A Survey of Clinical Perspectives on Rosuvastatin and Ezetimibe Combination Therapy in Current Clinical Practice

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Background and Objective of the Survey

Rosuvastatin and ezetimibe combination therapy represents a powerful approach in managing dyslipidemia, particularly in patients who require additional LDL-C lowering beyond what can be achieved with statin monotherapy. Here are some clinical perspectives on this combination therapy in current clinical practice:

Rosuvastatin, a potent statin, primarily acts by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. Ezetimibe, on the other hand, works by blocking intestinal absorption of cholesterol. Combining these agents provides complementary mechanisms of action, resulting in greater reductions in LDL-C levels compared to either agent alone. Clinical trials have demonstrated that the combination of rosuvastatin and ezetimibe leads to significant reductions in LDL-C levels, often exceeding the reductions achieved with high-dose statin monotherapy. This makes it an attractive option for patients with severe hypercholesterolemia or those who are statin-intolerant.

Lowering LDL-C levels with statin therapy has been shown to reduce the risk of cardiovascular events. The addition of ezetimibe to statin therapy further lowers LDL-C levels and may offer additional cardiovascular risk reduction benefits, although definitive data from outcome trials specifically evaluating this combination are limited.

In conclusion, rosuvastatin and ezetimibe combination therapy offers a valuable treatment option for patients with dyslipidemia, particularly those who require additional LDL-C lowering beyond what can be achieved with statin monotherapy. As with any therapeutic approach, careful consideration of individual patient characteristics and preferences is essential in guiding treatment decisions.

The objective of the survey is:

To evaluate the clinical perspectives on rosuvastatin and ezetimibe combination therapy in current clinical practice

Methodology of the Survey

A survey was conducted to evaluate the clinical perspectives on rosuvastatin and ezetimibe combination therapy in current clinical practice. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Rosuvastatin
- The “pleiotropic effects” of rosuvastatin
- Rosuvastatin in High CV Risk Patients
- Effect of rosuvastatin on lipid profile and atherosclerosis
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- Evaluation of Statin Monotherapy Treatment Compared to Combination Therapy with Ezetimibe
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- Increasing Statin Monotherapy Dosing Compared to Statin Ezetimibe Combinations

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Ischaemic heart disease (IHD) is the leading cause of mortality worldwide and constitutes a major health burden. According to World Health Organisation (WHO) statistics, it accounts for 12.8% of deaths, with stroke and other cerebrovascular diseases accounting for a further 10.8%. In the United Kingdom, data from the Health Surveys for England suggest that while mortality may be declining, cardiovascular disease morbidity continues to rise. Epidemiological studies have established a strong correlation between cholesterol and the incidence of cardiovascular disease. The associated morbidity and mortality are positively correlated to low-density lipoprotein cholesterol (LDL-C) and inversely related to high-density lipoprotein cholesterol (HDL-C).

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors that are effective in the reduction of total and LDL cholesterol. A number of large randomized control trials have demonstrated unequivocally that lowering LDL-C, particularly with statins reduces the risk of cardiovascular deaths and events. HMG CoA inhibitors have been shown to prevent initial cardiovascular events and subsequent cardiovascular events in ischaemic heart disease patients, irrespective of the cholesterol concentration. In addition to the beneficial cholesterol-lowering effects, statins improve endothelial function, enhance the stability of atherosclerotic plaques, and inhibit inflammatory as well as thrombogenic responses in arterial walls. Furthermore extensive post-marketing surveillance has shown that long-term statin therapy is generally well tolerated.

The lipid-lowering arms of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed the benefit of statin therapy in primary prevention of cardiovascular events. The 4S study was the first study conclusively linking a statin with improved outcomes in patients with coronary heart disease. It established simvastatin as the most common LDL-C lowering treatment for patients with CHD in northern Europe. Subsequently, more studies including results of the Treating to New targets (TNT) trial have shown that intensive lipid-lowering (atorvastatin 80 mg) significantly reduces the risk of recurrent cardiovascular events compared to standard lipid-lowering (atorvastatin 10 mg) in stable CHD patients. Other clinical trials using various statins have confirmed similar beneficial effects for ameliorating cardiovascular risk in specific groups such as patients with diabetes, heart failure, and renal failure. Early detection and treatment with statins have been shown to reduce morbidity and mortality in those with heterozygous familial hypercholesterolemia.

The reduction in cardiovascular events from statin therapy is proportional to the LDL-C reduction. A 1.0 mmol/L reduction in LDL-C results in a 20% decrease in major coronary events and revascularization. Larger reductions in LDL-C are associated with greater reductions in cardiovascular events, so more potent statins result in greater cardiovascular risk reduction. The drive towards more stringent goals for LDL-C lowering in cardiovascular risk prevention has brought high-impact statin therapy into focus. Different statins have varying effects on LDL-C reduction with rosuvastatin producing the greatest reduction and fluvastatin the least. Statins vary in their lipophilicity and metabolism. These affect their extrahepatic tissue penetration and drug interactions with potential safety implications.

Rosuvastatin[1]

Rosuvastatin which is a new-generation HMG-CoA reductase inhibitor exhibits some unique pharmacologic and pharmacokinetics properties. It has low extrahepatic tissue penetration, low potential for CYP3A4 interactions, and substantial LDL-C lowering capacity and may therefore have some advantages. Its potential impact in primary and secondary prevention of cardiovascular disease in different groups including heart failure, elderly, renal failure, and diabetes, and also in combination with other lipid-lowering drugs is the subject of ongoing clinical studies.

Rosuvastatin is a fully synthetic HMG-CoA reductase inhibitor. Other HMG-CoA reductase inhibitors are either natural, mevinic acid derived (lovastatin, simvastatin pravastatin) or synthetic, heptenoic acid derived (atorvastatin, fluvastatin). Rosuvastatin belongs to a new generation of methane-sulphonamide pyrimidine and N-methane sulfonyl pyrrole-substituted 3, 5- dihydroxy-heptenoates. Although the characteristic statin pharmacophore remains similar to other statins, the addition of a stable polar methane-sulphonamide group provides low lipophilicity and enhanced ionic interaction with HMG-CoA reductase enzyme thus improving its binding affinity to this enzyme.

Pharmacodynamics[1]

Rosuvastatin competitively inhibits the HMG-CoA reductase enzyme selectively and reversibly. This enzyme converts HMG-CoA to mevalonic acid in the cholesterol biosynthetic pathway which is the rate-limiting step in cholesterol synthesis. Rosuvastatin therefore decreases hepatic sterol synthesis, which, in turn, leads to a decreased concentration of hepatocellular cholesterol. Hepatocytes respond to this decreased intracellular cholesterol concentration by increased synthesis of LDL receptors to enhance hepatic LDL reuptake from the circulation. The net result of this process is increased fractional catabolism of LDL which reduces serum LDL-C concentration and total cholesterol. Statins also reduce production of ApoB leading to reduced hepatic output of very low-density protein cholesterol (VLDL-

C) and triglycerides. In patients with homozygous familial hypercholes-terolaemia, rosuvastatin decreases LDL-C despite absence of functional LDL receptors. This may be sec-ondary to marked inhibition of cholesterol synthesis which decreases LDL production. Rosuvastatin has demonstrated comparable reductions in triglyceride (TG) concentrations to other statins with the greatest benefit seen in patients with high baseline TG levels. Studies have shown rosuvastatin to increase HDL-C by 8–12% with no clear relationship between the dose and response, although the increase is greatest in patients with low baseline HDL-C levels. This may be due to reduction of cholesterol ester transfer protein (CETP). The affinity of rosuvastatin for the active site of the enzyme is four times greater than the affinity of HMG-CoA for the enzyme. It has the highest affinity for HMG-CoA reductase among statins marketed in Europe. This high affinity coupled with tight ionic interaction result in a slow recovery of enzyme activity after removal of rosuvastatin. Since it is a hyhydrophilictatin, rosuvastatin relies on the organic anion transporting polypeptide-1B1 (OATP-1B1), which is strongly expressed on the hepatocyte basolateral membrane, as the key mechanism for active transport into hepatocytes. Its affinity for OATP-1B1 is comparable to atorvastatin but significantly greater than pravastatin or simvastatin. Rosuvastatin is therefore primarily distributed to hepatocytes while peripheral concentrations are low. As observed with other statins, rosuvastatin has pleiotropic effects independent of HMG-CoA reductase inhibition. These include improvements in endothelial function, anti-inflammatory, antithrombotic and anti-oxidant effects. Rosuvastatin and other statins improve endothelial function by increasing the production of endothelial nitric oxide and reducing the production of oxygen-derived free radicals. This in turn reduces endothelial dysfunction that has been implicated in atherosclerosis. Rosuvastatin reduces high sensitivity C reactive protein (hsCRP) which is a marker of inflammation and an independent cardiovascular risk predictor and other inflammatory markers. Rosuvastatin inhibits platelet aggregation to leukocytes which inhibit formation of clots in injured endothelium.

Pharmacokinetics[1]

The oral bioavailability of rosuvastatin is 20%, which is comparable to atorvastatin, pravastatin and fluvastatin, and qualitatively higher than simvastatin and lovastatin. After a single oral dose the peak plasma concentration is reached at 5 hours. This is longer than other HMG-CoA inhibitors which achieve maximum plasma concentrations in less than 3 hours. In compiled data from pharmacokinetic trials, the peak plasma concentration and area under the concentra-tion time curve show a largely linear relationship as the dose of rosuvastatin increases from 5 to 80 mg. Food intake decreases the rate of absorption of rosuvastatin by 20% but not the extent of absorption. This does not reduce the cholesterol lowering potency; therefore rosuvastatin can be taken with or without food, and in the morning or evening. Approximately 90% of rosuvastatin is protein bound mainly to albumin; other statins have

approximately 95% protein binding except pravastatin which has lower protein binding of 50%. The mean of volume distribution is 134 litres in steady state. Rosuvastatin is less lipophilic than other statins such as atorvastatin and simvastatin but more lipophilic than pravastatin. Penetration of statins into extra-hepatic tissues occurs by passive diffusion and is dependent on their lipophilicity. This has implications on their muscle safety as increased rhabdomyolysis was reported in patients on lipophilic agents like cerivastatin and lovastatin. Human hepatocyte studies indicate that rosuvastatin is a poor substrate for metabolism by cyto-chrome P450 and hence 90% of the drug is excreted unchanged. CYP2C9 is the main isoenzyme involved in metabolism with minimal effect from CYP2C19. Rosuvastatin is metabolised to an N-desmethyl metabolite which is less potent than the parent drug in inhibiting HMG-CoA reductase activity. The parent drug rosuvastatin is responsible for approximately 90% of plasma HMG-CoA inhibitor activity. Rosuvastatin is less likely to cause metabolic drug to drug interactions since it has limited metabolism by CYP isoenzymes. Other HMG-CoA reductase inhibitors such as atorvastatin and simvastatin are metabolised via CYP3A4. Their plasma concentrations are increased by inhibitors of CYP3A4 such as itraconazole, protease inhibitors and macrolide antibiotics. Rosuvastatin has a plasma half-life of 19 hours which is longer than atorvastatin (15 hours) and simvastatin (2–3 hours). It is primarily eliminated in the faeces (90%) compared with 10% renal excretion. Approximately 72% of absorbed rosuvastatin is eliminated in bile and 28% via renal excretion.

The "pleiotropic effects" of rosuvastatin[2]

Like other drugs of this class, the benefits of rosuvastatin are independent of LDL-C baseline levels but they even exceed the predicted lowering effect of plasma LDL-C, suggesting other significant clinical beneficial effects in addition to the cholesterol-lowering one. These ancillary properties, other than those for which statins were specifically developed, are known as "pleiotropic effects" and significantly contribute to the statin efficacy in CV disease prevention and treatment. Atherosclerosis represents an inflammatory disease associated in its earliest phase with endothelial dysfunction and a higher risk of CV events. Statins ancillary properties are involved in all the CV diseases pathophysiological stages: initially by the reducing the oxidative stress and inflammation and improving endothelial function; then acting on the progression and rupture of plaque by inhibiting smooth muscle cell proliferation, promoting the stability of atheroma and inhibiting the thrombogenic response.

The pleiotropic effects of statins may be linked or not to the primary mechanism of action of these drugs. In fact, an association has been demonstrated with the faculty to inhibit the formation of mevalonate and its downstream products, the isoprenoid molecules. The non-sterol intermediates of the cholesterol synthesis pathway, farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), play important roles as regulators of essential signaling proteins in vascular cells.

They represent lipid binding sites for transmembrane movement and activity of several proteins including Rho and Ras, which are crucial components of various protein kinase signaling patways. In fact while Ras system is essential for cell growth and intracellular signaling, Rho proteins have a crucial role in the inflammatory process at the base of atherosclerosis pathophysiology.

Rho kinase (ROCK) are serine/threonine kinases, downstream effectors of the small GTPase Rho. They play key roles in a variety of cellular functions, and are also involved in basic processes of atherosclerosis. ROCK is able to promote the contraction of vascular smooth cell, through the stimulation of the myosin light chain phosphorylation. It can acts by directly phosphorylate the myosin light chain or alternatively by phosphorylating and then inactivating the myosin light chain phosphatase, an enzyme responsible for the dephosphorylation of the activated myosin light chain and consequently able to determine the relaxation of smooth muscle cells. ROCK activity is therefore responsible for the persistence of a state of smooth muscle cells contraction, closely related to the onset and development of CV diseases. Furthermore, evidences suggest that statins are able to determine an increased production of nitric oxide (NO) through the inhibition of the ROCK system that, by decreasing post-transcriptional stabilization of endothelial NO synthase (eNOS) mRNA, down-regulates eNOS expression. In vitro trials demonstrated that the increased NO production in cultured cells incubated with HMG-CoA inhibitors was completely reversed by the presence of L-mevalonate, trought the activation of the ROCK system.

Furthermore experiments with human vascular smooth muscle and mononuclear cells showed a great reduction, induced by statins, of interleukin-6 (IL-6) synthesis, a key molecule in chronic inflammation, strongly involved in atherosclerotic development and progression.

The inhibition of the ROCK system induced by statin treatment has proven to positively modulate the prothrombotic condition associated with atherosclerosis. In vivo and in vitro studies showed the ability of HMG-CoA reductase inhibitors to improve the fibrinolytic activity: on the one hand, the administration of statins is in fact associated with an increase of tissue plasminogen activator inhibitor, and with a reduction of activator inhibitor type-1 levels on the other hand. Moreover, clinical concentrations of statins showed to determine a reduction of matrix metalloproteinase-1 expression in human and animal cells, influencing plaque stability and progression of coronary artery disease.

Rosuvastatin in High CV Risk Patients

Rosuvastatin in patients with HF[2]

It is well known the positive prognostic impact of rosuvastatin in primary and secondary prevention of CAD in patients at high CV risk. Also in the HF management the role of statins seems to be crucial, as showed by several observational studies in which incident statin administration, in patients with no

prior statin use, was related with lower risks of death and hospitalization, independently of cholesterol levels, age and a history of ischemic heart disease. In patients with nonischemic HF atorvastatin 20 mg/day for 1 year increased left ventricular ejection fraction from 0.33 +/- 0.05 to 0.37 +/- 0.04 (p = 0.01) compared to placebo, in addition to effects on soluble inflammatory markers (increase erythrocyte superoxide dismutase activity and reduction in serum levels of hs-CRP, IL-6 and tumor necrosis factor-alpha receptor II). Neverthless the small sample (108 subjects) and the short follow-up period, the study suggests the role of statins in this subpopulation of patients. In a large randomized controlled trial (CORONA) which recruited 5011 elderly patients with ischemic disease and systolic HF, rosuvastatin 10 mg/day compared to placebo, over a median follow-up of 32.8 months, reduced the number of CV hospitalizations but not death from CV causes, nonfatal MI or stroke, death from any cause and any coronary event. Moreover, patients in the rosuvastatin group showed lower serum levels of LDL-C and hsCRP (P <0.001) with no significant rate of adverse events.

Similar findings emerged from GISSI-HF trial that enrolled patients with chronic HF of any etiology: in a median follow-up of 3.9 years, rosuvastatin 10 mg (2285 subjects) per day did not influence primary endpoints (time to death, and time to death or admission to hospital for CV reasons) and showed a good safety (the most frequent adverse reaction reported were gastrointestinal disorders with no statistically significant difference between rosuvastatin and placebo groups). Furthermore, an interesting result of GISSI-HF trial was the effectiveness of n-3 polyunsaturated fatty acids in decreasing the endpoint death or admission to hospital for CV reasons. The disappointing results of these two trials give rise to several interpretations. May exist varying extra-hepatic effects of statins due to their lipophilicity/hydrophilicity. Therefore, hydrophilic statins, to which the rosuvastatin belongs, could exert their effects especially in the liver, instead lipophilic statins, such as atorvastatin, affect also myocardium.

Moreover, the benefits of rosuvastatin may occur only for particular subgroups of HF patients, or for different degree of disease severity, and thus it could be a specific clinical and histopathological stage of cardiac pathology, previously or after which, rosuvastatin is ineffective.

Rosuvastatin in patients with chronic renal failure[2]

Likewise, in patients with end-stage renal disease on chronic haemodialysis, who represent a category of subjects at high CV risk, rosuvastatin is effective in decreasing LDL-C and CRP levels with no significant effects on death from CV causes, nonfatal MI infarction or nonfatal stroke. These were the conclusions of AURORA trial, performed on 2776 patients undergoing hemodialysis and treated with rosuvastatin 10 mg daily over a median follow-up period of 3.8 years compared to placebo. However, this study enrolled patients aged between 50 to 80 years old, omitting younger hemodialytic patients which, anyway, represent a subclass at high CV risk. Furthermore, the mean baseline LDL-C levels

within the study population were not high (99 mg/dl), so we can conclude that in renal failure patients, unlike general population, the CV disease is attributable also to non-traditional risk factors such as arterial calcification and arrhythmias. These reasons may be adduced to explain the disappointing results of this trial and to support the primary prevention and statin use in these patients, on the basis of magnitude of CV risk factors and of specific pathophysiology of uremia. This concept is in accordance with a post hoc analysis of AURORA trial that showed in participants with DM (n=731) a 32% reduction in fatal and nonfatal cardiac events rates with rosuvastatin therapy. Nevertheless, in patients at high CV risk rosuvastatin showed reno-protective effects, evaluated by means of GFR, compared to placebo treated subjects.

However dose adjustment is necessary in patients with kidney disease. In particular, while no modifications are needed in presence of mild renal impairment (GFR ≥60 mL/min/1.73 m2), 40 mg dose is contraindicated in presence of GFR ranging from 30 to 60 mL/min/1.73 m2 (moderate renal impairment), and finally no administration is permitted in presence of severe renal impairment (GFR 80 mL/min/1.73 m^2).

In hemodialytic patients rosuvastatin contraindicated but caution is needed as steady-state plasma concentrations are approximately 50% greater compared with subjects with normal renal function.

Rosuvastatin in patients with diabetes[1]

Type 2 diabetes is associated with increased risk of coronary heart disease. In the UK Prospective Diabetes Study (UKPDS), every 1 mmol/L increment in LDL-C was associated with a 57% increase in relative risk of coronary heart disease. Furthermore, the LDL-C of diabetic patients predicted their risk of stroke. CARDS (Collaborative Atorvastatin Diabetes Study) showed that atorvastatin 10 mg led to a reduction in cardiovascular events and strokes in diabetes patients without high HDL-C and no prior history of cardiovascular disease. This has strengthened the need for statin therapy for primary prevention in diabetes patients. Sub-group analyses of 4S showed the benefits of simvastatin in reducing major coronary events and revascularisation in diabetic patients with coronary heart disease. However, the reduction in total and cardiovascular mortality was not significant due to the small sample size.

A randomised double blind double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of rosuvastatin (10 mg and 20 mg), and atorvastatin (10 mg and 20 mg) in patients with type 2 diabetes mellitus (ANDROMEDA) showed that rosuvastatin produced greater reductions in LDL-C, ApoB and total cholesterol when compared with equal doses of atorvastatin. A greater proportion of patients on rosuvastatin achieved European LDL-C goals compared to those on atorvastatin. The CORALL (Cholesterol Lowering Effects of Rosuvastatin compared with Atorvastatin in patients with type 2 diabetes) study showed that rosuvastatin produced greater reductions in

ApoB:ApoA-1 ratios, LDL-C and total cholesterol in diabetic patients with moderate dyslipidaemia. The superior effect of rosuvastatin compared with atorvastatin in reduction of LDL-C was also demonstrated in the URANUS (Use of Rosuvastatin versus Atorvastatin in type 2 diabetes mellitus) study.

Rosuvastatin in atrial fibrillation patients[2]

Patients suffering from atrial fibrillation (AF), the most common cardiac arrhythmia and important risk factors for ischemic stroke, benefit from treatment with rosuvastatin. Data from several trials show that statin therapy determines a 50-60% decrease of recurrent AF risk and incidence of postoperative AF, but it is not significantly effective in preventing new-onset AF. These benefits occur in a dose-independent manner, and seem attributable to well-known anti-inflammatory and antioxidant properties of this statin able to counteract atrial structural remodeling. In fact, in subjects with high hsCRP serum value (> 2 mg/l), a further increase has been associated with a 36% higher risk of developing AF, and administration of rosuvastatin 20 mg once a day has been shown to reduce the relative risk of new AF of 27% compared with placebo group. Furthermore, in AF patients, rosuvastatin, administrated before elective electrical cardioversion, was able to reduce the risks of AF recurrence during the following 3 months. This antiarrhythmic action is due to the reduction of serum asymmetric dimethylarginine levels, a marker associated with higher risk of early recurrence of AF after electrical cardioversion, and the impaired endothelium-dependent vasodilatation. The GISSI-HF trial also demonstrated the favorable effect of rosuvastatin 10 mg once daily in preventing new-onset and recurrent AF (13% relative risk reduction, 2.1% absolute risk reduction) in patients with HF. At any rate, as the weight of the evidences is weak, the 2012 European Guidelines for the management of AF do not recommend the use of statins in the “upstream therapy” of AF, the nonantiarrhythmic treatment able to prevent its recurrence.

Rosuvastatin for prevention in special populations[3]

On the other hand, two important studies, ie, AURORA (A study evaluating the Use of Rosuvastatin in patients requiring Ongoing Renal dialysis: an Assessment of survival and cardiovascular events) and CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure), evaluating the efficacy of rosuvastatin in specific populations found that while rosuvastatin did reduce the levels of LDL-C and hsCRP, there was no difference in the rate of primary endpoints in the rosuvastatin groups compared with placebo.

Several studies have shown that patients undergoing maintenance hemodialysis have an increased risk of CVD, and observational studies have suggested that statin therapy can have survival benefits in patients undergoing hemodialysis. AURORA was a prospective trial that randomized 2776 patients,

aged 50–80 years (mean baseline age 64 years), who were undergoing maintenance hemodialysis for advanced renal failure to receive rosuvastatin 10 mg daily or placebo. After three months of treatment, patients randomized to the rosuvastatin group had LDL-C levels that were 43% lower than their baseline level as compared with only a 2% reduction from baseline in the placebo group. The median hsCRP level decreased by 12% in the rosuvastatin group (by 0.65 mg/L, versus an increase of 0.21 mg/L in the placebo group, $P < 0.001$).

After a median follow-up of 3.8 years, the primary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 396 patients in the rosuvastatin group (0.2 events per 100 patient-years) versus 408 patients in the placebo group (9.5 events per 100 patient-years), with no significant effect of treatment (HR 0.96, 95% CI 0.84–1.11, $P = 0.59$). The lack of an effect of rosuvastatin therapy on the primary endpoint was consistent in all the pre-specified subgroups, including patients younger than 65 years and those aged ≥65 years.

These findings suggest that the CVD process in patients undergoing hemodialysis differs from that in other patient populations. In the general population, a majority of cardiovascular events are coronary events such as myocardial infarctions. In the hemodialysis population, however, only approximately 25% of cardiovascular events are myocardial infarctions. Rather, heart failure, sudden cardiac death, and arrhythmias predominate in this population. Therefore, the anti-inflammatory and lipid-lowering effects of statins may not benefit a population in which myocardial infarctions do not predominate.

CORONA investigated the use of rosuvastatin in older patients with systolic heart failure, a population also generally excluded from statin trials. The study randomized 5011 patients aged at least 60 years (mean baseline age 73 years, with 41% at least 75 years) with New York Heart Association Class II, III, or IV ischemic systolic heart failure to rosuvastatin 10 mg daily or placebo. After a median follow-up of 32.8 months, patients in the rosuvastatin group had decreased levels of LDL-C (45% difference between groups, $P < 0.001$) and hsCRP (37% difference between groups) compared with placebo. However, there was no statistically significant decrease in the primary outcome, that included death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR 0.92, 95% CI 0.83–1.02, $P = 0.12$). On the other hand, there was a statistically significant reduction in the number of hospitalizations for cardiovascular causes in the rosuvastatin group compared with the placebo group ($P < 0.001$), which was a secondary endpoint for this trial.

The authors of the study had hypothesized that statin use would stabilize coronary plaques and reduce myocardial ischemia and infarction, and thereby decrease the rate of sudden death in patients with ischemic heart failure, a population in which half of the sudden deaths are caused by plaque rupture. While it is unclear why treatment with rosuvastatin did not decrease the rate of the primary outcome, the authors suggested that alternative mechanisms of death, such as pump failure rather than

atherosclerotic causes, effects of other drugs the patients were on, and the need for a longer follow-up period to see beneficial effects of treatment as possible explanations.

A post hoc analysis from CORONA did suggest a significant interaction by hsCRP status (*P* interaction = 0.026) with rosuvastatin benefitting those with hsCRP ≥2 mg/L but not those with low hsCRP. Furthermore, an economic analysis of the overall CORONA cohort, including both the primary outcome and the secondary outcome of hospitalizations, did find that the overall reduction in CVD events with rosuvastatin partially offset the costs of rosuvastatin treatment by 44%, thus finding rosuvastatin treatment to be a cost-effective treatment for older patients with systolic heart failure.

Effect of rosuvastatin on lipid profile and atherosclerosis[2]

Several RCTs showed the beneficial effects of rosuvastatin on both lipid profile and atherosclerosis. Nissen SE et al. in their prospective, open-label blinded end-points trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden 14 [ASTEROID]) highlighted as the intensive rosuvastatin therapy (40 mg/d) performed on 507 patients for 24 months is associated with a decline of mean LDL-C value from 130.4 mg/dL to 60.8 mg/dL with a reduction of 53.2% when compared to the baseline, a 14.7% increase of HDL-C levels (from 43.1 mg/dL, to 49.0 mg/dL), and a regression of coronary atherosclerosis assessed by IVUS imaging (a 6.8% median reduction of total atheroma volume) and by quantitative coronary angiography (decrease of mean percentage of diameter stenosis from 35.7% to 34.5%, p 2 mg/l] were treated with rosuvastatin 20 mg daily or placebo and followed for a median of 1.9 years for the occurrence of the combined primary end point of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes.

These results reinforce the axiom “lower is better” about the predictive role of LDL-C values for CV events, and confirm that the beneficial effects on CV prevention go beyond the merely lipidlowering action, as shown by a reduced rate of major CV events also in patients with acute MI and low baseline LDL-C levels. In a Korean study, in fact, 1.054 patients with acute MI and baseline LDL-C levels below 70 mg/dl were divided into two groups according to the prescribing of statins at discharge (statin group n = 607; non statin group n = 447). The one-year follow-up showed a significant reduction of major adverse cardiac events, including death, recurrent MI, target vessel revascularization, and coronary artery bypass grafting in the statin group compared to no statin one (adjusted hazard ratio [HR]: 0.56; 95% confidence interval [CI]: 0.34 to 0.89; p = 0.015); with a reduction of the risk of cardiac death (HR: 0.47; 95% CI: 0.23 to 0.93; p = 0.031) and coronary revascularization (HR: 0.45, 95% CI: 0.24 to 0.85; p = 0.013).

Ezetimibe[4]

Ezetimibe inhibits intestinal and biliary cholesterol absorption and can significantly lower LDL-C and nonhigh-density lipoprotein cholesterol (non-HDL-C, defined as total cholesterol minus high-density lipoprotein cholesterol) when used alone or in combination with statin therapy. Despite the established cholesterol-lowering benefits of ezetimibe, significant controversy exists with respect to ezetimibe's vascular and clinical benefit, particularly in light of the Ezetimibe and Simvastatin in Hypercholesterolemic Enhances Atherosclerosis Regression (ENHANCE) trial, which showed no difference in carotid atherosclerosis burden as measured by carotid intima-media thickness (CIMT) in patients with heterozygous familial hypercholesterolemia who were treated with simvastatin plus either ezetimibe or placebo.' Based upon this controversy, some providers eliminated or reserved the use of ezetimibe as a last-line agent in lipid management. This review aims to detail the biological mechanisms, lipid effects, and safety of ezetimibe treatment and discuss the vascular and clinical outcomes data that may impact the use of ezetimibe in clinical practice.

Mechanism of action[4]

Circulating plasma levels of cholesterol are derived from two primary sources: cholesterol production from the liver and peripheral tissues, and the absorption of dietary and biliary cholesterol in the gastrointestinal tract ().' Cholesterol synthesis begins with the conversion of acetyl-CoA to mevalonate, a reaction catalyzed by the enzyme HMG-CoA reductase. Cholesterol synthesized by hepatocytes undergoes esterification by acyl-CoA acyl transferase (ACAT) and is incorporated into apolipoprotein B (ApoB)-containing lipoproteins such as very-low-density lipoprotein (VLDL) via microsomal transfer protein.' Subsequent modification of VLDL with hydrolysis of triglycerides by the enzymes lipoprotein lipase and hepatic lipase produces intermediate-density lipoprotein (IDL) and LDL. The transfer of cholesterol from the peripheral tissues to the liver is mediated by HDL. Nascent pre-β HDL particles accept free cholesterol from peripheral tissues via ATP-binding cassette transporter A1 (ABCA1). The cholesterol undergoes subsequent esterification by lecithin– cholesterol acetyltransferase. The esterified cholesterol moves into the hydrophobic core of the HDL particle, and as the particles become progressively more lipidated, they mature and become progressively larger and more spherical. The cholesteryl esters in these mature HDL particles can be removed from the circulation by hepatic scavenger receptor BI or undergo transfer of cholesterol to apolipoprotein B-containing lipoproteins such as LDL and IDL via the activity of cholesteryl ester transfer protein. The liver clears LDL particles from the circulation by the LDL receptor and the LDL receptor-related protein.'

Intestinal cholesterol absorption, occurring primarily in the duodenum and proximal jejunum, can also contribute to serum cholesterol levels.[,] Dietary intake provides about a quarter of the cholesterol entering the intestinal lumen, while the remaining three-quarters are derived from biliary cholesterol excretion from the liver. A distinction must be drawn between cholesterol entry into enterocytes and systemic cholesterol absorption, which refers to the appearance of cholesterol within lymphatic vessels, as not all of the cholesterol that makes its way into enterocytes will be absorbed into plasma. Intestinal cholesterol absorption is a complex process involving incorporation of free cholesterol, the majority of which is of biliary origin, into mixed biliary micelles, and the subsequent delipidation of micelles via intestinal enterocyte membrane sterol influx transporters. Once in the enterocyte, free cholesterol can be effluxed to ApoA-1, prebeta HDL, or ApoE, esterified by ACAT into cholesteryl ester for incorporation into ApoB48-containing chylomicrons, or effluxed back to the gut lumen by ABC transporters G5 and G8. Genetic mutations in ABCG5 and ABCG8 proteins result in sitosterolemia, which is associated with an increase in phytosterol accumulation and intestinal cholesterol absorption resulting in significantly elevated plasma cholesterol and plant sterol levels and clinical development of early atherosclerotic heart disease.[–] After secretion into the lymphatic system and drainage via the thoracic duct, chylomicrons and their remnants are cleared from the circulation by the liver. The triglycerides and cholesterol esters derived from chylomicrons can be repackaged into VLDL and secreted.

In 2004, Altmann et al reported the discovery of the Niemann–Pick C1-like 1 protein (NPC1L1) as the human sterol transport protein that was expressed at the enterocyte/ gut lumen (apical) as well as the hepatobiliary (canalicular) interface. NPC1L1 has a sterol-sensing domain, which is a region consisting of around 180 amino acids that form five predicted membrane-spanning helices with short intervening loops.[,] Current evidence points to the NPC1L1 protein working in conjunction with the adaptor protein 2 (AP2) complex and clathrin to facilitate internalization of free cholesterol into the enterocyte (). AP2 is a classical AP that facilitates the internalization of molecules into cells, such as cholesterol entering clathrin-coated pits. The AP2 complex consists of four proteins forming a core and appendage domains. The core carries cholesterol, and the appendage or “ears” bind to clathrin, which has a triskelion shape (three interlocked spirals) composed of three heavy chains and three light chains, which align to form small vesicles capable of internalizing cholesterol. Cholesterol in the gut lumen or bile incorporates into the cell membrane, where it can bind to the sterol-sensing domain of NPC1L1. The NPC1L1/cholesterol complex is internalized or endocytosed by joining to AP2 clathrin, creating a vesicle complex that then translocates with the help of myosin along microfilaments in the cytosol to a storage endosome called the endocytic recycling compartment. When intracellular cholesterol becomes low the NPC1L1 is released from the endocytic recycling compartment and traffics back along microfilaments to the cell membrane.Serum cholesterol levels are regulated based upon an interactive relationship between hepatic cholesterol production and intestinal cholesterol absorption. Statin therapy reduces serum LDL-

C by inhibiting hepatic cholesterol production through inhibition of the rate-limiting step in cholesterol synthesis catalyzed by HMG-CoA reductase. In response to the decrease in hepatic cholesterol production, the liver upregulates hepatic LDL receptors, leading to an increase in LDL-C removal from the blood. Additionally, studies have shown that in response to statin treatment, there is a compensatory increase in intestinal cholesterol absorption, possibly through the induction of gene expression of such proteins such as NPC1L1.[7] As a corollary, increases in intestinal absorption can lead to downregulation of intrinsic hepatic cholesterol production.[7]

Ezetimibe, or 1-(4-fluorophenyl)-(3R)-[3-{4-fluorophenyl}-{3S}-hydroxyprophyl]-(4S)-(4-hydroxyphenyl)-(2-azetidinone), inhibits intestinal cholesterol absorption by selectively blocking the NPC1L1 protein in the jejunal brush border, integral to the uptake of intestinal lumen micelles into the enterocyte.[7,8] The exact mechanism by which ezetimibe reduces the entry of cholesterol into both enterocytes and hepatocytes is not completely understood. Ge et al suggest ezetimibe prevents the NPC1L1/sterol complex from interacting with AP2 in clathrin coated vesicles. Ezetimibe may change the shape of NPC1L1 so as to render it incapable of binding to sterols or may interfere with the binding of free cholesterol to the cell membrane. Other hypotheses have been proposed. Kramer et al described a 145-kDa integral membrane-bound ectoenzyme called aminopeptidase N ([alanyl]-aminopeptidase) to which ezetimibe binds. Annexins are a family of calcium-and phospholipid-binding proteins that mediate cholesterol uptake. Caveolin-1 (CAV1) is a small 22-kDa protein that forms at least two distinct chaperone complexes that regulate both total cellular and caveolar cholesterol levels. A complex consisting of annexin 2, cyclophilin A, and cyclophilin 40, traffics exogenous cholesterol from caveolae to the endoplasmic reticulum. The other CAV1 complex includes heat-shock protein 56, cyclophilin A, and cyclophilin 40, and traffics newly synthesized cholesterol from the endoplasmic reticulum to caveolae. It has been shown that ezetimibe effectively disrupts the CAV1– annexin 2 heterocomplex in vivo and thereby reduces sterol absorption. By reducing enterocyte cholesterol absorption, chylomicron formation and secretion, as well as the back flux of cholesterol from the bile, ezetimibe depletes hepatic pools of cholesterol and increases expression of the LDL receptor on the surface of hepatocytes, resulting in reductions in serum levels of LDL-C. Ezetimibe does not appear to affect the absorption of dietary triglycerides, fat-soluble vitamins, or drugs such as warfarin. After being metabolized through glucoronidation in the small intestine and liver, ezetimibe is excreted in the bile back into the intestinal lumen, where it again can inhibit the NPC1L1 protein.[7] It is eventually excreted predominantly in the feces, with a minor 10% excretion in the urine. This enterohepatic circuit allows ezetimibe to have a long half-life of 22 hours. Ezetimibe does not undergo metabolism via the cytochrome P450 pathway, and therefore does not have significant interactions with other medications that are metabolized by the cytochrome P450 pathway, such as statins, fibrates, amiodarone, and amlodipine. Medications such as fibrates and cyclosporine, though, have been shown to increase the bioavailability of ezetimibe. In

addition to inhibition of intestinal cholesterol absorption, ezetimibe also interacts with hepatic NPC1L1, whereby it may reduce biliary cholesterol absorption and further reduce serum cholesterol levels.

A number of preclinical animal studies have shown a consistent reduction in LDL-C levels and vascular benefit with treatment with ezetimibe.[3] Studies using animals fed cholesterol-rich diets showed that ezetimibe effectively lowered serum cholesterol levels. In ApoE double-knockout mice characterized by severely elevated cholesterol levels and early development of atherosclerosis, ezetimibe at a dosing of 10 mg/kg per day inhibited cholesterol intestinal absorption by greater than 90%, with significantly reduced levels of chylomicron and VLDL by 87%. A synergistic effect of cholesterol lowering was found in dogs treated with a combination of ezetimibe and statin. In addition to the antilipidemic effects, ezetimibe has been shown to inhibit the progression of aortic and carotid atherosclerosis in ApoE knockout mice treated with varying diets.

Ezetimibe appears to have reported marked variability in intestinal cholesterol absorption and serum cholesterol levels. Genomic studies have identified over 140 polymorphisms in the *NPC1L1* gene and shown that common variants in this gene are associated with differing treatment responses.[3] For example, one identified gene variant, single-nucleotide polymorphism g. − 18C > A, was associated with a 15% further reduction in LDL-C as compared to the most common allele after 6 weeks of ezetimibe added on to a background of statin treatment.

Statin therapy significant lowers LDL-C cholesterol levels by 35%–60%.[3] While inhibition of hepatic cholesterol production by statins results in a compensatory increase in the production of hepatic LDL receptors and enhanced uptake of serum LDL-C into the liver, there is also an increase in intestinal cholesterol absorption. Likewise, in animal models, treatment with ezetimibe as monotherapy has been shown to induce HMG-CoA reductase expression. Given these compensatory effects, the adjunctive treatment of hypercholesterolemia using inhibitors of cholesterol absorption such as ezetimibe with statins yields an additive effect on lowering serum cholesterol levels.

Efficacy and indications[4]

Ezetimibe is indicated in the treatment of disorders of elevated cholesterol levels, including LDL-C and ApoB, as monotherapy or in combination with statins. The effectiveness of ezetimibe to lower cholesterol and positively change lipid profiles has been noted in a number of clinical trials.[3] Given the preponderance of data demonstrating the clinical effectiveness of statin therapy and the current NCEP ATP recommendations for the primary use of statin medications to achieve LDL-C targets, there have only been a small number of clinical trials testing ezetimibe as monotherapy versus placebo. A meta-analysis of eight randomized placebo controlled trials that included over 2700 subjects showed that monotherapy with ezetimibe 10 mg daily in hypercholesterolemic subjects for a minimum of 12 weeks

was associated with a significant 18.5% reduction in LDL-C as compared to placebo. In addition, there was a significant 3% increase in HDL-C, a significant 8% reduction in triglycerides, and a 13% reduction in total cholesterol with ezetimibe as compared to placebo. Combination therapy trials using ezetimibe plus statin have shown greater efficacy in terms of LDL-C reduction than monotherapy with ezetimibe or statin alone." A recent meta-analysis was completed of 27 double-blind, placebo-controlled, or active comparative studies of over 21,000 subjects randomized to ezetimibe 10 mg daily plus statin or statin alone for a mean treatment of 9 weeks. Overall, there was a significant 15.1% greater observed reduction in LDL-C in the combination therapy with ezetimibe as compared monotherapy with statin. Also, there was a significant 13.5% greater decrease in non-HDL-C and 8.6% reduction in high-sensitivity – C-reactive protein. With a greater effect on cholesterol values, the study showed that a higher percentage of subjects were able to reach ATP III treatment targets with the addition of ezetimibe therapy. In subjects with established CHD, only 10.3% of subjects on statin monotherapy were able to reach an LDL-C goal of <70 mg/dL, while 32.1% of subjects on combination therapy with ezetimibe were able to reach this target.

The effectiveness of ezetimibe in lowering cholesterol has been tested in various dyslipidemic populations, including familial hypercholesterolemia (FH). FH is an autosomal dominant hereditary disorder caused predominantly by mutations in the LDL-receptor gene resulting in less functional hepatic LDL receptors and subsequent decreased uptake of LDL-C from the blood. It has a prevalence of 1:500 for heterozygotes and 1:1 million for homozygotes who have almost complete loss of hepatic LDL-receptor activity. FH subjects are often characterized by severely elevated LDL-C, dermatologic findings with xanthomas, and early onset atherosclerotic vascular disease. While statin therapy is the recommended initial treatment of choice along with lifestyle intervention, many FH subjects are frequently unable to reach LDL-C goals even on high-dose statin. The additive effect of the addition of ezetimibe to statin therapy therefore makes ezetimibe an attractive add-on option for undertreated FH subjects. In ENHANCE, 720 heterozygous FH subjects were randomized to simvastatin 80 mg daily plus either ezetimibe 10 mg daily or placebo. After 24 months of treatment, the simvastatin plus ezetimibe group had significantly greater LDL-C reduction as compared to the statin-only group (−55.6% vs −39.1%; $P < 0.01$). Given the low prevalence of homozygous FH subjects, there have been only a small number of randomized controlled trial trials testing ezetimibe in this population. One such trial randomized 50 homozygous FH subjects who were already receiving a background of 40 mg daily of simvastatin or atorvastatin to either increased statin to 80 mg daily, 40 mg daily of statin plus ezetimibe 10 mg daily, or to 80 mg of statin plus ezetimibe 10 mg daily. After 12 weeks of therapy, there was a greater decrease in LDL-C with addition of ezetimibe to either 40 or 80 mg of statin as compared to doubling of statin to 80 mg from 40 mg daily without the addition of ezetimibe (21%–27% vs 7%).

Ezetimibe can effectively lower sterol levels in subjects with sitosterolemia by inhibiting intestinal plant sterol absorption.[–] An autosomal recessive disorder, sitosterolemia is a condition caused by mutations in the ABC transporter genes, *ABCG5* and *ABCG8*, which reduce the ability of intestinal cells to transfer free cholesterol back to the intestinal lumen and from the liver into the bile. This reduction leads to an increase in serum sterol levels of sitosterol and campesterol, and results in the development of early onset atherosclerotic vascular disease. Given the inability of statins to reduce plant sterol levels and the incomplete lowering of sterol levels with other treatments such as low-sterol diets and bile-acid binding resins, ezetimibe has emerged as an effective alternative strategy. In hypercholesterolemic subjects without a diagnosis of sitosterolemia, ezetimibe therapy for 2 weeks was shown to lower sitosterol and campesterol levels by 41% and 48%, respectively. In one small multicenter study, 37 subjects with sitosterolemia were randomized to placebo or ezetimibe 10 mg daily. After 8 weeks of therapy, sterol levels were reduced by 21% in the ezetimibe group and increased by 4% in the placebo group. The reduction in sterols with ezetimibe was seen despite subjects concurrently taking bile-acid binders or statins.

Several trials have evaluated the use of ezetimibe in patients with diabetes or metabolic syndrome who often have an atherogenic lipid profile consisting of elevated LDL-C and triglycerides and low HDL-C.[–] The diagnosis of diabetes is considered a CHD-risk equivalent, and current NCEP guidelines recommend a similar LDL-C goal for patients with established CHD or diabetes. Metabolic syndrome is characterized by a combination of risk factors, including dyslipidemia with elevated triglycerides and low HDL-C, hypertension, obesity based upon waist circumference, and insulin resistance with impaired fasting glucose. Similar to diabetes, the presence of metabolic syndrome is associated with a high risk of cardiovascular events. In the Vytorin vs Atorvastatin in Patients with Type 2 Diabetes Mellitus and Hypercholesterolemia (VYTAL) trial, 1229 subjects with diabetes and dyslipidemia were randomized to combination therapy with ezetimibe 10 mg/day plus simvastatin 20 mg/day vs atorvastatin 10–20 mg/day or to ezetimibe 10 mg/day plus simvastatin 40 mg/day vs atorvastatin 40 mg/day. After 6 weeks of therapy, combination therapy with ezetimibe plus simvastatin had greater LDL-C reduction as compared with atorvastatin both at the low dose (−53.6% vs −38.3%, respectively) and the high dose (−57.6% vs −50.9%, respectively). In addition to a greater ability to lower LDL-C, combination therapy with ezetimibe was better in lowering total cholesterol and non-HDL-C and in raising HDL-C. As compared to the atorvastatin 10-mg dose, ezetimibe 10-mg/simvastatin 20-mg dose was associated with a greater reduction in triglyceride levels. In another study testing an identical protocol as VYTAL in subjects with metabolic syndrome, a similar result was documented with combination therapy, with ezetimibe and simvastatin achieving a greater reduction in LDL-C and non-HDL-C and greater increase in HDL-C as compared to atorvastatin monotherapy.

Safety

Though side effects have been reported with all lipid-altering therapies such as statins, niacin, and fibrates, life-threatening toxicities are rare and the overall safety profile of these therapies is quite favorable.[–] The safety of ezetimibe as monotherapy or in combination with other lipid-modifying agents such as statins has been well documented.[,] In terms of elevations in liver function tests, ezetimibe appears to cause similar elevations in transaminases (three times the upper limit of normal with alanine transaminase or aspartate transaminase) as compared to placebo when given as monotherapy. Also, as combination therapy with statins, ezetimibe does not significantly cause an increase in liver enzymes more than is observed with statin therapy alone. In a meta-analysis of 18 randomized controlled trails evaluating statin plus ezetimibe or placebo in 14,471 subjects, the incidence of elevations in liver enzymes was not statistically different between the two groups. Life-threatening liver failure with ezetimibe as monotherapy or in combination with statins is extremely rare, with only a handful of published reported cases.[–] Myalgias with or without myositis and elevations in creatinine kinase are commonly reported with treatment with statins. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated creatinine kinase levels beyond what is noted with treatment with statin alone. A meta-analysis of seven randomized controlled trials showed that monotherapy with ezetimibe or in combination with statin was not associated with an increased risk of myositis as compared to placebo or monotherapy with statin.

Several epidemiological trials have raised concerns of an increased risk of cancer associated with low total serum cholesterol levels that have been reproduced in a small number of randomized controlled statin trials.[,–] The recent publication of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study raised similar concerns for cancer with treatment with ezetimibe plus statin. In SEAS, 1873 subjects with a history of asymptomatic aortic stenosis were randomized to ezetimibe 10 mg/day and simvastatin 40 mg/day or placebo. There was a higher rate of cancer incidence in the ezetimibe/simvastatin group (11.1%) than in the placebo group (7.5%). However, a combined analysis of two larger ezetimibe-plus-statin trials that were ongoing at the time of the analysis did not support such a hypothesis. In this interim analysis, incident cancer cases from the Study of Heart and Renal Protection (SHARP) and Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) studies with 20,617 subjects showed no increased risk of cancer with treatment with ezetimibe plus statin as compared to statin alone. Also, the study showed that there was no increased risk of new cancer diagnosis associated with duration of treatment. Since the publication of this combined analysis, the SHARP trial has been completed and confirmed no difference in cancer rates between the combination therapy and placebo (9.4% vs 9.5%, $P = 0.89$). Final cancer-event data is not yet available for the IMPROVE-IT trial, which is ongoing, but no recommendations for early termination of the trial have been reported by the data-monitoring and safety board, which suggests that no significant increase in cancer risk has been detected.

Imaging trials evaluating effects on atherosclerosis[4]

The vascular effects of ezetimibe on atherosclerosis progression have been investigated in several trials using ultrasound measurements of CIMT.[,,] Numerous population studies have documented CIMT as a marker for CHD risk. Documenting changes to CIMT has become a common surrogate marker of atherosclerosis progression or regression in evaluating the clinical effectiveness of lipid-altering therapies. The ENHANCE study investigated the vascular effect as measured by CIMT of combination therapy with simvastatin 80 mg/day plus either ezetimibe 10 mg/day or placebo in subjects with heterozygous FH. After 24 months of treatment and despite a significant difference in LDL-C lowering (−55.6% vs −39.1%, $P < 0.01$) favoring combination therapy with ezetimibe, there was no significant difference in CIMT measurements (+0.0033 mm for placebo vs 0.0182 mm for ezetimibe, $P = 0.15$). This negative finding was contrary to the prior Atorvastatin Versus Simvastatin on Atherosclerosis Progression (ASAP) trial, which showed that high-dose treatment using atorvastatin 80 mg/day in subjects with heterozygous FH led to a greater reduction in LDL-C as compared to treatment with moderate-dose simvastatin of 40 mg/day. This difference in LDL-C reduction was associated with regression of CIMT of −0.031 mm in the atorvastatin group and progression of +0.036 mm in the simvastatin group ($P = 0.0001$ for between-group comparison). Though ENHANCE failed to produce similar effects on CIMT as seen in ASAP, several fundamental differences exist between the two study populations that may account for the discordant findings. The baseline CIMT seen in ENHANCE (0.70 mm) was significantly thinner than in ASAP (0.92 mm). In addition, the change in CIMT over 2 years in the monotherapy groups treated with simvastatin was significantly less in ENHANCE (0.0058 mm) than ASAP (0.0360 mm), despite similar effects on LDL-C. These findings in ASAP and ENHANCE suggest that the heterozygous FH subjects in ENHANCE had been previously well treated with chronic statin therapy and may have entered the study with carotid arteries already depleted of lipid and therefore resistant to further changes in response to new lipid therapies. Support for this hypothesis was provided by data from the Carotid Atorvastatin Study in Hyperlipidemic post-Menopausal Women: A Randomized Evaluation (CASHMERE) trial. CASHMERE randomized 398 postmenopausal women with moderate hypercholesterolemia to treatment with atorvastatin 80 mg daily, hormone replacement therapy alone, combination, or placebo and measured change in CIMT as a vascular outcome. After 12 months of therapy, there was no reported change in CIMT despite greater LDL-C reduction on high-dose atorvastatin as compared to placebo. The mean baseline CIMT was 0.69 mm, which was similar to that of ENHANCE. This low baseline CIMT measurement observed in both trials likely limited the measurable incremental change to carotid atherosclerosis in response to additional lipid-lowering therapy.

A positive impact on carotid atherosclerosis using ezetimibe was observed in the Stop Atherosclerosis in Native Diabetics Study (SANDS).[,] SANDS randomized diabetic subjects to aggressive care with target LDL-C <70 mg/dL and systolic blood pressure <115 mmHg or to standard care with target LDL-

C < 100 mg/dL and systolic blood pressure < 130 mmHg. Ezetimibe was added on to statin therapy in subjects not able to meet LDL-C targets. Change in carotid IMT was compared between the aggressive versus standard treatment groups and between subjects receiving statins plus ezetimibe versus statins alone. After 36 months of therapy, LDL-C was reduced similarly in the aggressive treatment group receiving statins plus ezetimibe (−31 mg/dL) or statins alone (−32 mg/dL). Mean baseline CIMT in SANDS was 0.81 mm as compared to 0.69 mm seen in ENHANCE. In the standard therapy group, there was progression of CIMT by +0.039 mm, while the aggressively treated group showed CIMT regression from baseline in both the ezetimibe (−0.025 mm) and nonezetimibe (−0.012 mm) subjects. In multivariate analysis, change in CIMT was related to degree of LDL-C reduction independent of specific choice of lipid-lowering therapy.

Further support for the vascular benefits of combination therapy with ezetimibe was reported in the Vytorin on Carotid Intima-Media Thickness and Overall Arterial Rigidity (VYCTOR) study, which randomized 90 coronary artery disease subjects to pravastatin 40 mg/day ± ezetimibe 10 mg/day, simvastatin 40–80 mg/day, or simvastatin 20–40 mg/day ± ezetimibe 10 mg/day with a primary end point of change in CMIT. After 1 year of therapy, there was significant reduction in LDL-C to a mean level of 45–48 mg/dL in the three groups. Baseline CIMT was 1.23–1.33 mm, almost twice that of the baseline in ENHANCE. Follow-up measurement of CIMT showed a significant reduction in all three groups to a level of 0.90–0.93 mm. The results of SANDS and VYCTOR are contradictory to the outcome observed in ENHANCE and suggest that treatment with ezetimibe can regress carotid atherosclerosis if there is a sufficiently thick CIMT at baseline.

Despite the positive results of the SANDS and VYCTOR trials, additional questions were raised regarding the vascular benefits of ezetimibe following the early termination of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies (ARBITER 6 – HALTS) study.[·] ARBITER 6 randomized 363 coronary artery disease subjects with CHD or CHD equivalent, treated LDL-C <100 mg/dL on background statin therapy and low HDL-C to treatment with ezetimibe 10 mg/ day or extended-release niacin target to 2000 mg/day. The primary end point of the study was change in mean CIMT. The study was stopped early after 14 months of follow-up after reaching a prespecified efficacy end point. Changes to lipid profiles were as expected with treatment, with niacin raising HDL-C by 18.4% to 50 mg/dL and ezetimibe lowering LDL-C by 19.2% to 66 mg/dL. A significant reduction in CIMT (−0.0142 mm, $P = 0.001$) in the niacin group was reported, while a nonsignificant reduction (−0.0007 mm, $P = 0.84$) was noted in the ezetimibe group. The authors concluded based upon these results that treatment with niacin in combination with statin was superior to ezetimibe on regression of CIMT. These results are consistent with prior data documenting niacin's ability to stabilize or regress atherosclerosis and lend support to the use of niacin in the treatment of low HDL-C. However, several issues exist in trying to extrapolate these findings to conclude on the effectiveness of ezetimibe on carotid atherosclerosis. First, ARBITER-

6 was designed to evaluate the treatment of subjects with low HDL-C and controlled LDL-C. Such a population was ideally suited for therapy with niacin and not with ezetimibe which is used primarily to reduce LDL-C. While niacin treatment raised HDL-C by 7.5 mg/ dL, therapy with ezetimibe lowered HDL-C by 2.8 mg/dL. Additionally, as noted in prior carotid imaging trials including ASAP and ENHANCE, changes in carotid atherosclerosis occur in the first 1–2 years after initiating LDL-C-lowering therapy and are not expected in subjects who have been on chronic lipid-lowering treatment. ARBITER 6 subjects were on a background of aggressive statin therapy for an average of 6 years prior to study enrollment, which could have impacted their capacity for additional LDL-C reduction with ezetimibe to reduce CIMT. Also, the trial was stopped prematurely, with over 40% of the subjects not having undergone follow-up CIMT measurements, and this could have minimized any possible vascular effects due to ezetimibe. Based on these methodological study design flaws, definitive conclusions on the presence or absence of vascular benefit of ezetimibe cannot be made using data presented in ARBITER-6.

Clinical outcome trials[4]

The clinical efficacy of ezetimibe treatment was evaluated in the SEAS study, where 1873 subjects with mild to moderate aortic stenosis without indication for lipid-lowering therapy were randomized to ezetimibe 10 mg/day plus simvastatin 40 mg/day or placebo. The primary end point was a composite of need for aortic valve surgery and cardiovascular events. After 4 years of therapy, combination therapy with ezetimibe reduced LDL-C by 61% as compared to placebo. While there was no significant difference in the primary end point, major cardiovascular events with fatal and nonfatal myocardial infarction were significantly reduced by 41% in the simvastatin plus ezetimibe group (). This cardiovascular event reduction was proportional to the magnitude of LDL-C change and was only apparent in subjects with less severe aortic stenosis, defined as tertiles 1 and 2 as based upon aortic jet velocity. This degree of event reduction based upon the level of LDL-C reduction was similar to what was previously observed in a meta-analysis of 14 statin trials showing the benefit of statin therapy versus placebo completed by the Cholesterol Treatment Trialists' Collaboration.

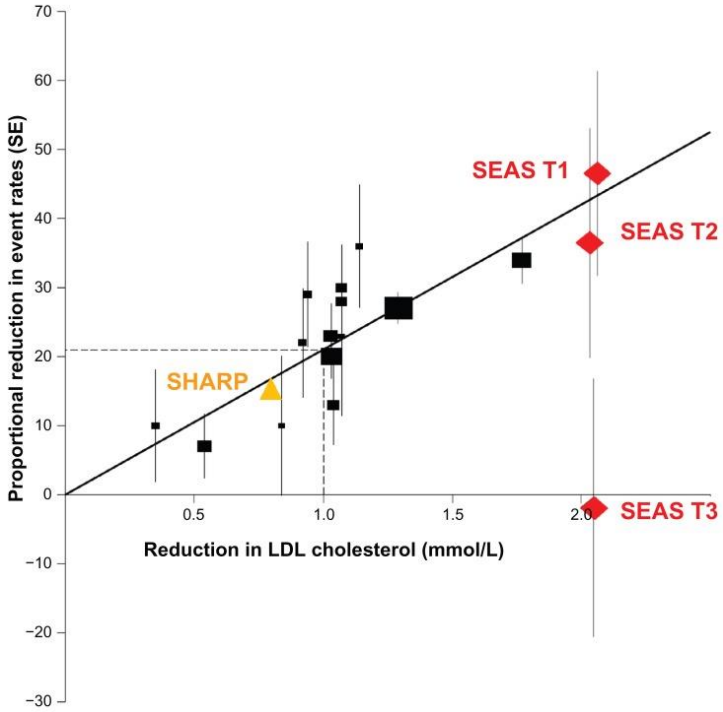

Figure 1. Proportional reduction in major ischemic events by mean decrease in LDL-C (mmol/L) in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (tertiles 1, 2, and 3 for severity of aortic valve stenosis) compared to 14 randomized trials in the Cholesterol Treatment Trialists meta-analysis.

Similar evidence supportive of a cardiovascular benefit in using statin plus ezetimibe treatment was noted in the SHARP trial. In SHARP, subjects with chronic kidney disease with and without dialysis dependence were randomized to simvastatin 20 mg/day plus ezetimibe 10 mg/day or placebo. After 5 years of therapy, there was a significant 17% reduction in major atherosclerotic events in the ezetimibe groups as compared to placebo (P = 0.0021). Risk reduction was again found to be proportional to magnitude of LDL-C reduction. No increased risk of adverse events was reported, including myopathy and rhabdomyolysis. This positive outcome was in contrast to two previously reported negative trials evaluating lipid-lowering with statins in renal disease subjects; A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) and German Diabetes and Dialysis Study (4D).[,] In addition to the fact that SHARP was a significantly larger trial with three times greater enrollment than AURORA and 4D combined, the likely main explanation for the discrepant findings was that the SHARP population had less advanced kidney disease. While AURORA and 4D evaluated lipid therapy in subjects who were already undergoing hemodialysis, the SHARP trial only had a third of its population being dialysis-dependent. Lipid therapy would be expected to benefit less advanced kidney disease subjects, who predominantly succumb to deaths related to atherosclerotic-based heart disease, but not in dialysis-dependent subjects, who experience more arrhythmia-related deaths.

Despite the atherosclerosis regression documented in SANDS and VYCTOR and cardiovascular benefit seen in SEAS and SHARP using combination therapy with ezetimibe, the negative outcomes reported from ENHANCE and ARBITER 6 produced significant controversy on the clinical value of ezetimibe in the treatment of hypercholesterolemia." Also, to date, no randomized trial has shown a significant reduction in clinical events with combination therapy using ezetimibe plus statin versus statin alone. Therefore, the results from the soon-to-be-completed IMPROVE-IT are highly anticipated. The goal of IMPROVE-IT is to evaluate the effect of additional LDL-C lowering using ezetimibe on top of intensive background statin therapy on cardiovascular events in 18,000 subjects who have had recent acute coronary syndromes. But while the trial is not expected to be completed until June 2013, questions already exist about the ability of the trial to detect incremental benefit of ezetimibe added on to statin therapy. Subjects in IMPROVE-IT were treated at baseline with optimal medical therapy post–acute coronary syndrome and were thought to be able to reach aggressive LDL-C targets based upon NCEP ATP III updated recommendations with treatment with simvastatin 40 mg/day plus placebo (the trial will be comparing mean attained LDL-C levels of 66 mg/dL and 52 mg/dL). Given the already low LDL-C levels and reduced cardiovascular events with simvastatin-only therapy in this population, the further reduction of cardiovascular events with the addition of ezetimibe will likely be of modest value. Beyond the large sample size, IMPROVE-IT will need an adequate number of events to provide enough power to detect the expected small difference between the ezetimibe and placebo groups. Ideally, a trial comparing ezetimibe monotherapy versus placebo in hypercholesterolemic subjects would provide the best answer on ezetimibe's ability to lower LDL-C and subsequently affect cardiovascular events. But unfortunately, given the long-established benefit of statin therapy, a cholesterol trial without statin therapy would not be possible today, particularly in subjects with CHD.

Evaluation of Statin Monotherapy Treatment Compared to Combination Therapy with Ezetimibe[5]

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 (). 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. 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 (). 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.

Table 1. Impact on Low-Density Lipoprotein

Study	**n**	**Regimens**	**LDL- C Lowering (mg/dL)**	**Achieve LDL-C Goal (% of Patients)**
EXPLORER	469	RSV/EZ 40 mg/10mg vs RSV 40 mg	RSV/EZ: 70.0[a] RSV: 57.0 p<0.001	RSV/EZ: 94.0% RSV: 79.1% p<0.001
Yang	337	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 59.5[a] RSV: 51.1 p<0.001	RSV/EZ: 90.7% RSV: 72.9% p=0.01
MRS-ROZE	407	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 59.1[b] RSV: 49.4 p<0.001	RSV/EZ: 94.1% RSV: 86.3% p<0.05
I-ROSETTE	396	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 75.4[a] RSV: 64.4 p<0.001	RSV/EZ: 92.3% RSV: 79.9% p<0.001
Kim W	712	RSV/EZ 5–20/10mg vs RSV 5–20mg	RSV/EZ: 56.5%[c] RSV: 45.2% p<0.01	RSV/EZ: 94.2% RSV: 86.6% P=0.0142

Hwang	36	RSV/EZ 5/10mg vs RSV 20mg	RSV/EZ: 94.3[a] RSV: 89.9 p=0.54	NR
Torimoto	79	RSV/EZ 2.5/10 mg vs RSV 5mg	RSV/EZ: 31.1%[c] RSV: 12.1% p<0.001	RSV/EZ: 89.7% RSV: 58.3% p=NR
Masuda	51	RSV/EZ 5/10mg vs RSV 5mg	RSV/EZ: 55.8%[c] RSV: 36.8% p=0.004	NR
Bays	440	RSV/EZ 5–10/10mg vs RSV 10–20 mg	RSV/EZ: 21.5%[d] RSV: 7.6% p<0.001	NR
Ambegaonkar	8667	Prior ST/EZ 10mg vs ST DD vs RSV 10mg vs SIM/EZ 20/10mg	Prior ST/EZ: 26.0[b] ST DD: 9.7 RSV: 19.7 SIM/EZ: 27.6	NR
GRAVITY	833	RSV/EZ 10–20/10 mg SIM/EZ 40–80/10 mg	RSV/EZ 10/10: 59.7[a] 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: [a]Data represented as mean change in mg/dL. [b]Data represented as least squares mean in mg/dL. [c]Data represented as percent change from baseline. [d]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.

Table 2. Impact on Non-LDL Laboratories

Study	Non-HDL Lowering	TC Lowering	TG Lowering	HDL Increasing	hs-CRP Lowering
EXPLORER	RSV/EZ: 65 RSV: 52 p<0.001	RSV/EZ: 51[a] 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	RSV/EZ: 54.9 RSV: 45.8 p<0.001	RSV/EZ: 39.6[a] 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	RSV/EZ: 53.2 RSV: 42.2 p<0.001	RSV/EZ: 38.8[b] 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	RSV/EZ: 52.8 RSV: 41.4 p<0.01	RSV/EZ: 39.0[b] 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	RSV/EZ: 100.8 RSV: 98.9 p=0.79	RSV/EZ: 98.4[a] 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	NR	NR	RSV/EZ: 13.8[c] RSV: 1.3 p=0.032	RSV/EZ: 1.1 RSV: 2.4 p=0.408	NR
Masuda	RSV/EZ: 50.3[b] 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	RSV/EZ: 17.1[c] 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	Prior ST/EZ: 22.6[d] ST DD: 8.5		Prior ST/EZ: 12.1 ST DD: 5.0	Prior ST/EZ: 1.7 ST DD: 0.8	

	RSV: 16.3 SIM/EZ: 22.8		RSV: 5.7 SIM/EZ: 8.0	RSV: 3.2 SIM/EZ: 2.5	
GRAVITY	RSV/EZ 10/10: 54.7[a] 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: [a]Data represented as mean change in mg/dL. [b]Data represented as percent change from baseline. [c]Data represented as least squares mean in mg/dL. [d]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.

A multicenter, randomized, double-blind, placebo-controlled study over 12-weeks was conducted in Korean patients with moderate or high cardiovascular risk. 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 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 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[5]

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. 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± standard deviation, SD) compared to monotherapy (59.1% ± 1.8% vs 49.4% ±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 ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg), abdominal obesity (waist circumference ≥90 cm in men, ≥80 cm in women), elevated TG (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), and elevated fasting glucose (≥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). Following 8 weeks of treatment, mean LDL-C concentration (±SD) decreased by 82.0 mg/dL (±30.3) in the combination groups compared to 64.4 mg/dL (±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). 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 ± SD) than those in the monotherapy group (56.47% ±16.13% vs 45.18% ±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[5]

Patients with type 2 diabetes have enhanced cholesterol absorption, and therefore may benefit from the addition of ezetimibe to the statin regimens., 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. 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). 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% (± 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. In patients with diabetes, it was determined that the combination lowered the mean (standard error) LDL-C more than rosuvastatin monotherapy (64.2%±2.0 vs 50.2%±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[5]

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. 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. 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%±7.2 vs 68.2%±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[5]

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. 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. 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[5]

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). 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. 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.

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Survey Form

1) What is the percentage of patients usually diagnosed with atherosclerotic cardiovascular disease (ASCVD) in your clinical practice?

a. <25%
b. 25-50%
c. >50-75%
d. >75%

2) Which is your preferred statin?

a. Rosuvastatin
b. Atorvastatin
c. Pravastatin
d. Simvastatin

3) In your opinion what is/are the advantage(s) of Rosuvastatin in comparison to other statins?

a. Higher LDL-C Lowering
b. Better Patient Compliance
c. Better Safety Profile

4) In your clinical practice, what percentage of patients with dyslipidemia have been prescribed with Rosuvastatin in combination with other lipid-lowering agents?

a. <25%
b. 25 to 50%
c. >50 to 75%
d. >75%

5) Which lipid-lowering agent is most commonly prescribed by you along with Rosuvastatin?

a. Ezetimibe
b. Fenofibrate
c. Bempedoic acid
d. Bile acid sequestrants
e. Niacin

6) Approx. what % of your patients have been prescribed with the Rosuvastatin and Ezetimibe combination therapy?

a. <25%
b. 25 to 50%
c. >50 to 75%
d. >75%

7) As per your opinion, which is the most preferred place of Rosuvastatin Plus Ezetimibe combination therapy?

a. As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce LDL-C.
b. Alone or as an adjunctto other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia to reduce LDL-C.
c. In patients unable to reach their LDL-C goal with the highest tolerated intensity of statin.
d. As a second-line agent when LDL-C reduction is inadequate with Rosuvastatin monotherapy in patients with primary hypercholesterolemia.

8) Which is the most suitable patient profile for Rosuvastatin/Ezetimibe combination therapy?

a. Patients with primary hypercholesterolemia
b. Dyslipidaemia patients with Ischemic Heart Disease
c. High risk patients (with an ASCVD risk over 20%)
d. Patients with Diabetic Dyslipidemia

9) Which is the most commonly prescribed strength of Rosuvastatin/Ezetimibe FDC by you?

a. 5 mg/10 mg
b. 10 mg/10 mg
c. 20 mg/10 mg
d. 40 mg/10 mg

10) How much is the average LDL-C reduction observed with the usage of Rosuvastatin and Ezetimibe combination therapy in your practice?

a. Up to 30%
b. 30-50%
c. 50-70%
d. >70%

11) At what frequency, the LDL-C levels are assessed during treatment with Rosuvastatin and Ezetimibe combination therapy?

a. After 2 weeks
b. Between 2 to 4 weeks
c. Between 4 to 6 weeks
d. After 6 weeks

12) How long do you use Rosuvastatin and Ezetimibe combination in ASCVD patients?

a. 6 months
b. 12 months
c. Life Long therapy

13) As per your opinion, what is the perceived clinical advantage of the Rosuvastatin and Ezetimibe combination in your practice?

a. Once daily dosing
b. Minimal drug–drug interaction potential
c. Superior LDL-C lowering and HDL-C increases
d. Beneficial pleiotropic effects

14) Which is the most common adverse effect observed with Rosuvastatin/Ezetimibe combination in your clinical practice?

a. Myalgia
b. Arthralgia
c. Headache
d. Gastrointestinal upset

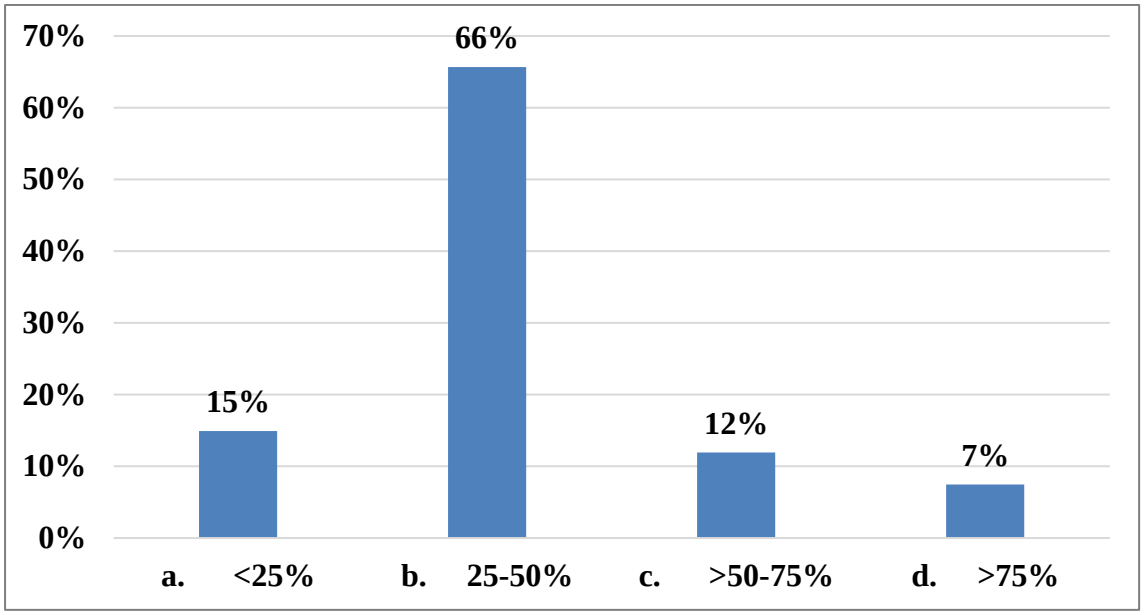
15) In your opinion, how is the long-term safety profile of Rosuvastatin and Ezetimibe combination therapy?

a. Excellent
b. Very Good
c. Good
d. Poor

Survey Findings

1) What is the percentage of patients usually diagnosed with atherosclerotic cardiovascular disease (ASCVD) in your clinical practice?

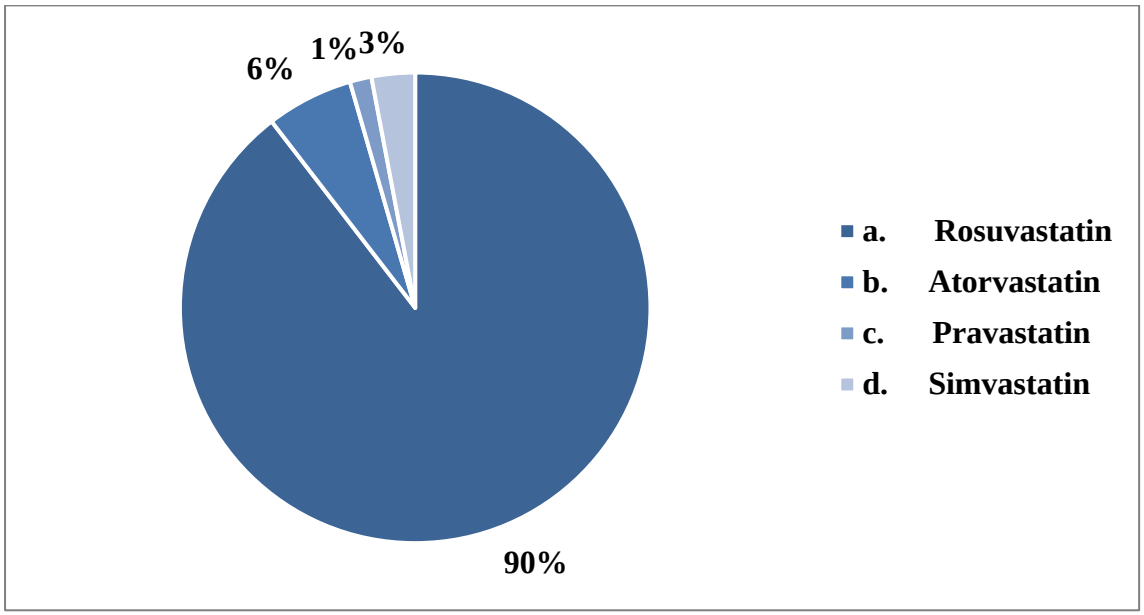
a. <25%
b. 25-50%
c. >50-75%
d. >75%



According to majority of doctors, 66%, the percentage of patients usually diagnosed with atherosclerotic cardiovascular disease (ASCVD) in their clinical practice is 25-50%.

2) Which is your preferred statin?

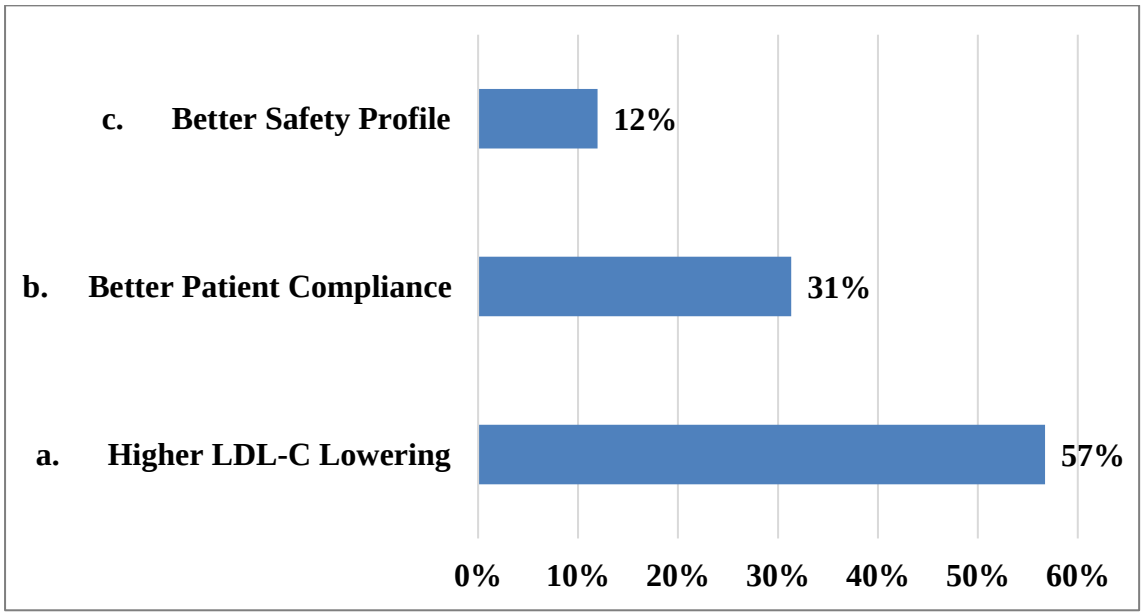
a. Rosuvastatin
b. Atorvastatin
c. Pravastatin
d. Simvastatin



According to majority of doctors, 90%, their preferred statin is Rosuvastatin.

3) In your opinion what is/are the advantage(s) of Rosuvastatin in comparison to other statins?

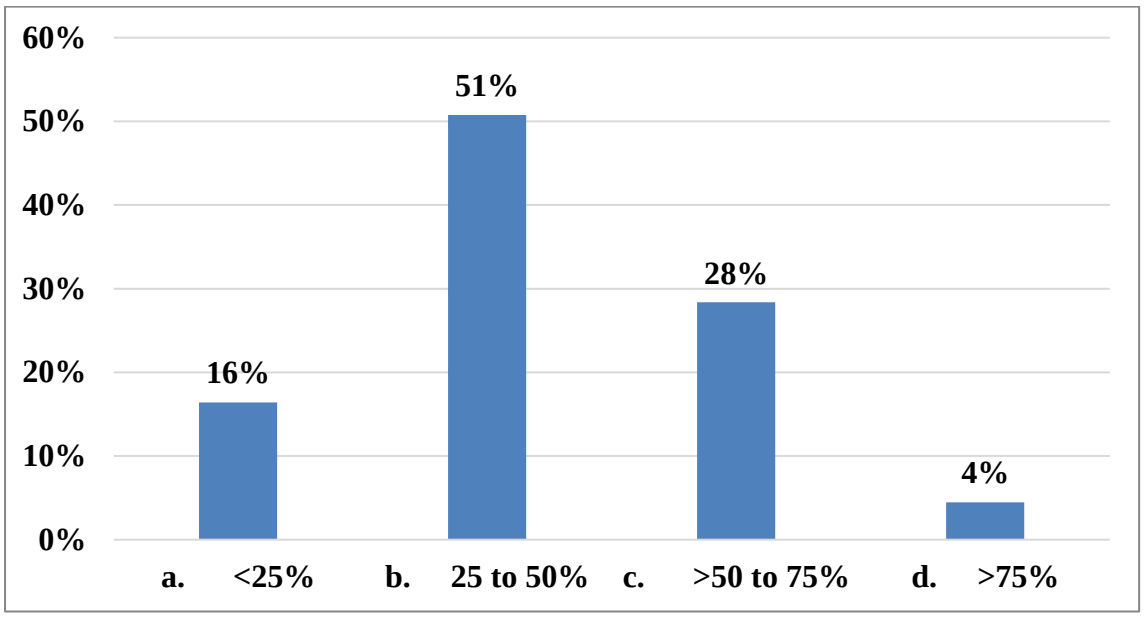
a. Higher LDL-C Lowering
b. Better Patient Compliance
c. Better Safety Profile



In the opinion of 57% of doctors, the advantage(s) of Rosuvastatin in comparison to other statins is higher LDL-C lowering,

4) In your clinical practice, what percentage of patients with dyslipidemia have been prescribed with Rosuvastatin in combination with other lipid-lowering agents?

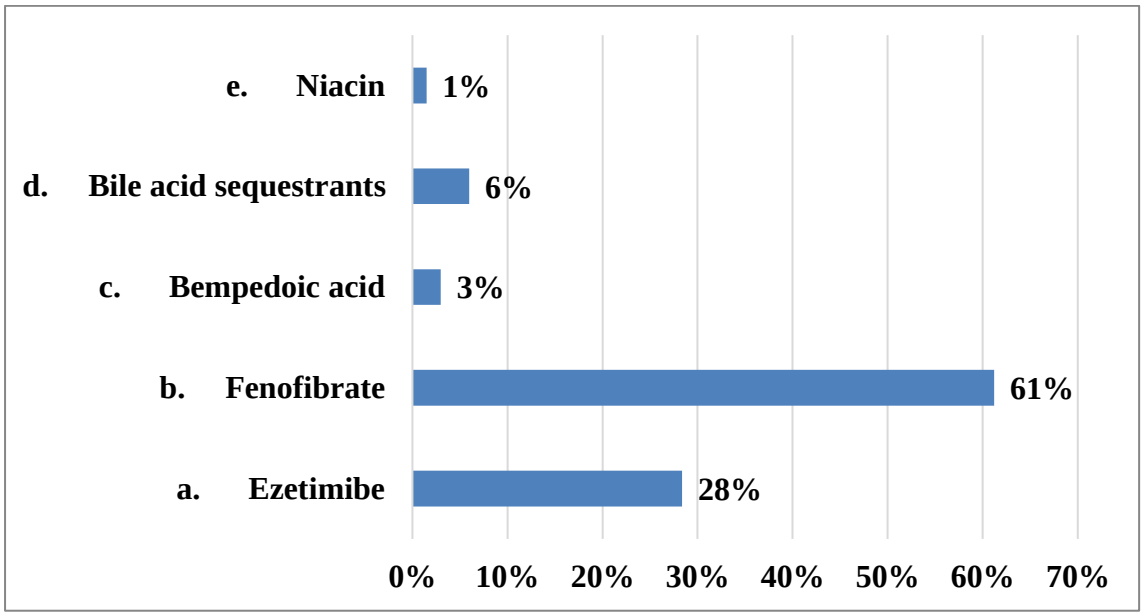
a. <25%
b. 25 to 50%
c. >50 to 75%
d. >75%



In the clinical practice of 51% of doctors, 25 to 50% of patients with dyslipidemia have been prescribed with Rosuvastatin in combination with other lipid-lowering agents.

5) Which lipid-lowering agent is most commonly prescribed by you along with Rosuvastatin?

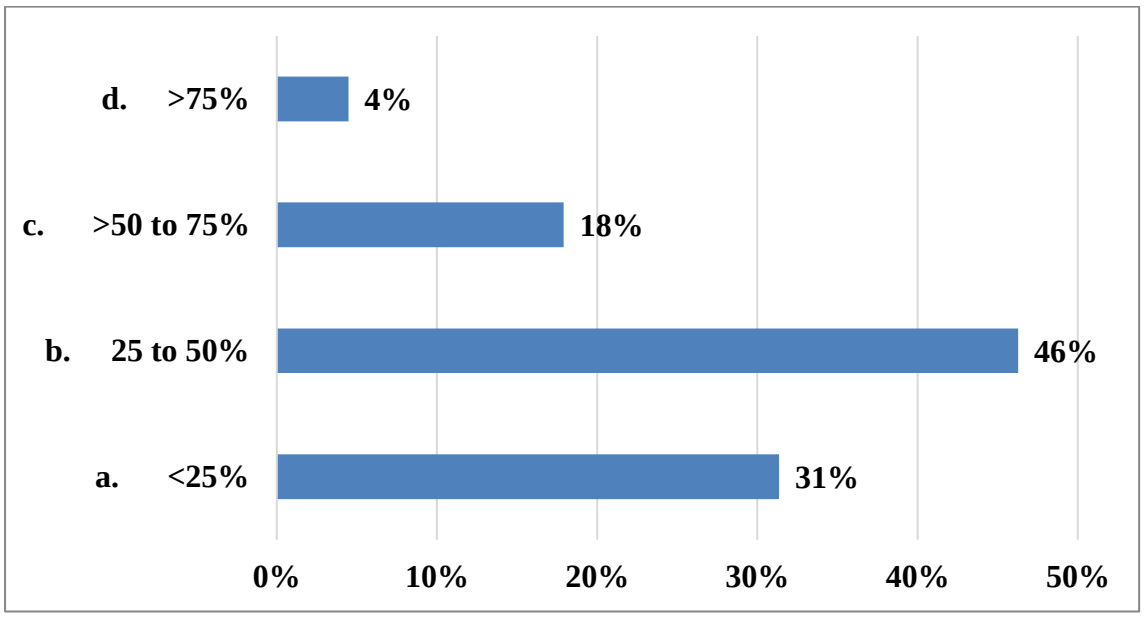
a. Ezetimibe
b. Fenofibrate
c. Bempedoic acid
d. Bile acid sequestrants
e. Niacin



As per 61% of doctors, Fenofibrate is most commonly prescribed by them along with Rosuvastatin.

6) Approx. what % of your patients have been prescribed with the Rosuvastatin and Ezetimibe combination therapy?

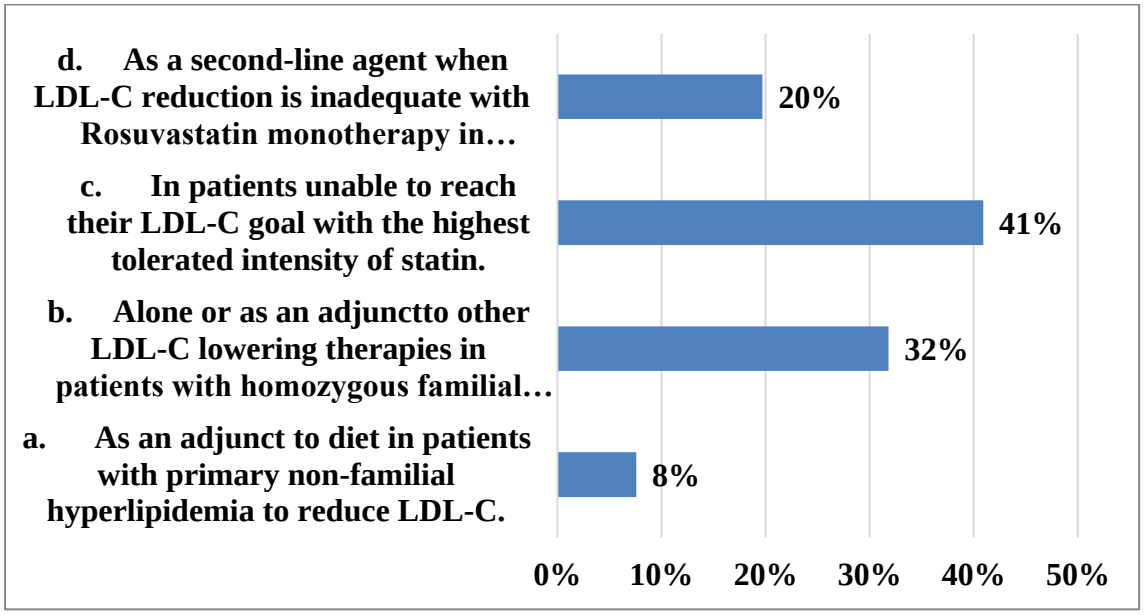
a. <25%
b. 25 to 50%
c. >50 to 75%
d. >75%



According to 46% of doctors, 25 to 50% of their patients have been prescribed with the Rosuvastatin and Ezetimibe combination therapy.

7) As per your opinion, which is the most preferred place of Rosuvastatin Plus Ezetimibe combination therapy?

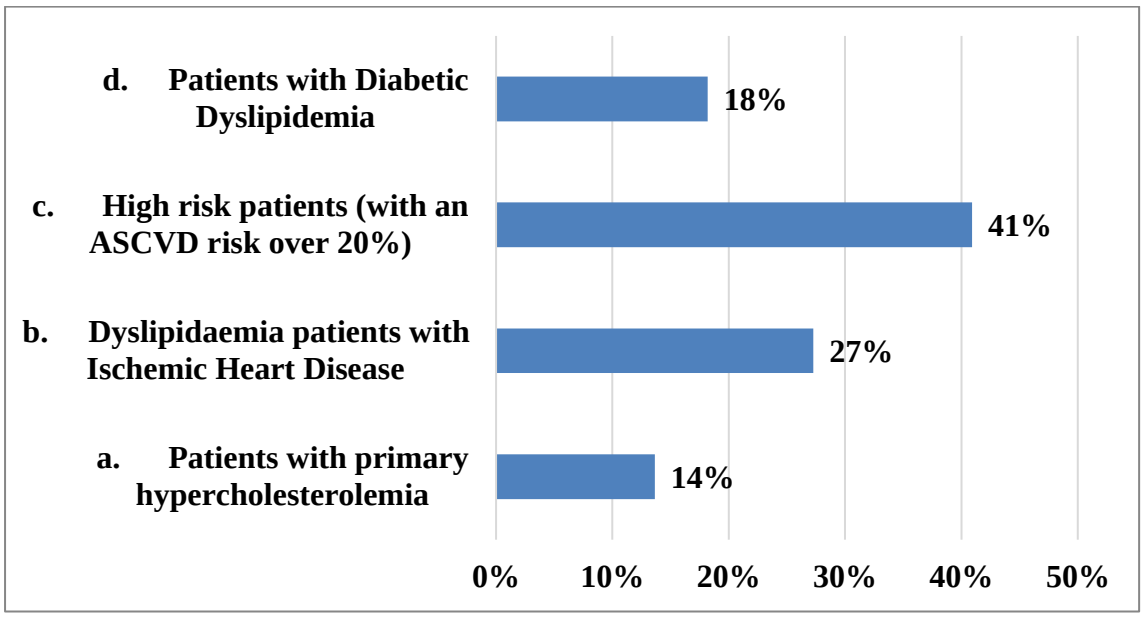
a. As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce LDL-C.
b. Alone or as an adjunctto other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia to reduce LDL-C.
c. In patients unable to reach their LDL-C goal with the highest tolerated intensity of statin.
d. As a second-line agent when LDL-C reduction is inadequate with Rosuvastatin monotherapy in patients with primary hypercholesterolemia.



In the opinion of 41% of doctors, the most preferred place of Rosuvastatin Plus Ezetimibe combination therapy is in patients unable to reach their LDL-C goal with the highest tolerated intensity of statin.

8) Which is the most suitable patient profile for Rosuvastatin/Ezetimibe combination therapy?

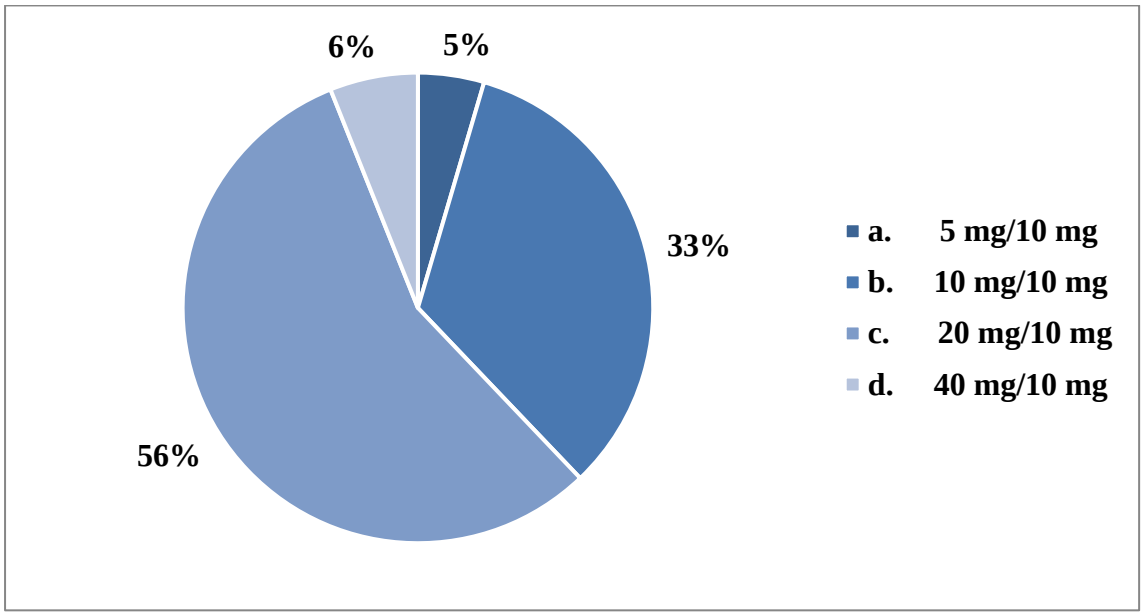
a. Patients with primary hypercholesterolemia
b. Dyslipidaemia patients with Ischemic Heart Disease
c. High risk patients (with an ASCVD risk over 20%)
d. Patients with Diabetic Dyslipidemia



According to 41% of doctors, high risk patients (with an ASCVD risk over 20%) is the most suitable patient profile for Rosuvastatin/Ezetimibe combination therapy.

9) Which is the most commonly prescribed strength of Rosuvastatin/Ezetimibe FDC by you?

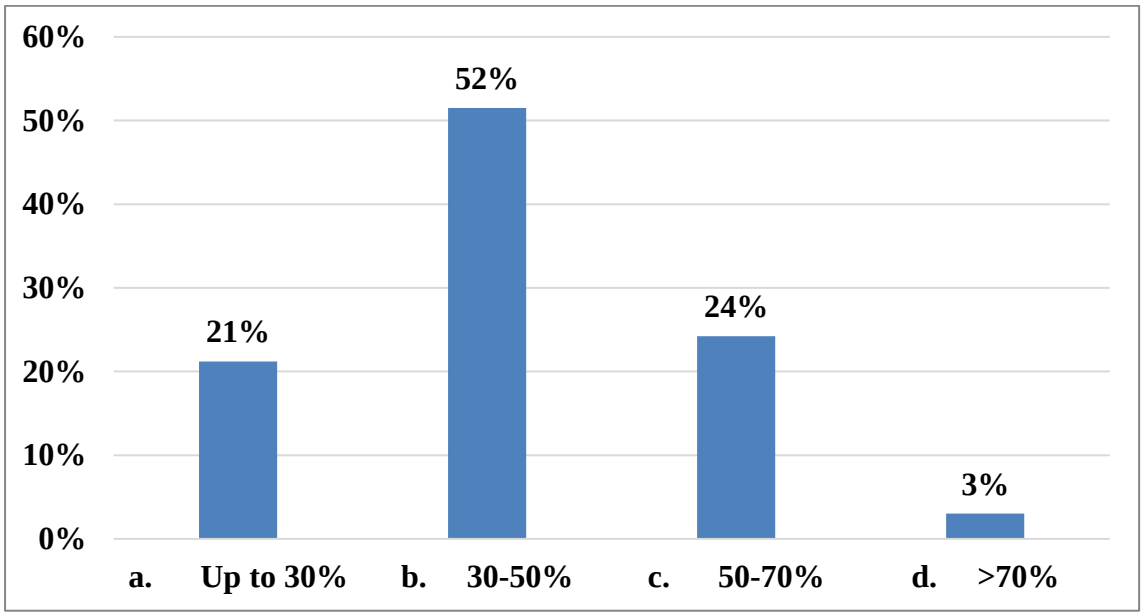
a. 5 mg/10 mg
b. 10 mg/10 mg
c. 20 mg/10 mg
d. 40 mg/10 mg



According to 56% of doctors, the most commonly prescribed strength of Rosuvastatin/Ezetimibe FDC by them is 20 mg/10 mg.

10) How much is the average LDL-C reduction observed with the usage of Rosuvastatin and Ezetimibe combination therapy in your practice?

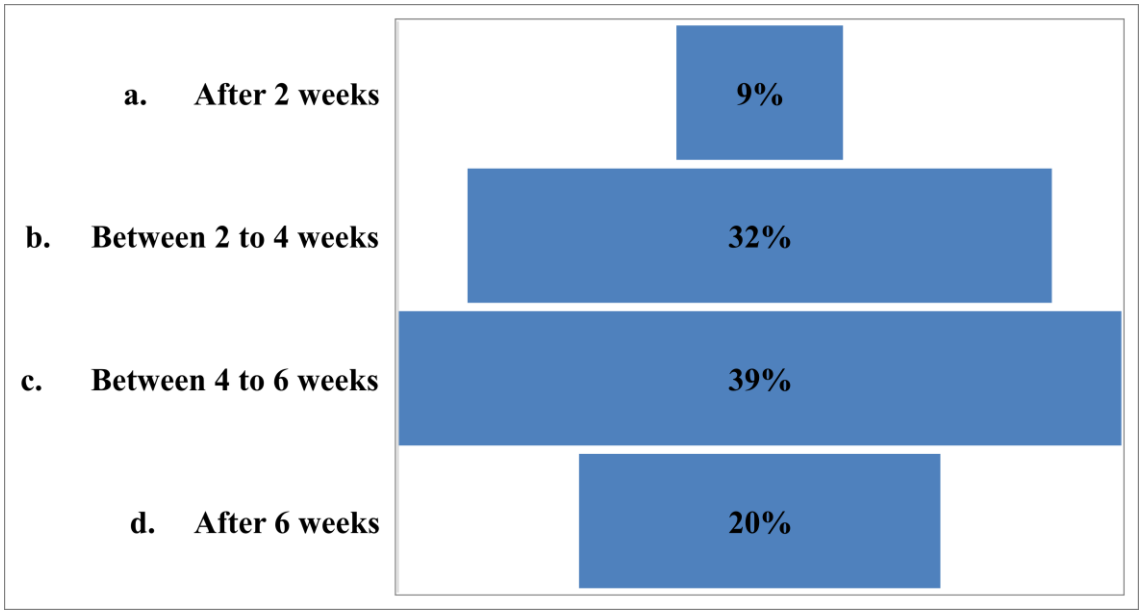
a. Up to 30%
b. 30-50%
c. 50-70%
d. >70%



As per 52% of doctors, the average LDL-C reduction observed with the usage of Rosuvastatin and Ezetimibe combination therapy in their practice is 30-50%.

11) At what frequency, the LDL-C levels are assessed during treatment with Rosuvastatin and Ezetimibe combination therapy?

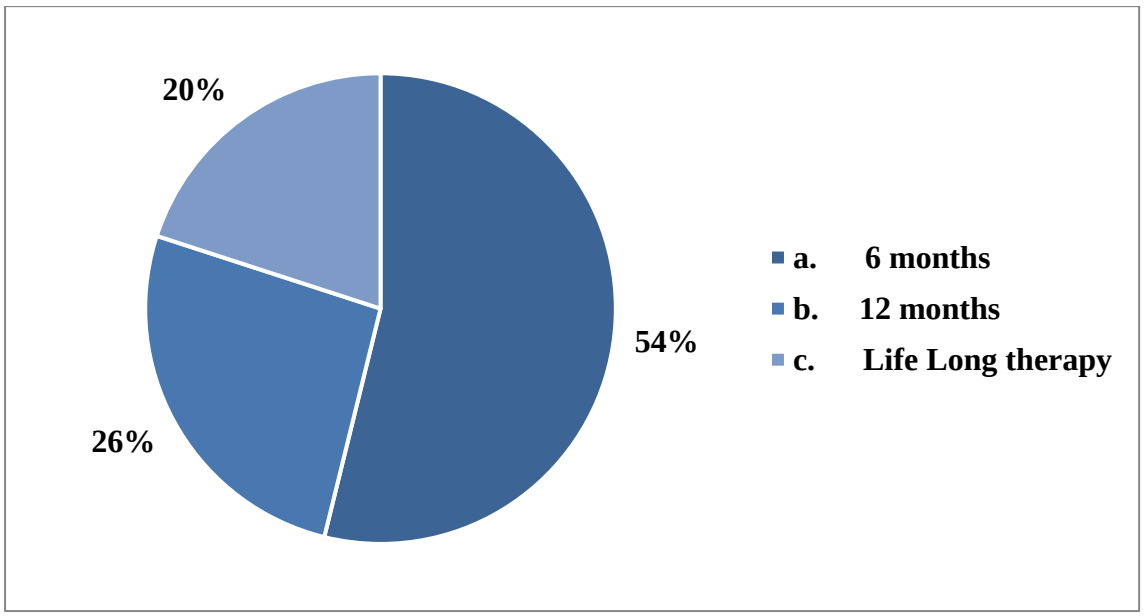
a. After 2 weeks
b. Between 2 to 4 weeks
c. Between 4 to 6 weeks
d. After 6 weeks



According to 39% of doctors, the LDL-C levels are assessed during treatment with Rosuvastatin and Ezetimibe combination therapy between 4 to 6 weeks.

12) How long do you use Rosuvastatin and Ezetimibe combination in ASCVD patients?

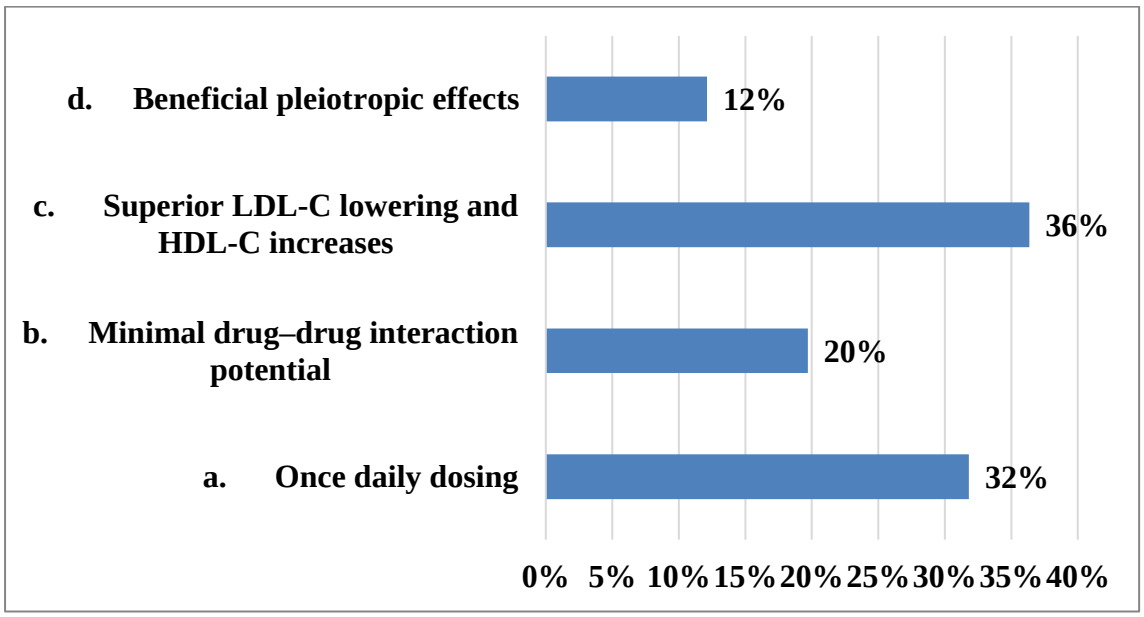
a. 6 months
b. 12 months
c. Life Long therapy



54% of doctors use Rosuvastatin and Ezetimibe combination in ASCVD patients for 6 months.

13) As per your opinion, what is the perceived clinical advantage of the Rosuvastatin and Ezetimibe combination in your practice?

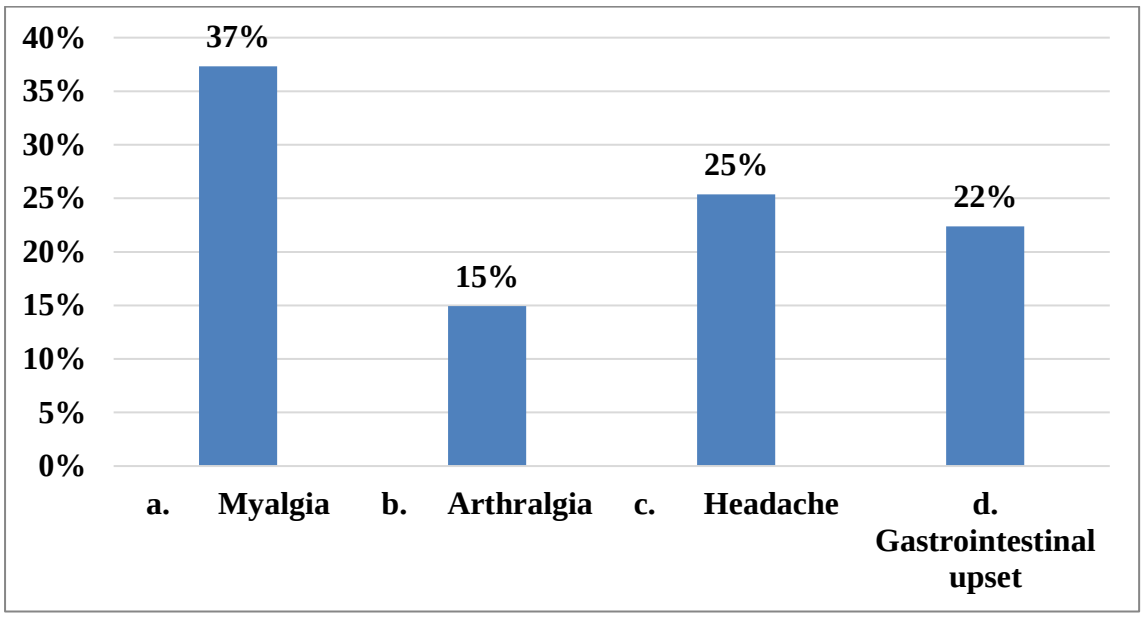
a. Once daily dosing
b. Minimal drug–drug interaction potential
c. Superior LDL-C lowering and HDL-C increases
d. Beneficial pleiotropic effects



As per the opinion of 36% of doctors, the perceived clinical advantage of the Rosuvastatin and Ezetimibe combination in their practice is superior LDL-C lowering and HDL-C increases.

14) Which is the most common adverse effect observed with Rosuvastatin/Ezetimibe combination in your clinical practice?

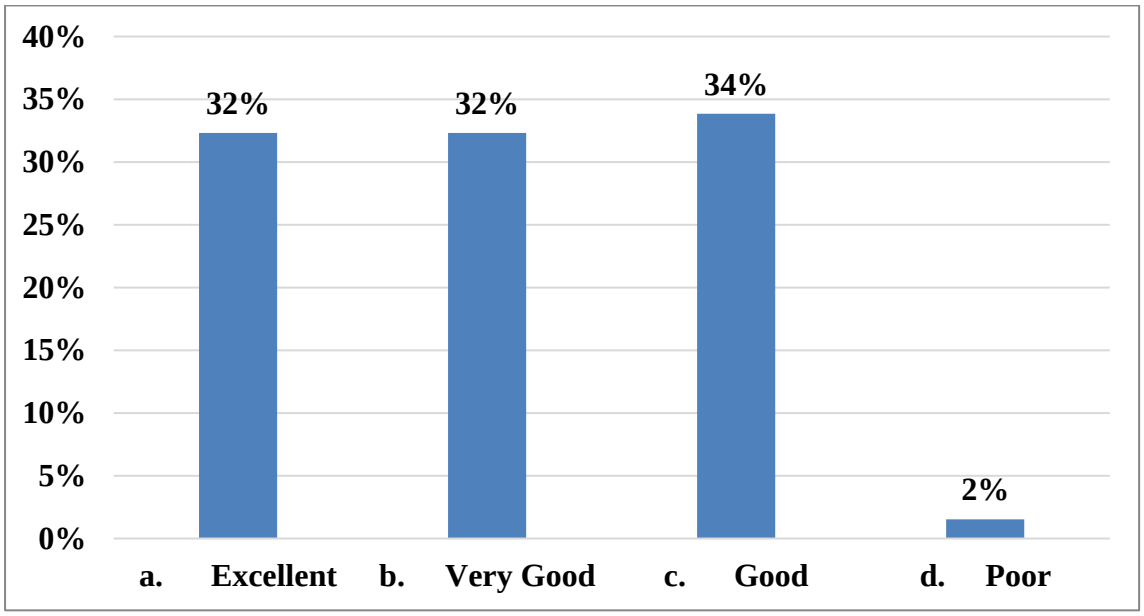
a. Myalgia
b. Arthralgia
c. Headache
d. Gastrointestinal upset



According to 37% of doctors, the most common adverse effect observed with Rosuvastatin/Ezetimibe combination in their clinical practice is myalgia.

15) In your opinion, how is the long-term safety profile of Rosuvastatin and Ezetimibe combination therapy?

a. Excellent
b. Very Good
c. Good
d. Poor



In the opinion f 34% of doctors, the long-term safety profile of Rosuvastatin and Ezetimibe combination therapy is good.

Summary

- According to majority of doctors, 66%, the percentage of patients usually diagnosed with atherosclerotic cardiovascular disease (ASCVD) in their clinical practice is 25-50%.
- According to majority of doctors, 90%, their preferred statin is Rosuvastatin.
- In the opinion of 57% of doctors, the advantage(s) of Rosuvastatin in comparison to other statins is higher LDL-C lowering,
- In the clinical practice of 51% of doctors, 25 to 50% of patients with dyslipidemia have been prescribed with Rosuvastatin in combination with other lipid-lowering agents.
- As per 61% of doctors, Fenofibrate is most commonly prescribed by them along with Rosuvastatin.
- According to 46% of doctors, 25 to 50% of their patients have been prescribed with the Rosuvastatin and Ezetimibe combination therapy.
- In the opinion of 41% of doctors, the most preferred place of Rosuvastatin Plus Ezetimibe combination therapy is in patients unable to reach their LDL-C goal with the highest tolerated intensity of statin.
- According to 41% of doctors, high risk patients (with an ASCVD risk over 20%) is the most suitable patient profile for Rosuvastatin/Ezetimibe combination therapy.
- According to 56% of doctors, the most commonly prescribed strength of Rosuvastatin/Ezetimibe FDC by them is 20 mg/10 mg.
- As per 52% of doctors, the average LDL-C reduction observed with the usage of Rosuvastatin and Ezetimibe combination therapy in their practice is 30-50%.
- According to 39% of doctors, the LDL-C levels are assessed during treatment with Rosuvastatin and Ezetimibe combination therapy between 4 to 6 weeks.
- 54% of doctors use Rosuvastatin and Ezetimibe combination in ASCVD patients for 6 months.
- As per the opinion of 36% of doctors, the perceived clinical advantage of the Rosuvastatin and Ezetimibe combination in their practice is superior LDL-C lowering and HDL-C increases.
- According to 37% of doctors, the most common adverse effect observed with Rosuvastatin/Ezetimibe combination in their clinical practice is myalgia.
- In the opinion f 34% of doctors, the long-term safety profile of Rosuvastatin and Ezetimibe combination therapy is good.

Consultant Opinion

Market Opportunities:

Recognize the high prevalence of ASCVD and dyslipidemia in clinical practice as an opportunity for pharmaceutical companies to develop and market combination therapies like Rosuvastatin and Ezetimibe, addressing the need for effective lipid-lowering options.

Value for Healthcare Professionals:

Provide healthcare professionals with updated guidelines and educational resources on the management of dyslipidemia and ASCVD, highlighting the role of combination therapies like Rosuvastatin and Ezetimibe in achieving LDL-C goals.

Adverse Effect Management:

Focus on educating healthcare providers about the potential adverse effects of Rosuvastatin and Ezetimibe combination therapy, such as myalgia, and provide guidance on monitoring and managing these side effects effectively.

Withdrawal Management:

Develop strategies and resources to support healthcare providers in optimizing treatment adherence and persistence with Rosuvastatin and Ezetimibe combination therapy, ensuring long-term effectiveness and patient satisfaction.

Market Positioning:

Position Rosuvastatin and Ezetimibe combination therapy as a preferred treatment option in high-risk patients with ASCVD who are unable to achieve LDL-C goals with statin monotherapy, emphasizing its superior LDL-C lowering efficacy and potential for improving cardiovascular outcomes.

Personalized Treatment Decisions:

Encourage healthcare providers to individualize treatment decisions based on patient characteristics, including ASCVD risk profile, comorbidities, and treatment tolerance, to optimize the benefits of Rosuvastatin and Ezetimibe combination therapy.

Improving Patient Outcomes:

Promote patient education and counseling about the importance of adherence to Rosuvastatin and Ezetimibe combination therapy, emphasizing its role in reducing cardiovascular risk and improving long-term health outcomes.

Innovation and Research:

Support ongoing research and clinical trials to further evaluate the efficacy, safety, and long-term benefits of Rosuvastatin and Ezetimibe combination therapy, providing additional evidence to guide treatment decisions and improve patient care.

By addressing these aspects, both healthcare professionals and pharmaceutical companies can collaborate to optimize the use of Rosuvastatin and Ezetimibe combination therapy in patients with ASCVD and dyslipidemia, leading to better cardiovascular outcomes and overall patient care.

NOTES

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