Appropriate use of PCSK9 Inhibitors in India

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Abstract

The burden of atherosclerotic cardiovascular (CV) disease is alarmingly high and increasing in our country. Dyslipidemia is one of the major modifiable risk factors, and INTERHEART study showed that dyslipidemia had the highest population attributable risk for myocardial infarction. In the management of dyslipidemia, low-density lipoprotein cholesterol (LDL-C) is the primary therapeutic target. In addition to therapeutic lifestyle changes, statins and ezetimibe effectively lower LDL-C and consequently improve CV outcomes. However, there are situations where these drugs fall short of achieving the target or they may not be well tolerated.

Human monoclonal proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody therapy has been found to be effective and safe in reducing LDL-C when added to statins and or ezetimibe or as a monotherapy, and these agents have been shown to improve CV outcomes. A PCSK9 inhibitor is now available in India and the Drug Controller General of India has approved its use. It is therefore timely and appropriate to disseminate information on this new class of drugs and on their appropriate use in clinical practice, especially in view of their high cost. Either the “drug cost has to be lowered” which the medical community hopes or else one has to plan to “limit its use to very high-risk patients”.

Introduction

Cardiovascular disease (CVD) currently accounts for approximately 33% of the total deaths around the globe. As of 2012, 17.5 million individuals died due to CVD1 and it is postulated that CVD will become the major cause of death and disability worldwide by 2020 with approximately 23.3 million deaths by 2030.2 The burden of CVD has risen dramatically in the past few decades with 80% of the burden now in low- and middle-income countries,3 due to the change in lifestyle and the demographic age shift.4 There has been a welcome decline in the incidence of CVD in many of the western countries between 1998-2008, but it has increased in low- and middle-income countries during the same period.5 According to the Global Burden of Diseases 2013 report, ischemic heart disease (IHD) was found to be the greatest contributor to death, amongst the middle-aged men, in all countries. Stroke, along with IHD, was the leading cause of death and a major cause of life years lost in Asia.6,7

Data for India in the Global Burden of Diseases study showed that absolute as well as age-adjusted mortality from various forms of CVD has significantly increased. The years of life lost has increased by 40.7% due to CVD, 33.7% due to IHD and 7% due to stroke.8 In contrast, overall cardiovascular (CV) mortality has decreased in the United States of America by 62.4% and in high-income European countries by 71.2%.9,10

Dyslipidemia is one of the major modifiable risk factors for CVD, or more precisely atherosclerotic CVD (ASCVD). The INTERHEART study reported on the relative importance of various conventional risk factors in causation of myocardial infarction (MI).11 Serum apolipoprotein A (apoA) and apolipoprotein B (apoB) ratio had the highest population attributable risk for MI. Accordingly, effective management of dyslipidemia forms the cornerstone of ASCVD prevention strategy.

In India, high cholesterol levels have been reported in 25–30% of urban and 15–20% rural population; most common dyslipidemia being borderline high low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C) and high triglycerides.12 Indian Council of Medical Research, in the ICMR-INDIAB (Indian Council of Medical Research-India DIABetes) study of prevalence of dyslipidemia in rural and urban India, involving 3 Indian states (Tamil Nadu, Maharashtra, Jharkhand) and the union territory of Chandigarh, reported an LDL-C level of ≥130 mg/dL in Tamil Nadu (15.8%), followed by Maharashtra (13.3%), Chandigarh (12%) and Jharkhand (3.4%), with higher rates in urban areas compared to rural areas, except in Maharashtra.13 Further, twenty-year trends in lipid levels reported by Jaipur Heart Watch studies show an increase in mean total cholesterol, LDL-C and triglyceride levels over the past couple of decades.14
In other studies, severe hypercholesterolemia (LDL-C ≥220 mg/dl; probably reflecting familial hypercholesterolemia [FH]) was estimated to be 1 in 357 (1 in 326 men, 1 in 402 women) in hospital-based subjects, demonstrating a significantly high prevalence of severe hyperlipidemia in Indian population. While dyslipidemia is widely prevalent, its management has remained rather dismal. A study looking at cross-sectional data across the Indian urban population showed that level of awareness, treatment and control of dyslipidemia was quite low. Awareness was seen in 17.5% men and 13.2% women with high cholesterol, treatment with statins was instituted in 7.5% men and 6.7% women, while goal of total cholesterol <200 mg/dl was achieved in only 4.5% men and 3.7% women.

To study the current status of lipid management by clinicians, a nationwide, cross-sectional physician survey was carried out recently in which 404 physicians participated from 23 sites in India. The data showed that 88% respondents ordered a lipid profile before starting statin therapy and 80% preferred to set lipid targets. Interestingly, high-intensity statins were preferred by 73.7% of respondents in post-acute coronary syndrome (ACS) cases. However, disappointingly, 50% clinicians chose not to use a statin in diabetic patients, irrespective of their LDL-C levels, and 52% chose not to alter pre-existing therapy in patients who had LDL-C levels at goal but elevated non-HDL-C levels. Thus, it is evident that although there were some positive trends in this survey, much remains to improve.

**Summary**

1. High prevalence and incidence of ASCVD and consequent mortality and morbidity are a cause of concern in India.
2. Level of awareness, treatment and control of dyslipidemia is disappointingly and alarmingly low in our population.

**Proprotein convertase subtilisin/kexin type 9 inhibitors - Pharmacology**

The discovery of a relationship between lipids, cholesterol and atherosclerosis was made in the 1960s which paved way for the development of lipid lowering drugs. But it was the discovery by Goldstein and Brown of the role of LDL receptors (LDLRs) which led to further discoveries including that of proprotein convertase subtilisin/kexin type 9 (PCSK9).

The PCSK9 journey began in 2003 and is still actively ongoing. PCSK9 gene is located on chromosome 1p32.3. Abifadel et al discovered that a gain of function mutation of gene encoding PCSK9 led to FH in a French family. Similar findings were reported from Oslo. In 2005, the Dallas Heart Study in Afro-Americans showed that loss of function mutation in the gene for PCSK9 was associated with low serum LDL-C levels and a reduced incidence of CVD. In 2006 itself, it was discovered that the PCSK9 acted extracellularly and that it facilitated LDLR degradation in hepatocytes. The molecular structure of PCSK9 was revealed in 2007 and 2008. Further animal studies in mice and primates using ribonucleic acid (RNA) inhibitors and monoclonal antibodies confirmed the relationship of PCSK9 and lipid lowering. These findings led to the development of several strategies to inhibit the PCSK9 protein or RNA using monoclonal antibodies or RNA interference drugs, respectively. Trials were conducted for 3 monoclonal antibodies, and two of them- evolocumab and alirocumab- are now available for clinical use, with further development of the third monoclonal antibody bococizumab having been stopped because of immunogenicity issues and attenuation of its LDL-C lowering effect with time.

**Mechanism of action**

PCSK9 facilitates degradation of the LDLRs, resulting in a reduced hepatic uptake of LDL-C and increased levels of circulating LDL-C (Figure 1).

PCSK9 binds to an extracellular portion of the LDLR. Once internalized in the hepatocytes, LDLR is transported to a lysosome, where it can either be degraded or recycled. PCSK9 prevents LDLR from forming a closed conformation, making it susceptible to enzymatic degradation. Inhibition of PCSK9 thus leads to a decrease in the LDLR breakdown, resulting in more LDLRs being recycled to the hepatocyte surface leading to an increased hepatic uptake of LDL-C and therefore a lower serum LDL-C level.

Evolocumab and Alirocumab bind selectively to the LDLR binding site of PCSK9 and prevent circulating...
shown in Table 1.28,29 evolocumab and alirocumab have been discontinued. Further development of the drug has been discontinued because of anti-drug antibodies which attenuated the effect on LDL-C lowering. For this reason, further development of the drug has been discontinued.

Table 1: Pharmacokinetic Properties of PCSK9 inhibitors

<table>
<thead>
<tr>
<th>Property</th>
<th>Evolocumab</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>4 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Peak</td>
<td>3-4 days</td>
<td>3-7 days</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>72%</td>
<td>85%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>3.3 L</td>
<td>0.04 to 0.05 L</td>
</tr>
<tr>
<td>Crosses Placenta</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Degradation to small peptides and individual amino acids.</td>
<td>Degradation to small peptides and individual amino acids.</td>
</tr>
<tr>
<td>Half life</td>
<td>11 to 17 days</td>
<td>17 to 20 days</td>
</tr>
<tr>
<td>Drug Interaction with statins</td>
<td>20% increase in the clearance; no dose adjustment needed; Belimumab: toxicity enhanced by Evolocumab</td>
<td>Decreased half-life of alirocumab to 12 days; no dose adjustment needed; Belimumab: toxicity enhanced by Evolocumab</td>
</tr>
</tbody>
</table>

PCSK9 from binding to the LDLRs on the hepatocytes, preventing PCSK9-mediated LDLR degradation. Increased liver LDLR levels result in corresponding reduction in serum LDL-C concentration.

Bococizumab is a third inhibitor of PCSK9 but unlike evolocumab and alirocumab, it is not a fully humanized monoclonal antibody with 3% of the murine sequence remaining in the molecule. Though it showed beneficial effects in high risk ASCVD patients, its use was associated with development of anti-drug antibodies which attenuated the effect on LDL-C lowering. For this reason, further development of the drug has been discontinued.

Pharmacokinetic properties of evolocumab and alirocumab have been shown in Table 1.28,29

Interaction with statins

It has been shown that statins increase the levels of PCSK9 in a dose-dependent manner, leading to attenuation of their lipid-lowering effect.30 So, conceptually inhibition of PCSK9 would have a synergistic effect, by increasing LDLR density and further maximize the LDL-C-lowering effect of statins (Figure 2).

Effect on other lipid fractions

In FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, as compared with placebo, at 48 weeks, evolocumab had reduced LDL-C by 59%, non-HDL-C levels by 52%, apoB levels by 49%, triglycerides by 16% and it increased HDL-C levels by 8%.32

PCSK9 inhibition also decreased the plasma concentrations of lipoprotein(a) (Lp[a]) by around 20–30%.33,34 The mechanism of Lp(a) lowering by PCSK9 inhibitors is not clear. Some claim that Lp(a) is not cleared by the LDLR, and statins, which upregulate the LDLR, do not substantially lower plasma concentrations of Lp(a). However, in vitro studies have suggested that the LDLR may play a role in Lp(a) clearance.35

Effect beyond lipid lowering

Apart from lipid-lowering, PCSK9 inhibition may have additional beneficial effects. There are data to support that reduced PCSK9 function increases LDLR-mediated pathogen lipid clearance and thus reduces the inflammatory response and improves outcomes in sepsis in both mice and humans.36

PCSK9 may also have interacting partners other than LDL-C in plasma that might contribute to its additional action. PCSK9 expression in hepatocytes may be increased by a small protein called resistin, secreted by human macrophages. The level of resistin is increased in obesity and may contribute to insulin resistance and inflammation in patients with metabolic syndrome. Resistin levels have also been linked to ASCVD in humans.37

It is also reported that PCSK9 may have a potential role in vascular inflammation in atherogenesis. Vascular smooth muscle cells have been shown to produce higher amounts of PCSK9 when compared to endothelial cells in an inflammatory environment.38

Dosing recommendations

Route of administration: PCSK9 inhibitors need to be administered subcutaneously, in the abdomen, thigh or upper arm. Injection sites should be rotated; injections should not be given into areas where the skin is tender, bruised, red, or hard. The drug should not be administered intravenously or intramuscularly.

Evolocumab (Repatha®) is available as 140mg/mL solution in a pre-filled SureClick® autoinjector; each autoinjector is to be used once only. The recommended dosages are-

- Primary hypercholesterolemia and mixed dyslipidemia in adults:
  - 140 mg every two weeks or 420 mg once monthly.
- Homozygous FH (HoFH) in adults and adolescents aged > 12 years:
  - The initial dose: 420 mg once monthly. After 12 weeks, dose frequency can be up-titrated to 420 mg once every 2 weeks, if a clinically meaningful response is not achieved,
  - In patients on apheresis, initiate treatment with 420 mg every 2 weeks to correspond with the apheresis schedule.

Alirocumab (Praluent®) is available as 75 and 150 mg/mL pre-filled syringes, made for single use. The recommended dosages are-

- 75 mg once every 2 weeks; measure LDL-C levels between 4 to 8 weeks. If response is inadequate, increase the dose to 150 mg every 2 weeks and reassess within 4 to 8 weeks,
As compared to 59 ml/min/1.73 m² safely lowered LDL-C in patients with severe hepatic impairment (Child-Pugh C). 42

Koren et al, 43 in their meta-analysis of patients ≥65 (n=1779) and ≥75 (n=223) years of age, enrolled in phase 2 and 3 studies of Evolocumab, concluded that PCSK9 inhibition with evolocumab potently reduced LDL-C with a side effect profile similar to placebo.

Pregnant and lactating mothers

Role of PCSK9 in neural tube development has been demonstrated in rats. Low levels of PCSK9 have been observed in pregnancies with neural tube defect in rats, 44 hypothesizing a possibility of neural tube defects in the newborn if administered to a pregnant woman. There is paucity of data regarding the use of PCSK9 inhibitors in pregnant and lactating women. Both these drugs cross the placenta. Alirocumab and evolocumab are to be avoided in pregnant and lactating women, unless absolutely necessary. 45

Evidence base

Imaging Studies

In a recent trial, a total of 968 statin-treated coronary artery disease (CAD) patients underwent serial coronary intravascular ultrasound imaging at baseline and following 76 weeks of treatment with placebo or evolocumab 420 mg monthly. 46 With statin monotherapy, baseline LDL-C was 89.9 mg/dL. Evolocumab further reduced it to 33.5 mg/dL, and reduced percent atheroma volume (−1.2% vs. +0.17%; p=0.0001) and total atheroma volume (−3.6 mm³ vs. −0.8 mm³; p=0.04). Evolocumab resulted in plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%). 46 However, there was no difference between the evolocumab and placebo groups in plaque composition. 46 An inverse correlation was observed between changes in LDL-C and plaque calcification.

CV outcomes studies

SPIRE-1 and SPIRE-2

The SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) program consisted of two clinical trials (SPIRE-1 and SPIRE-2) that were stopped prematurely. 27 These trials evaluated 27,438 patients of ASCVD randomized to receive bococizumab or placebo. Bococizumab is a humanized monoclonal antibody to PCSK9 but contains 3% of the murine sequence. The LDL-C was significantly lowered in the treatment group, and in higher-risk patients with baseline LDL-C >100 mg/dL, there was a reduction in major ASCVD events as well. However, the major limitation of SPIRE was the development of antidrug antibodies, which attenuated the effect of bococizumab on LDL-C lowering. Further clinical development of bococizumab has been stopped due to its tendency to stimulate development of antidrug antibodies.

FOURIER

The FOURIER trial 32 was a randomized, double-blind, placebo-controlled trial that enrolled patients aged 40–85 years with- (1) established ASCVD [MI, non-hemorrhagic stroke, or symptomatic peripheral artery disease (PAD)], and (2) LDL-C level ≥70 mg/dL or non-HDL-C ≥100 mg/dL while taking an optimized lipid-lowering therapy with statin. A total of 27,564 patients were randomly assigned

- An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once monthly.

- PCSK9 Inhibitors in India: The Drug Controller General of India has approved Evolocumab in April 2018 for the treatment of-

- Adult patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, alone or in combination with other lipid lowering drugs,

- Adults and adolescents ≥12 years of age with HoFH in combination with other lipid-lowering drugs.

Use in Special Population

Patients with renal impairment

No dose adjustment is required with evolocumab in patients with renal impairment, despite lower exposure. 39 From pooled data of eight phase 3 ODYSSEY trials (double-blind treatments of 24-104 weeks), it was seen that alirocumab consistently and safely lowered LDL-C in patients with renal dysfunction (defined as an eGFR 30 to 59 ml/min/1.73 m²) as compared to control. 40 Efficacy and safety of both these drugs did not differ significantly with respect to renal function. 41 Rise in creatine kinase was seen in 84 and 124 participants treated with alirocumab and evolocumab, respectively.

Patients with hepatic impairment

Caution is to be maintained while administering these drugs in patients with severe hepatic impairment (Child-Pugh C). 42

Elderly (age ≥65years)

Advanced age is a highly prevalent and arguably, a strong risk factor for CVD. Koren et al, 43 in their meta-analysis of patients ≥65 (n=1779) and ≥75 (n=223) years of age, enrolled in phase 2 and 3 studies of Evolocumab, concluded that PCSK9 inhibition with evolocumab potently reduced LDL-C with a side effect profile similar to placebo.

Clinical use of PCSK9 inhibitors

Patients with ASCVD

A number of imaging studies and CV outcome trials have established the safety and efficacy of PCSK9 inhibitors in patients with ASCVD.
subtilisin/kexin type 9

OUTCOMES- Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9- Proprotein convertase

IMPROVE-IT- IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; MI- myocardial infarction; NNT- numbers needed to treat; ODYSSEY OUTCOMES (52)

FOURIER (32) Stable atherosclerotic
coronary disease with additional risk factors

Hospitalization for unstable angina

Coronary revascularization

Death from any cause, nonfatal MI and nonfatal ischemic stroke

CV death, MI, or stroke

CHD death

Death from any cause

MI

Stroke

Elevated Risk; MI- myocardial infarction, ODYSSEY OUTCOMES- Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment

1- Primary end-point in FOURIER was a composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, whereas in ODYSSEY OUTCOMES it was a composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization; 2- death from CHD, nonfatal MI, unstable angina requiring hospitalization, and an ischemia-driven coronary revascularization procedure; 3- death from CHD, nonfatal MI; 4- death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, unstable angina requiring hospitalization, or nonfatal ischemic stroke; 5- this was the key secondary end-point in FOURIER trial; CHD- coronary heart disease, CV- cardiovascular, FOURIER- Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; MI- myocardial infarction, ODYSSEY OUTCOMES- Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab

Table 2: Clinical outcomes with alirocumab and evolocumab in FOURIER and ODYSSEY OUTCOMES trials

<table>
<thead>
<tr>
<th></th>
<th>FOURIER (52)</th>
<th>ODYSSEY OUTCOMES (52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evolocumab</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CHD event</td>
<td>5.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Major CHD event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CV event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause, nonfatal MI and nonfatal ischemic stroke</td>
<td>1.3</td>
<td>3.4</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
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<tr>
<td>Hospitalization for unstable angina</td>
<td></td>
<td></td>
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<tr>
<td>Coronary revascularization</td>
<td></td>
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</tbody>
</table>

Table 3: Number needed to treat for preventing one adverse outcome with ezetimibe or PCSK9 inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study populations</th>
<th>Therapeutic intervention</th>
<th>Duration</th>
<th>Study subgroup</th>
<th>NNT</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE-IT (56,61)</td>
<td>Acute coronary syndrome within the preceding 10 days</td>
<td>Ezetimibe (10 mg daily) or a placebo added on to simvastatin 40 mg daily</td>
<td>7 years</td>
<td>3 or more risk factors</td>
<td>16</td>
<td>CV death, MI ischemic CVA</td>
</tr>
<tr>
<td>FOURIER (32)</td>
<td>Stable atherosclerotic vascular disease with additional risk factors</td>
<td>Evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or a matching placebo added on to statin therapy</td>
<td>2.2 years</td>
<td>Overall</td>
<td>74</td>
<td>Death, MI stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>37  (yes), 62 (no)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI duration</td>
<td>35 (&lt;2 years), 101 (&gt;2 years)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of prior MIs</td>
<td>38 (2 or more), 60 (&lt;2)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multivessel disease</td>
<td>29 (yes), 78 (no)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peripheral arterial disease</td>
<td>29 (yes), 63 (no)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
<td>49</td>
<td>Primary end-point</td>
</tr>
<tr>
<td>ODYSSEY OUTCOMES (52)</td>
<td>Acute coronary syndrome 1 to 12 months earlier</td>
<td>Alirocumab 75 mg every 2 weeks or a matching placebo added on to statin therapy</td>
<td>4 years</td>
<td>Overall</td>
<td>49</td>
<td>Primary end-point</td>
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Table 3: Number needed to treat for preventing one adverse outcome with ezetimibe or PCSK9 inhibitors

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CV- cardiovascular; CVA- cerebrovascular event; FOURIER- Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; IMPROVE-IT- IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; MI- myocardial infarction; NNT- numbers needed to treat; ODYSSEY OUTCOMES- Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9- Proprotein convertase subtilisin/kexin type 9

to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo. The primary efficacy endpoint was the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy endpoint was the composite of CV death, MI, or stroke.

Treatment with evolocumab reduced LDL-C by 59% from a median of 92 mg/dL to 30 mg/dL (Figure 3). LDL-C level was reduced to 70 mg/dL or lower in 87% of the patients, to 40 mg/dL or lower in 67% of the patients, and to 25 mg/dL or lower in 42% of the patients receiving evolocumab. Ezetimibe was used only in about 5% of patients.

After a median follow-up of 2.2 years, both primary and secondary endpoints were significantly reduced (15% and 20% respectively, both P values <0.001) in the evolocumab group, as compared with placebo (Table 2). For individual outcomes, evolocumab treatment reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%. Relative risk reductions in primary and secondary endpoints were 15%–20% and absolute risk reduction (ARR) was 1.5% for both endpoints. The number-needed-to-treat (NNT) was 74 patients for 2 years to prevent one CV death, MI or stroke (Table 3).

Evolocumab showed greater risk reduction in the second year of follow-up and the benefit seemed to grow over time. The key secondary end-point benefit (risk reduction in CV death, MI and stroke) increased from 16% during the first year to 25% beyond 12 months.

Injection site reaction was the only significant adverse event as compared to the placebo. There was no difference between evolocumab and placebo for muscle related events, cataract, new
onset diabetes, and neurocognitive events.

**Sub-studies of FOURIER**

- **Diabetes**: In FOURIER trial, there were 11031 patients with diabetes mellitus and 16533 patients without diabetes mellitus (of whom 10344 had prediabetes and 6189 had normoglycemia). The prespecified sub-analysis found that evolocumab significantly reduced CV risk in patients with and without diabetes, but there was a greater ARR in patients with diabetes compared to those without diabetes (2.7% vs. 1.6%).

- **High risk coronary artery disease**: Analyses in high-risk subgroup with recent MI (<2 years), multiple prior MIs (≥2), and residual multivessel CAD also demonstrated greater ARR than that in low-risk group (3.4% vs. 0.8%, 3.7% vs. 1.3%, and 3.6% vs. 1.2%, respectively).

- **Peripheral artery disease**: In the FOURIER trial, out of 27564 patients, 3642 (13.2%) patients had PAD as diagnosed by leg claudication, ankle-brachial index of less than 0.85 and/or history of previous vascular procedure. Of these, 1505 had no prior MI or stroke. Patients with PAD showed greater ARR for the primary end point (3.5% with PAD, 1.6% without PAD) and the key secondary end point (3.5% with PAD, 1.4% without PAD), implying higher risk in this group. Evolocumab reduced the risk of major adverse limb events in all patients consistently. There was a consistent relationship between lower achieved LDL-C and lower risk of limb events that extended down to LDL-C of <10 mg/dL.

- **Metabolic syndrome**: Nearly 60% subjects in the FOURIER trial had metabolic syndrome at baseline. The degree of LDL-C reduction was less in patients with metabolic syndrome (58% vs 61%). Despite this, the patients with metabolic syndrome had greater risk reduction for the primary (17% vs. 11%) and secondary end-points (24% vs. 16%) as compared to those without metabolic syndrome (51). There was no increased risk for new onset diabetes in this subgroup.

**The EBBINGHAUS Study**: The EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) study investigated the effect of low LDL-C levels on cognitive function in 1204 patients enrolled in the FOURIER study over a median follow-up of 20 months, using the Cambridge Neuropsychological Test Automated Battery (CANTAB), that assessed cognitive functions in the context of episodic and working memory, executive function, psychomotor speed, and attention. No clinically relevant or statistically significant changes were observed with the addition of evolocumab to statin therapy.

The findings from the EBBINGHAUS study strongly support the safety of lowering LDL-C levels below the currently recommended targets.

**ODYSSEY OUTCOMES study**

ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial was a randomized, double-blind, placebo-controlled trial that enrolled 18924 patients aged 40 years or older with 1) a recent ACS (acute MI or unstable angina) event within the preceding 1–12 months, and 2) LDL-C level ≥70 mg/dL, non-HDL-C ≥100 mg/dL, or apoB ≥80 mg/dL while taking a high-intensity or maximum tolerated dose of statin. The subjects were randomly assigned to receive subcutaneous injections of alirocumab (either 75 or 150 mg every 2 weeks) or placebo. The dose of alirocumab was adjusted or the statin dose further or adding a non-statin drug further reduces CV risk and helps mitigate the “residual cholesterol risk”. The earlier trials such as PROVE-IT TIMI 22 (Pravastatin or
Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) and TNT (Treating to New Targets) compared standard dose pravastatin/atorvastatin with high-dose atorvastatin (80 mg daily), which resulted in lowering of LDL-C from 100 mg/dL to roughly 70 mg/dL and provided greater protection against death or major CV events.55,56

IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial),57 which enrolled 18144 patients, showed further benefit beyond statin therapy by achieving LDL-C levels lower than previous trials in persons with recent ACS. The median time-weighted average LDL-C level during the study was 53.7 mg/dL in the simvastatin-monotherapy group. There was a 6% relative risk reduction and 2% ARR, translating in to NNT of 50 at 7 years. These findings indicate that early and aggressive lowering of LDL-C to levels substantially below the currently recommended target levels would be of benefit in a population of high-risk ASCVD.

Figure 4 shows a recommended approach for the use of PCSK9 inhibitors in ASCVD patients; SCVD-atherosclerotic cardiovascular disease; LDL-C- low density lipoprotein cholesterol; PCSK9- Proprotein convertase subtilisin/kexin type 9

**Summary**

- PCSK9 inhibitors - evolocumab and alirocumab significantly and safely reduce major ASCVD events achieving very low LDL-C levels, which could effectively manage the “residual cholesterol risk”. LDL-C lowering with PCSK9 inhibitors is intensive, but the drug is expensive. Thus, keeping cost factor in context and medical economics in mind, we should embrace an approach of “highest risk, highest benefit” for using PCSK9 inhibitors. Table 4 outlines a “very high-risk” population that is most likely to benefit from PCSK9 inhibitors. It is a valuable exercise to look at NNT and ARR for various therapies as they assist in therapeutic decision-making in clinical practice and also serve as supportive tools for regulatory policies. Based on IMPROVE-IT, which looked at NNT based on the TIMI Risk Score for Secondary Prevention (TRS 2°P)62 and the results of the studies and sub-studies from FOURIER and ODDESSEY OUTCOMES, the Table 3 lists the risk factors and NNT/ARR for ezetimibe and PCSK9 inhibitors.
when added to statin therapy and/or ezetimibe.

- Imaging studies and CV outcome trials with PCSK9 inhibitors have shown that there is a continued CV benefit with LDL-C going down to 20-25 mg/dL. These trials have clearly demonstrated two points—
  - LDL-C: “Lower is better”
  - All reductions in LDL-C levels, regardless of mechanism, are of equivalent benefit.

- However, these CV outcome studies had a few limitations—
  - These were not long-term studies.
  - The usage of ezetimibe was quite low, and there was no mortality benefit (except in some subgroups).

- Nonetheless, the achieved benefit further validates the LDL-C principle, and also shows that LDL-C may now be reduced to levels much below the currently recommended targets, safely and with benefit.

- To maximize CV benefit, we should strive to achieve very low levels of LDL-C early in individuals who are at high risk.

- NNT derived from various studies and subgroups helps in identifying high risk group for PCSK9 inhibitor therapy.

- LDL-C target when using PCSK9 inhibitors—
  - The median LDL-C achieved in FOURIER trial was 30 mg/dL.
  - The ODESSEY OUTCOMES trial had the LDL-C target as 25 to 50 mg/dL, and if on two occasions, the LDL-C was below 25 mg/dL, the dose was down-titrated.
  - The latest (2018) American College of Cardiology/American Heart Association guidelines recommend at least 50% reduction from the baseline in LDL-C or to <70 mg/dL in all high-risk individuals.

**Recommendations**

- Since cost is a constraint, PCSK9 inhibitors should be used in those who are likely to benefit most i.e. in very high ASCVD risk population (Figure 4).

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 3).

- LDL-C target recommended in this very high-risk group on being treated with PCSK9 inhibitor in addition to statin and/or ezetimibe is 25 to 50 mg/dL or at least 50% reduction from baseline in LDL-C.

- The patient should diligently follow therapeutic lifestyle changes - an integral part of therapy.

- Associated ASCVD risk factors should be meticulously managed.

- The patient should receive maximum tolerated statin dosage.

- If LDL-C is 70 mg/dL or more despite these measures, ezetimibe should be added.

- If it still fails to reach the LDL-C target, shared decision should be taken by the physician and patient after a detailed discussion and PCSK9 inhibitors should be prescribed.

**Familial hypercholesterolemia**

“You never find an individual with FH. You always find a family.”

-Katherine A Wileman, Founder and President, FH Foundation

FH is one of the most common genetic metabolic disorders characterized by elevated plasma levels of LDL-C due to defective clearing, resulting in premature ASCVD. There are unmet needs in LDL-C-lowering therapies in this population.

The majority of the cases of FH have an autosomal dominant pattern of inheritance with 90% penetrance. Autosomal dominant FH is attributed to mutations in three different genes coding for LDLR, apoB and PCSK9. Rarely, it could be autosomal recessive. Despite being the most common monogenic disorder, FH is underdiagnosed and undertreated globally.

Telomere length is a biological index of ageing. A recent study found that FH subjects have significantly shorter length of telomere. An increased oxidative stress due to hypercholesterolemia could result in shorter telomere length. These findings indicate that FH accelerates ageing, and untreated FH markedly reduces life expectancy.

The prevalence of FH in India amongst young CAD patients has been found to be around 15%, as shown by a study from a tertiary care hospital. A total of 635 patients with premature CAD were studied, and on applying Dutch Lipid Clinic Network criteria, 4% were diagnosed to be having definite FH and 11% probable FH. In another study, the same investigators studied genetic mutations in 100 patients with FH (definite, probable and possible) and found abnormal mutations in LDLr, apoB or PCSK9 genes in 47% of the patients (Setia et al, 2018, under publication). A previous publication described the spectrum of mutations in sixteen Indian HoFH subjects. Ten mutations were detected in LDLR gene but none in apoB and PCSK9 genes. Fourteen subjects had homozygous mutations and one had compound heterozygous mutation, while no mutation was detected in one subject despite being clinically homozygous.

High prevalence of FH mutations has been reported in family members of FH patients in India. Cascade screening by molecular testing was carried out in 133 family members of 31 probands with FH having a pathogenic mutation in LDLR/apoB gene. Nearly two-thirds of them (88 subjects, 66.1%) were found to carry the family mutation. ASCVD was present in 15 (11.2%) subjects and 63 (47.4%) were already on lipid lowering therapy. Four children were found to have HoFH, who were treated with high-intensity statin therapy.

**HoFH and ASCVD**

A systematic review from 19 studies and 2458456 individuals found that FH currently affects 1 in 250 people in the adult population. Left untreated, nearly 85% of males and 50% of females with FH are expected to suffer coronary events prior to age 65.

**HoFH and ASCVD**

HoFH is rare and should be considered as a life-threatening disease. HoFH patients have a very high levels of plasma LDL-C levels (usually >500 mg/dL), extensive xanthomas, and marked premature and progressive ASCVD. Untreated, most of these patients develop overt ASCVD before the age of 20 years, and generally do not survive past 30 years.
FH is often associated with increased plasma levels of Lp(a), the mechanism of which is not fully understood. Lp(a) levels tend to be higher in patients with HoFH than HeFH and are independent of genetic variation in apolipoprotein(a). HoFH patients also usually have low levels of HDL-C, probably due to accelerated turnover of HDL apoA1, and defective HDL-driven cholesterol efflux.72

### Diagnostic criteria

There are a number of well-established and validated criteria for the diagnosis of FH. Of these, Dutch Lipid Clinic Network criteria are easy to use and very popular (Table 5).73

### Management

Patients suspected to be having HoFH should be referred to specialist centers for further evaluation and clinical management. Lifestyle intervention and maximal statin therapy are the mainstays of treatment, ideally started in the first year of life or at an initial diagnosis, often with ezetimibe and other lipid-modifying therapy.

Other ASCVD risk factors should be meticulously assessed. Doppler echocardiographic evaluation of the heart and aorta annually, stress testing and, if available, computed tomography coronary angiography every 5 years, or less if deemed necessary, should be performed.

In a retrospective study, case records of 149 patients (81 females, 68 males) of HoFH from South Africa were reviewed. Statin was the lipid lowering therapy in most. The mean reduction in LDL-C was 26.4% (from 15.9±3.9 to 11.7±3.4 mmol/L; P<0.0001) with lipid-lowering therapy. The lipid-lowering therapy was associated with delaying of CV events and survival benefit in these patients with HoFH.73

It needs to be acknowledged that moderate intensity statin therapy can reduce ASCVD mortality by 70%74 and that recent data suggest a 44% reduction in ASCVD events with statins and ezetimibe.75

LDL-C apheresis is an expensive and time-consuming therapeutic approach, and when available is an important adjunctive treatment for HoFH.

Lomitapide and mipomersen were recently approved by the United States Food and Drug Administration as adjunct therapy for HoFH in patients aged ≥18 and ≥12 years, respectively; lomitapide is also approved by the European Medicines Agency. These agents carry substantial risk of side effects.

In the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) registry,76 2404 adult patients with FH were followed up for a mean of 5.5 years. Age, male gender, history of previous ASCVD, high blood pressure, increased body mass index, active smoking, and LDL-C and Lp(a) levels were independent predictors of incident ASCVD. The authors concluded that the risk of incident ASCVD in patients with FH could be estimated using simple clinical predictors. This finding may improve risk stratification and could be used to guide therapy in patients with FH.

### Role of PCSK9 inhibitors

Availability of PCSK9 inhibitor in our country is definitely going to brighten up the prospects of treatment of patients with FH.

In a randomized controlled trial (RCT) carried out at 17 sites in ten countries in North America, Europe, the Middle East, and South Africa,50 eligible (aged ≥12 years) patients with HoFH, on stable lipid-regulating therapy for at least 4 weeks, and not receiving lipoprotein apheresis, were randomly allocated to evolocumab or placebo.77 Evolocumab was administered at a dose of 420 mg once in 4 weeks for 12 weeks. All had genetic testing- 92% had mutations in LDLR gene, 4% apoB mutations and 1% had autosomal recessive hypercholesterolemia. The primary endpoint was percentage change in serum LDL-C levels from baseline through week 12. Compared with placebo, evolocumab significantly reduced serum LDL-C at 12 weeks by 30-9% (95% confidence interval -43-9% to -18-0%; p<0.0001). There were no serious clinical or laboratory adverse events.

In another RCT of 440 patients with HeFH, followed up to 48 weeks, there was a persistent and marked lowering of LDL-C by 53% in the evolocumab arm.78 The drug was well tolerated and was safe.

In SPIRE-2 study,79 patients had higher LDL-C levels (mean at baseline 133 mg/dL) and 7.3% of them had FH. In spite of the fact that there was a progressive attenuation of LDL-C

### Table 5: Dutch Lipid Clinic Network criteria for diagnosis of familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature coronary and vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with known LDL-C level above the 95th percentile</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis</td>
<td>2</td>
</tr>
<tr>
<td>Children aged less than 18 years with LDL-C level above the 95th percentile</td>
<td>2</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>Patient with premature coronary artery disease</td>
<td>2</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td>LDL-C level</td>
<td></td>
</tr>
<tr>
<td>&gt;330 mg/dL</td>
<td>8</td>
</tr>
<tr>
<td>250-329 mg/dL</td>
<td>5</td>
</tr>
<tr>
<td>190-249 mg/dL</td>
<td>3</td>
</tr>
<tr>
<td>155-189 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td>DNA analysis</td>
<td></td>
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<tr>
<td>Functional mutation in the LDLR, apoB or PSCK9 gene</td>
<td>8</td>
</tr>
<tr>
<td>Interpretation based on total score</td>
<td></td>
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<td>Possible FH</td>
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<tr>
<td>Unlikely FH</td>
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*Premature = < 55 years in men; <60 years in women; ApoB- apolipoprotein B; FH- familial hypercholesterolemia; LDL-C- low density lipoprotein cholesterol; LDLR- low density lipoprotein receptor; PCSK9- Proprotein convertase subtilisin/kexin type 9

Historically, HoFH can be diagnosed on the basis of an untreated LDL-C plasma concentration >500 mg/dL, or a treated LDL-C concentration of ≥280 mmol/L (≥300 mg/dL), and the presence of cutaneous or tendon xanthomata before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents.

HoFH may affect as many as 1 in 160000-300000 people. There is a higher prevalence in specific populations, such as French Canadians, Afrikaners in South Africa, or Christian Lebanese, due to founder effect.

Most patients with genetically confirmed HoFH have mutation in LDLR gene and their parents each have HeFH. Other mutations described are in the genes coding for apoB, PCSK9, and LDLR adapter protein 1 (a recessive form).75

### Table 6: American College of Cardiology and American Heart Association criteria for diagnosis of familial hypercholesterolemia

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lowering with bococizumab due to neutralizing antibodies, SPIRE 2 study showed significant clinical benefit within 12 months (absolute event rates for major CV events 3.32% vs. 4.19% on placebo, relative risk reduction of 21%, P= 0.02).

An updated re-analysis of data from a Canadian registry of FH showed that following the introduction of inhibitors of PCSK9 into clinical use, lipid levels improved in patients. Among those patients who received PCSK9 inhibitors, >85% met the lipid targets, compared to only 50% of the patients who did not receive PCSK9 inhibitor.

These studies have shown that PCSK9 inhibitors are safe and effective in patients with FH.

Role of PCSK9 inhibitors in pediatric population: There exists a paucity of data as far as the use of PCSK9 inhibitors in the pediatric population is concerned. The previous studies with evolocumab in HoFH and HeFH patients have been done in subjects 12 years or older. The HAUSER-RCT (NCT02392559) study is designed to assess the efficacy, safety, and tolerability. In RCTs, adverse event rates (including complaints of muscle pain) have generally been similar in statin and placebo groups. Rarely, however, statins do cause “muscle related symptoms” which may lead to discontinuation of the drug and consequent increase in the risk of ASCVD events. These muscle related events may be associated with elevated serum creatine kinase. Creatine kinase elevations >10 times the upper limit of normal is reported to occur in 1 per 1000 to 1 per 10 000 people per year. As compared to RCTs, patient registries and clinical experience indicate that 7–29% of patients complain of “statin associated muscle symptoms”. In an Indian physicians’ survey, statin intolerance was reported in 0-20% of the patients. Statin intolerance has been defined as inability to tolerate at least two statins, one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation. The adverse reaction to statin therapy partly depends on the statin preparation used, its intensity of dosing, and the presence of other risk factors like hypothyroidism, vitamin D deficiency and alcohol intake (Table 6).

Statin intolerance often leads to lack of adherence and consequently increases the risk of ASCVD events. In an analysis of more than 100,000 patients who were on statins following myocardial infarction (MI), 1741 patients (1.65%) had statin intolerance. These patients when followed up for 2 years were found to have a 36% higher rate of recurrent MI, and a 43% higher rate of coronary events. American Heart Association has published a comprehensive scientific statement on Statin Safety and Associated Adverse Events.

In a national survey from India, physicians chose the following actions on encountering statin intolerance in their patients:

- reducing statin dose- 39.0 %,
- stopping statin and restarting at a lower dose- 34.5%,
- using alternative statin- 22.3%,
- using non-statin drugs- 10.9%,
- other options (e.g. more aggressive lifestyle modification)- 1.4%.

These steps taken by the physicians in the survey are generally in line with the standard guidelines.

In the GAUSS-3 (Goal Achievement after Utilizing an anti-PSCK9 antibody in Statin-intolerant Subjects) RCT, 491 subjects who were established to have statin intolerance were randomized to ezetimibe or evolocumab for 24 weeks. Muscle symptoms were reported in 28.8% of the ezetimibe-treated patients and 20.7% of the evolocumab-treated patients (log-rank P=0.17). Active study drug had to be discontinued for muscle symptoms in 5 of the 73 ezetimibe-treated patients (6.8%) and in only 1 of the 145 evolocumab-treated patients (0.7%). Lipid lowering efficacy was superior with evolocumab.

In a study “Efficacy and safety of alirocumab vs ezetimibe in statist-
intolerant patients, with a statin rechallenge arm, alirocumab produced greater LDL-C reductions than ezetimibe in these statin-intolerant patients, and there were fewer skeletal-muscle adverse events as compared to atorvastatin.

When faced with a challenge of lowering LDL-C in a patient with statin intolerance, ezetimibe and PCSK9 inhibitors come to the rescue; PCSK9 inhibitors will more effectively lower LDL-C.

**Recommendations**

- Statin intolerance must be clearly established.

**Use of PCSK9 inhibitor** is recommended if the patient is at a very high risk and requires LDL-C to be substantially lowered further.

**Conclusions**

Introduction of PCSK9 inhibitors heralds the onset of an exciting time in lipid therapeutics. However, the cost comes in the way of its widespread use. The cost effectiveness of these expensive drugs can be improved by selecting patients who are at a very high risk of ASCVD events. The results of the many western studies on full economic evaluations of PCSK9 inhibitors have generally concluded that they are not cost effective at the current pricing. The manufacturers are already in the process of reducing the prices, which might favourably impact the pricing in our country also. Hopefully, PCSK9 inhibitors would prove to be cost effective in patients with FH and high risk ASCVD patients. Appropriate and judicious use should be the guiding factor in using these agents in the present circumstances.

**Abbreviations**

ACS: Acute coronary syndrome; ARR: Absolute risk reduction; ASCVD: Atherosclerotic cardiovascular disease; CAD: Coronary artery disease; CANTAB: Cambridge Neuropsychological Test Automated Battery; CHD: Coronary heart disease; CV: Cardiovascular; CVD: Cardiovascular disease; EBBINGHAUS: Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; FH: Familial hypercholesterolemia; FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GAUSS-3: Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin-intolerant Subjects; HDL-C: High-density lipoprotein cholesterol; HeFH: Heterozygous familial hypercholesterolemia; HoFH: Homozygous familial hypercholesterolemia; ICMR-INDIAB™: Indian Council of Medical Research-India DIABetes; IHD: Ischemic heart disease; IMPROVE-IT: IMP proved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein receptor; Lp(a): Lipoprotein(a); MI: Myocardial infarction; NNT: Number-needed-to-treat; ODYSSEY OUTCOMES: Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During Treatment with Alirocumab; PAD: Peripheral artery disease; PCSK9: Proprotein convertase subtilisin/kexin type 9; PROVE-IT TIMI 22: Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; RCT: Randomized controlled trial; RNA: Ribonucleic acid; SAFEHEART: Spanish Familial Hypercholesterolemia Cohort Study; SPIRE: Studies of PCSK9 Inhibition and the Reduction of Vascular Events; TNT: Treating to New Targets

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