

Pharmacotherapy of Dyslipidemia: An Overview of New Cholesterol Treatment Guidelines - The Big Statin Debate.

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Abstract : Numerous pathological, epidemiological, genetic and interventional trials have validated the central tenet of the lipid hypothesis, which proposes a causal relationship between dyslipidaemia and atherogenesis and identifies lipid modification as a risk reducing strategy for coronary heart disease (CHD). In 1984, National Institute of Health (NIH), Coronary Primary Prevention Trial, an NIH Consensus Conference convened concluded that lowering elevated LDL cholesterol with diet and drugs would reduce the risk of CHD. Since then, the National Cholesterol Education Programme-Adult Treatment Panel (NCEP-ATP) has been instrumental in developing and formulating guidelines for management of the dyslipidemia both in patients with established cardiovascular disease and for primary prevention in individuals with increased risk. In 1988, NCEP-ATP developed its first set of guidelines, followed in 1993 by NCEP-ATP-II recommendations and ATP-III guidelines in 2002. On November 12, 2013, updated guidelines for the treatment of high blood cholesterol levels were released by the American College of Cardiology – American Heart Association (ACC-AHA) Task Force on Practice Guidelines. This update represents the first major guidelines revision since the National Cholesterol Education Program released its Adult Treatment Panel III report in 2002. The previous guidelines were widely accepted and applied with relative consistency. The new guidelines rely heavily on randomized controlled trials that largely involved fixed doses of HMG CoA reductase inhibitors (statins) in patient populations that are at risk for atherosclerotic cardiovascular disease. Overall, the current American College of Cardiology–American Heart Association (ACC-AHA) recommendations will move treatment toward statins and deemphasize other agents for a broader range of patients than the previous recommendations did.

INTRODUCTION

Following the first convincing trial in humans on the benefits of cholesterol lowering for prevention of atherosclerotic events, in 1985, director of the United States heart, Lung and Blood institute Robert Lewy asserted that cholesterol “question” was no longer whether to treat high levels, but rather when, in whom, and how. For thirty years, it has been well known that atherosclerotic cardiovascular disease can be prevented by lowering cholesterol levels by statin drugs, in broad segments of general population. However critical questions—when, in whom, and how to lower cholesterol still remain.¹

The 20th century saw unparalleled increase in life expectancy and major shift in the causes of illness and death throughout the world². Ecological analyses of major CHD risk factors and mortality demonstrate that there is high co-relations between expected and observed mortality rates for three main risk factors – smoking, serum cholesterol and hypertension²⁻¹⁰.

Even when the basic lipid hypothesis has been validated, the movement towards treating hypercholesterolaemia came under fire from a number of sources. Overviews of various trials based on the efficacy of cholesterol lowering drugs, published in last decade of 20th century, indicated that although there were less CHD events in treated patients, the survival was not improved. This led Davey Smith and Pekkanen¹¹ to title their 1992 overview as “Should there be a moratorium on cholesterol lowering drugs”.

While this controversy raged, the adoption of lipid lowering

therapy slowed even when some evidence of benefit of statins in slowing the progression of atherosclerotic lesions was demonstrated with the help of quantitative angiography and ultrasound¹²⁻¹⁵.

However, in 1994, after the publications of results of the Scandinavian Simvastatin Survival Study (4S)¹⁶ and later on, the Heart Protection Study (HPS)¹⁷, a new beginning in dyslipidemia management was made. This trial showed an unequivocal 30% reduction in all cause mortality (p=0.0003) due to 42% reduction in coronary deaths in studied population.

CHOLESTEROL AND ATHEROSCLEROSIS

Although, the relationship between cholesterol and atherosclerosis currently enjoys wide acceptance, this has not always been the case. In 1850's, the observations of German pathologist Virchow and in 1913, experiments of Russian scientists Anitschkov and Chalotov established the role of cholesterol in pathogenesis of human atheromata¹⁸⁻²¹.

The first step in human atherogenesis remains largely conjectural, but it appears to be aggregation of small lipoproteins particles in the intima of the arteries. Another hallmark of atherogenesis, leukocytes recruitment and accumulation, also occurs early in lesion generation^{20,21}.

The serum levels of lipids and lipoprotein lipids have proven to be among the most potent and best substantiated risk factors for atherosclerosis in general and coronary heart disease in particular. The major types of lipids that circulate in plasma include cholesterol and cholesterol esters, phospholipids and triglycerides. Cholesterol is a lipid that is an essential component of mammalian cell membranes and many cell function depend critically on it, in addition to its role as a precursor of bile acids and steroid hormones.

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The lipoproteins are complex macromolecular structures, composed of an envelope of phospholipids and free cholesterol and a core of cholesterol esters and triglycerides. The apolipoproteins comprise the protein moiety of lipoproteins. The lipoproteins transport hydrophobic lipids, primarily triglycerides, cholesterol and fat soluble vitamins through body fluids, and to and from tissues. The classification of lipoproteins reflects their density in plasma (1.006 gm/ml) as gauged by floatation in the ultracentrifuge. There are five types of lipoproteins- Chylomicrons (the triglyceride-rich lipoproteins), Very low density lipoproteins (VLDL) (<1.006 gm/ml), Low density lipoprotein (LDL), High density lipoprotein (HDL) and Lipoprotein - LP.

So to summarise in short

- Chylomicrons carry diet-derived lipids to body cells.
- VLDLs carry lipids synthesized by the liver to body cells.
- LDLs carry cholesterol around the body.
- HDLs carry cholesterol from the body back to the liver for breakdown and excretion [Reverse cholesterol transport]²²⁻²⁷.

ROLE OF HDL AND TRIGLYCERIDES IN CORONARY HEART DISEASE^{27,28}

Although elevated plasma levels of LDL-c are clearly associated with increased CVD events, HDL-c has also emerged as an independent predictor of CHD along with fasting triglyceride (TGs) levels. However, as large number of completed large scale primary and secondary prevention trials have demonstrated significant reduction in cardiovascular events after the reduction in plasma levels of LDL, same is not true for triglyceride-HDL axis and data supporting pharmacologic intervention to decrease HDL-TG is far less compelling than data supporting LDL-C reduction.

DIET AND DYSLIPIDEMIA

The relationship between dietary fats and CHD, has been extensively investigated²⁸. As part of its first-line therapeutic lifestyle changes, the NCEP recommends a diet that includes 25 to 35 percent of calories from fats, with saturated fats accounting for less than 7 percent of fat intake²⁸.

The meta-analysis of more than 60 controlled trials in a study in 2003, showed that increased fat intake was not associated with increased risk of acquiring CHD. After that, many systematic reviews concluded that "substantial health benefits can occur from increase or decrease in specific type of fat consumed either as a replacement for other fats or for carbohydrates." This effect is thought to come about by changes in the quantity of cholesterol and lipoproteins that are synthesized by the body²⁹⁻³¹, limited to less than 200mg/day.

SECONDARY CAUSES OF HYPERLIPIDEMIA

1. Hormonal causes

- **Hypothyroidism:** cause elevated levels of LDL, triglycerides or both.
- **Pregnancy:** it can sometimes cause severe increase in plasma triglyceride levels on a background of lipoprotein lipase deficiency or unidentified genetic effect.
- **Estrogens:** they can elevate plasma triglyceride and HDL cholesterol levels, probably because of increases in hepatic VLDL and apo A-I production.

- **Renal disorders:** patients with chronic renal failure have a pattern of hypertriglyceridemia with reduced HDL level.

2. Liver disease

Obstructive liver disease, especially primary biliary cirrhosis, may lead to formation of an abnormal lipoprotein termed lipoprotein-X, it consists of an LDL like particle but with a marked reduction in cholesterol esters.

3. Medication

- **Thiazide diuretics:** can increase plasma triglyceride level.
- **Beta-adrenergic receptor blockers:** increase triglyceride and lower HDL levels.
- **Corticosteroids and immunosuppressive agents:** increase plasma triglyceride and lower HDL cholesterol levels.
- **Anti HIV drugs:** can cause severe lipoprotein disorders and increase in the prevalence of CHD among patients with chronic HIV infection treated with such agents³³.

DRUGS USED FOR THE TREATMENT OF DYSLIPIDEMIA

As discussed previously, the Lipid Research Clinic study³⁴ showed that bile acid binding resins could lower cholesterol levels in individuals with high baseline levels, but before 1987, the lipid lowering armamentarium was essentially limited to dietary changes, the bile acid sequestrants, the nicotinic acid derivatives, the fibrates and probucol.

History of discovery of hydroxymethylglutarate co-enzyme (HMG-CoA) reductase inhibitors

Cholesterol biosynthesis is a complex process involving more than 30 enzymes. The compound triparanol, which inhibits a late step in the pathway, was introduced into clinical use in mid 1960s, but was withdrawn shortly afterwards because of the development of cataract and other cutaneous adverse effects; attributed to tissue accumulation of desmosterol, the substrate for the inhibited enzyme^{35,36}. In contrast to desmosterol and other late stage intermediates, hydroxymethylglutarate, another substrate, is water soluble and there are alternative metabolic pathway for its breakdown. So inhibition of HMG-CoA reductase does not lead to build up of potentially toxic precursors^{35,36}.

The natural products with a powerful inhibitory effect on HMG-CoA reductase (compactin), were first discovered by the Japanese microbiologists Akira Endo³⁷ in a fermentation broth of *Penicillium citrinum* in the 1970s, during a search for antimicrobial agents. In 1978, Alberts, Chen and others found a potent inhibitor of HMG-CoA reductase in a fermentation broth of *Aspergillus terreus*, mevinoлин, which was later changed officially to lovastatin³⁸⁻⁴⁰. In February 1987, USFDA advisory panel voted unanimously for the approval of the drug lovastatin, after fully considering the various safety issues arising out of animal toxicology studies⁴¹⁻⁴³.

The second entrant, simvastatin was introduced in 1988, followed by pravastatin in 1991, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998, and finally rosuvastatin in 2003. The mean reduction in LDL cholesterol attainable with maximal recommended dose of different statins ranges from 35-55%.

Mechanism of action of Statins

The mechanism of decrease in plasma cholesterol by statins is not simply the reduction in cholesterol biosynthesis. It has been shown that inhibition of HMG-CoA reductase reduces levels of mevalonate, leading to a reduction in the regulatory sterol pool,

which in turn causes up-regulation of other enzymes of cholesterol biosynthesis and most importantly the LDL receptor. So statins in addition to above, also lower human plasma cholesterol by increasing uptake of LDL by LDL receptor. Statins also decrease the production of apolipoprotein B containing lipoproteins by the liver⁴⁴⁻⁴⁷.

Adverse effects of Statins

Statins produce significant toxicity at high doses in a variety of animal species. These effects include: increase in hepatic transaminases, atypical focal hyperplasia of the liver, squamous epithelial hyperplasia of the rat fore stomach (an organ not present in man), cataract, vascular lesions in the central nervous system, skeletal muscle toxicity and testicular degeneration, but fortunately most of these harmful effects have not been observed in patients of dyslipidemia taking these drugs.

Overall adverse reactions occur in less than 2 % of treated individuals⁴⁷⁻⁴⁹. It has been seen that around 1% to 3% of persons taking a statin will have dose-related elevated hepatic enzyme levels and require monitoring. The other important adverse effect of statins, the myopathy was first reported in a cardiac transplant patient receiving the immunosuppressive cyclosporine, in addition to gemfibrozil⁵⁰⁻⁵². There is a slight but statistically significant increase in physician reported diabetes in patients who were on long term statins⁵³.

OTHER AGENTS USED TO TREAT DYSLIPIDEMIA

Nicotinic acid derivatives: Its predominant effect on plasma lipid levels is to reduce production of VLDL particles in the liver, with subsequently results in reduced production of LDL particles. It is particularly effective in increasing HDL-c and in lowering triglyceride level, although exact mechanism of this action is not known. The major adverse effects are cutaneous flushing, GIT symptoms, liver enzyme elevation and an increase in uric acid⁵⁴⁻⁵⁶.

Fibric acid derivatives: Fibrates stimulate LPL activity thereby enhancing triglyceride hydrolysis and may decrease synthesis of VLDL triglyceride. Adverse effects occur in 5-10% of patients, gastrointestinal side effects are the most common, and at high doses fibrates may cause myositis and rhabdomyolysis. (may be specifically related to the concomitant use of statins and fibrates^{57,58}.)

Bile acid-sequestering agents (resins) These polymers have a molecular weight of over and function by binding the bile acids in the gastrointestinal lumen. An increase in bile acid excretion causes an increase production of bile acids in the liver. This result in a relative depletion of cholesterol from the liver cells, thereby inducing an increased level of hepatic LDL receptor activity and increase in catabolism of LDL-C and decreased plasma levels⁵⁹.

Fish oils: Fish oils contain polyunsaturated fatty acids, such as eicosapentanoic acid or docosahexaenoic acid; these fatty acids lower plasma triglyceride level and also have antithrombotic properties. They also decrease VLDL synthesis and VLDL apo B. A daily dose of 10g is required for maximal benefit on plasma triglyceride level⁶⁰.

Phytosterols: These are derivatives of cholesterol from plants and trees. They interfere with formation of micelles in the intestine and prevent intestinal cholesterol absorption.

NOVEL AGENTS TO TREAT DYSLIPIDEMIA

Although statins have been successful in reducing the cardiovascular events in a large patient population, there remains a large burden of residual cardiovascular risk. Some patients fail to attain desirable benefits from statins or combination therapies. Thus, there continues to a search for additional safe and effective lipid lowering drugs to modify atherosclerotic disease and reduce cardiovascular risk.

The majority of new compounds are in various stages of development and in initial phases of clinical testing with limited information about their safety and efficacy in human population. Presently only two compounds, mipomersen and MTP inhibitor lomitapide have received recommendations for use in patients of homozygous familial hypercholesterolemia by the drug advisory committee of United States Food and Drug Administration (USFDA) in Oct 2012 and both drugs are currently under FDA review.

A. Potential therapies to lower serum LDL-C⁶¹⁻⁶⁶

- 1. Apolipoprotein B Antisense (mipomersen):** It is a second generation antisense oligonucleotide causing inhibition of Apo B 100 production resulting in decrease in apo B, LDL-C and lipoprotein (a) in humans. The drug was approved by USFDA for the treatment of familial hypercholesterolemia with the boxed warning of liver toxicity. It is available for clinical use in many countries including India and is administered once weekly by subcutaneous injections. It has been shown to lower LDL-c by about 25% from the baseline and side effects include increase in liver transaminases level and increase in liver fat.
- 2. Microsomal triglyceride transfer protein (MTP) inhibitors:** MTP is lipid transfer protein necessary for formation of chylomicrons, VLDL and downstream remnants. Lomitapide which inhibits MTP was approved for the treatment of homozygous familial hypercholesterolemia and is available as oral formulation for clinical use. The increase in transaminases and liver fat accumulation is also seen with this compound.
- 3. Proprotein convertase subtilisin/kexin type-9:** Also known as PCSK9, is an enzyme that in humans is encoded by the PCSK9 gene. This gene encodes a proprotein convertase which leads to synthesis of a protein, which plays a major regulatory role in cholesterol homeostasis PCSK9. Drugs can inhibit PCSK9, leading to lower circulating levels of cholesterol. A number of monoclonal antibodies that bind to PCSK9 near the catalytic domain, that interact with the LDLR and hence inhibit the function of PCSK9, are in clinical trials. These include Evolocumab, bocoizumav and alirocumab⁶⁴⁻⁶⁶.
- 4. Squalene synthase inhibitors:** Squalene synthase is an enzyme localized to the membrane of endoplasmic reticulum. Squalene inhibitors have been shown to decrease the cholesterol as well as plasma triglycerides levels and may provide an alternative to HMG-CoA reductase inhibitors in some statin-intolerant patients. However after some promising initial trials with squalene synthase inhibitors like TAG-475, Zoragozic acid and RPR-107393, further progress has been extremely slow.
- 5. Thyroid hormone analogue:** The thyroid hormone lowers LDL-c by increasing expression of LDL receptor gene in the

liver, but causes undesirable effects on the heart and other tissues. Eprotrirome was developed to circumvent those problems. However clinical trials with eprotrirome in patients with heterozygous familial hypercholesterolemia, were discontinued after animal studies indicated that long term exposure could result in cartilage damage.

B. Investigational Therapies for Modulating HDL-C^{61,62,66,67}

1. **Cholesteryl ester transfer protein (CETP) inhibitor:** This class of drugs inhibits CETP which normally transfers cholesterol from HDL-c to very low density or low density lipoprotein. Inhibition of this process results in higher HDL levels and reduced LDL levels. Two compounds Anacetrapib and evacetrapib are presently undergoing clinical trials, the result of which will be known in 2017.
2. **ApoA-1 mimetics:** Apolipoprotein A-1 Milano (ETC-216, MDCO-216) is a naturally occurring mutated variant of the apolipoprotein A1 protein found in HDL-C. In 1990s, researchers at the Cedars-Sinai medical center showed that injection of synthetic version of the mutant apoA-1 into rabbits and mice could reverse vascular plaque build up. Currently no drug based on apoA-1 milano is available for clinical use. The progress with production and clinical trials is slow as it is a complex protein, which is very expensive to produce and also intravenous administration makes it less desirable for routine use.
3. **Liver X Receptor Agonists:** The liver x receptor is a member of the nuclear receptor family of transcription factors and is closely related to nuclear receptors such as PPAR, FXR and RXR. Liver x receptors are important regulators of cholesterol, fatty acids and glucose hemostasis. The treatment with LXR agonists lowers the cholesterol level in serum and liver and inhibits the development of atherosclerosis in murine disease models. LXR agonists which are currently undergoing clinical trials are GW3965 and hypocholeamide.
4. **Novel Peroxisome Proliferator-Activated Receptor Agonists (PPAR-a):** Fibrates, which are PPAR-alpha activators are well recognized for increasing HDL-c and lowering triglycerides. PPAR alpha is a nuclear receptor involved in the regulation of lipid metabolism. However, as they are only weak agonists of PPAR-a, the selective agonists are in phase of development, which are more potent than fibrates like dual PPAR-a/d agonists GFT50, which has been shown to decrease the triglycerides by 21% and increase HDL-c by 9% as compared to placebo.

DYSLIPIDEMIA MANAGEMENT AS HAS BEEN IN PRACTICE FOR PAST THREE DECADES.

National Cholesterol Education Programme (NCEP) has been instrumental in developing and formulating guidelines for management of the dyslipidemia both in patients with established cardiovascular disease and for primary prevention; in past 25 years. In 1988, NCEP-ATP-1 developed its first set of guidelines, followed in 1993 by NCEP-ATP-II recommendations. ATP-III guidelines, released in 2002, identify elevated LDL-C as the primary target of cholesterol lowering therapy and maintain attention on intensive treatment of patients with CHD^{68,69}. NCEP recommendations for primary prevention advises screening of all adults after 20 years of age, at least once in 5 years, as majority

of patients with lipoprotein disorders are asymptomatic, except for individuals with severe hypertriglyceridemia who can present with acute pancreatitis and those with familial lipoprotein disorders who may present with cutaneous manifestations [xanthoma]. The diagnosis of lipoprotein disorders depends on laboratory measurements and fasting lipid profile generally suffices for most lipoprotein disorders.

RISK ASSESSMENT: FIRST STEP IN RISK MANAGEMENT

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants. To better identify risk, physicians are advised to use an assessment tool that determines global risk calculated based on the data from the Framingham Heart Study (FHS). The tool calculates 10-year CHD risk or Framingham risk score (FRS) separately for men and women who do not have diabetes or cardiovascular disease (CVD) on the basis of presence of following risk factors-age, total cholesterol, HDL-c, systolic blood pressure, and cigarette smoking. The FRS consists of points that are allocated for various degree of risk associated with these five categories and summation of these points result in a percentage risk of having a cardiac event in next 10 years.

High risk: Patients with established CVD and diabetes plus patients with an estimated 10 year risk of more than 20% based on FRS. All individuals with established cardiovascular disease (CVD) and diabetes are placed under high risk group as these patients have exceedingly high risk for CVD events occurring in future.

Moderate risk: presence of 2 or more risk factors.

Low risk: presence of 0 to 1 risk factor.

For high risk patient, the NCEP recommended target for LDL-c was less than 100 mg/dl, with optional target of less than 70 mg/dl (which was considered desirable when the results of five major clinical outcome trials became available since the ATP-III guidelines were published (AHA/ACC update in 2006). In **moderate risk** patients, for primary prevention, the recommended LDL-c target was less than 130mg/dl and with the patients at **lowest risk**, the LDL-c target of less than 160mg/dl was considered desirable^{68,69}.

THE NEW GUIDELINES

On November 12, 2013 updated guidelines for the treatment of high blood cholesterol levels were released by the American College of Cardiology-American Heart Association Task force on Practice Guidelines. [first major guideline revision since 2002]. The new guidelines rely heavily on randomized controlled trials that involved fixed doses of HMG-CoA reductase inhibitors in patient population that is at risk of atherosclerotic cardiovascular disease. In this report, expert panel identified four subgroups of patients for whom the benefit of statins clearly outweighs the risk^{69,70}:

1. Individuals with clinically evident atherosclerotic cardiovascular disease (ASCVD).

2. Individuals with LDL - cholesterol level of > 190 mg/dl, such as those with familial hypercholesterolemia.
3. Individuals with type 1 or type 2 diabetes who are 40 to 75 years of age with LDL-c levels between 70 and 189 mg/dl and without evidence of atherosclerotic cardiovascular disease.
4. Individuals without diabetes and ASCVD but who a 10 year risk of atherosclerotic cardiovascular disease of at least 7.5% and LDL cholesterol level of > 70 mg/dl.

(The 10 year risk of atherosclerotic CVD is calculated with the use of new risk calculator available at <http://my.americanheart.org/cvriskcalculator>). The statin therapy is started in dyslipidemic patients based on new treatment guidelines⁷⁰ as follows:

% High intensity Statin therapy: For all high risk patients.

% Moderate intensity Statin therapy: For all those high risk patients who fail to tolerate high intensity therapy or patients with a 10 yr risk of ASCVD of less than 7.5%^{70,71}

% Low intensity treatment is recommended for all other patients.

The meaning of high intensity statin therapy is that the daily dose of drug is expected to lower LDL-C level by approximately e"50% on an average from the baseline. [Atorvastatin in the dose of 40-80 mg and Rosuvastatin 20-40 mg are recommended]. In moderate- intensity statin therapy, the daily dose of drug is expected to lower LDL-C level by approximately e"30% on an average. (Atorvastatin 10-20 mg, Rosuvastatin 5-10 mg, and Simvastatin 20-40 mg). Low intensity statin therapy is expected to lower LDL-C level by approximately <30% on an average^{70,71}.

The Patients who are unlikely to benefit from statin therapy :

1. The Patients with age of >75 years, unless clinical atherosclerotic cardiovascular disease is present.
2. The patients of end stage renal disease [ESRD] on hemodialysis: It has been stated in guidelines, that insufficient evidence was found for or against the use of statin therapy for the purpose of ASCVD risk reduction in this population⁷².
3. NYHA class II, III and IV heart failure patients: Again insufficient evidence was found for or against the use of statins in this group of patients⁷³.

Key Implication of new guidelines for medical professionals and how do they differ from existing guidelines in management of patients with dyslipidemia.

1. **Elimination of routine assessment of LDL cholesterol levels:** this is the most important and controversial recommendation of new guidelines, thus shifting the focus away from specific LDL goals to identifying those patients who are in need of high intensity, moderate intensity or no statin therapy. Instead of target levels (LDL levels of less than 100 in high risk and less than 130 in moderate risk patients as advocated by ATP III), percent reduction is intended to be used as an indication of response and adherence to therapy. According to Dr. Richard W. Grant of ADA, "That's the thing we struggle with the largest and the most. We have always checked LDL levels and on the basis of LDL-c level, started and adjusted the dose of statin to get under a certain level. That has been tattooed in every doctor's brain for past 15 yrs or so."⁷⁴ As cardiologist Harlan Krumholz summarized the changes, "The new message is don't chase targets, know your risk and - if you need drug therapy-use statins"⁷⁴. However how low is too low (for LDL levels) has not been clearly

defined in new guidelines. A systematic review did not identify any evidence of harm when LDL levels remain below 40mg/dl on statin therapy. The guidelines however provide a weak recommendation that the statin dose may be reduced if two consecutive LDL levels are below 40mg/dl.

2. **The use of new risk calculator:** immediately after the release of guidelines, there was considerable controversy and scrutiny regarding the fourth clinical scenario; the primary prevention in adults without established ASCVD and diabetes but with an estimated 10 year ASCVD risk of 7.5% Or higher. Uncertainties about the accuracy of new risk calculator (as the calculator itself has not been prospectively tested in clinical trials) have raised concerns about the wisdom of the newly lowered treatment threshold. On the basis of comparisons with findings in several large cohorts of persons without cardiovascular disease, the new calculator appears to overestimate the observed risks. Would the new guidelines lead to massive and unjustified overtreatment of millions of people? It has been estimated that about 33 millions Americans in the age group of 40-70 years are predicted to have 10 year risk of CVD 7.5% or higher based on new guidelines. Therefore evaluation of the cost effectiveness of plasma cholesterol lowering therapy assumes enormous importance because of the size of the potential population for intervention of what can be a lifelong medical therapy. To summarise, the main criticism of the guidelines focused on flawed methods (problem with the risk calculation), ethics (conflicts of interest with involvement of pharmaceutical companies) and inferences (too many people offered treatment)⁷⁵. However two new studies published in second half of 2015, have come up with important evidence to back up the recommendations with researchers reporting that new guidelines were more accurate and efficient at identifying people with increased risk of cardiovascular disease^{76,77}.
3. **The CVD Vs ASCVD:** In new guidelines the term ASCVD has been used instead of CVD, as previous recommendations focused on coronary artery disease outcomes of non-fatal myocardial infarction and CVD deaths. The new guidelines also incorporate non-fatal and fatal stroke as an outcome. As a result, baseline risk may increase for certain patient population and benefit of treating with specific doses of statin therapy also increases. ASCVD events include acute coronary syndrome, h/o myocardial infarction (MI), stable or unstable angina, coronary revascularization, stroke or TIA and peripheral revascularization.
4. **Avoidance of cholesterol lowering therapy** in certain patient groups who have not been shown to get any benefit from these drugs from extensive review of clinical trials. This will help clinicians in reducing the cost of treatment and also the undesirable side effects in an important group of patients who was being prescribed these drugs before the publication of new guidelines. The new guidelines may help reduce some under-treatment and some over-treatment of patients with CVD with evidence based proven therapy. However, for primary prevention these guidelines may lead to some over-treatment.
5. **Avoidance of non-statin LDL-c lowering agents:** The new guidelines released by ACC-AHA task force noted that data available from the review of clinical trials, did not support the use of non-statin cholesterol lowering drugs, either

- combined with statin therapy or in statin-intolerant patients-
6. These guidelines also advise clinicians on trying **alternative formulations of statins** in difficult patients (who are unable to tolerate these agents because of side effects) before calling it quits, thus ensuring that benefits reach those who need them most.
 7. **Diminished use of surrogate markers** like C-reactive protein or calcium scores in new guidelines as opposed to previous one, which advocated consideration of these markers of risk apart from Framingham risk score while assessing the patient's overall risk.
 8. **Monitoring of treatment:** Persons receiving statin therapy should be monitored for muscle and hepatic injury and for new onset diabetes, although both primary and secondary prevention trials indicate that no clinically significant liver problems are associated with statin therapy. Moreover, to avoid unnecessary discontinuation of statins, it is desirable to obtain a history of prior or current muscular symptoms to establish a baseline creatinine kinase (CK) levels before initiating statins.
 9. **Hypertriglyceridemia :** In new guidelines, the medication to lower triglyceride levels are advocated only when serum triglyceride level is above 1000mg/dl for lowering the risk of pancreatitis ; instead of 500mg/dl as recommended in ATP III guidelines.
 10. In the end, the most convincing argument in favour of new guidelines is that they are based on the results and analysis of more than two decades of randomized, controlled clinical trials and thus claim to provide evidence based proven therapy to individuals at risk of CVD. But **the final verdict** will only be known when large number of patients will receive recommended high doses for prolonged periods with the anticipated fall in cardiovascular event rates.

SOME UNRESOLVED ISSUES AND FUTURE DIRECTIONS

Although CHD is still the leading cause of death in most industrialized countries, in many western countries age adjusted CHD mortality has declined by a about a half from its peak in the 1960's. There are many reasons for this, not all well understood, but certainly the availability and use of drugs including not only statins, but also α -adrenoreceptor antagonist, aspirin and angiotensin converting enzymes inhibitors, all proven by multiple large placebo controlled trials to reduce risk, is a major contributor. The following are going to be major points of interest as for as future research is concerned:

- Given trial evidence that some patients with low global risk benefit markedly from statin therapy⁷⁸, where as some patients with very high risk, like those suffering from chronic kidney disease on maintenance dialysis and chronic heart failure don't get desired benefit from statins, it becomes necessary to reconsider methods for selecting populations for treatment with statin therapy.
- Role of high-sensitivity C-reactive protein (hs-CRP levels higher than 2 mg/L) levels⁷⁹ as an independent risk factor and identification of other nobel risk factors as large number of patients of coronary artery disease do not have dyslipidemia.
- Are these guidelines, which are based on the clinical trials involving mainly the western white population, applicable to other ethnic groups like Indians?

- Importance of quality of LDL particles rather than quantity in cardiovascular diseases as some clinical studies have indicated that people with small size and more dense LDL particles exhibit an increased propensity for oxidative damage⁸⁰.
- Genetic understanding of cardiovascular risk and gene therapy.

REFERENCES

1. Philip Greenland,MD, Michael S,Lauer, MD. Cholesterol lowering in 2015, *Still Answering Questions About How and in Whom*, JAMA2015;314(28);127-128doi:10.1001/jama.2015.7434
2. Murrarv C JL, Lopez AD. *The Global Burden of Disease*, Cambridge. Mass, Harvard School of public Health.1996
3. *World Health Report 2003: Shaping the Future*, Geneva, World Health Organisation, 2003.
4. Yousuf S, Hawken S, Ounpuv S, et al. Effect Of potentially modifiable risk factors associated with myocardial infarction in 52 countries (The interheart study) - A Case control study. *Lancet*, 364:937, 2004.
5. NIH consensus development conference. Lowering blood cholesterol to prevent heart disease. NIH consensus development conference statement. *Nutr. Rev.* 43, 283-291, 1985.
6. Jonathan A. Tobert. *Lovastatin and beyond: The history of HMG-CoA reductase inhibitors*. *Nature reviews/drug discovery*, Volume 2, July 2003.
7. Bhatt DL, Steg PG, Ohmen E, Rother J, Wilson PW et al. International prevalence, recognition and treatment of cardiovascular risk factors in outpatients with atherothrombosis, *JAMA*, 295:180; 2006.
8. Kuulasmaar, Tunstall – Pedoe A, Dobson A et al. Estimation of contribution of changes in classic risk factors to trends in Coronary event rates across the WHOMONICA Project Populations. *Lancet*, 355: 675; 2000.
9. Steinberg D and Gotto, AM Jr. Preventing coronary artery disease by lowering cholesterol levels: fifty years from bench to bedside - An excellent concise historical overview. *JAMA*, 282, 2043-2050; 1999.
10. Kannel, WB. Clinical misconceptions dispelled by epidemiological research. *Circulation* 92, 3350-3360; 1995.
11. Davey-Smith G and Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ*, 304, 431-434; 1992.
12. Blankenhorn, DH et al. Coronary angiographic changes with lovastatin therapy. *The monitored Atherosclerosis Ann. Intern. Med.*, 119, 969-976; 1993.
13. MAAS investigators. Effect of simvastain on coronary atheroma: the multicenter Anti-Atheroma study (MAAS). *Lancet*, 334, 663-638; 1994.
14. Jukema, JW et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels - The Regression Growth Evaluation Statin Study (REGRESS). *Circulation*, 91, 2528-2540; 1995.
15. Walters D et al. Effect of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. *The Canadian coronary atherosclerosis intervention trial*. *Circulation* 89, 959-968 (1994).
16. Scandinavian simvastain survival study group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastain survival study (4s). *Lancet*, 334, 1383-1389; 1994.
17. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial, *Lancet* 360, 7-22; 2002.
18. Sarci-Thomas MG, Curtiss I, Parks JS et al. The Hydrophobic face orientation of apolipoprotein A-I Amphipathic helix domain 143:164 regulates lecithin: cholesterol acyltransferase activation, *J Biol Chem*, 273: 11776; 1998.
19. Hiltunen TP, Luoma JS, Nikkari T, Yia-Hertuala S. Expression of LDL receptor, VLDL receptor, LDL receptor- related protein, and scavenger receptor in Rabbit atherosclerosis lesions. Marked Induction of scavenger receptor and VLDL receptor Expression during lesion development. *Circulation*, 97: 1079; 1998.
20. Nimpf J, Schneider WJ. The VLDL receptor: an LDL receptor relative with eight ligand binding repeats. *LR8. Atherosclerosis*, 141: 191, 1998.
21. Kruth HS. Sequestration of aggregated low density lipoproteins by macrophages. *Curr Opin Lipidol*, 13:483, 2002
22. Radar DJ. Mechanism of disease: HDL metabolism as a target for novel therapies. *Nat Clin Pract Cardiovasc Med*, 4: 102, 2007
23. Mensic R P, Rock PL, Kester AD, Katan MBV. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and serum lipids and apolipoproteins. A meta analysis of 60 controlled trials. *Am J Clin Nutr*, 77: 1146, 2003.
24. Kris-Etherton P, Daniels SR, Eckel RH et al. For the Nutrition Committee of the American Heart Association. Summary of the Scientific Conference on Dietary Fatty Acids and Cardiovascular Health. *Circulation*; 103: 1034-39, 2001.
25. Grundy S, Vega GL. Plasma Cholesterol responsiveness to saturated fatty acids. *Am*

- J Clin Nutr*, 47: 822-24, 1998.
26. Mozaffarian D. Effects of dietary fats versus carbohydrates on coronary heart disease: A review of the evidence. *Curr Atheroscler Rep*, 7: 435, 2005.
 27. Mozaffarian D, Wallace S, Micha R. Effects on coronary heart disease of increasing polyunsaturated fats in place of saturated fat: A systematic review and meta-analysis of randomized controlled trials. *Plos Med* 7: e1000250, 2010.
 28. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of high Blood Cholesterol in Adults. (Adults Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of high Blood Cholesterol in Adults. (Adults Treatment Panel III) final report. *Circulation*; 106: 3143-421, 2002.
 29. Riccardi G, Rivellese AA, Giacco R. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr*, 87: 269S, 2008.
 30. Mensink RP, Zock PL, Kaster AD et al. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta analysis of 60 control trials. *Am J Clin Nutr*, 77: 1146, 2003.
 31. Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. *Eur J Clin Nutr*, 63(suppl 2): S22, 2009.
 32. Whelton SP, Hyre AD, Pedersen B et al: Effect of dietary fibre intake on blood pressure. A meta-analysis of randomized, controlled clinical trials. *J Hypertension* 23:475, 2005.
 33. DAD Study Group: Friis-Moller N, Reiss P, Sabin CA et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Eng J Med*, 356: 1723, 2007.
 34. Lipid research clinics program. The Lipid Research Clinics Coronary Primary Prevention Trial Results. Reduction in incidence of coronary heart disease. *JAMA*, 251, 351-364, 1984.
 35. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 360, 2-3; 2002.
 36. Kirby TJ. Cataracts produced by Triparanon (Mer 29): *Trans. Am. Ophthalmol, Soc*, 65, 494-543; 1967.
 37. Endo A, Kuroda M. & Tsujita Y. ML-236A, ML-236B, ML-236C, new inhibitors of cholesterol synthesis produced by penicillium citrinium. *J. Antibiot. (Tokyo)*, 29, 1346-1348, 1976.
 38. Havel, RJ et al. Lovastatin (mevinolin) in the treatment of heterozygous familial hypercholesterolaemia. *Q. J. Med*, 107, 609-615; 1987.
 39. Tobert, JA et al. Cholesterol-lowering effects of mevinolin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, in healthy volunteers. *J. Clin. Invest.* 69, 913-919, 1982.
 40. Lovastatin study group 2. Therapeutic response to lovastatin (mevinolin) in non familial hypercholesterolemia. A Multicenter study. *JAMA*, 256, 2829-2834; 1986.
 41. Pappu, AS and Illingworth DR. Contrasting effects of lovastatin and cholestyramine on low density lipoprotein cholesterol and 24-hour urinary mevalonate excretion in patients with heterozygous familial hypercholesterolemia. *J. Lab. Clin. Med.*, 114, 554-562, 1989.
 42. Nourmova, RP et al. Plasma mevalonic acid, an index of cholesterol synthesis in vivo, and responsiveness of HMG CoA reductase inhibitors in familial hypercholesterolaemia. *Atherosclerosis* 119, 203-213, 1996.
 43. Illingworth DR and Sexton GJ: Hypercholesterolemic effects of Mevinolin in patients with heterozygous familial hypercholesterolemia *J Clin. Invest.* 74, 1972-1978; 1984.
 44. Brown MS and Goldstein JL. Multivalent feedback regulation of HMG CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. *J. Lipid Res.* 21, 505-517, 1980.
 45. Vita JA et al. Effects of cholesterol-lowering therapy on coronary endothelial vasomotor function in patients with coronary artery disease. *Circulation* 102, 846-851; 2000.
 46. Alberts AW et al. Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl - Coenzyme A reductase and a cholesterol lowering agent: *Proc Nat Acad Sci*; 77, 3957-3961; 1980.
 47. Beard SL. HMG-CoA reductase inhibitors: assessing differences in drug interaction and safety profiles. *J Am Pharm Assoc*; 40: 637-44; 2000.
 48. Gerson RJ et al. Animal safety and toxicology of simvastatin and related 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Am. J. Med*; 87, 28s-38s; 1989.
 49. Smith PF et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors induced myopathy in the rat: cyclosporine A interaction and mechanism studies. *J. Pharmacol. Exp. Ther.* 257, 1225-1235, 1991.
 50. Norman DJ, Illingworth DR, Munson J and Hosenpud J. Myolysis and acute renal failure in a heart transplant receiving lovastatin. *N. Engl J. Med*, 318, 46-47, 1988.
 51. Pierce LR, Wysowski DK and Gross TP. Myopathy and Rhabdomyolysis associated with lovastatin-Gemfibrozil combination therapy. *JAMA*, 264, 71-75, 1990.
 52. Ballantyne, CM et al. Risk of myopathy with statin therapy in high-risk patients. *Arch. Intern. Med.*, 163, 553-564, 2003.
 53. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359: 2195, 2008.
 54. Carlson LA, Hampsten A, Asplund A. Effects of hyperlipidemic drugs on serum levels of lipoprotein LP (a) in hyperlipidemic subjects treated with nicotinic acid. *J Int Med*, 226, 271-76, 1989.
 55. Guyton JR, Bays HE. Safety consideration with niacin therapy. *Am J Cardiol*, 99 (suppl):22C, 2007.
 56. Knopp RH: Evaluating Niacin in its various forms. *Am J Cardiol*, 86: 51L-56L, 2000.
 57. Frick MJ, Elo O, Haapa K et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*, 317:1237-45, 1987.
 58. Robins SJ, Collins D, Wittes JT et al: VA-HIT Study Group-Veterans Affairs high Density Lipoprotein Intervention Trial: Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*, 285; 1585-91, 2001.
 59. Hunnigake DB. *Bile Acid Sequestrants*. In: Rifkind BM ed. *Drug Treatment of Hyperlipidemia* New York: Marcel Dekker 1991.
 60. He K, Song Y, Davigulus ML et al: Accumulated Evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* 109: 2705, 2004.
 61. Berter PJ, Caulfield M, Eriksen M et al. Effect of Torcetrapib in patients at high risk for coronary events. *N Engl J Med*, 357: 2109, 2007.
 62. Nissen SE, Tardif JC, Nicholls SJ et al. Effects of Torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*, 356: 1620; 2007.
 63. Stein EA. Other Therapies for reducing low-density lipoprotein cholesterol: medication in development. *Endocrinol Metab Clin North Am*, 38: 99-119, 2009.
 64. Davidson MH. Novel nonstatin strategies to lower low density lipoprotein cholesterol. *Curr Atheroscler Rep.*, 11: 67-70, 2009.
 65. doi:10.2146/ajhp130592 *American journal of Health System Pharmacy* June 15, 2014 Vol 71 no 12 1001-1008
 66. Peter P Toth. The impact of HDL-C Elevation on Patient outcomes: What do the data tell us? *Medscape Education Cardiology, CME Released 09/07/2010*.
 67. Ladenson PW, Kristensen JD, Ridgway EC, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med*, 362: 906-916, 2010.
 68. Grundy, SM, Cleeman, JJ, Bairer Merz, CN et al. Implications of recent clinical trials for the National Cholesterol Education Programme Adult Treatment Panel III Guidelines. *Circulation*, 100: 227-39; 2004.
 69. Marra AK, Lloyd-Jones DM. Systematic Examination of updated Framingham Heart Study General cardiovascular risk profile. *Circulation*, 120: 384-390, 2009.
 70. Keaney, JF Jr, Curfman GD and Jarcho JA. A Pragmatic view of the New Cholesterol Treatment Guidelines. *N Eng J Med*, 370: 3, 275-278, January 16, 2014
 71. Stone NJ, Robinson J, Lichtenstein AH et al. ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, 129 (25 Suppl 2): S1-S45, June 24, 2014.
 72. Fellstrom BC, Jardine AG, Schmieder RE et al. Rosuvastatin and cardiovascular disease in patients undergoing hemodialysis. *N Engl J Med*, 360: 1395, 2009
 73. Tavazzi L, Maggioni AP, Marchioli R et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): A randomised double blind, placebo controlled trial. *Lancet*, 372: 1231, 2008.
 74. ADA endorses ACC/AHA Guidelines, with caveats. *Medscape Medical News* December 24, 2014.
 75. John P.A. Loannidis, MD, DSc: More Than a Billion People Taking Statins? Potential Implications of the New Cardiovascular Guidelines. *JAMA*. 2014;311(5):463-464. doi:10.1001/jama.2013.28465
 76. Amit Pursnani, MD^{1,2}; Joseph M. Massaro, PhD^{3,4}; Ralph B. D'Agostino Sr, PhD, Christopher J. O'Donnell, MD, MPH^{4,6,7}; Udo Hoffmann, MD, MPH, Guideline-Based Statin Eligibility, Coronary Artery Calcification, and Cardiovascular events *JAMA* 2015; 314(2):134-141 doi:10.1001/jama.2015.7515
 77. Ankur Pandya, PhD¹; Stephen Sy, MS¹; Sylvia Cho, MHS¹; Milton C. Weinstein, PhD¹; Thomas A. Gaziano, MD, MSc. Cost-Effectiveness of 10 year Risk Thresholds for Initiation of Statin Therapy for Primary Prevention of Cardiovascular Disease. *JAMA* 2015; 314(2):142-150. doi:10.1001/jama.2015.6822
 78. Nakamura H, Arakawa K, Itakura H, et al: Primary prevention of cardiovascular disease with pravastatin in Japan. (MEGA Study): A prospective randomised controlled trial. *Lancet*, 368: 1155, 2006.
 79. McMurray JJ, Kjekshus J, Gullestad L, et al. Effects of statin therapy according to plasma high-sensitivity C-reactive protein concentration in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA):
 80. JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-Density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA*, 260 (13), 1917-1921, 1988.