

# Combination Therapy of Ezetimibe and Rosuvastatin for Dyslipidemia: Current Insights

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**Abstract:** Cardiovascular disease is one of the leading causes of death around the world with various efforts being made to reduce risk in patients through preventive measures. One major method for prevention has been managing cholesterol, particularly low-density lipoprotein to decrease atherosclerotic plaque burden, potentially decreasing future cardiac complications. Statins have been the gold standard therapy for hypercholesterolemia treatment due to their ease of dosing, limited drug interactions, and favorable safety profile. Unfortunately, statin therapy alone is not always effective enough to adequately control a patient's elevated lipid levels and combination therapy may be warranted. Ezetimibe is commonly added to regimens to help augment cholesterol lowering by inhibiting the absorption of cholesterol. The recent approval of a combination tablet of high-intensity rosuvastatin and ezetimibe has introduced a potentially more beneficial option for cholesterol management in addition to the only available combination of moderate intensity simvastatin and ezetimibe. We aimed to identify potential beneficial effects of ezetimibe by comparing its use in combination with high-intensity rosuvastatin compared to a statin therapy alone or in combination with moderate intensity simvastatin through a literature review. The current evidence indicated that combination therapy outperformed statin monotherapy in reduction of low-density lipoprotein cholesterol and patients were more likely to achieve their target low-density lipoprotein cholesterol goal level. This suggests rosuvastatin/ezetimibe combination holds a potential place in therapy for patients requiring a more aggressive reduction in cholesterol to help prevent atherosclerotic disease.

**Keywords:** hypercholesterolemia, hyperlipidemia, cardiac events, lipid biomarkers, atherosclerosis

## Introduction

Ischemic heart disease (IHD) affects over 10 million patients per year, resulting in over 8 million deaths globally with incidences varying by sex and geographical region.<sup>1</sup> A high circulating level of low-density lipoprotein cholesterol (LDL-C) is a significant risk factor for atherosclerotic plaque formation resulting in ischemic heart disease, peripheral artery disease, and ischemic stroke. The mainstay of both primary and secondary prevention treatment to lower LDL-C are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, which inhibit the synthesis of cholesterol in the liver.<sup>2,3</sup> Multiple guidelines on management of blood cholesterol recommend an LDL-C goal of less than 100 mg/dL for primary prevention and 70 mg/dL for secondary prevention. If patients were unable to tolerate statins or statins do not lower their LDL-C to the target goals, then a second-line agent such as ezetimibe can be added to the regimen.

Ezetimibe is a Niemann-Pick C1-Like 1 (NPC1L1) inhibitor that works by blocking absorption of cholesterol at the brush border of the small intestine. The combination of a statin and ezetimibe has been studied historically with simvastatin, a moderate intensity statin, with positive outcomes.<sup>4</sup> More recently, a combination of rosuvastatin, a high-intensity statin, and ezetimibe has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Therefore, the purpose of this review is to summarize current evidence with this combination, particularly regarding its impact on laboratory markers, clinical outcomes, and plaque burden in comparison to monotherapy with statins and the simvastatin/ezetimibe combination.

## Basic Characteristics of Rosuvastatin and Ezetimibe

Rosuvastatin is one of the most potent HMG-CoA reductase inhibitors available and can lower LDL-C up to 55%.<sup>5</sup> Additional beneficial impacts on the cholesterol panel include an increase in HDL-C by approximately 6% and lowering of triglycerides (TG) by 15% or greater as well as a decrease in the cholesterol content in atherosclerotic plaques.<sup>6</sup> Rosuvastatin also exerts pleiotropic effects including anti-inflammatory effects, endothelial protection, and antioxidant effects.<sup>7,8</sup> Benefits of rosuvastatin over other statins include its hydrophilicity which is associated with very low rates of myopathy and rhabdomyolysis as well as its long duration of action allowing it to be taken at any time of day.<sup>9</sup> Additionally, only approximately 10% of the drug is transformed by the Cytochrome P450 enzymes and the other 90% is excreted via biliary means leading to very few drug–drug interactions.

Ezetimibe is the only drug in its class and works by inhibiting NPC1L1 leading to a decrease in absorption of cholesterol by up to 67% resulting in a lowering of LDL-C by about 15–20%.<sup>10</sup> The impact on HDL-C is an increase of about 3% with no impact on TG. In addition to its anti-inflammatory effects, the combination of ezetimibe and statin lower high sensitivity CRP approximately 10% more than statin monotherapy.<sup>11</sup> Ezetimibe is metabolized via glucuronidation and thus has minimal drug interactions, like rosuvastatin.<sup>12</sup>

A combination product of rosuvastatin and ezetimibe has become commercially available in doses of 10/10 mg, 20/10 mg, and 40/10 mg.<sup>13</sup> These exert complementary mechanisms of action, allowing for a lower dose of each individual agent to achieve the same changes in the lipid panel. When statins exert their lipid-lowering action by reducing endogenous cholesterol synthesis in the liver, the body responds by increasing cholesterol absorption which in turn can decrease the efficacy of statins. Therefore, the addition of ezetimibe can provide additional benefit by blocking the absorption of cholesterol, thus improving the ability of statins to reduce LDL-C.

## Evaluation of Statin Monotherapy Treatment Compared to Combination Therapy with Ezetimibe

### High Risk or Underlying Cardiovascular Disease

Multiple studies have compared the combination of rosuvastatin with ezetimibe to the corresponding doses of rosuvastatin alone in patients at a high risk or with underlying cardiovascular disease (Table 1). The “EXamine of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone” (EXPLORER) trial was a 6-week open-label, randomized parallel group study conducted in the United States, Germany, Austria, Switzerland, and South Africa.<sup>14</sup> This study assessed the lipid panel and compared rosuvastatin combination therapy with ezetimibe (40/10 mg) to rosuvastatin monotherapy (40 mg). Patients were included if they had hypercholesterolemia and a history of coronary artery disease (CAD) or an atherosclerotic cardiovascular disease (ASCVD) risk score over 20% with an LDL-C between 160 and 250 mg/dL (n = 469). Patient’s mean LDL-C levels significantly decreased in the combination group at 69.8% (mean 189 to 57 mg/dl) compared to 57.1% (mean 191 to 82 mg/dl) in the monotherapy group (p < 0.001). Most patients on combination therapy were able to achieve their LDL-C goal of less than 100 mg/dL in comparison to patients on monotherapy (94.0% vs 79.1%, p < 0.001). Similarly, in very high-risk patients, the optimal LDL-C goal (<70 mg/dl) was achieved in a significantly greater proportion of patients in the combination therapy group compared to monotherapy (79.6% vs 35.0%, p < 0.001). The combination therapy group also had a significantly greater decrease in non-HDL-C, total cholesterol (TC), and triglycerides (TG) while both treatment groups had similar increases in HDL-C concentrations (Table 2). When assessing pleiotropic effects, high-sensitivity C-reactive protein (hs-CRP) was significantly lower in combination therapy compared to monotherapy (46.6% vs 28.6%, p < 0.001). Both treatment regimens were well tolerated with similar safety profiles, with the most reported adverse event reported being myalgias (2.9% of patients taking combination therapy vs 3.0% of patients taking monotherapy). In conclusion, combination therapy with rosuvastatin/ezetimibe compared to rosuvastatin alone is more likely to achieve LDL-C targets, exert beneficial impacts on the lipid panel and inflammation, while being similarly tolerable in patients with CAD or high-risk ASCVD.

A multicenter, randomized, double-blind, placebo-controlled study over 12-weeks was conducted in Korean patients with moderate or high cardiovascular risk.<sup>15</sup> The patients were split into two treatment groups comparing rosuvastatin/ezetimibe (5/10 mg, 10/10 mg, and 20/10mg) to rosuvastatin (5, 10, and 20 mg) (n = 337). The rosuvastatin/ezetimibe

**Table I** Impact on Low-Density Lipoprotein

Study	n	Regimens	LDL- C Lowering (mg/dL)	Achieve LDL-C Goal (% of Patients)
EXPLORER <sup>14</sup>	469	RSV/EZ 40 mg/10mg vs RSV 40 mg	RSV/EZ: 70.0 <sup>a</sup> RSV: 57.0 p<0.001	RSV/EZ: 94.0% RSV: 79.1% p<0.001
Yang <sup>15</sup>	337	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 59.5 <sup>a</sup> RSV: 51.1 p<0.001	RSV/EZ: 90.7% RSV: 72.9% p=0.01
MRS-ROZE <sup>16</sup>	407	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 59.1 <sup>b</sup> RSV: 49.4 p<0.001	RSV/EZ: 94.1% RSV: 86.3% p<0.05
I-ROSETTE <sup>17</sup>	396	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 75.4 <sup>a</sup> RSV: 64.4 p<0.001	RSV/EZ: 92.3% RSV: 79.9% p<0.001
Kim W <sup>18</sup>	712	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 56.5% <sup>c</sup> RSV: 45.2% p<0.01	RSV/EZ: 94.2% RSV: 86.6% P=0.0142
Hwang <sup>20</sup>	36	RSV/EZ 5/10mg vs RSV 20mg	RSV/EZ: 94.3 <sup>a</sup> RSV: 89.9 p=0.54	NR
Torimoto <sup>21</sup>	79	RSV/EZ 2.5/10 mg vs RSV 5mg	RSV/EZ: 31.1% <sup>c</sup> RSV: 12.1% p<0.001	RSV/EZ: 89.7% RSV: 58.3% p=NR
Masuda <sup>22</sup>	51	RSV/EZ 5/10mg vs RSV 5mg	RSV/EZ: 55.8% <sup>c</sup> RSV: 36.8% p=0.004	NR
Bays <sup>19</sup>	440	RSV/EZ 5–10/10mg vs RSV 10–20 mg	RSV/EZ: 21.5% <sup>d</sup> RSV: 7.6% p<0.001	NR
Ambegaonkar <sup>25</sup>	8667	Prior ST/EZ 10mg vs ST DD vs RSV 10mg vs SIM/EZ 20/10mg	Prior ST/EZ: 26.0 <sup>b</sup> ST DD: 9.7 RSV: 19.7 SIM/EZ: 27.6	NR
GRAVITY <sup>26</sup>	833	RSV/EZ 10–20/10 mg SIM/EZ 40–80/10 mg	RSV/EZ 10/10: 59.7 <sup>a</sup> RSV/EZ 20/10: 63.5 SIM/EZ 40/10: 55.2 SIM/EZ 80/10: 57.4 p<0.001	RSV/EZ 10/10: 93.3 RSV/EZ 20/10: 95.6 SIM/EZ 40/10: 67.7 SIM/EZ 80/10: 88.6 p<0.007

**Notes:** <sup>a</sup>Data represented as mean change in mg/dL. <sup>b</sup>Data represented as least squares mean in mg/dL. <sup>c</sup>Data represented as percent change from baseline. <sup>d</sup>Data represented as percent change from baseline as a least squares mean.

**Abbreviations:** RSV, rosuvastatin; EZ, ezetimibe; SIM, simvastatin; LDL, low-density lipoprotein; ST, statin; DD, double-dose statin.

combination therapy group had significantly better lipid-lowering effects over monotherapy with a mean (range) LDL-C lowering of 59.5% (57.6–62.7%) versus 51.1% (45.3–56.0%) in the monotherapy group ( $p < 0.001$ ). The combination therapy also achieved the target LDL-C among 90.7% (86.8–94.7%) of participants compared to 72.9% (64.1–87.2%) in the monotherapy group ( $p = 0.01$ ). Musculoskeletal adverse events were low in both groups and not statistically different

**Table 2** Impact on Non-LDL Laboratories

Study	Non-HDL Lowering	TC Lowering	TG Lowering	HDL Increasing	hs-CRP Lowering
EXPLORER <sup>14</sup>	RSV/EZ: 65 RSV: 52 p<0.001	RSV/EZ: 51 <sup>a</sup> RSV: 42 p<0.001	RSV/EZ: 35 RSV: 25 p<0.001	RSV/EZ: 11 RSV: 9 p=0.151	RSV/EZ: 46 RSV: 29 p<0.001
MRS-ROZE <sup>16</sup>	RSV/EZ: 54.9 RSV: 45.8 p<0.001	RSV/EZ: 39.6 <sup>a</sup> RSV: 32.9 p<0.001	RSV/EZ: 22.7 RSV: 13.4 p=0.003	RSV/EZ: 14.1 RSV: 11.7 p=0.171	NR
I-ROSETTE <sup>17</sup>	RSV/EZ: 53.2 RSV: 42.2 p<0.001	RSV/EZ: 38.8 <sup>b</sup> RSV: 30.2 p<0.001	RSV/EZ: 19.2 RSV: 11.9 p=0.024	RSV/EZ: 13.6 RSV: 11.3 p=0.200	NR
Kim W <sup>18</sup>	RSV/EZ: 52.8 RSV: 41.4 p<0.01	RSV/EZ: 39.0 <sup>b</sup> RSV: 30.7 p<0.01	RSV/EZ: 19.9 RSV: 9.4 p<0.05	RSV/EZ: 10.8 RSV: 9.4 p=0.14	RSV/EZ: 69.4 RSV: 66.1 p=0.95
Hwang <sup>20</sup>	RSV/EZ: 100.8 RSV: 98.9 p=0.79	RSV/EZ: 98.4 <sup>a</sup> RSV: 99 p=0.77	RSV/EZ: 49.5 RSV: 10.5 p=0.01	RSV/EZ: 0.5 RSV: 0.5 p=0.99	RSV/EZ: 0.15 RSV: 0.49 p=0.35
Torimoto <sup>21</sup>	NR	NR	RSV/EZ: 13.8 <sup>c</sup> RSV: 1.3 p=0.032	RSV/EZ: 1.1 RSV: 2.4 p=0.408	NR
Masuda <sup>22</sup>	RSV/EZ: 50.3 <sup>b</sup> RSV: 34.8 p=0.037	RSV/EZ: 35.8 RSV: 25.2 p=0.048	RSV/EZ: 17.5 RSV: 4.6 p=0.029	RSV/EZ: 8.8 RSV: 4.3 p=0.490	RSV/EZ: 18.8 RSV: 14.4 p=0.764
Bays <sup>19</sup>	RSV/EZ: 17.1 <sup>c</sup> RSV: 5.2 p<0.001	RSV/EZ: 12.6 RSV: 3.9 p<0.001	RSV/EZ: 6.3 RSV: 3.2 p=NS	RSV/EZ: -0.5 RSV: 1.7 p=NS	RSV/EZ: 14.1 RSV: 13.0 p=NS
Ambegaonkar <sup>25</sup>	Prior ST/EZ: 22.6 <sup>d</sup> ST DD: 8.5 RSV: 16.3 SIM/EZ: 22.8		Prior ST/EZ: 12.1 ST DD: 5.0 RSV: 5.7 SIM/EZ: 8.0	Prior ST/EZ: 1.7 ST DD: 0.8 RSV: 3.2 SIM/EZ: 2.5	
GRAVITY <sup>26</sup>	RSV/EZ 10/10: 54.7 <sup>a</sup> RSV/EZ 20/10: 58.9 SIM/EZ 40/10: 49.9 SIM/EZ 80/10: 52.4	RSV/EZ 10/10: 43.0 RSV/EZ 20/10: 46.6 SIM/EZ 40/10: 39.6 SIM/EZ 80/10: 41.7	RSV/EZ 10/10: 28.9 RSV/EZ 20/10: 35.0 SIM/EZ 40/10: 23.0 SIM/EZ 80/10: 25.8	RSV/EZ 10/10: 6.4 RSV/EZ 20/10: 7.5 SIM/EZ 40/10: 3.9 SIM/EZ 80/10: 4.3	RSV/EZ 10/10: 25.2 RSV/EZ 20/10: 34.1 SIM/EZ 40/10: 28.5 SIM/EZ 80/10: 30.6

**Notes:** <sup>a</sup>Data represented as mean change in mg/dL. <sup>b</sup>Data represented as percent change from baseline. <sup>c</sup>Data represented as least squares mean in mg/dL. <sup>d</sup>Data represented as percent change from baseline as a least squares mean.

**Abbreviations:** RSV, rosuvastatin; EZ, ezetimibe; SIM, simvastatin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglycerides; hs-CRP, high sensitivity c-reactive protein.

with 2.4% in the combination group versus 0.8% in the monotherapy group ( $p = 0.62$ ). These results suggest improved efficacy of the combination therapy over monotherapy for this high-risk population with similar rates of adverse effects.

## Hypercholesterolemia

This combination was also studied in patients with hypercholesterolemia in trials conducted in South Korea. The “Multicenter Randomized Study of Rosuvastatin and eZetimibe” (MRS-ROZE) was an 8-week double blind parallel group Phase III study.<sup>16</sup> It aimed to compare fixed-dose combination of rosuvastatin/ezetimibe (5/10 mg, 10/10 mg, and 20/10 mg) with rosuvastatin alone (5, 10, and 20 mg) in patients with primary hypercholesterolemia ( $n = 407$ ). The combination led to additional lowering of LDL-C (mean  $\pm$  standard deviation, SD) compared to monotherapy ( $59.1\% \pm$

1.8% vs 49.4%  $\pm$  1.9%,  $p < 0.001$ ) as well as achievement of LDL-C goals (94.1% vs 86.3%,  $p = 0.009$ ). It was observed that there was a greater reduction in LDL-C for patients with diabetes or metabolic syndrome, defined as the presence of at least three of the following five factors: elevated blood pressure (systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 85$  mm Hg), abdominal obesity (waist circumference  $\geq 90$  cm in men,  $\geq 80$  cm in women), elevated TG ( $\geq 150$  mg/dL), reduced HDL cholesterol ( $< 40$  mg/dL in men,  $< 50$  mg/dL in women), and elevated fasting glucose ( $\geq 100$  mg/dL or receiving treatment for elevated glucose). The fixed-dose combination therapy also showed a significant reduction in TC and TG levels compared to rosuvastatin alone, but HDL-C and apolipoprotein A (ApoA) levels did not significantly differ. Both safety and tolerability profiles were similar between the two groups with no serious adverse events related to the medications reported.

The “Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia” (I-ROSETTE) trial was an 8-week, double-blind, multicenter phase III randomized controlled trial to compare different dosing combinations of rosuvastatin/ezetimibe (5/10 mg, 10/10 mg, and 20/10 mg) with monotherapy rosuvastatin (5, 10, and 20mg) in patients with hypercholesterolemia ( $n = 396$ ).<sup>17</sup> Following 8 weeks of treatment, mean LDL-C concentration ( $\pm$ SD) decreased by 82.0 mg/dL ( $\pm 30.3$ ) in the combination groups compared to 64.4 mg/dL ( $\pm 31.3$ ) in the rosuvastatin monotherapy groups ( $p < 0.001$ ). The target LDL-C goal was achieved in a greater percent of patients receiving rosuvastatin/ezetimibe than rosuvastatin alone (92.3% vs 79.9%,  $p < 0.001$ ). A greater percent decrease was observed in total cholesterol, TG, non-HDL-C, and apolipoprotein B (ApoB) than those in the rosuvastatin group; however, there were no significant differences in HDL-C and apolipoprotein AI (ApoAI) and hs-CRP. Both safety and drug tolerability were favorable in both groups, with musculoskeletal impacts shown in 2% of patients receiving combination therapy versus 0.5% receiving monotherapy ( $p = 0.372$ ).

A multicenter, randomized, double-blind 8-week study was conducted comparing rosuvastatin/ezetimibe (5/10 mg, 10/10 mg, and 20/10 mg) to rosuvastatin alone (5, 10, and 20 mg).<sup>18</sup> Patients with hypercholesterolemia and an LDL-C less than 250 mg/dL were included. Seven-hundred and twelve patients were enrolled, and those receiving combination therapy had a significantly better reduction in LDL-C level (mean  $\pm$  SD) than those in the monotherapy group (56.47%  $\pm$  16.13% vs 45.18%  $\pm$  14.74%,  $p < 0.01$ ). The addition of ezetimibe resulted in significantly more patients achieving their LDL-C goal (94.15% vs 86.63%,  $p = 0.0142$ ). Overall, the adverse event rate was comparable in both treatment groups and the most frequently reported was increased alanine aminotransferase levels (1.05% in pooled monotherapy groups and 1.57% in pooled combination groups).

## Patients with Type II Diabetes

Patients with type 2 diabetes have enhanced cholesterol absorption, and therefore may benefit from the addition of ezetimibe to the statin regimens.<sup>19,31</sup> Three studies have been completed to date to assess whether additional benefits might result from the combination among patients with diabetes. In a small study in Korea ( $n = 36$ ), the efficacy of rosuvastatin/ezetimibe 5/10 mg was compared to rosuvastatin 20 mg monotherapy in this population.<sup>20</sup> Interestingly, after 6 weeks of treatment, there was a similar decrease in LDL-C, TC, TG, ApoB, and ApoB/ApoAI in both treatment groups, though this lack of difference may have been due to small numbers of patients studied. Both regimens were noted to have tolerable side effects and did not cause elevations in muscle or liver enzymes.

Subsequently, a randomized trial conducted by Torimoto et al assessed patients with type II diabetes on rosuvastatin 2.5 mg daily with an LDL greater than or equal to 80 mg/dL ( $n = 79$ ).<sup>21</sup> Patients were randomly assigned to two groups, addition of ezetimibe to their rosuvastatin therapy or double the rosuvastatin dose to 5 mg. At week 12, adding ezetimibe to rosuvastatin 2.5 mg further decreased the LDL-C level at a mean of 31% ( $\pm$  SD 13.1%), significantly better than that with the dose escalation group at 12.1% (15.6%,  $p < 0.001$ ). More patients in the combination therapy group achieved their LDL-C goal, though statistical significance was not reported (89.7% vs 58.3%). No patients experienced an elevation in creatinine kinase or liver function tests. It was concluded that in patients with type 2 diabetes, it might be more effective to add ezetimibe to rosuvastatin rather than up-titration of the rosuvastatin dose, supported by the stronger LDL-C lowering effects.

The MRS-ROZE study, described above, completed a subgroup analysis on patients with type II diabetes.<sup>16</sup> In patients with diabetes, it was determined that the combination lowered the mean (standard error) LDL-C more than rosuvastatin monotherapy (64.2% $\pm$ 2.0 vs 50.2% $\pm$ 1.8,  $p < 0.001$ ), supporting the conclusion that patients with diabetes may benefit from the combination of rosuvastatin/ezetimibe.

## Studies Assessing Atherosclerotic Plaque Burden

Additional benefits of LDL reduction therapy include a prevention of ASCVD events which are often mediated via reduction of atherosclerotic plaque volume. Masuda et al conducted a prospective, open-label, randomized, single-center study examining the effect of 6 months of rosuvastatin 5 mg and ezetimibe 10mg to rosuvastatin 5 mg alone on coronary plaque regression.<sup>22</sup> Patients were eligible if they had stable angina and were to receive an elective percutaneous coronary intervention (PCI) with at least one obstructive lesion and an LDL-C greater than 100 mg/dL. A total of 51 patients were randomized, and while reductions in plaque volume were seen in the combination arm as measured by intravascular ultrasound (IVUS), statistical significance was not seen ( $-13.2\%$  vs  $-3.1\%$ ;  $p = 0.05$ ) which may be due to the small number of patients studied. Despite not reaching statistical significance in the primary measure, secondary measures of correlation between percent change in plaque volume and LDL ( $r = 0.384$ ,  $p = 0.015$ ) and non-HDL ( $r = 0.334$ ,  $p = 0.035$ ) both reached statistical significance.

A prospective, single center, randomized study in China compared patients with borderline or severe atherosclerosis receiving either rosuvastatin/ezetimibe 10/10 mg or rosuvastatin 10 mg.<sup>23</sup> A total of 106 patients were randomized and atherosclerotic plaque measurement was completed via IVUS 12 months post treatment with combination versus monotherapy as a secondary outcome. This assessment determined a statistically significant reduction in percent plaque burden ( $62.1\% \pm 7.2$  vs  $68.2\% \pm 8.3$ ) in those receiving combination rosuvastatin/ezetimibe ( $p < 0.05$ ), suggesting that the combination may impact coronary plaque burden in patients with coronary artery disease.

## Studies Assessing Clinical Outcomes

The first published study assessing clinical outcomes comparing rosuvastatin/ezetimibe combination therapy to monotherapy was a prospective, randomized, open-label study conducted in patients within 12 months of vascular surgery.<sup>24</sup> The primary outcome assessed cardiovascular events including death from cardiac causes, non-fatal myocardial infarction (MI), ischemic stroke, and unstable angina in patients receiving rosuvastatin/ezetimibe 10/10 mg compared to rosuvastatin 10 mg alone ( $n = 262$ ). The study concluded that addition of ezetimibe to rosuvastatin therapy did not decrease cardiovascular events within the first month of surgery ( $5.6\%$  vs  $6.6\%$ ,  $p = 0.72$ ), but did significantly decrease events in months 1–12 after surgery ( $7.1\%$  vs  $1.7\%$ ,  $p = 0.04$ ). Additionally, both treatments showed significant decrease in TC and LDL-C levels. Rates of myopathy were not reported between groups.

In the Chinese study described above by Wang et al assessing patients with borderline or severe atherosclerosis, the primary endpoint was a new or recurrent myocardial infarction, unstable angina pectoris, cardiac death, or stroke.<sup>23</sup> Of those receiving combination therapy, two (3.6%) events occurred while 6 (11.8%) occurred in the monotherapy group ( $p < 0.05$ ). Additionally, reductions in LDL-C, total cholesterol, and high-sensitivity CRP were all statistically significantly lower in the combination therapy arm compared to that of monotherapy. One incidence of myalgias occurred in each group.

## Increasing Statin Monotherapy Dosing Compared to Statin Ezetimibe Combinations

Outside of investigating the safety and efficacy of combination therapy of rosuvastatin and ezetimibe, several studies have been conducted to explore the potential benefit of combination therapy compared to an increased dosing, monotherapy rosuvastatin regimen. One such study by Bays et al was a randomized, double-blind, parallel-group investigation to assess a treatment difference in adults with hypercholesterolemia ( $n = 440$ ).<sup>19</sup> The addition of ezetimibe 10 mg daily to rosuvastatin showed a statistically significant least square mean LDL-C percent reduction compared to that of doubling the rosuvastatin dose ( $21.5\%$  vs  $7.6\%$ ,  $p < 0.001$ ). Additionally, more patients were able to achieve their LDL-C goal in the combination therapy group ( $59.4\%$  vs  $30.9\%$ ,  $p < 0.001$ ). One patient in each group experienced a myalgia.

These results were echoed in a meta-analysis carried out by Ambegonkar et al in which 17 double-blind, active, or placebo-controlled trials were analyzed with a collection of 8667 patients with hypercholesterolemia.<sup>25</sup> Patients were all on a moderate intensity statin but required additional therapy to meet cholesterol goals. Patients either received ezetimibe ( $n = 4582$ ), doubled their statin dose ( $n = 2336$ ), switched to moderate intensity rosuvastatin 10 mg monotherapy ( $n = 571$ ), or were transitioned to simvastatin/ezetimibe combination therapy ( $n = 1178$ ). The least squares mean (95% CI) percent reduction in LDL from baseline was  $-26\%$  ( $-26.8$ ,  $-25.2$ ) with the addition of ezetimibe,  $-9.7\%$  ( $-10.7$ ,  $-8.6$ ) with doubling the dose of their statin,  $-19.7\%$



(−21.7, −17.7) with a switch to rosuvastatin 10 mg, and −27.6% (−29.2, −26.0) with a switch to ezetimibe/simvastatin. The most benefit observed in patients adding ezetimibe to their regimen either as an addition to their current statin or by switching to the simvastatin/ezetimibe combination suggested the possible additional benefit of adding ezetimibe to any statin therapy over increasing statin doses.

## Evaluation of Therapy of Ezetimibe in Combination with Rosuvastatin versus Simvastatin

The combination of ezetimibe with statin therapy has been evolving. Prior to the approval of rosuvastatin/ezetimibe, the combination tablet delivery of a moderate intensity statin, simvastatin, and ezetimibe was commercially available as Vytorin<sup>®</sup>.<sup>26</sup> Gauging the lipid effects of Rosuvastatin plus ezetimibe Versus simvastatin plus ezetimibe Therapy (GRAVITY) was a multicenter, randomized, open-label, parallel group trial which sought to compare the combinations of ezetimibe with rosuvastatin versus ezetimibe with simvastatin. The doses compared included rosuvastatin/ezetimibe 20/10 mg versus simvastatin/ezetimibe 40/10 mg and simvastatin/ezetimibe 80/10 mg, as well as rosuvastatin 10/10 mg versus simvastatin/ezetimibe 40/10 mg. In total, 833 patients were randomized in the United States, South America, and Europe, who were included if they had hypercholesterolemia with an LDL-C between 130 and 200 with a history of coronary heart disease or an ASCVD 10-year risk score of 20% or greater. A mean (±SD) reduction in LDL-C was 63.5% (±16.7%) with rosuvastatin/ezetimibe 20/10, 55.2% (±15.8%) with simvastatin/ezetimibe 40/10 mg, and 57.4% (±20.5%) with simvastatin/ezetimibe 80/10 mg, and both comparisons were statistically significant ( $p < 0.001$ ). Rosuvastatin/ezetimibe 10/10 mg showed a mean (±SD) reduction in LDL-C of 59.7% (±14.2%) compared to simvastatin/ezetimibe 40/10 mg ( $p = 0.002$ ). In addition to LDL-C reduction, secondary markers of achieving LDL-C, increases in HDL-C, and reductions in total cholesterol, triglycerides, and non-HDL-C were all statistically significant in the rosuvastatin arms compared to that of simvastatin. Only one case of myopathy was reported which was in the rosuvastatin/ezetimibe 20/10 mg group. This trial demonstrated that statin/ezetimibe combinations with a high-intensity statin overall had better efficacy on the lipid reduction than with a moderate intensity statin.

## Discussion

Rosuvastatin/ezetimibe has demonstrated satisfactory efficacy and safety in a multitude of populations compared to statin monotherapy at the same or higher doses as well as compared to the ezetimibe/simvastatin combination. The rosuvastatin/ezetimibe combination is a valuable and appealing addition to medication regimens due to its once daily dosing and minimal drug–drug interaction potential. Rosuvastatin/ezetimibe provides superior LDL-C lowering and HDL-C increases as well as exerts beneficial pleiotropic effects compared to statins alone. International Guidelines have suggested ezetimibe as an add-on therapy to statins in patients unable to reach their LDL-C goal with the highest tolerated intensity of statin in various populations, and expert opinion supports its use.<sup>2,3,30</sup> It has been well demonstrated that high-intensity statins are underused, which may result in inferior clinical outcomes.<sup>31–33</sup> Underuse is due to a variety of factors including lack of awareness of guidelines by providers, patient fear of side effects, and inability of the patient to tolerate high-intensity statins. The use of a statin in combination with ezetimibe may provide a reasonable alternative in the latter two scenarios.

Ezetimibe is a cost-effective option to improve LDL-C lowering in patients at risk for, with cardiovascular disease, or those who are statin intolerant.<sup>27,30</sup> This agent should be utilized prior to a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for most patients with primary hyperlipidemia or cardiovascular disease. PCSK9-inhibitors are an injectable medication which may be undesirable for patients to administer at home. Though they do exert significant LDL-C lowering and cardiovascular benefit, they have not been determined to be cost-effective in some populations.<sup>28</sup> Due to the benefits of ezetimibe outlined above, paired with the cost-effectiveness, this agent has been determined to be the optimal add-on therapy to statins for patients requiring additional LDL-C lowering.<sup>2,3,27,30</sup>

In patients with ischemic heart disease or at high risk (ASCVD > 20%), combination rosuvastatin/ezetimibe showed superior LDL-C lowering and increased the likelihood that patients would achieve their LDL-C goal over rosuvastatin monotherapy.<sup>15,26</sup> This population is at the highest risk of future cardiovascular events and should be considered for ezetimibe add-on therapy if unable to reach LDL-C goals.<sup>2,3</sup> The combination also showed superior LDL-C lowering and improvement in achieving LDL-C goals in patients with primary hypercholesterolemia.<sup>16–18</sup> This population is at high

risk of having a future cardiovascular event, and those at intermediate risk or higher should consider ezetimibe if unable to tolerate a statin, or unable to achieve their LDL-C goal on the highest intensity statin tolerated.<sup>2,3</sup> In patients with type II diabetes, it is hypothesized that the complementary mechanisms of action of these two agents would be particularly beneficial as this population experiences an upregulation of cholesterol absorption at the brush border of the intestine, which is blocked by ezetimibe. To date, only small trials have assessed this, one with neutral results and two showing benefits of the combination.<sup>20,21,23</sup> Regardless, based on the tolerability and simple use of the combination, it should still be considered in patients with type II diabetes per the European guidelines, and particularly those with an ASCVD risk over 20% to reduce LDL-C by 50% or more per the United States guidelines.<sup>2,3</sup>

Additional studies have been conducted investigating the beneficial effects of high-intensity statin therapy with atorvastatin in combination with ezetimibe that have similar results that were seen with rosuvastatin.<sup>34</sup> In 2018, a meta-analysis involving 11 studies assessing combination therapy with atorvastatin and ezetimibe versus atorvastatin monotherapy at various doses. The addition of ezetimibe was found to be statistically significant at all comparator doses for lowering LDL-C, total cholesterol, and triglycerides compared to atorvastatin monotherapy. These data are supportive of the approach to combine high-intensity statins with ezetimibe for further improvement in laboratory markers.

Further research is still warranted to understand the true impact of this combination on treatment. Most trials assessing the combination of rosuvastatin and ezetimibe are relatively short in duration, up to 12-weeks, which questions the durability of the LDL-C response.<sup>14–21</sup> Though, studies of each individual agent do suggest benefit on a longer-term basis which could reasonably be extrapolated to this population.<sup>4,29</sup> Most studies were completed in Asian populations which may bring into question the external validity of the study to other patient populations. Additionally, there is limited representation of certain subgroups in clinical trials assessing lipid lowering therapy as a whole. A systematic review conducted by Khan et al evaluated if women and older participants were properly represented in lipid-lowering therapy randomized clinical trials.<sup>35</sup> These subgroups were underrepresented compared to the relative risk for disease burden. Thus, the efficacy and safety data of rosuvastatin monotherapy and the combination with ezetimibe may not be generalizable in all populations. Lastly, the clinical cardiovascular impact of the combination has been minimally studied. A study was completed in patients receiving simvastatin/ezetimibe which did show a decrease in major cardiovascular events at 6 months, so it is reasonable to suggest that this impact would be similar or better with a high-intensity statin (rosuvastatin).<sup>4</sup>

## Conclusion

It is clear that combination rosuvastatin/ezetimibe is effective at lowering LDL-C in patients at risk, or with cardiovascular disease, and is a compelling option for those unable to achieve LDL-C goal levels with the highest tolerated statin potency. The combination is well tolerated and a simple once daily regimen with few drug interactions which is beneficial for patients who require therapy. Ezetimibe, though already recommended in the guidelines, should be considered in patients who would benefit more from further LDL-C lowering. More research on clinical outcomes such as major adverse cardiovascular event rate should be completed to further elucidate the benefit of this combination therapy and proper place in therapy.

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