	AKI 5.45 vs 4.07/1,000 person-years, aHR=1.32; ESKD 0.41 vs 0.54/1,000 person-years, aHR=0.76.	AKI: P=0.004; ESKD: P=0.369
Group 3. Statin–fibrate combination in general				
David L. McClure et al. (2007) (17)	Statin + fibrate	Statin monotherapy/no drug	Myositis: 12 cases in the combination group; adjusted RR 9.06 vs no drug; rhabdomyolysis very rare, NNH about 10,000.	P<0.01
Yohei Sobukawa et al. (2024) (18)	Statin added to fibrate or fibrate added to statin	Corresponding monotherapy	Adding a statin to a fibrate increased liver injury (1.2% vs 0.3%) and AKI (1.3% vs 0.3%), with no increase in pancreatitis/rhabdomyolysis. Adding a fibrate to a statin did not significantly increase the evaluated events.	Liver: P<0.01; AKI: P=0.01; other outcomes: P>0.05

3.3. Study quality assessment

The risk of bias assessment rated the 3 RCTs (9–11) as low risk according to RoB 2, owing to appropriate randomization, blinding, low loss to follow-up, and complete outcome reporting. Among the 7 non-RCT studies, risk of bias varied by design: the two large retrospective cohorts by Hong (2024) and Kim (2025) (15,16) were rated low risk because of 1:1 propensity score matching and adjustment for multiple confounders; the studies by Jones (2010) (14), Farnier (2012) (12), Papadopoulos (2024) (13), and Sobukawa (2024) (18) were rated moderate risk, mainly because of their pooled-analysis or real-world observational designs and possible residual confounding; McClure (2007) (17) had a high risk of bias because of limited control of confounding and reliance on retrospective administrative data. Overall, most of the evidence included in the review had a low to moderate risk of bias, with the RCTs and some large cohorts being more reliable.

4. DISCUSSION

This review showed that FDC fenofibrate/pravastatin 160/40 mg improved lipid parameters compared with statin monotherapy, reducing non-HDL-C by 12.9–16.3%

and triglycerides by 22.6–31.6% and increasing the rate of dual lipid target attainment (9–11). This is explained by the complementary mechanisms of pravastatin, which inhibits cholesterol synthesis, and fenofibrate, which activates PPAR-α. The POSE study also showed that lipid control was maintained for up to 3 years without a significant increase in cardiovascular events (13).

Studies of fenofibrate/fenofibric acid combined with a statin as separate drugs add evidence on clinical outcomes. Jones reported a 5- to 7-fold higher rate of simultaneous attainment of multiple lipid targets compared with monotherapy (14), while Hong and Kim showed that fenofibrate–statin combination therapy was associated with approximately 9.9–20.0% lower risks of selected cardiovascular events and 27.0–28.4% lower risk of all-cause mortality in patients with type 2 diabetes (15,16). However, this is mainly observational evidence, so the cardiovascular outcome benefits cannot be attributed directly to FDC fenofibrate/pravastatin alone.

Regarding safety, FDC fenofibrate/pravastatin was generally well tolerated; adverse event rates did not differ significantly from those with statin monotherapy, and no myopathy or rhabdomyolysis was reported in the RCTs (9–11). Nevertheless, some observational studies found signals of increased risks of acute kidney injury, myositis, or liver injury with statin–fibrate combinations (16–18), indicating that liver and kidney function and muscle symptoms should be monitored during treatment.

A strength of this review is that it combines evidence from RCTs and clinical practice data. The main limitations are the short follow-up of the RCTs, the risk of residual confounding in the observational studies, and the lack of studies directly comparing the FDC with other forms of fenofibrate–statin combination therapy.

5. CONCLUSION

Combination therapy with fenofibrate and a statin, particularly the fixed-dose combination (FDC) of fenofibrate/pravastatin, improves the overall lipid profile and, in large observational studies, is also associated with fewer major cardiovascular events, hospitalizations for heart failure, and deaths in patients with diabetes. The combination is well tolerated, with a very low risk of serious musculoskeletal events in RCTs. However, liver and kidney function should be monitored regularly, especially early in treatment, to detect laboratory changes early; these changes are mostly reversible.

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