

REVIEW ARTICLE



Rosuvastatin and Fenofibrate Combination in The Treatment of Mixed Hyperlipidemia: A Narrative Review

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Abstract

Introduction: Patients with mixed dyslipidemia are presented with high levels of low-density lipid cholesterol (LDL-C), triglycerides (TG), and reduced high-density lipid cholesterol (HDL-C). Though useful in lowering LDL-C, therapy with rosuvastatin is insufficient in optimizing the overall lipid profile, thus putting the patient at risk of residual cardiovascular risk. A combination of statin with other lipid-modifying agents has been used with more efficient lipid control and cardiovascular risk prevention. Of these, fenofibric acid is the most frequently used, along with rosuvastatin.

Methods: Authors conducted a literature search of published literature to assess the use of rosuvastatin and fenofibrate combination in the management of mixed hyperlipidaemia.

Results and discussion: The authors selected a total of 46 articles to be included in the review. Due to the small number of articles and heterogeneity on the combination of rosuvastatin and fenofibrate combination in mixed hyperlipidemia, the findings herein are presented using narrative summaries. Based on the thorough assessment of the selected literature, the essential themes that emerged from the review include safety and efficacy of rosuvastatin and fenofibrate combination, place of therapy of rosuvastatin, and fenofibrate combination, and potential cardiovascular risk reduction with rosuvastatin and fenofibrate combination.

Conclusion: Based on the review, the authors suggested that the combination therapy with fenofibric acid was beneficial, well-tolerated with a similar safety profile compared with statin monotherapy. The combination therapy of moderate dose rosuvastatin and fenofibric acid led to a reduction of cardiovascular risk factors via several pathways.

Keywords: Rosuvastatin, fenofibric acid, Mixed dyslipidemia, LDL-C, HDL-C, triglycerides

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1 | INTRODUCTION

The management of coronary heart disease has transformed with statin therapy as the reduction of low-density lipoprotein cholesterol (LDL-C) is an essential factor. Studies have shown that the use of statins leads to a 20-40% reduction in LDL-C levels, which further led to a 25-35% lowering of the risk of myocardial infarction and stroke. Despite this protection, there remains a 65-75% risk of myocardial infarction and stroke in patients treated with statins (1, 2).

Currently, high LDL-C, triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C) are considered to be risk factors for coronary heart disease (CHD) (3). The significant features of patients with mixed dyslipidemia are raised TGs (≥ 150 mg/dL), low HDL-C (<40 mg/dL men, <50 mg/dL women), and a moderate increase in LDL-C with a high concentration of small LDL particles. The presence of this abnormal 'lipid triad,' along with abdominal obesity, impaired fasting glucose, and high blood pressure, leads to an increased risk for CHD in patients with mixed dyslipidemia (4, 5).

Hence, it becomes imperative to strategically use aggressive lipid-altering therapy to manage cardiovascular risk profiles in individuals with mixed dyslipidemia. In such cases, monotherapy, often with statins, is unable to achieve the targeted optimisation of increased LDL-C and TG levels along with the low levels of HDL-C. In such a situation, the use of combination therapy becomes imperative (6). The combination of statins with fibric acid derivatives is a commonly used therapy in individuals with mixed dyslipidemia (6). Rosuvastatin has demonstrated significant superiority over other statins used routinely (7) The STELLAR trial has depicted that rosuvastatin reduced non-HDL-C by 42.0% to 50.9% compared with 34.4% to 48.1% with atorvastatin, 26.0% to 41.8% with simvastatin, and 18.6% to 27.4% with pravastatin. Similarly, adult treatment panel III LDL cholesterol goals were achieved in 82 to 89% of patients treated with rosuvastatin (10 to 40 mg), compared with 69 to 85% patients treated with 10 mg to 80 mg atorvastatin; rosuvastatin reduced apo B protein by 36.7% to 45.3% compared with 29.4% to 42.9% with atorvastatin, 22.2% to 34.7%

with simvastatin, and 14.7% to 23.0% with pravastatin (8).

Fenofibric acid is frequently used in combination therapy with a statin. Both the drugs have different mechanisms of action and exhibit a complementary pharmacodynamic effect on lipid levels. Fibrates change the lipid levels via activation of peroxisome proliferator-activated receptors (PPARs), which regulate gene transcription. On the other hand, statins affect lipid levels by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (9).

In this article, the authors have attempted to throw insight on the place of therapy of rosuvastatin and fenofibrate combination therapy versus statin monotherapy, the safety profile of the combination, and its potential role in reducing the cardiovascular risk in patients of mixed dyslipidemia.

2 | METHODS

The authors conducted a detailed review of published literature to evaluate the place of therapy of rosuvastatin and fenofibrate combination therapy compared with statin therapy, safety, efficacy, and the reduction of cardiovascular side effects in patients with mixed hyperlipidemia.

A search was conducted on PubMed, Medline, and Google Scholar with the search terms (Rosuvastatin) AND (Fenofibrate) between 2003 and 2020. The author's goal was to analyze all the published literature comprising randomized controlled trials, clinical trials, retrospective and prospective research, systematic reviews, and meta-analysis for rosuvastatin and fenofibrate combination in managing mixed hyperlipidemia. The search returned 32 results, out

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of which 27 articles were screened and selected. Further, in a backward chronological search, the lists of all relevant articles were checked for citations that could not be identified in the primary search. Titles and abstracts from the electronic search were screened, and full-text articles meeting the selection criteria were obtained. The study data were extracted by reading the complete article.

Title and abstracts from the electronic search were checked, and full-text articles on the treatment of rosuvastatin and fenofibrate in mixed hyperlipidemia were obtained. Crucial information from all the articles was extracted. Two investigators independently extracted data from eligible studies, and any differences were resolved through discussion and consensus between the authors. Where an agreement was not reached, arbitration was done by the third author. The selected articles were then qualitatively analyzed by the investigators.

3 | RESULTS AND DISCUSSION

Based on the search, a total of 46 articles were selected to be included in the review. Due to the small number of articles and heterogeneity on the combination of rosuvastatin and fenofibrate combination in mixed hyperlipidemia, the findings herein are presented using narrative summaries. Based on the thorough assessment of the selected literature, the essential themes that emerged from the review include safety and efficacy of rosuvastatin and fenofibrate combination, place of therapy of rosuvastatin, and fenofibrate combination, and potential cardiovascular risk reduction with rosuvastatin and fenofibrate combination.

Rosuvastatin-fenofibrate pharmacokinetic interactions

In a multiple-dose, open-label, 3-period, randomized, cross-over design assessing the pharmacokinetic interaction between the two drugs, the authors suggested that they showed no clinically significant pharmacokinetic interaction between fenofibric acid at the full clinical dose and rosuvastatin at the highest approved dose. The findings of the above study demonstrated that co-administering the two

drugs had no substantial effect on the steady-state C_{min} or AUC 24 of rosuvastatin ($p>.05$), but the C_{max} was found to be raised by 20% (99% CI: 12%-18%) (6). Similar results were obtained from another open-label, randomized, 3-way cross-over trial consisting of three 7-day treatment periods. The study findings showed that coadministration of rosuvastatin and fenofibrate produced minimal changes in rosuvastatin and fenofibric acid exposure about a minor increase in the AUC from 0 to 24 hours and C_{max} of rosuvastatin; the respective geometric least-square means increased by 7% (90% CI, 1.00-1.15) and 21% (90% CI, 1.14-1.28). The pharmacokinetic parameters of fenofibric acid were similar when fenofibrate was administered alone and with rosuvastatin: the geometric least-square mean for fenofibric acid AUC from 0 to 8 hours and C_{max} decreased by 4% (90%CI, 0.90-1.02) and 9% (90% CI, 0.84-1.00), respectively (10).

Place of therapy of rosuvastatin and fenofibrate combination

One of the key factors in preventing cardiovascular disease prevention is the reduction of low-density lipoprotein cholesterol, and it also forms the main aspect of hypolipidemic therapy. (11, 12). The treatment of the lipid triad calls for the use of combination therapy. Evidence has suggested that the concomitant use of statins and fibrates may lead to a positive effect on the lipid triad. The combination of rosuvastatin and fenofibrate assumes significance here, given the potency of rosuvastatin to lower LDL-C and fenofibrate's efficacy in reducing triglycerides. Rosuvastatin is known to reduce LDL-C by 45%-63% with doses of 5-20 mg per day, a much higher mean reduction compared with equivalent doses of other statins (13). Fenofibric acid has an increased efficacy in reducing triglycerides and increasing HDL-C in patients on rosuvastatin therapy with a favorable safety profile. Rosuvastatin-fenofibric acid fixed-dose combinations have significantly improved triglycerides, HDL-C, non-HDL-C, apolipoprotein B, and high sensitivity C-reactive protein levels compared with simvastatin monotherapy ($P\leq.04$ for all comparisons) (14). The safety and efficacy studies have shown that there are no major adverse reactions following the use of combination and rosuvastatin, and fenofibrate is a

safe combination to treat difficult to manage mixed dyslipidemia patients (13).

The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol and the 2019 ESC/EAS guidelines for the management of dyslipidaemias recommend that it is safer to use fenofibrate with a statin since it has a lower risk of severe myopathy. It is vital to reduce triglycerides whenever levels exceed 500 mg/dL (5.6 mmol/L) to prevent pancreatitis in patients with severe hypertriglyceridemia. This can be achieved by prescribing a very low-fat diet and adding fibrates or omega-3 fatty acids for patients with persistently high severe hypertriglyceridemia (15, 16).

Efficacy of rosuvastatin and fenofibrate in diabetes

The first open-label randomized study to directly compare the high doses of rosuvastatin (40 mg) [R] with low doses of statin (10 mg) plus fenofibrate (200 mg) [RF] or Ω -3 fatty acids (2 g) [RN] in the treatment of mixed hyperlipidemia showed that non-HDL-C levels were reduced in all groups: in R group by 54%, in RF group by 42% and RN group by 42%. Significant reductions in total cholesterol, LDL-C and triglyceride levels were observed in all groups. At the end of the 3-month treatment duration, there was a significant reduction of non-HDL-C in all treatment groups ($p < 0.001$ compared to baseline values) with a more significant decrease in the R group ($p < 0.05$ compared to RF and RN groups). The proportion of patients reaching the non-HDL-C target value was significantly more in the R group than the RF group ($p < 0.05$) but not in the RN group. While the monotherapy was more effective in reducing non-HDL-C, the combination of rosuvastatin plus fenofibrate led to a more potent effect in lowering triglyceride levels and raising HDL-C values compared with the other two treatment groups (LDL-C: R group-304 \pm 69 to 164 \pm 37, Group RF-300 \pm 45 to 197 \pm 40, Group RN-284 \pm 42 to 185 \pm 37; HDL-C: R group- 50 \pm 8 to 52 \pm 8, RF Group-52 \pm 10 to 56 \pm 12, RN Group 48 \pm 10 to 50 \pm 10; non-HDL-C: R Group 253 \pm 60 to 117 \pm 32, RF Group 247 \pm 38 to 141 \pm 39, RN Group 235 \pm 38 to 135 \pm 33) (17).

A randomized trial showed that when a comparative assessment was made between the effect of

high dose rosuvastatin monotherapy with moderate dosing combined with fenofibrate or ω -3 fatty acids on the lipoprotein subfraction profile in patients with mixed dyslipidemia and metabolic syndrome, rosuvastatin + fenofibrate was the most effective treatment. The findings of the study showed that the mean low-density lipoprotein and HDL-C level were significantly increased while insulin resistance was reduced (18). Similar results were seen when high doses of rosuvastatin (40 mg) [R] or a combination of low doses of rosuvastatin (10 mg) with fenofibrate (200 mg) [RF] were proven to be superior to the rosuvastatin (10 mg)-Omega 3 fatty acid (2 g) combination [R Ω] treatment given daily in reducing inflammatory indices. The HDL-LpPLA2 activity was raised more in the RF group (+43%) compared with the R and R Ω groups (+18% and +35%, respectively; $p < 0.05$ for both comparisons) (19).

It was seen in many comparative assessments that the use of rosuvastatin and fenofibric acid was more efficacious than rosuvastatin alone in patients with mixed dyslipidemia. In a post hoc analysis of patients with mixed dyslipidemia, the combination therapy compared with rosuvastatin monotherapy showed comparable effects in achieving risk-stratified low-density lipid-C goals. However, measures of total atherogenic burden were improved (20). In a study where 1-year therapy with rosuvastatin and fenofibric acid was conducted, the results showed the combination to be well-tolerated (21).

Current evidence suggests that statin/fibrate combination therapy is favorable in changing the lipid profile of T2Dm patients with high TG and low HDL-C profile, which is linked with increased cardiovascular risk (22). A post hoc analysis was done in trials led by Jones et al. and Rosenson et al., including type 2 diabetes patients with mixed dyslipidemia treated with rosuvastatin (5, 10, or 20 mg) fenofibric acid 135 mg, or the combination of them for 12 weeks. The results revealed that the combination therapy with rosuvastatin and fenofibric acid led to a significantly higher proportion of type 2 diabetes mellitus patients achieving the individual and lipid targets than the corresponding monotherapies (23).

These results were consonant in patients with diabetes too, who, when treated with a combination of

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rosuvastatin and fenofibric acid, achieved individual and combined lipid targets as compared with the corresponding dose of rosuvastatin monotherapy (24).

Elderly patients

Sub-analysis of two randomized controlled trials showed that the combination of rosuvastatin 5, 10, or 20 mg with fenofibric acid 135 mg improved the overall lipid profile when given to elderly patients (age 65 years or older) with mixed dyslipidemia. The study findings demonstrated that the combination therapy reduced LDL-C by 31.8%-47.2% vs. 10.6% with fenofibric acid monotherapy ($P<0.001$). Combination therapy also raised HDL-C by 21.9%-27.0% vs. 5.9%-9.9% with rosuvastatin monotherapy ($P<0.001$) and reduced triglycerides by 48.3%-53.5% vs. 20.7%-32.8% with rosuvastatin monotherapy ($P<0.001$). There were no new or unexpected safety issues observed with the combination therapy (25).

Effects on biomarkers

Another benefit of the combination therapy with rosuvastatin and fenofibric acid is the improvement in the inflammatory biomarker, high sensitivity C-reactive protein (hsCRP), and other lipid abnormalities in patients with mixed dyslipidemia and high hsCRP. Increased levels of hsCRP are indicative of an increased risk of cardiovascular events. The post hoc analysis reported that 65% (1416/2182) of patients had pre-treatment baseline $hsCRP \geq 2$ mg/L. Among all treatment groups, groups, higher reduction in hsCRP was seen in patients with greater baseline hsCRP; however, improvements in other lipids/apolipoprotein were comparable between the baseline hsCRP categories. In patients with high hsCRP (≥ 2 mg/L) remaining after 12 weeks of rosuvastatin 10, 20, or 40 mg monotherapy, hsCRP was lowered by ~36% after changing to rosuvastatin 20 mg and fenofibric acid 135 mg for up to 52 weeks, and ~36 of patients shifted from $hsCRP \geq 2$ mg/L to <2 mg/L. Thus, combination therapy with rosuvastatin and fibrates is more effective than statin monotherapy for reducing hsCRP and hence a potential treatment option for patients with several lipid risk factors (26).

Rosuvastatin has shown a beneficial effect on oxidative stress markers, while fenofibrate is associated

with reduced oxidative stress. In a randomized, open-label, blinded endpoint (PROBE) study, patients with mixed dyslipidemia on a standard statin dose on uncontrolled lipid targets were randomly selected to transition to a higher dose of rosuvastatin or add-on-statin extended-release nicotinic acid /laropiprant for the first four weeks followed by 2000/40 mg/day for the next eight weeks OR to add-on-statin micronized fenofibrate (200 mg/day) for a total of 3 months. Study findings showed that all treatment interventions reduced the assessed oxidative stress markers (27).

Long-term and short-term therapy

While assessing the role of combination (statin + fenofibrate) in long-term and short-term therapy of mixed dyslipidemia, a post hoc analysis was conducted. The results showed that in the controlled studies, remarkably reduced level of high-risk patients treated with fenofibric acid + moderate dose statin [rosuvastatin 10, 20 or 40 mg, simvastatin 20, 40 or 80 mg, or atorvastatin 20, 40 or 80 mg] and a substantially higher percentage of high-risk patients treated with fenofibric acid and low dose statin compared with monotherapies were able to achieve their LDL-C (51.3% vs. 72.9%, $p<0.001$) and non-HDL-C targets (53% vs. 38%, $p<0.02$), respectively. This was suggestive of the fact that short-term treatment with fenofibric acid and low or moderate dose statin led to a comparable or higher number of patients attaining individual targets of non-HDL-C, ApoB, HDL-C, and TG, and combined targets for these values and LDL-C, compared with corresponding monotherapy with any of the statins used in the study (rosuvastatin, simvastatin or atorvastatin). (28, 29). Another long-term study conducted to evaluate the safety and efficacy of combination lipid therapy reported that fenofibric acid and a moderate-dose statin (Rosuvastatin 20 mg/Atorvastatin 40 mg/ Simvastatin 40 mg) exhibited good tolerance and did not cause any new or unanticipated adverse reactions. This phase 3, open-label, year 2 extension study in patients who had completed one of the three double-blind, 12-week, controlled studies and the subsequent open-label, year 1 extension study also showed that the combination lipid therapy, when used for over 2 years, led to a sustained improvement in HDL-C (+17.4%), TG (-46.4%) and LDL-C (-40.4%).

Hence, long-term therapy resulted in elaborate and sustained lipid improvements in patients with mixed dyslipidemia (30).

Safety and efficacy of rosuvastatin and fenofibrate combination

An acceptable safety profile of fenofibric acid and rosuvastatin has been established in a multicentre, randomized study. The study was conducted to evaluate the short-term efficacy and safety profile of fenofibric acid + rosuvastatin combination therapy for improving lipid parameters in patients with stage 3 chronic kidney disease and mixed dyslipidemia. Study findings showed that fenofibric acid (45 mg) and rosuvastatin (5 mg) compared with only rosuvastatin 5 mg led to a significant improvement in triglycerides (median % changes: week 8, -38.0% vs -22%, $P < 0.001$; week 16, -42.6% vs -29.7%, $P < 0.001$) and HDL-C (mean % changes: week 8, 16.9% vs 7.8%, $P < 0.001$; week 16, 17.3% vs 8.9%, $P < 0.001$) (31).

In another study, following three months of treatment with the highest dose of rosuvastatin (40 mg/day) or to add-on-statin extended-release nicotinic acid (ER-NA)/laropiprant (LRPT) or add-on-statin micronized fenofibrate, results revealed that add-on ER-NA/LRPT followed by switching to the highest dose rosuvastatin brought about significant benefits in emerging cardiovascular risk factors compared with add-on fenofibrate in patients with mixed dyslipidemia. However, another important finding was that ER-NA/LRPT was linked with more side effects than rosuvastatin and add-on fenofibrate (32).

In a study conducted among high-risk Asian patients with mixed hyperlipidemia, the rosuvastatin-fenofibrate combination led to an incidence of myo- or hepatotoxicity as compared with rosuvastatin monotherapy. Additionally, the combination group was associated with higher increases in homocysteine, blood urea nitrogen, serum creatinine, and much larger reductions in leukocyte and hemoglobin levels. However, it was suggested that the combination might require caution in individuals with underlying pathologies such as renal dysfunction. The study findings revealed that the combination group had higher, but not significantly, common treatment-related adverse events (13.3% and 5.6% respectively) and drug discontinuation due to ad-

verse events (10.0% and 3.3%, respectively) (33).

In a randomized clinical study, where 1,377 patients with mixed hyperlipidemia were treated with either fenofibric acid 135 mg, rosuvastatin 10, 20, or 40 mg, or fenofibric acid plus rosuvastatin 10 or 20 mg, fenofibric acid plus rosuvastatin 20 mg led to more significant improvements in triglyceride levels (-42.9% versus -25.6%, $p < 0.001$) and HDL-c (+19.0% versus +10.3%, $p < 0.001$) compared with rosuvastatin 20 mg monotherapy. A significantly higher LDL-C reduction (-38.8% versus -6.5%, $p < 0.001$) compared with fenofibric acid monotherapy was observed. The levels of hsCRP were significantly lowered with fenofibric acid plus rosuvastatin 10 or 20 mg treatment compared with the corresponding dose of rosuvastatin monotherapy ($p < 0.05$) (34).

In phase 3, multicentre, randomized, double-blind study conducted on patients with mixed dyslipidemia with high low-density lipoprotein cholesterol, triglycerides, and low level of high-density lipoprotein cholesterol, the results revealed that the combination of rosuvastatin 5 mg/day with fenofibric acid 135 mg/day for 12 weeks in patients with mixed dyslipidemia led to a significant increase in HDL-C plasma concentration (+23.0% versus +12.4%, $p < 0.001$) and a significant lowering of the TG levels (-40.3% versus -17.5%, $p < 0.001$) compared with rosuvastatin monotherapy. These results suggested that rosuvastatin 5 mg + fenofibric acid 135 mg led to substantial improvement in the lipid profile of the patients with mixed dyslipidemia and did not cause any unwarranted adverse effects (35). Similar results were obtained in phase 3, multicentre, randomized, double-blind, active-controlled study, where the combination formulation of choline salt of fenofibric acid given with two doses of rosuvastatin showed that the combination therapy led to significantly ($p < 0.001$) greater improvements in HDL-C (20.3% vs. 8.5%) and TG (-47.1% vs. -24.4%) compared to rosuvastatin 10 mg, and fenofibrate. Based on the above, the authors concluded that the combination caused a better optimization of many lipid parameters than monotherapy (34).

When assessed in patients with high low-density lipid and triglyceride levels, combination treatment with rosuvastatin/fenofibric acid was reported to

be well-tolerated. The results of this randomized, double-blind study also showed that the combination therapy with statin (rosuvastatin) and fibrate (fenofibric acid) doses led to a higher reduction in the low-density lipid-cholesterol and improved other efficacy parameters, compared with simvastatin 40 mg (36). An open-label, randomized, parallel-group, comparative, prospective clinical study was conducted to compare the effects of atorvastatin and rosuvastatin in combination with fenofibrate in patients with mixed hyperlipidemia. The results showed that patients who received a combination of atorvastatin (10 mg) with fenofibrate (160 mg) demonstrated a lowering of total cholesterol by 39%, triglycerides by 47%, LDL-C by 50%, and VLDL-C by 35%. Simultaneously, in the rosuvastatin (10 mg) and fenofibrate (160 mg) group, a reduction of total cholesterol occurred by 54%, TGs by 58%, LDL-C by 52%, and VLDL-C by 56%. The authors concluded that both the treatment regimens led to a considerable reduction in TC, TG, LDL-C, and VLDL-C; however, the reduction was more pronounced and statistically significant rosuvastatin fenofibrate combination group when compared with atorvastatin and fenofibrate after the 12-week treatment period (37).

Effect of Rosuvastatin and Fenofibrate combination on Potential cardiovascular disease markers

Mixed dyslipidemia, oxidative stress, and inflammation are linked to an increased risk for cardiovascular disorders. Being a common metabolic disorder with notable features such as increased cholesterol and triglycerides presents a therapeutic challenge wherein monotherapy with statins may only be useful in the partial treatment of the underlying metabolic disorders. (38).

The mixed dyslipidemia phenotype comprises increased triglyceride levels, reduced high-density lipid cholesterol, and increased ApoB linked with diabetes and increased coronary artery disease risk. Fenofibric acid is commonly used to treat individuals with mixed dyslipidemia, and it decreases triglycerides, ApoB containing VLDL particles, and APOC-III while increasing HDL-C. A study showed that using a combination of fenofibric acid and statins in individuals with mixed dyslipidemia might cause an attenuated ApoB reduction if they are homozygous for the minor allele of single nucleotide

polypeptide in both the ANGPTL3 and RXRA gene regions. This may lead to the diminution of cardiovascular risk (39, 40).

The low levels of 25 (OH) vitamin D may be a novel risk factor for cardiovascular disease, the metabolic syndrome and other aspects associated with it (hypertension, atherogenic dyslipidemia, impaired glucose tolerance, and central obesity), diabetes mellitus, and even for cancer, autoimmune diseases, infections, and overall mortality (41). Results from many large, cross-sectional studies found an association of 25 (OH) Vit D deficiency with an increased rate of myocardial infarction (42, 43). Initially, it was proposed that the cause for the rise in 25 (OH) vitamin D levels in patients on statin combination therapy may be due to the competition in the cytochrome P450 3A4 (CYP3A4) catabolic pathway, which breaks down 25 (OH) vitamin D levels (44). Another possible mechanism may be the inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins, which may lead to an increase in the 7-dehydrocholesterol levels, which in turn acts as the common precursor of cholesterol and 25 (OH) vitamin D (45). In a randomized trial, high dose rosuvastatin monotherapy and the usual dose of rosuvastatin + fenofibrate or omega-3 fatty acid was associated with a significant and similar increase in the 25(OH) vitamin D levels. In this study, 60 patients with dyslipidemia were randomly allocated to receive rosuvastatin 40 mg, rosuvastatin 10 mg plus fenofibrate 200 mg, or rosuvastatin 10 mg plus omega-3 fatty acids 2 g daily for three months. Rosuvastatin monotherapy led to a 53% increase in 25 (OH) Vit D (from 14.6 [1.0-38.0] to 17.8 [5.3-49.6] ng/mL; $P=0.000$). The combination of rosuvastatin with fenofibrate and omega-3 fatty acids were related with increase of 64% (from 14.1 [1.0-48.0] to 18.4 [6.7-52.4] ng/mL; $P=0.001$) and 61% (from 10.4 [6.6-38.4] to 14.0 [9.6-37.6] ng/mL; $P=0.04$), respectively (41). The study results are important from a clinical perspective since low levels of 25 (OH) Vit D have been identified as an independent CVD risk factor (43, 44).

The two hypolipidemic drugs also reduce Lipoprotein-associated phospholipase A2 (Lp-PLA2) activity and mass associated with atherogenic apoB-lipoproteins is a predictor for incident

atherosclerotic disease. Additionally, fenofibrate was also found to improve the enzyme-specific activity on apoB-lipoproteins and induce HDL-Lp-PLA2 (46).

4 | CONCLUSION

Statins are established to be the standard-of-care therapy for lowering the low-density lipoprotein cholesterol; however, in patients with mixed dyslipidemia experiencing the abnormal ‘lipid triad,’ monotherapy alone becomes inadequate. In such cases, combining other lipid-modifying agents is needed to optimize lipid profiles in patients with mixed dyslipidemia. The combination therapy with fenofibric acid has been proven beneficial, well-tolerated with a similar safety profile compared with statin monotherapy. The combination therapy of moderate dose rosuvastatin and fenofibric acid leads to a diminution of cardiovascular risk factors via several pathways.

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Kaushik Biswas (KB): Literature search, data extraction of the relevant articles, qualitative assessment of the eligible articles, drafting and critically revising the article, and final approval of the version to be published.

Prachi Jadhav (PJ): Critical review of the article, data extraction from the relevant article, and final approval of the version to be published.

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