Positioning of Rosuvastatin 40mg + Bempedoic Acid 180mg in ASCVD Patients

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Background and Objective of the Survey

The combination of rosuvastatin 40mg and bempedoic acid 180mg holds a strategic position in the management of atherosclerotic cardiovascular disease (ASCVD) patients, particularly those with elevated LDL cholesterol levels despite maximally tolerated statin therapy or those who are intolerant to statins.

Rosuvastatin, a potent statin, effectively lowers LDL cholesterol levels by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. It has demonstrated cardiovascular benefits in reducing major adverse cardiovascular events (MACE) and mortality rates in patients with ASCVD.

Bempedoic acid, a first-in-class ATP citrate lyase inhibitor, complements the action of statins by inhibiting cholesterol synthesis at an earlier step in the pathway. This dual mechanism of action leads to additional LDL cholesterol reduction beyond what can be achieved with statin therapy alone, making it an attractive option for patients with persistent hypercholesterolemia.

The combination of rosuvastatin and bempedoic acid offers a convenient once-daily oral therapy that can significantly reduce LDL cholesterol levels, improve lipid profiles, and potentially reduce the risk of cardiovascular events in ASCVD patients. This combination is particularly beneficial for patients who require additional LDL cholesterol lowering beyond what can be achieved with statin monotherapy or who are unable to tolerate high-dose statins due to side effects.

The objective of the survey is:

To evaluate the positioning of Rosuvastatin 40 mg + Bempedoic acid 180 mg in ASCVD patients

Methodology of the Survey

A survey was conducted to evaluate the positioning of Rosuvastatin 40mg + Bempedoic acid 180mg in ASCVD patients. 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
- Role of Rosuvastatin in Primary and Secondary Prevention[2]
- Rosuvastatin in High CV Risk Patients
- Bempedoic acid
- Monotherapy in patients with statin intolerance
- Combination therapy with statins
- Phase III trials
- FDA-approved indication
- Current guideline recommendations

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]

LDL cholesterol (LDL-C) plays a key role in the development of atherosclerotic plaques and, subsequently, cardiovascular events. Lowering LDL-C levels reduces the risk of atherosclerotic cardiovascular disease proportionally to the absolute reduction in LDL-C.' Statins remain the cornerstone of lipid-lowering therapy.' Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for *de novo* cholesterol synthesis, resulting in up-regulation of hepatic LDL receptors and a reduction in circulating LDL-C.

Many patients with hypercholesterolaemia remain above guideline-recommended LDL-C thresholds despite treatment with maximally tolerated statin doses with or without the addition of non-statin agents (e.g. ezetimibe) and thus remain at elevated risk for cardiovascular disease. Adverse effects (primarily muscle symptoms) can limit the maximally tolerated statin dose to low-dose therapy, or may make patients not adhere to their treatment or stop their statin therapy completely. Therefore, there is a high unmet need for additional non-statin therapies to help patients achieve lipid-lowering goals.

Bempedoic acid, an oral, once-daily medication that lowers LDL-C in patients with hypercholesterolaemia, is approved for use in the United States and Europe with varying indications. Bempedoic acid is a competitive inhibitor of ATP citrate lyase, an enzyme two steps upstream of HMG-CoA reductase (the target of statins), and lowers LDL-C by decreasing cholesterol synthesis and up-regulating LDL receptors, thus impacting LDL metabolism through this well-established pathway

Rosuvastatin

Pharmacology and Pharmacodynamics[2]

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.

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[2]

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.

Role of Rosuvastatin in Primary and Secondary Prevention[2]

There have been a number of clinical studies evaluating rosuvastatin on its own, against placebo and against other statins in various clinical settings.

Rosuvastatin in primary prevention

Clinical studies have demonstrated the benefits of statins in primary prevention. This is believed principally to be secondary to reduction in LDL-C, high sensitivity C-reactive protein (hsCRP) and elevation of HDL-C though other effects are recognised. The Cholesterol Treatment Trialists' Collaborators (CTT) meta-analysis established that a 1 mmol/L reduction in LDL cholesterol results in a 20% reduction in cardiovascular risk. The benefit of statins in low risk populations was demonstrated in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study where reduction of cholesterol using pravastatin 10 mg reduced cardiovascular events by 33%.

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) marked an important juncture in primary cardiovascular disease prevention with statins. The participants had a mean Framingham risk score at baseline of 11.6% and would otherwise not have qualified for lipid lowering therapy. They were apparently healthy individuals with normal levels of LDL-C (<3.4 mmol/L) and increased hsCRP (>2 mg/L). The hsCRP threshold value of 2 mg/L is the approximate median hsCRP value after 30 days of statin therapy. It originated from secondary prevention trials and in particular the PROVE-IT-TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis In Myocardial Infarction) and A to Z (Aggrastat to Zocor) which showed that achieving this level of hsCRP was associated with improved cardiovascular outcomes. JUPITER was a randomised, double blind, placebo-matched, multicentre trial conducted at 1315 sites in 26 countries. 17,802 participants received either 20 mg of rosuvastatin, or matched placebo, and were followed up every six months. 12 months into the study, the rosuvastatin group had a 50% lower median LDL-C, 37% lower median hsCRP and 17% lower median triglyceride level ($P < 0.001$ for all three comparisons) which persisted to study completion. The observed increase in HDL-C was transient. Results showed that rosuvastatin was associated with a significant reduction in first major cardiovascular events (HR 0.56; 95% CI, 0.46 to 0.69; $P < 0.00001$) which was the primary endpoint. Reductions were further seen in the incidence of the individual components of the trial end point including myocardial infarction (54%), stroke (48%), arterial revascularisation (47%), unstable angina and death from cardiovascular causes. This is important as up to 50% of all myocardial infarctions and strokes occur in patients with LDL cholesterol concentrations that are considered normal. The benefits were largely similar for men and women, and were observed in all subgroups

including age, ethnicity, region and cardiovascular risk score. Previously, there has been limited data on statin benefits in women, black and Hispanic patients.

Since the results of JUPITER were initially published, several secondary subgroup analyses of the study population have been reported. Participants with a 10 year low baseline risk (<5%) benefited less than those with risk >5%. Participants with a 10 year intermediate baseline risk by Framingham (5%–20%) experienced incremental absolute risk reductions that were proportional to their global risk. In a different subgroup analysis, participants at high global risk (10 year Framingham score >20%) showed no additional benefit for the combined endpoint of myocardial infarction, stroke and cardiovascular death (HR 0.50; 95% CI, 0.27 to 0.93) when compared with subjects who had an intermediate Framingham risk score.

Another series of sub analyses have looked at lipid profiles and hsCRP particularly in relation to residual cardiovascular risk. In all of them, participants who achieved low concentrations of hsCRP in addition to low values of the lipid parameters of interest had the best outcome. When hsCRP is included in enrolment of primary prevention, rosuvastatin produced greater benefit when compared with other statins.

These results compare favourably with other primary prevention trials using different statins. WOSCOPS (West of Scotland Coronary Prevention Study) showed that pravastatin 40 mg in men with moderate hypercholesterolaemia reduced incidence of myocardial infarction and cardiovascular death by 31%. Similarly, AFCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) demonstrated that lovastatin 20–40 mg daily reduced risk of first major coronary event by 37% in men and women with average LDL-C and below average HDL-C when compared with placebo. In the ASCOT lipid lowering arm, atorvastatin 10 mg reduced the incidence of myocardial infarction, stroke and cardiovascular death by 36% compared to placebo.

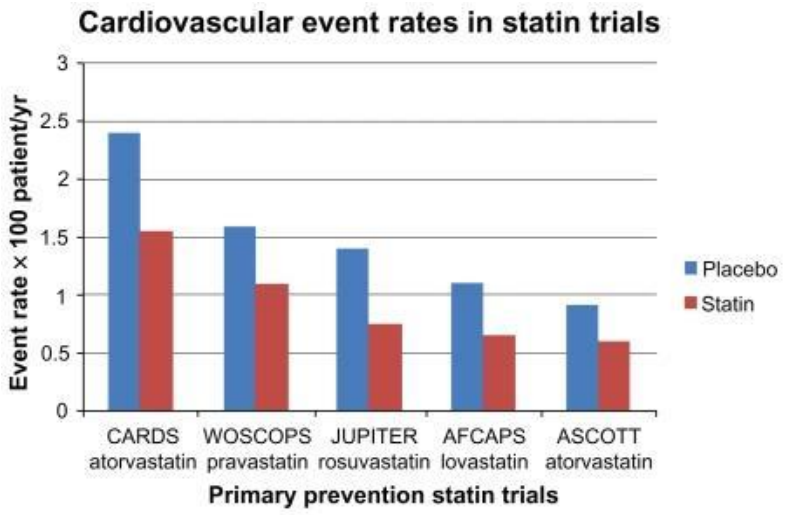

Figure 3. CHD event rate in primary prevention trials.

Rosuvastatin in secondary prevention

The beneficial effects of statin therapy in patients with ischaemic heart disease are well known. The 4S study showed that simvastatin 20 mg to 40 mg daily significantly reduced major coronary events, coronary death and overall mortality in patients post-MI or those with ischaemic heart disease. In the LIPID study (Long-term Intervention with Pravastatin in Ischaemic Disease), pravastatin 40 mg reduced cardiovascular events and mortality in patients with history of myocardial infarction or unstable angina with different baseline lipid profiles. Other studies have also established the benefits of treatment after myocardial infarction.

a) Stable coronary heart disease (CHD)/Arrest and regression of atherosclerosis

The TNT trial comparing atorvastatin 80 mg with atorvastatin 10 mg, investigated whether intensive treatment to achieve LDL-C <1.81 mmol/L was associated with better outcomes. Mean LDL-C of 2 mmol/L was realised with intensive treatment. A relative risk reduction of 22% was achieved for the primary outcome which was the occurrence of a first major cardiovascular event. The IDEAL study (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) compared the effect of atorvastatin 80 mg and simvastatin 20 mg on cardiovascular outcomes. There were significant reductions in non-fatal acute myocardial infarction and in other secondary composite endpoints, with no difference in cardiovascular or all-cause mortality. Statistical significance was not demonstrated for the prespecified primary clinical outcome which was time to first occurrence of major coronary event. In as much as there have been no clinical outcome data for secondary prevention with rosuvastatin, a number of studies have compared their effect on surrogate markers and achievement of treatment goals. The STELLAR study (Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses) showed that at different doses, rosuvastatin reduced total cholesterol better than other statins, and triglycerides better than simvastatin and pravastatin. Additionally a larger proportion of rosuvastatin patients achieved National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C targets when compared with atorvastatin. PULSAR (Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin) showed that in hypercholesterolaemic patients with vascular occlusive disease rosuvastatin 10 mg was better than atorvastatin 20 mg at reducing LDL-C, improving other lipid parameters and enabling achievement of US and European treatment goals.

Several studies have suggested that reduction in plaque volume is linked to the clinical outcome. ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden) investigated the impact of high dose rosuvastatin on regression of atherosclerosis. The results showed that rosuvastatin 40 mg produced significant reduction in LDL-C (53% from baseline; $P < 0.001$), increase in HDL-C (14.7% from baseline; $P < 0.001$) and regression

of atheroma volume in the most diseased coronary arteries in 78% of participants. A median reduction of 6.8% in atheroma volume was recorded by IVUS (intravascular ultrasound). It must be noted that the study was non-comparative and open label. Other studies including ORION (Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation) and METEOR (Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin) demonstrated that rosuvastatin 40 mg achieved a 49% LDL-C reduction and slowed progression of atherosclerosis as assessed by carotid intima-media thickness (CIMT) but did not result in regression of CIMT. The lack of plaque regression may have occurred because low risk patients with minimal subclinical carotid atherosclerosis were used in the study. The COSMOS (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) study found that rosuvastatin achieved significant reduction of coronary plaque volume with good safety in stable Japanese CHD patients. The recently concluded SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) study compared maximal doses of rosuvastatin and atorvastatin on coronary atheroma. It reported that although rosuvastatin achieved lower LDL-C and higher HDL-C, both agents produced similar percentage reduction in atheroma volume.

b) Acute coronary syndrome (ACS)

The NCEP ATP III guidelines recommend that intensive statin treatment should be used in patients admitted with acute coronary syndrome. The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have recommended LDL-C levels of 1.8 mmol/L as the optimal target for very high risk patients (established CHD, type I diabetes with end organ damage, moderate to severe chronic kidney disease (CKD) or a SCORE level >10%). Several studies have provided evidence of the additional LDL-C lowering achieved by intensive statin therapy.

The PROVE-IT study found that intensive treatment with atorvastatin 80 mg was better than pravastatin 40 mg at preventing death and major cardiovascular events following ACS. The A to Z study which compared 40 mg and 80 mg of simvastatin demonstrated a benefit which did not reach statistical significance, while the MIRACL (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering) study showed that early intensive treatment with atorvastatin 80 mg after ACS led to a 16% reduction in death, acute MI, unstable angina and cardiac arrest, compared with placebo. Meta-analyses of intensive statin trials have also shown that intensive treatment provides benefit above lower intensity treatment in prevention of myocardial infarction and strokes in patients with known coronary disease irrespective of the baseline LDL-C. The CENTAURUS (Comparison of the Effects Noted in The ApoB:ApoA-1 ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome) study showed that 20 mg rosuvastatin produced similar changes in ApoB:ApoA-1 ratio at 3 months

when compared with atorvastatin 80 mg. Previous studies have identified ApoB:ApoA-1 ratio as an important predictor of myocardial infarction. In the same study rosuvastatin 20 mg achieved similar LDL-C reduction as atorvastatin 80 mg. This study therefore showed that rosuvastatin 20 mg is as effective as atorvastatin 80 mg in intensive statin therapy. In SPACEROCKET (Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets Trial), a larger proportion of patients on rosuvastatin 10 mg achieved ESC, ACC and American Heart Association (AHA) optimal LDL-C target of less than 1.81 mmol/L when compared to those on simvastatin 40 mg. A crucial observation of this study was that in both treatment arms, most patients did not achieve these targets, highlighting the importance of intensive statin therapy to meet these goals. The superior lipid lowering effect of rosuvastatin makes it a good candidate for intensive lipid lowering.

Rosuvastatin in High CV Risk Patients

Rosuvastatin in patients with HF[3]

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[3]

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 atrial fibrillation patients[3]

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.

Bempedoic acid[4]

Mechanism of action

Bempedoic acid was developed under the name ETC-1002 and its chemical name is 8-hydroxy-2,2,14,14-tetramethylpentadecaned-ioic acid. It is a prodrug that, once activated, decreases LDL-C by inhibition of adenosine triphosphate-citrate lyase (ACL) in the liver. By inhibiting ACL, an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzme A reductase, bempedoic acid decreases the conversion of mitochondrial-derived citrate to cytosolic ACL, creating less substrate for cholesterol and fatty acid synthesis., This ultimately decreases liver cholesterol synthesis and decreases serum LDL-C levels by upregulating LDL receptors., Additionally, bempedoic acid activates adenosine monophosphate-activated protein kinase, which has been demonstrated in mice models to inhibit acetyl-CoA carboxylase and hydroxymethylglutaryl-CoA reductase, decreasing the synthesis of fatty acids and cholesterol. Bempedoic acid and its active metabolite, , require activation by very long-chain acyl-CoA synthetase I (ACSVL1) to ETC-1002-CoA and -CoA, respectively, in order to exert their therapeutic effects. The enzyme

ACSVL1 is present in the liver but not in skeletal muscle, decreasing the risk for muscle-related adverse effects.

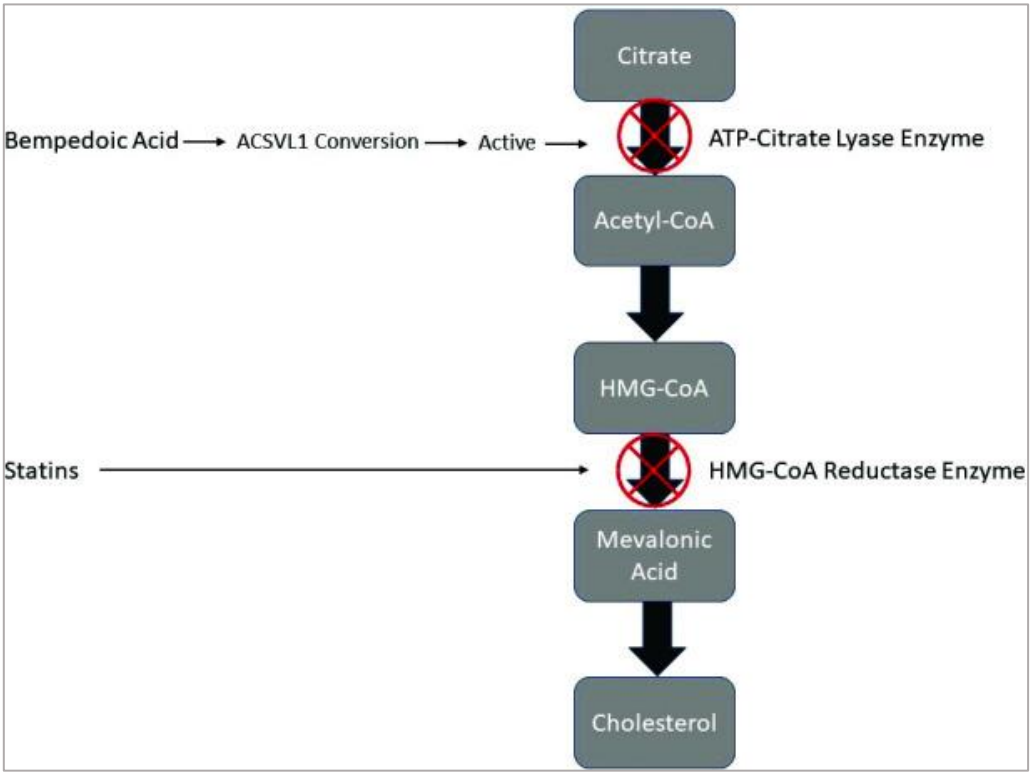

Figure 1. Mechanism of action of cholesterol lowering with bempedoic acid versus statins.

Phase I trials

Following completion of *in vitro* and *in vivo* animal studies, bempedoic acid was studied in humans in phase I and II clinical trials. Two phase Ia studies evaluated the effect of a single dose of bempedoic acid in healthy volunteers. In the first phase Ia study, 18 healthy volunteers were given a bempedoic acid dose of 2.5, 10, 45, 125, or 250 mg and pharmacokinetic data were collected. In the second phase Ia study, 6 healthy male volunteers were given a carbon-14 radiolabeled dose of bempedoic acid to evaluate the absorption, metabolism, and excretion of the drug. Two phase Ib multiple ascending dose studies evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of bempedoic acid in patients with mild dyslipidemia (*n*=39) and healthy volunteers (*n*=18), respectively., Mild dyslipidemia in the first study was defined as a fasting LDL-C level of 100–160 mg/dL or fasting triglyceride levels of 100–350 mg/dL, and patients received the drug for either 14 or 28 days. The study of healthy

volunteers demonstrated a mean decrease in LDL-C levels of 36% in the bempedoic acid group compared to a 4% increase in the placebo group (40% placebo-adjusted LDL-C reduction; $p<0.0001$)., The phase I trials demonstrated that there were no adverse effects related to bempedoic acid dosing and bempedoic acid was overall determined to be safe to proceed with phase II trials.

Phase II trials

Phase II clinical trials of bempedoic acid were conducted in patients with dyslipidemia, with or without other common comorbidities, to assess the efficacy and safety of the drug in its intended population. Bempedoic acid was studied both as monotherapy and in combination with other lipid-lowering agents.

Monotherapy

The first phase II study evaluated 177 patients with dyslipidemia, defined as LDL-C levels of 130–220 mg/dL and triglyceride levels of either <150 mg/dL or 150–400 mg/dL, treated with bempedoic acid monotherapy or placebo for 12 weeks. Patients treated with bempedoic acid, 40, 80, or 120 mg, daily experienced a reduction in LDL-C levels of 18%, 25%, and 27%, respectively, compared with a 2% reduction in the placebo group ($p<0.0001$). Levels of atherogenic biomarkers apolipoprotein B (apo B), non-high-density lipoprotein C (non-HDL-C), and LDL particle number were significantly reduced in the bempedoic acid-treated patients compared to those who received placebo ($p<0.0001$). There was a trend of reduction in high-sensitivity C-reactive protein (hsCRP) levels in patients treated with bempedoic acid *versus* those treated with placebo (26% *versus* 2%), which was further amplified in patients with elevated hsCRP at baseline (43–64% *versus* 7%).

A second phase II monotherapy study evaluated bempedoic acid specifically in patients with type 2 diabetes. Patients were randomized to placebo or bempedoic acid 80 mg daily with a run-in period of 2 weeks and a subsequent 2-week period of 120 mg daily. Bempedoic acid demonstrated a 43% reduction in LDL-C levels compared to a 4% reduction in the placebo arm at 4 weeks ($p<0.0001$). In patients who had a baseline LDL-C level of >100 mg/dL, 88% of those treated with bempedoic acid achieved an LDL-C level of <100 mg/dL compared to only 4% of those who received placebo ($p<0.0001$). Similar to the previous trial, hsCRP levels

decreased by 41% in the bempedoic acid treatment arm compared to 11% in the placebo treatment arm. A 24-hour continuous glucose monitoring assessment demonstrated a non-significant trend toward improved glycemia in the bempedoic acid group.

Lastly, bempedoic acid monotherapy was evaluated in 143 patients with both dyslipidemia and hypertension. Before study entry, all patients enrolled were taken off their blood pressure-lowering and lipid-lowering medications for a washout period. After 6 weeks, there was a statistically significant lowering of LDL-C compared to placebo, with a respective decrease of 21% *versus* an increase of 3% ($p<0.0001$). Further, levels of hsCRP increased by 20% in the placebo-treated patients compared to a 25% lower level in patients treated with bempedoic acid ($p<0.0001$). There was no change in blood pressure in the bempedoic acid group.

Monotherapy in patients with statin intolerance[4]

Bempedoic acid has been hypothesized to yield little-to-no risk of muscle-related side effects. The rationale for this hypothesis is that bempedoic acid does not get converted to the active form in skeletal muscle by the enzyme ACSVL1, and only gets converted to its active form in the liver. Two phase II trials of patients with dyslipidemia and a history of statin intolerance aimed to explore this. Thompson et al. randomized 56 patients with dyslipidemia and a history of statin intolerance (defined as new myalgia, muscle cramps, muscle aches, or muscle weakness that developed during statin treatment and resolved within 4 weeks of statin discontinuation) to either bempedoic acid or placebo for 8 weeks. Patients in the bempedoic acid group received increasing doses of 60, 120, 180, and 240 mg for 2 weeks each during the course of the study. A reduction in LDL-C levels from baseline to week 8 was the designated primary endpoint. Patients treated with bempedoic acid had lowered LDL-C levels by a mean of 32% compared to 3% in patients treated with placebo ($p<0.0001$). None of the patients treated with bempedoic acid dropped out of the study due to a muscle-related adverse effect. Similar to the previous phase II studies,, hsCRP levels decreased by 42% in the bempedoic acid group compared to no change in the group that received placebo ($p=0.0022$).

Another study by Thompson et al. compared bempedoic acid *versus* ezetimibe *versus* the combination of the two agents in 177 patients with a history of statin intolerance ($n=177$) and in 171 patients without a history of statin intolerance. Statin intolerance was defined as an intolerance to ≥2 statins, with at least one at the lowest therapeutic dose. Patients were stratified 1:1 by history of statin intolerance and then randomized 4:4:4:1 to bempedoic acid 120 mg

daily, bempedoic acid 180 mg daily, ezetimibe 10 mg daily, bempedoic acid 120 mg daily plus ezetimibe 10 mg daily, or bempedoic acid 180 mg daily plus ezetimibe 10 mg daily. In the bempedoic acid monotherapy groups, the reduction in LDL-C levels was 27.5% for 120 mg daily and 30.1% for 180 mg daily (p=0.15) and this reduction was similar in statin-intolerant *versus* statin-tolerant patients. The reduction in LDL-C was 21.2% for the ezetimibe monotherapy group. There were significantly greater LDL-C reductions in the bempedoic acid plus ezetimibe groups (43.1% for the 120 mg daily group and 47.7% for the 180 mg daily group), with the decrease being approximately equal to a sum of each individual drug's LDL-C lowering ability. There was no difference noted in the incidence of adverse effects between bempedoic acid and ezetimibe. More statin-intolerant patients experienced an adverse effect that led to discontinuation (n=7) compared to statin-tolerant patients (n=3). Muscle-related adverse effects were less frequent and caused fewer study discontinuations in the bempedoic acid monotherapy group and were more common in statin-intolerant patients. The authors concluded that bempedoic acid monotherapy (or in combination with ezetimibe) is a safe and efficacious treatment in patients with or without a statin intolerance.

Combination therapy with statins[4]

Bempedoic acid has been studied in two phase II trials where it was added to statin therapy in patients with dyslipidemia. In one 8-week study, bempedoic acid in escalating doses (60 mg daily for 2 weeks, 120 mg daily for 2 weeks, 180 mg daily for 2 weeks, and 240 mg daily for 2 weeks) was added to atorvastatin 10 mg daily and compared against daily placebo added to atorvastatin 10 mg daily. LDL-C levels were lowered by 22% in the bempedoic acid arm and no reduction was seen in the placebo arm (p<0.0001)., In a study by Ballantyne et al., 134 patients with LDL-C levels between 115 and 220 mg/dL while taking atorvastatin ≤20 mg daily, pravastatin ≤40 mg daily, rosuvastatin ≤10 mg daily, or simvastatin ≤20 mg daily were randomized to receive bempedoic acid 120 mg, 180 mg, or placebo daily for 12 weeks. Patients who had bempedoic acid added onto concurrent statin therapy experienced an LDL-C reduction of 17% (120 mg daily) and 24% (180 mg daily) compared to 4% with placebo (p=0.0055 and p<0.0001, respectively). Bempedoic acid also decreased apo B, non-HDL-C, and total cholesterol (TC) levels to a greater extent than placebo (p<0.05). The overall incidence of adverse effects was similar between groups and muscle-related adverse effects were more common in the placebo group (13%) than in either bempedoic acid group (2–5%). The authors

concluded that in patients with elevated LDL-C levels despite statin therapy, bempedoic acid was an efficacious and safe addition to therapy for additional lipid lowering.

Phase III trials[4]

Following successful completion of phase II clinical trials, bempedoic acid was studied in the phase III trial series named 'CLEAR'.

Table 1. Summary of dyslipidemia phase III trials with bempedoic acid.

Trial	Design	Participants	Duration, weeks	Intervention, total daily mg (*n*)	Primary outcome	Secondary outcome
CLEAR HARMONY (2019)	MC, OL	ASCVD and/or HeFH on MTS with LDL-C ≥70 mg/dL	52	BA 180 (1488), P (742)	Number of participants with treatment-related adverse events (78.7% P *versus* 78.5 % BA; *p*=0.91)	Percentage change in LDL-C at 52 weeks (1.6% P *versus* −16.5 % BA; *p*<0.001)
CLEAR WISDOM (2019)	MC, DB, PC	ASCVD and/or HeFH on MTS with LDL-C ≥70 mg/dL	52	BA 180 (522), P (257)	Percentage change in LDL-C at 12 weeks (2.4% P *versus* −15.1 % BA; *p*<0.001)	Percentage change in LDL-C at 24 weeks (2.7% P *versus* −12.1 % BA; *p*<0.001) significant reductions in non-HDL-C,

						TC, Apo B, and hsCRP at 12 weeks
CLEAR SERENITY (2019)	MC, DB, PC	Primary prevention with LDL-C ≥130 mg/dL or HeFH with LDL-C ≥100 mg/dL or ASCVD with a history of statin intolerance	24	BA 180 (234), P (111)	Percentage change in LDL-C at 12 weeks (−1.3% P *versus* −23.6 % BA; p<0.001)	Percentage change in non-HDL-C at 12 weeks (−0.4% P *versus* −19.0 % BA; p<0.001) Percentage change in TC at 12 weeks (−0.6% P *versus* −16.1 % BA; p<0.001) Percentage change in Apo B at 12 weeks (−0.2% P *versus* −15.5 % BA; p<0.001) Percentage change in hsCRP at 12 weeks (2.7% P *versus* −25.4 % BA; p<0.001)

CLEAR TRANQUILITY (2018)	MC, DB, PC	LDL-C ≥100 mg/dL with a history of statin intolerance on stable LLT 12	BA 180 + E 10 (181), P+E 10 (88)	Percentage change in LDL-C at 12 weeks (5.0% P+E *versus* −22.5% BA+E; $p<0.001$)	Percentage change in non-HDL-C at 12 weeks (5.2% P+E *versus* −18.4% BA+E; $p<0.001$) Percentage change in TC at 12 weeks (2.9% P+E *versus* −15.1% BA+E; $p<0.001$) Percentage change in Apo B at 12 weeks (4.7% P+E *versus* −14.6% BA+E; $p<0.001$) Percentage change in hsCRP at 12 weeks (2.1% P+E *versus* −32.5% BA+E; $p<0.001$)

Ballantyne et al., (2020)	MC, DB, PC	ASCVD or HeFH or multiple CV risk factors on MTS	12	BA 180 + E 10 (108), BA 180 (111), E 10 (109), P (55)	Percentage change in LDL-C (1.6% P *versus* −36.2 % BA+E; *p*<0.001), (−23.2% E *versus* −36.2 % BA+E; *p*<0.001), (−17.2% BA *versus* −36.2% BA+E; *p*<0.001)	Percentage change in hsCRP (21.6% P *versus* −35.1 % BA+E; *p*<0.001), (−8.2% E *versus* −35.1 % BA+E; *p*=0.002), (−31.9% BA *versus* −35.1% BA+E; NS)
CLEAR OUTCOMES (anticipated completion 2022)	RC, MC, DB, PC	ASCVD or high CV risk with LDL-C ≥100 mg/dL with a history of statin intolerance	Anticipated 3.75 years	BA 180, P (14,014 enrolled)	First occurrence of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization	Percentage change in LDL-C, non-HDL-C, TC, Apo B, hsCRP

Apo B = apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CLEAR, Cholesterol Lowering via Bempedoic Acid, an ACL-inhibiting Regimen; CV, cardiovascular; DB, double blind; E, ezetimibe; HDL-C, high-density lipoprotein-cholesterol; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; MC, multicenter; MTS, maximum tolerated statin; NS, not significant; OL, open label; PC, placebo controlled; R, randomized; TC, total cholesterol.

CLEAR HARMONY

The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) HARMONY trial was a phase III trial of bempedoic acid that assessed its safety and efficacy over 1 year. The randomized, placebo-controlled trial enrolled 2230 patients with ASCVD, heterozygous familial hypercholesterolemia (HeFH), or both. The mean age was 66.1 years with a baseline mean LDL-C level of 103.2 mg/dL. Patients were randomized to bempedoic acid 180 mg daily or placebo with two bempedoic acid participants for every one placebo participant. Patients had to be receiving maximally tolerated statin therapy with an LDL-C level of at least 70 mg/dL. The primary endpoint assessed the number of participants with treatment-related adverse events. No difference in the incidence of adverse events was seen between the bempedoic acid group (78.5%, 1167/1487) and the placebo group (78.7%, 584/742) (p=0.91). The secondary endpoint of change in LDL-C at 12 weeks demonstrated a reduction in LDL-C levels by 19.2 mg/dL in the bempedoic acid arm and lowered LDL-C levels by 16.5% more than placebo (p<0.001). Additional secondary endpoints of non-HDL-C, TC, and apo B demonstrated statistically significant improvements compared to placebo. Similar rates of serious adverse events occurred in bempedoic acid and placebo groups (14.5 and 14.0%, respectively). There was a slightly higher rate of discontinuation in the bempedoic acid group (10.9%) compared to that in the placebo group (7.1%). Of note, there was a small, but statistically significant increase in uric acid in the bempedoic acid group compared to placebo. Overall, the positive safety and LDL-C efficacy findings of CLEAR HARMONY led to the 2020 FDA approval of bempedoic acid in addition to statin therapy to further lower LDL-C in patients with HeFH or established ASCVD.

CLEAR WISDOM

The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) WISDOM trial was a phase III trial of bempedoic acid that assessed its efficacy over 1 year. The randomized, double-blind, placebo-controlled trial enrolled 1049 patients with ASCVD, HeFH, or both. The mean age was 64.3 years with a baseline mean LDL-C level of 120.4 mg/dL. Patients were randomized to bempedoic acid 180 mg daily or placebo with two bempedoic acid participants for every placebo participant. Patients had to be receiving maximally tolerated statin therapy with an LDL-C of at least 70 mg/dL. A reduction in LDL-C levels at 12 weeks was the primary endpoint. The bempedoic acid treatment arm

demonstrated a 15.1% reduction in LDL-C levels *versus* a 2.4% reduction with placebo ($p<0.001$). The secondary endpoints of non-HDL-C (−13.0%; $p<0.001$), TC (−11.2%; $p<0.001$), apo B (−13.0%; $p<0.001$), and hsCRP (−8.7%, $p=0.04$) levels demonstrated statistically significant improvements compared to placebo. Common adverse events included hyperuricemia (4.2% bempedoic acid *versus* 1.9% placebo), nasopharyngitis (5.2% bempedoic acid *versus* 5.1% placebo), and urinary tract infections (5.0% bempedoic acid *versus* 1.9% placebo). Overall, the findings of CLEAR WISDOM aligned with those of CLEAR HARMONY, demonstrating the LDL-C-lowering ability of bempedoic acid in a high CV risk population.

CLEAR SERENITY

The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) SERENITY trial was a phase III trial of bempedoic acid that assessed its efficacy and safety over 24 weeks. The double-blind, placebo-controlled trial enrolled 345 patients with hypercholesterolemia and a history of intolerance to at least two statins with one at the lowest available dose. Both primary and secondary prevention patients were enrolled. Primary prevention patients needed to have an LDL-C level of ≥130 mg/dL. Patients with HeFH or ASCVD needed to have an LDL-C level of ≥100 mg/dL to be enrolled. The mean age was 65.2 years with a baseline mean LDL-C level of 157.6 mg/dL and 93% of patients had a history of statin-associated muscle symptoms. As in the previous CLEAR trials, patients were randomized to bempedoic acid 180 mg daily or placebo with double the number of patients enrolled in the bempedoic acid arm compared to the placebo arm. The primary endpoint was percent change in LDL-C levels from baseline at 12 weeks. The bempedoic acid treatment arm demonstrated a 23.6% reduction in LDL-C levels *versus* a 1.3% reduction in the placebo treatment arm ($p<0.001$). The additional secondary endpoints of non-HDL-C (−18.6%; $p<0.001$), TC (−15.5%; $p<0.001$), apo B (−15.3%; $p<0.001$), and hsCRP (−28.1%, $p<0.001$) levels demonstrated statistically significant improvements compared to placebo. Myalgia was the most common muscle-related adverse event and occurred in 4.7% of patients treated with bempedoic acid compared to 7.2% in patients treated with placebo. The findings of CLEAR SERENITY demonstrated that bempedoic acid could be considered a safe and effective LDL-C-lowering therapy for patients with a history of statin intolerance.

CLEAR TRANQUILITY

The Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) TRANQUILITY trial was a phase III trial of bempedoic acid plus ezetimibe that assessed its efficacy and safety over 24 weeks. The multicenter, randomized, double-blind, placebo-controlled trial enrolled 269 patients with a history of statin intolerance and an LDL-C level of ≥100 mg/dL on stable lipid-lowering therapy. The mean age was 63.8 years with a baseline LDL-C level of 127.6 mg/dL and 25% had established ASCVD. All patients received a 4-week run-in with ezetimibe 10 mg daily and were then randomized to bempedoic acid 180 mg daily or placebo. Percent change in LDL-C from baseline at 12 weeks was the primary efficacy endpoint. The bempedoic acid treatment arm demonstrated a 23.5% reduction in LDL-C levels *versus* a 5.0% increase in the placebo treatment arm ($p<0.001$). The additional secondary endpoints of non-HDL-C (−23.6%; $p<0.001$), TC (−18.0%; $p<0.001$), apo B (−19.3%; $p<0.001$), and hsCRP (−34.5%, $p<0.001$) levels demonstrated statistically significant improvements compared to placebo. Muscle-related treatment-emergent adverse events occurred in 3.3% of patients treated with bempedoic acid and in 3.4% of those treated with placebo. The findings of CLEAR TRANQUILITY additionally support the fact that bempedoic acid can be safely used in patients with a history of statin intolerance who need LDL-C lowering.

Ballantyne CM, et al

Ballantyne et al. conducted a phase III trial of bempedoic acid plus ezetimibe that assessed their efficacy and safety over a 24-week trial. The multicenter, double-blind, placebo-controlled trial enrolled 301 patients with established ASCVD, HeFH, or multiple CV risk factors. The mean age was 64.3 years with most patients having a baseline LDL-C level of >130 mg/dL and 62.5% having established ASCVD and/or HeFH. All patients were randomized and received either bempedoic acid 180 mg daily and ezetimibe 10 mg daily (fixed dose combination), bempedoic acid 180 mg daily, ezetimibe 10 mg daily, or placebo. Percent change in LDL-C levels from baseline at 12 weeks was the primary efficacy endpoint. The bempedoic acid and ezetimibe treatment arm demonstrated a 36.2% reduction in LDL-C levels *versus* a 17.2% reduction in the bempedoic acid arm ($p<0.001$) *versus* a 23.2% reduction in the ezetimibe arm ($p<0.001$) *versus* a 1.0% increase in the placebo treatment arm ($p<0.001$). There was a 35.1% reduction in the secondary endpoint of hsCRP in the bempedoic acid and

ezetimibe treatment arm compared to a reduction of 31.9% in the bempedoic acid arm (non-significant) compared to a reduction of 8.2% in the ezetimibe arm (p=0.002) compared to a 21.6% increase in the placebo treatment arm (p<0.001). Treatment-related adverse events were more common in the bempedoic acid plus ezetimibe (62.4%) and the bempedoic acid (65.9%) arms than in the ezetimibe (54.7%) or placebo (43.9%) arms. When assessing muscle-related adverse events, there was no difference between arms and the incidence was within 7–8%. Overall, the findings from this study support the LDL-C-lowering ability of the combination with bempedoic acid plus ezetimibe and did not elucidate any safety issues with this combination.

FDA-approved indication[4]

The US Food and Drug Administration (FDA) approved bempedoic acid in February 2020, for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C. The FDA-approved dose combination with maximally tolerated statin therapy is 180 mg administered orally once daily. Following the approval of bempedoic acid by just a few days was the combination product of bempedoic acid and ezetimibe as a single tablet. The combination product was approved by the FDA for the same indication as bempedoic acid.

Current guideline recommendations[4]

No recommendations for the use of bempedoic acid are available for any of the major cholesterol guidelines from AHA/ACC, the National Lipid Association, or the European Society of Cardiology. It is anticipated that, with the recent FDA approval of bempedoic acid, there will be future recommendations for the role of bempedoic acid in managing dyslipidemia. Guideline recommendations should continue to be followed, within which the only non-statin therapy recommendations at this time are for the addition of ezetimibe and/or PCSK9 inhibitors to maximally tolerated statin therapy in patients with established ASCVD and/or FH considered high risk or very high risk. It is likely that future recommendations for the role of bempedoic acid will include recommendations for patients with statin intolerance.

References:

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4. Marrs JC, Anderson SL. Bempedoic acid for the treatment of dyslipidemia. *Drugs Context*. 2020;9:2020-6-5.

Survey Form

1) In your clinical practice, how many patients on an average do you see with ASCVD in a month?

a. <5
b. 5-10
c. 10-15
d. >15

2) Which is your preferred statin in your patients?

a. Rosuvastatin
b. Atorvastatin
c. Simvastatin

3) In your opinion, what do you consider as the advantage of Rosuvastatin in comparison to other statins?

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

4) Which patients in your practice require additional LDL-c reduction?

a. Patients with existing ASCVD
b. Heterozygous familial Hypercholesterolemia
c. Patients with diabetes and elevated LDL-c
d. Any other

5) What is the most common Rosuvastatin dose that you prescribe in your patients?

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

6) What percent of your patients with ASCVD do you prefer initiating high intensity statin?

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

7) In which patient profiles do you prefer high intensity statins, in your clinical practise?

a. Existing clinical ASCVD
b. Those with LDL-C levels of 190 mg/dl or more
c. Diabetic patients aged 40-75 years with LDL-C levels ≥70 mg/dL
d. Any other

8) What percent of your patients achieve LDL-c levels after treatment with high intensity statins?

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

9) Which is your preferred non-statin agent that you prescribe for patients with ASCVD and uncontrolled LDL-c levels?

a. Bempedoic Acid
b. Ezetimibe
c. Fenofibrate

10) In your opinion, what are the benefits of using Bempedoic acid as an add-on therapy?

a. BA is a prodrug and gets activated only in liver and not muscle, hence less risk of myopathy
b. Better LDL-c reduction
c. BA is not associated with increased incidence of new onset diabetes or worsening glycemic control in diabetic patients.
d. Any other

11) In your clinical practise, have you used Rosuvastatin in combination with Bempedoic acid?

a. Yes
b. No

12) What percent reduction of LDL-c have you seen with High intensity Rosuvastatin and Bempedoic acid combination in your patients with ASCVD?

a. <40%
b. 40-60%
c. 60-70%
d. >70%

13) In which patient profile do you think would the combination of Rosuvastatin and Bempedoic Acid be preferred?

a. Intolerance to high intensity statin
b. Patients requiring a LDL-c reduction of 65-75%
c. Patients with ASCVD and Heterozygous familial hypercholesterolemia
d. All of the above

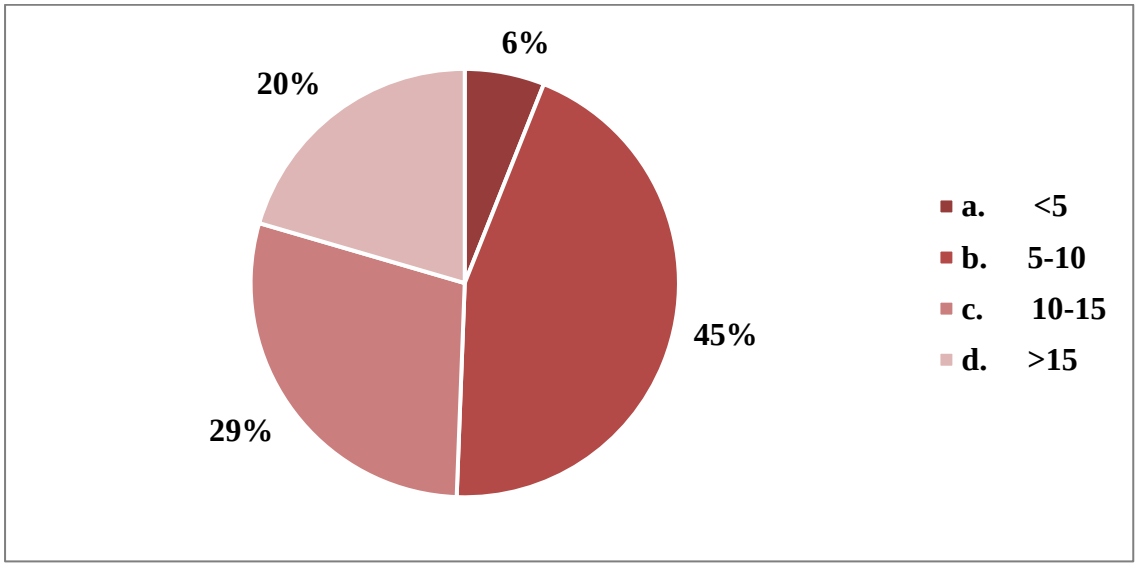
14) In your opinion what is your experience observed with Rosuvastatin 40mg and Bempedoic acid tolerability?

a. Well tolerated
b. Occasional Side effects
c. Frequent Side effects

Survey Findings

1) In your clinical practice, how many patients on an average do you see with ASCVD in a month?

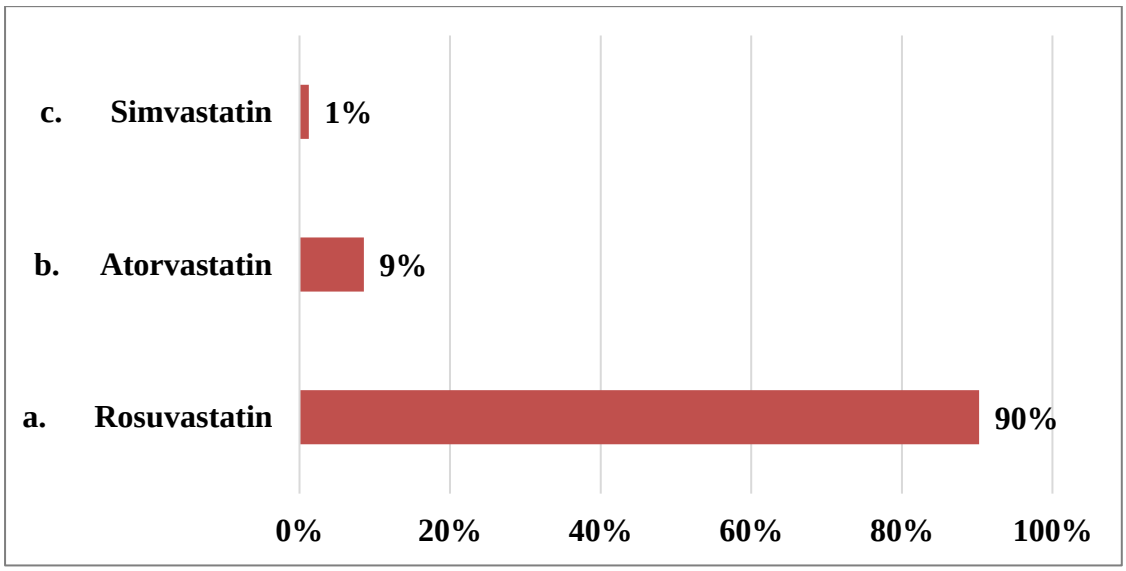
a. <5
b. 5-10
c. 10-15
d. >15



According to 45% of doctors, on an average they see 5 – 10 patients with ASCVD in a month.

2) Which is your preferred statin in your patients?

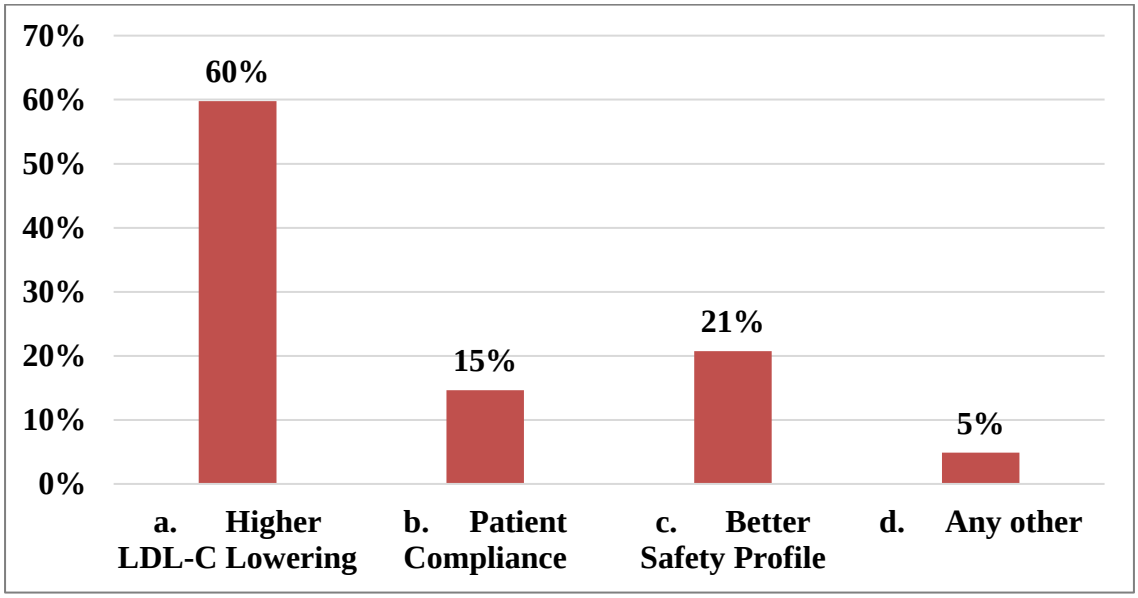
a. Rosuvastatin
b. Atorvastatin
c. Simvastatin



As per majority of doctors, 90%, their preferred statin in their patients is Rosuvastatin.

3) In your opinion, what do you consider as the advantage of Rosuvastatin in comparison to other statins?

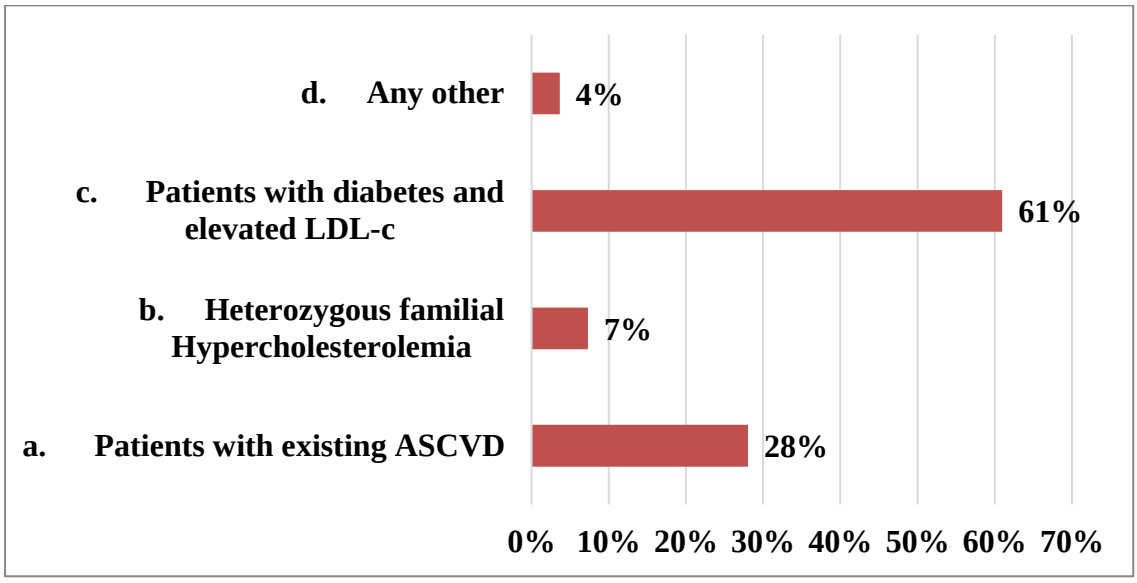
a. Higher LDL-C Lowering
b. Patient Compliance
c. Better Safety Profile
d. Any other



According to 60% of doctors, they consider Higher LDL-C Lowering as the advantage of Rosuvastatin in comparison to other statins.

4) Which patients in your practice require additional LDL-c reduction?

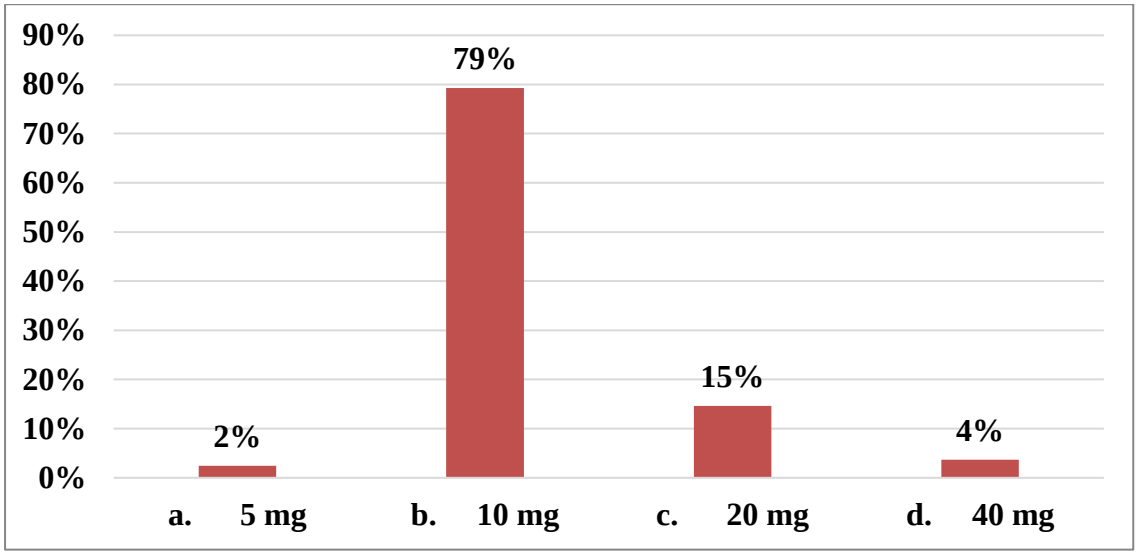
a. Patients with existing ASCVD
b. Heterozygous familial Hypercholesterolemia
c. Patients with diabetes and elevated LDL-c
d. Any other



As per 61% of doctors, patients with diabetes and elevated LDL-c require additional LDL-c reduction.

5) What is the most common Rosuvastatin dose that you prescribe in your patients?

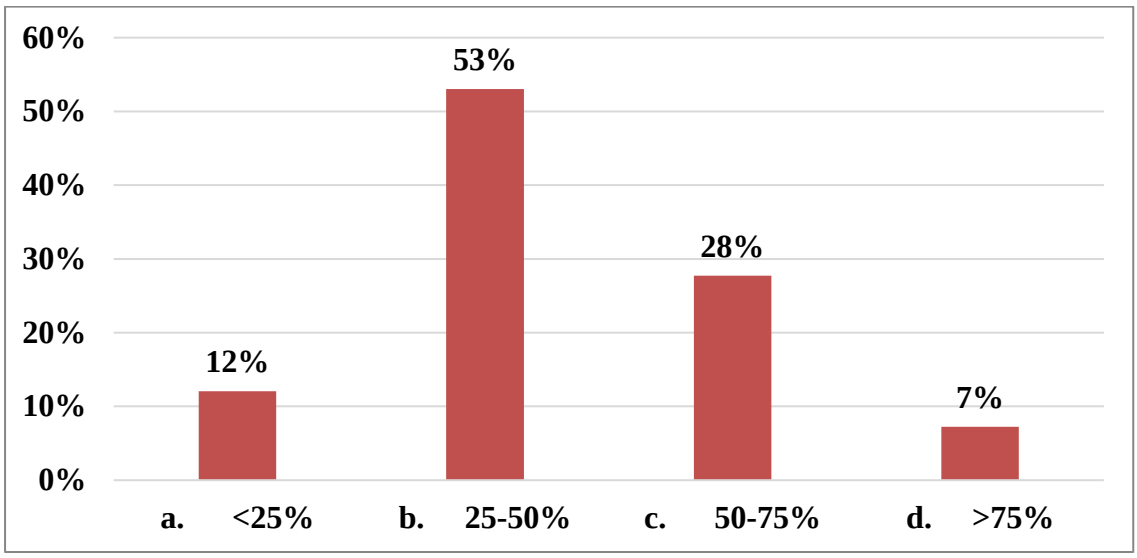
a. 5 mg
b. 10 mg
c. 20 mg
d. 40 mg



As per majority of doctors, 79%, the most common Rosuvastatin dose that they prescribe in your patients is 10mg.

6) What percent of your patients with ASCVD do you prefer initiating high intensity statin?

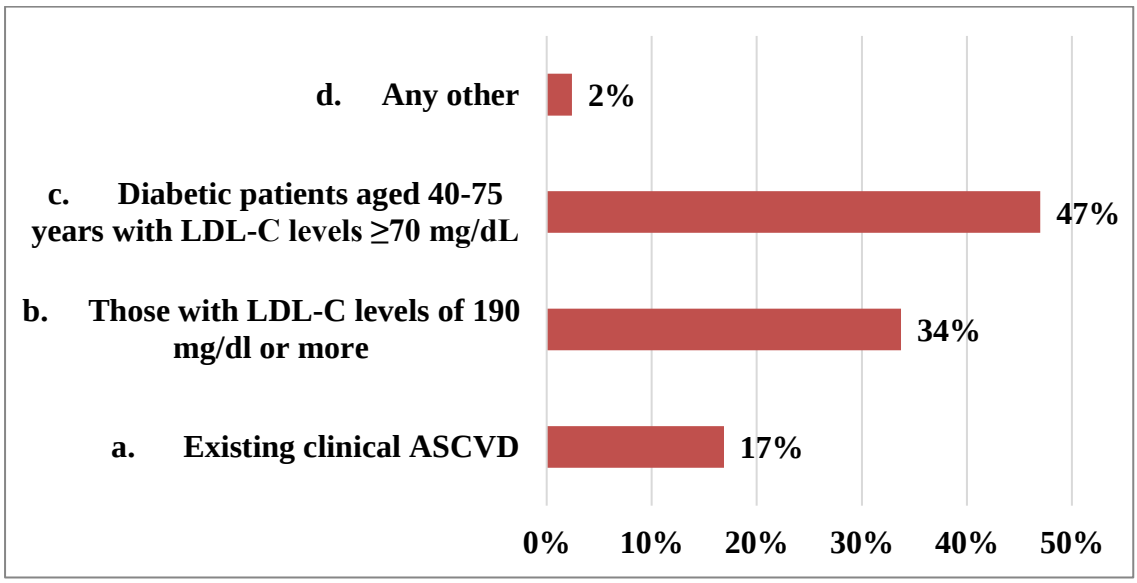
a. <25%
b. 25-50%
c. 50-75%
d. >75%



According to 53% of doctors, they prefer initiating high intensity statin for 25-50% of their patients with ASCVD.

7) In which patient profiles do you prefer high intensity statins, in your clinical practise?

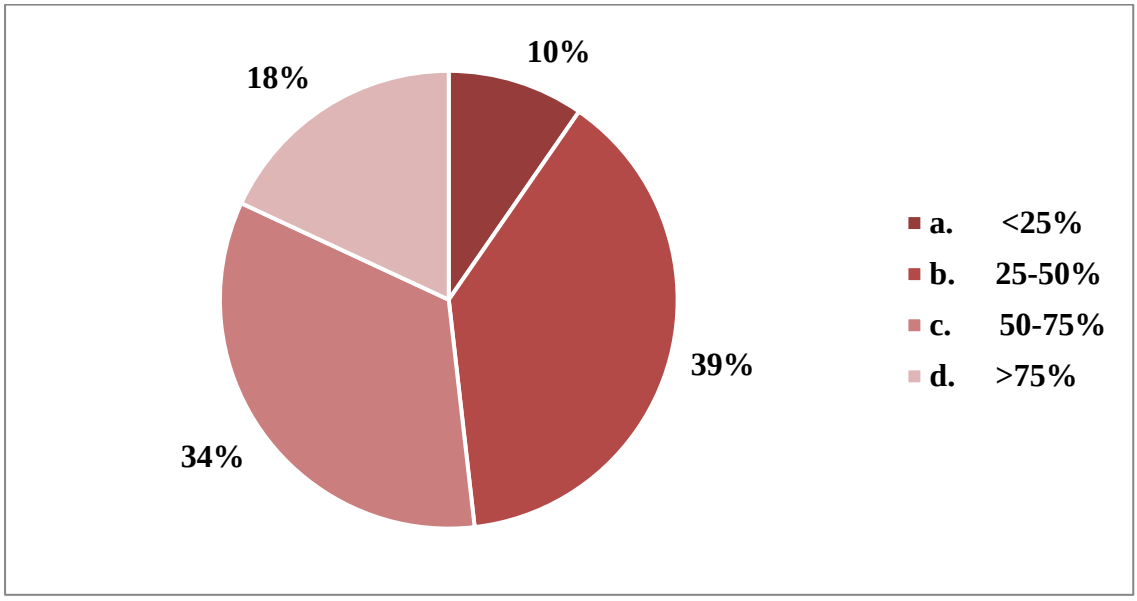
a. Existing clinical ASCVD
b. Those with LDL-C levels of 190 mg/dl or more
c. Diabetic patients aged 40-75 years with LDL-C levels ≥70 mg/dL
d. Any other



According to 47% of doctors, they prefer high intensity statins in diabetic patients aged 40-75 years with LDL-C levels ≥70 mg/dL

8) What percent of your patients achieve LDL-c levels after treatment with high intensity statins?

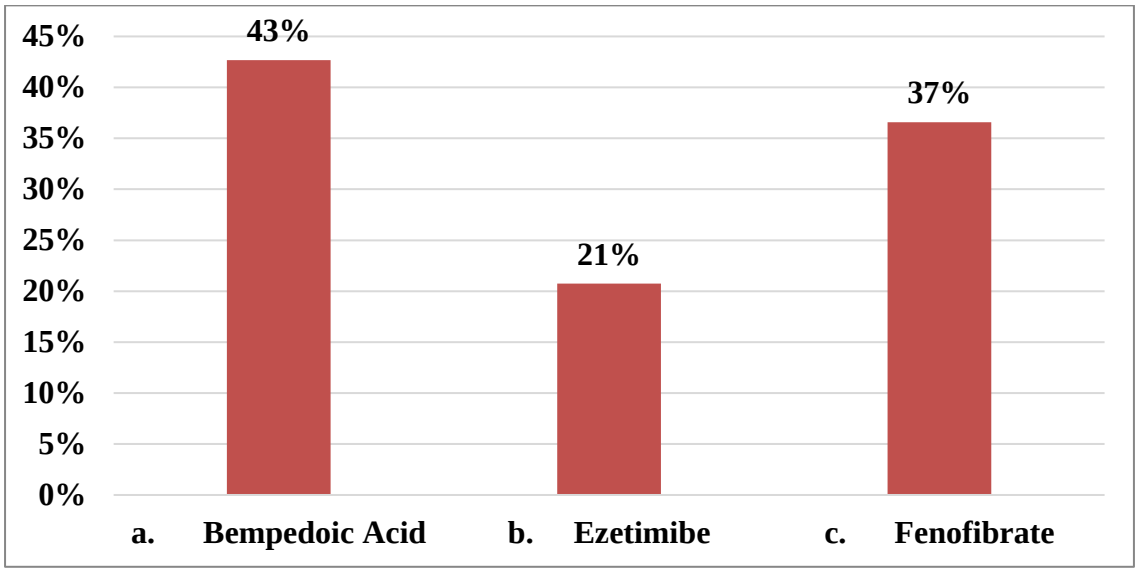
a. <25%
b. 25-50%
c. 50-75%
d. >75%



As per 39% of doctors, 25-50% of their patients achieve LDL-c levels after treatment with high intensity statins.

9) Which is your preferred non-statin agent that you prescribe for patients with ASCVD and uncontrolled LDL-c levels?

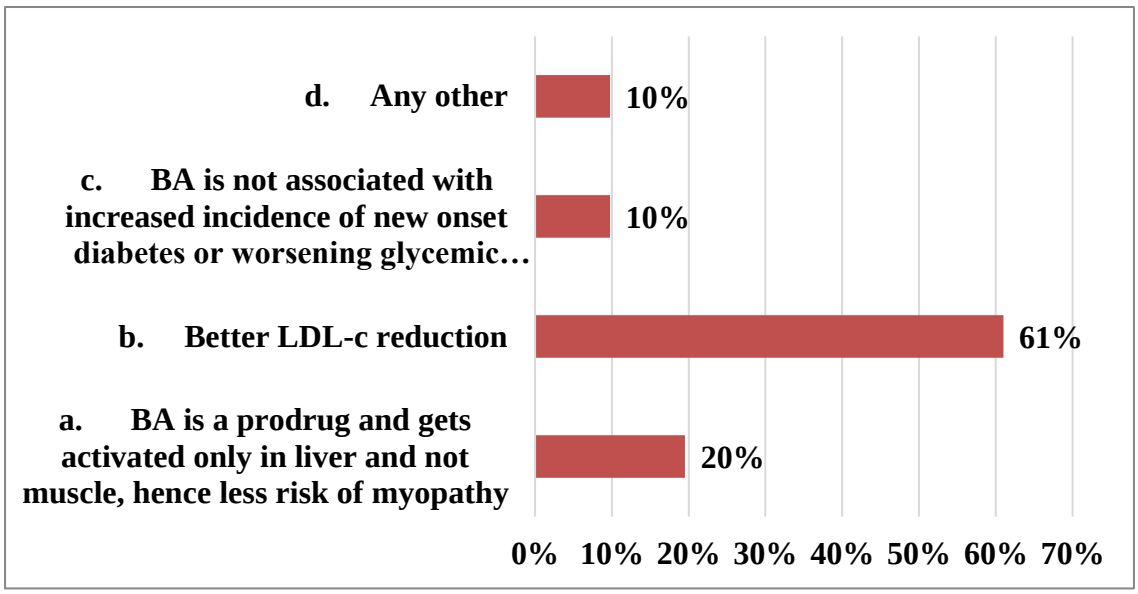
a. Bempedoic Acid
b. Ezetimibe
c. Fenofibrate



According to 43% of doctors, their preferred non-statin agent that they prescribe for patients with ASCVD and uncontrolled LDL-c levels is bempedoic acid.

10) In your opinion, what are the benefits of using Bempedoic acid as an add-on therapy?

a. BA is a prodrug and gets activated only in liver and not muscle, hence less risk of myopathy
b. Better LDL-c reduction
c. BA is not associated with increased incidence of new onset diabetes or worsening glycemic control in diabetic patients.
d. Any other

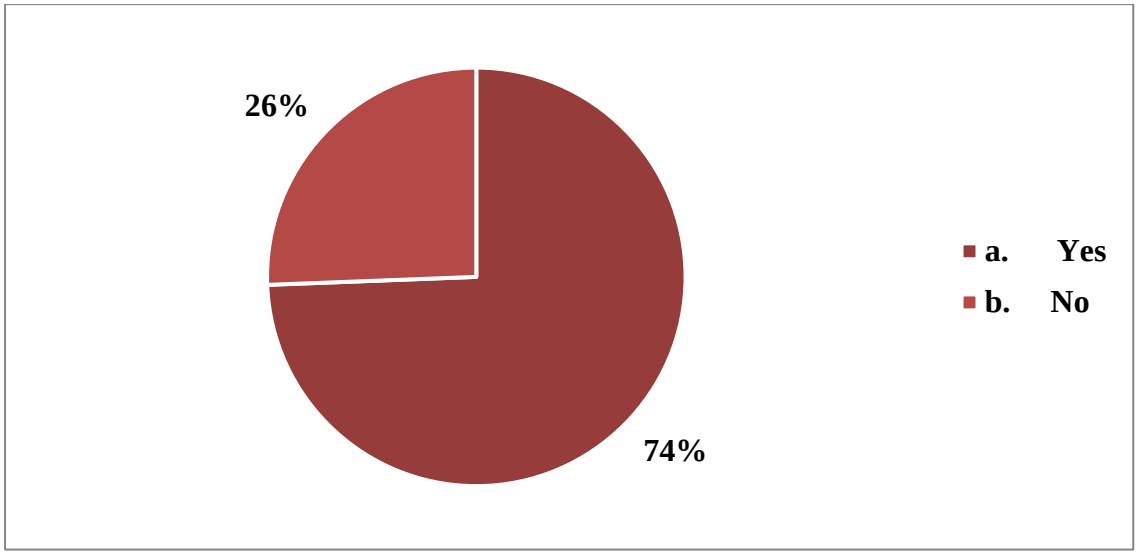


As per majority of doctors, 61%, the benefits of using Bempedoic acid as an add-on therapy is better LDL-c reduction.

11) In your clinical practise, have you used Rosuvastatin in combination with Bempedoic acid?

a. Yes

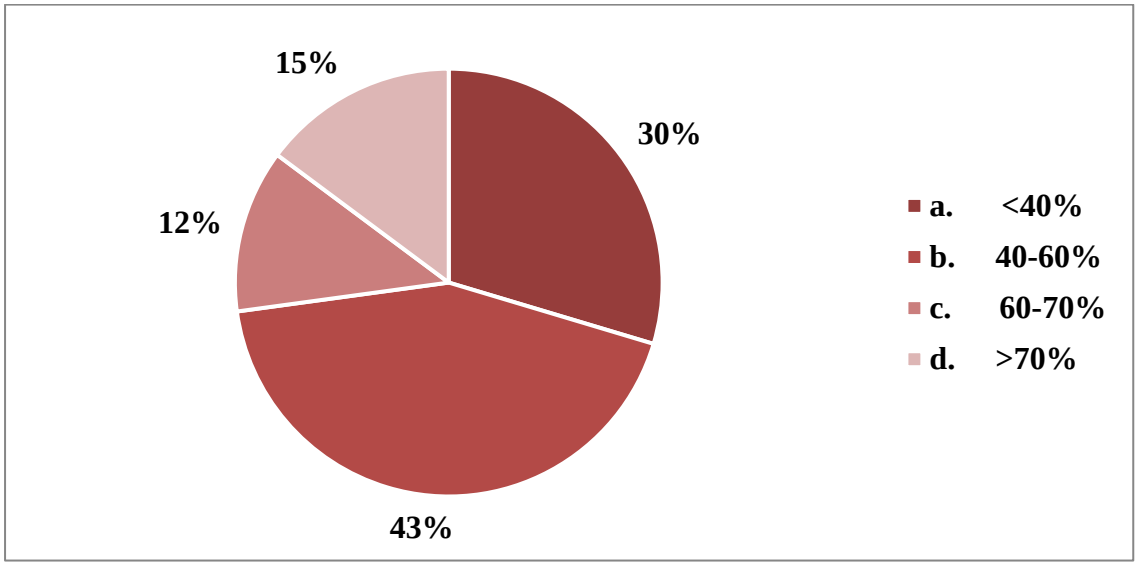
b. No



As per majority of doctors, 74%, they have used Rosuvastatin in combination with bempedoic acid.

12) What percent reduction of LDL-c have you seen with High intensity Rosuvastatin and Bempedoic acid combination in your patients with ASCVD?

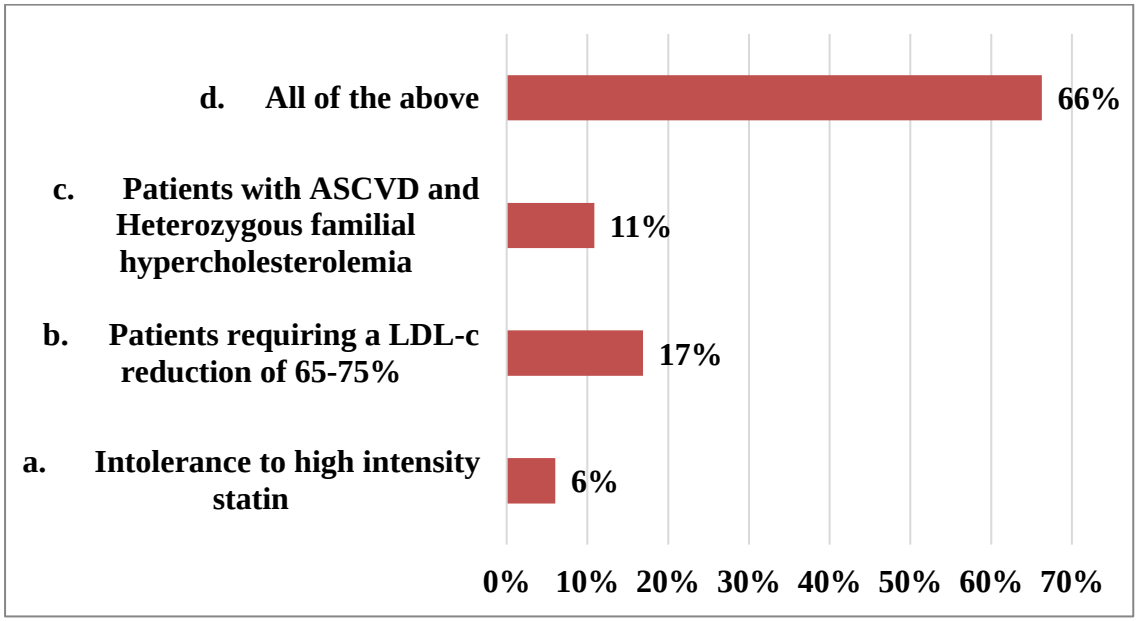
a. <40%
b. 40-60%
c. 60-70%
d. >70%



According to 43% of doctors, they have seen 40-60% reduction with High intensity Rosuvastatin and Bempedoic acid combination in their patients with ASCVD.

13) In which patient profile do you think would the combination of Rosuvastatin and Bempedoic Acid be preferred?

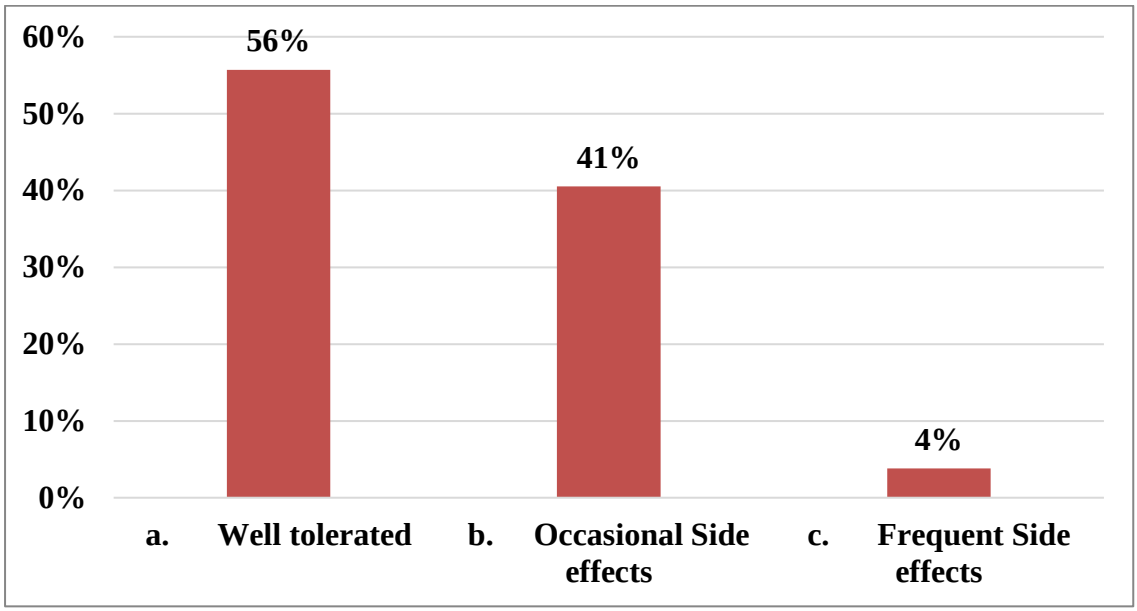
a. Intolerance to high intensity statin
b. Patients requiring a LDL-c reduction of 65-75%
c. Patients with ASCVD and Heterozygous familial hypercholesterolemia
d. All of the above



As per majority of doctors, 66%, the combination of Rosuvastatin and Bempedoic Acid would be preferred for patients with intolerance to high intensity statin, patients requiring a LDL-c reduction of 65-75% and patients with ASCVD and Heterozygous familial hypercholesterolemia.

14) In your opinion what is your experience observed with Rosuvastatin 40mg and Bempedoic acid tolerability?

a. Well tolerated
b. Occasional Side effects
c. Frequent Side effects



As per 56% of doctors, in their experience they have observed that Rosuvastatin 40mg and Bempedoic acid are well tolerated.

Summary

- According to 45% of doctors, on an average they see 5 – 10 patients with ASCVD in a month.
- As per majority of doctors, 90%, their preferred statin in their patients is Rosuvastatin.
- According to 60% of doctors, they consider Higher LDL-C Lowering as the advantage of Rosuvastatin in comparison to other statins.
- As per 61% of doctors, patients with diabetes and elevated LDL-c require additional LDL-c reduction.
- As per majority of doctors, 79%, the most common Rosuvastatin dose that they prescribe in your patients is 10mg.
- According to 53% of doctors, they prefer initiating high intensity statin for 25-50% of their patients with ASCVD.
- According to 47% of doctors, they prefer high intensity statins in diabetic patients aged 40-75 years with LDL-C levels ≥70 mg/dL
- As per 39% of doctors, 25-50% of their patients achieve LDL-c levels after treatment with high intensity statins.
- According to 43% of doctors, their preferred non-statin agent that they prescribe for patients with ASCVD and uncontrolled LDL-c levels is bempedoic acid.
- As per majority of doctors, 61%, the benefits of using Bempedoic acid as an add-on therapy is better LDL-c reduction.
- As per majority of doctors, 74%, they have used Rosuvastatin in combination with bempedoic acid.
- According to 43% of doctors, they have seen 40-60% reduction with High intensity Rosuvastatin and Bempedoic acid combination in their patients with ASCVD.
- As per majority of doctors, 66%, the combination of Rosuvastatin and Bempedoic Acid would be preferred for patients with intolerance to high intensity statin, patients requiring a LDL-c reduction of 65-75% and patients with ASCVD and Heterozygous familial hypercholesterolemia.
- As per 56% of doctors, in their experience they have observed that Rosuvastatin 40mg and Bempedoic acid are well tolerated.

Consultant Opinion

Market Opportunities:

The survey indicates that a significant number of doctors see patients with ASCVD each month. This represents a substantial market opportunity for pharmaceutical companies to develop and market treatments for ASCVD.

Value for Healthcare Professionals:

Healthcare professionals highly prefer Rosuvastatin as their statin of choice, mainly due to its efficacy in lowering LDL cholesterol levels. Continuing education on the benefits of Rosuvastatin and its role in ASCVD management can further enhance its value for healthcare professionals.

Adverse Effect Management:

Healthcare professionals should be educated on the management of adverse effects associated with statin therapy, such as myalgia and liver function abnormalities. Additionally, monitoring for adverse effects and adjusting treatment accordingly can help optimize patient safety and tolerability.

Withdrawal Management:

Clear guidelines and protocols should be established for initiating high-intensity statin therapy, particularly in diabetic patients with ASCVD. Additionally, guidance on when to consider non-statin agents, such as bempedoic acid, for patients with uncontrolled LDL cholesterol levels can assist healthcare professionals in making informed treatment decisions.

Market Positioning:

Pharma companies can position bempedoic acid as a valuable add-on therapy for patients with ASCVD and uncontrolled LDL cholesterol levels, particularly in combination with Rosuvastatin. Emphasizing the benefits of combination therapy, such as better LDL cholesterol reduction, can differentiate these treatments in the market.

Personalized Treatment Decisions:

Personalized treatment approaches should be considered based on individual patient characteristics, such as intolerance to high-intensity statins or the need for specific LDL cholesterol reduction targets. Healthcare professionals should tailor treatment regimens to meet the unique needs of each patient with ASCVD.

Improving Patient Outcomes:

Improving patient outcomes in ASCVD management requires a comprehensive approach that includes aggressive LDL cholesterol lowering and addressing other cardiovascular risk factors. Healthcare professionals should prioritize LDL cholesterol reduction and utilize combination therapies, such as Rosuvastatin and bempedoic acid, to achieve optimal outcomes for patients with ASCVD.

NOTES

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