Statins in CVD prevention

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Abstract

Cardiovascular diseases are one of the leading causes of mortality and morbidity worldwide. Dyslipidemia, particularly LDL cholesterol, being an important major risk factor, plays a robust role in the pathogenesis of atherosclerosis. Different drugs have shown variable efficacy in clinical trials in treating dyslipidemia. Statins have been the most effective and best tolerated agents amongst them. Statins have proved their efficacy in slowing progression and even inducing regression of atherosclerotic plaque. These drugs also have a pleiotropic effect, e.g., improvement of endothelial function, anticoagulant of atherosclerotic plaque. These drugs also have a pleiotropic effect, e.g., improvement of endothelial function, anticoagulant of atherosclerotic plaque. These drugs also have a pleiotropic effect, e.g., improvement of endothelial function, anticoagulant

Key Words

• Dyslipidemia
• Statins
• Primary prevention
• Secondary prevention

Introduction

Today, cardiovascular diseases (CVD) are the leading cause of mortality as well as morbidity worldwide. In 2001, CVD was responsible for 29% of all deaths. By 2020, the world population is expected to reach 8.2 billion, 33% of all deaths will be caused by CVD. By 2030, WHO predicts that worldwide, CVD will be responsible for 24.2 million deaths.1

Lipids and atherosclerosis

Dyslipidemia is among the most important and major risk factor of cardiovascular diseases and has been addressed continuously for decades. Hypercholesterolemia was linked to atherosclerosis long back in 1940s and this was followed by discovery of abnormal lipoprotein fractions (low HDL and high LDL levels) as culprit agents.

In the late 1970s, the Pooling Project made the assertion that LDL among the different lipoprotein fractions, had the strongest association with CHD. Meanwhile, the Framingham Study demonstrated the cardioprotective role of HDL, noting that it was inversely related to CHD risk independent of LDL levels.2

Lowering lipids with drugs specifically targeting cholesterol was initially attempted with fibrates. Clofibrate was studied in a World Health Organisation initiated randomized controlled primary prevention trial and it was found that 9% reduction in cholesterol level resulted in 25% decrease in myocardial infarction and 20% decrease in CHD events after more than 5 years of follow-up.3 It was soon followed by another, the Coronary Drug Project using niacin, estrogen, or dextrothyroxine or placebo. This study, however, failed to demonstrate any mortality.

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References

benefit with fibrates, rather increased prevalence of CVD and gall bladder stones were found. Niacin was found to reduce recurrent MI but without any benefit in 5 year mortality rate largely because of non compliance with the drug for its side effects. Search for safer and more effective drug continued and cholestyramine, a bile acid sequestrant, was introduced in Lipid Research Clinics Coronary Primary Prevention Trial which resulted in 12% reduction in LDL-C level along with 19% decrease in CHD events.

As compared to clofibrate, gemfibrozil—a fibric acid derivative, showed a better safety and tolerability profile in Helsinki Heart Study. In addition to LDL-C lowering by 10% it also showed rapid increase in HDL-C by almost 16% and triglyceride reduction by 43%. There was 34% decrease in CHD events, however, mortality benefit was still a dream till 1980s when the latest class of drug, statins, were introduced. It was found that statins have been one of the landmark events of last century. Lovastatin was the first approved molecule for clinical use and its dramatic efficacy of different statins on serum lipid levels and to explore the association between those changes and cardiac events were soon recognized. It not only reduced LDL-C by 28–45%, but also was far more effective than cholestyramine, probucol and gemfibrozil.

**Evolution**

Statins have been the most effective and best tolerated agents for treating dyslipidemia. These drugs competitively inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis. They also reduce triacylglycerol and raise HDL-C. Although the exact mechanism is yet to be established. Historically, statins were first isolated from Penicillium citrinum, a mold, which wasamed, as inhibitors of cholesterol biosynthesis. Although mevastatin was the first drug to be studied in human, lovastatin was the first to be approved for human use, followed by simvastatin, fenofibrate, fluvastatin, atorvastatin, pitavastatin and rosuvastatin were introduced. A recent comparative study was done to compare the efficacy of different statins on serum lipid levels and to explore the association between these changes and cardiac events in patients after percutaneous coronary intervention (PCI). Each statin significantly prevented major adverse cardiac events compared with no statin, and pitavastatin was the most effective of all. It was concluded that the extent of changes in LDL-C and HDL-C with statins would independently alter the risk of cardiac events.

The cardioprotective effects of statins have been found to be due to factors beyond lipid lowering. These pleiotropic effects include improvement of endothelial function, anticoagulant and anti-inflammatory properties of statins. Reduction in LDL-C level and improvement of lipid profile with statins have substantially reduced clinical events beyond that could be expected with improvement of angiographic patterns alone. In the setting of acute coronary syndrome, statins have been found to stabilize vulnerable plaque by reducing the lipid core, lipid laden macrophages, and thereby causing sizable reduction in clinical events.

**Primary prevention – Evidence**

Almost all primary prevention studies have demonstrated significant mortality benefits. In the West of Scotland Coronary Prevention Study (WOSCOPS), 6595 patients with LDL-C values of 192 mg/dl were treated with Pravastatin 40 mg/day against placebo. There was 31% (p<0.001) relative and 2.4% absolute risk reduction in CHD-death and nonfatal myocardial infarction. In another placebo controlled trial, Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex-CAPS), done on 6605 patients with low HDL-C, and of LDL-C at 150 mg/dl Lovastatin after an average follow-up of 5.2 years was found to be beneficial in reducing major cardiac events by 37%. The MEGA study done with pravastatin in relatively older population with a total cholesterol of 220–270 mg/dl revealed similar benefits. The lipid lowering arm of the Anglo-Scandinavian Cardiovascular Outcome Trial (ASCOT-LLA) recruited over 10,000 hypertensive patients with three or more CHD risk factors, to low dose atorvastatin or placebo in patients having relatively average LDL cholesterol levels of 133 mg/dl yet high global risk of CHD. The Atorvastatin versus Diabetes Study (CARDS) was conducted in smaller (2838) number of patients with type 2 diabetes with one or more of the following cardiovascular risk factors: retinopathy, albuminuria, current smoking or hypertension. Both these placebo controlled studies with atorvastatin showed significant risk reduction in CHD death, nonfatal MI and acute coronary syndrome, coronary revascularization, and stroke.

In recent years, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin, JUPITER 31, has been a landmark trial which revolutionized the concept of primary prevention. It was conducted in over 18,000 healthy individuals with normal cholesterol levels and high reactive protein levels. The study was terminated prematurely as significant reduction in myocardial infarction, stroke and total mortality was evident. In a criticism, it was shown that the study population was more intent on actually low risk and the benefit of statin therapy, in the form of reduction in CVD events by 45–49%, were restricted to the intermediate risk group only. In general, all evidences are in favor of using statins in all diabetic individuals and women, non-whites and older individuals were equally benefited as their counterparts. So there is ample trial data evidence to suggest the unquestionable benefit of statins in the primary prevention of CHD. Trials have also been conducted in special population with statins as a primary preventive strategy like the 4D study done in diabetics undergoing dialysis with atorvastatin. The AURORA study done in patients with acute coronary syndrome with rosuvastatin and the CORONA study done in patients of heart failure, however, failed to demonstrate any significant decrease of CV events, although ongoing trials are in place to address the role of statins as a primary prevention tool in these diverse population groups.

**Secondary prevention**

Studies done in stable CHD patients also have consistently shown the benefits. In Scandinavian Simvastatin Survival Study (4S), Simvastatin was tried in CHD patients with high LDL, all group of patients experienced similar benefits including those whose baseline LDL was <100 mg/dl and total mortality reduction was found to be quite significant, relative reduction of total mortality was 30% and absolute reduction 3.3%. Other studies have also convincingly demonstrated that not only those with hypercholesterolemia but also those with normal lipid profile are benefited from statin therapy. Cholesterol and Recurrent Events (CARE) study showed that the benefit of cholesterol-lowering therapy extends to the majority of patients with coronary disease who have average cholesterol levels. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, statin therapy reduced mortality from coronary heart disease and overall mortality, as compared with the rates in the placebo group, as well as the incidence of all the prespecified cardiovascular events in patients with a history of myocardial infarction or unstable angina who had a broad range of initial cholesterol levels. Pravastatin treatment in patients with average cholesterol levels undergoing their first successful PCI significantly reduces the risk of major adverse cardiac events and overall mortality by 20%. In another study, ALLIANCE, an aggressive, focused atorvastatin therapy management strategy outperformed usual care in health maintenance organization and Veterans Administration clinic patients with CHD.

A number of trials have evaluated the concept of ‘the lower the better’. Treat to New Targets (TNT), a large trial done with 10,001 patients evaluating efficacy of higher dose 80 mg atorvastatin with standard 10 mg dose, found that intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day. A head to head trial with atorvastatin 80 mg/day vs. simvastatin 20 mg/day, Incremental Decrease in End Points throughAggressive Lipid Lowering (IDEAL) study showed more favorable result for atorvastatin in respect to reduction in CHD death, nonfatal MI or resuscitated cardiac arrest and stroke.

A study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trials have shown that more intensive reduction of LDL-C in patients at high or very high risk of recurrent CAD events reduces risk further compared with more modest LDL-C lowering. There are also robust evidences of the benefit of statins in high risk ACS patients as evidenced in the following three major landmark trials.

Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) was a landmark trial in patients with acute coronary syndrome which demonstrated dramatic reduction of total mortality, nonfatal MI, resuscitated cardiac arrest, or recurrent acute coronary syndrome with high dose (80 mg) atorvastatin as early as 4 months of treatment. Comparative evaluation of high dose atorvastatin 80 mg/day and pravastatin 40 mg in Pravastatin or Atorvastatin: Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI 22) found superiority of atorvastatin in achieving primary and all-cause mortality benefits in acute coronary syndrome. In Aggrastat-to-Zocor (A-to-Z) study, patients on tirofiban or heparin were randomized to receive either simvastatin, 40 or 80 mg/day or diet plus simvastatin, 20 mg/day. The observed reduction in cardiovascular death, nonfatal MI, acute coronary syndrome or stroke events, however, did not reach statistical significance.

The multicenter, randomized Clinical Outcomes Utilizing Rosuvastatin Evaluation of the Effectiveness and Safety (COURAGE) trial tested the hypothesis that revascularization plus optimal medical therapy, of course including statins, would be superior to optimal medical therapy alone. After 5 years, there were no significant differences in any of the prespecified outcomes.

Continuous endeavor has been dedicated in search of discovering newer actions of this miraculous molecule. Statins have also been found to cause regression of atherosclerotic plaque. The Reversal of Atherosclerosis with Lipitor (REVERSAL) trial used intravascular ultrasoundography (IVUS) to examine the effect of differing degrees of lipid lowering on plaque volume using

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### Evolution

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### Secondary prevention

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Table 1: The NECP-ATP III goals for LDL cholesterol and cutpoints for therapeutic lifestyle changes (TLCs) and drug therapy in different risk categories

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL goal</th>
<th>LDL level at which to initiate TLCs</th>
<th>LDL level at which to consider drug therapy</th>
<th>Therapeutic lifestyle change (Lifestyle intervention)</th>
<th>Drug intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents (10 year risk &gt;20%)</td>
<td>&lt;100 mg/dl</td>
<td>&gt;100 mg/dl</td>
<td>+100 mg/dl (100–129 mg/dl)</td>
<td>Drug optional</td>
<td>Lifestyle intervention</td>
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<tr>
<td>2+ risk factors (10 year risk &gt;20%)</td>
<td>&lt;130 mg/dl</td>
<td>&gt;130 mg/dl</td>
<td>+130 mg/dl</td>
<td>Drug optional</td>
<td>Lifestyle intervention</td>
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<tr>
<td>0-1 risk factor</td>
<td>&lt;160 mg/dl</td>
<td>&gt;160 mg/dl</td>
<td>+160 mg/dl</td>
<td>Lipid lowering drug optional</td>
<td>Lifestyle intervention</td>
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Table 2: ESC: Intervention strategy as a function of total CV risk and LDL-C level

<table>
<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C level</th>
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<tbody>
<tr>
<td>&lt;70</td>
<td>100 to &lt;155</td>
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<tr>
<td>70 to &gt;100</td>
<td>155 to &gt;190</td>
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<td>&gt;190</td>
<td>&gt;190</td>
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</table>

Class/Level | I/C | I/C | I/C | I/C | I/C | I/C | I/C | I/C |
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</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>No lipid intervention</td>
<td>No lipid intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Drug intervention</td>
<td></td>
</tr>
<tr>
<td>&gt;1 to 5</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Consider drug if uncontrolled</td>
<td>Lifestyle intervention</td>
<td>Consider drug if uncontrolled</td>
<td>Lifestyle intervention</td>
<td>Drug intervention</td>
</tr>
<tr>
<td>&gt;5 to 10</td>
<td>Lifestyle intervention</td>
<td>Consider drug</td>
<td>Lifestyle intervention</td>
<td>Consider drug</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Lifestyle intervention</td>
<td>Consider drug</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Lifestyle intervention</td>
<td>Consider drug</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
<td>Drug intervention</td>
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Table 3: ESC: Recommendation for treatment targets for LDL-C

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at very high CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE &gt;10%)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients at high CV risk (high baseline risk, cardiovascular disease, moderate to severe CKD or a SCORE &gt;7%)</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>In patients at moderate high CV risk (moderate baseline risk, cardiovascular disease)</td>
<td>IIb</td>
<td>B</td>
</tr>
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Panel III (NCEP-ATP III) guidelines recommend initiation of lipid-lowering drug therapy if LDL level is more than 190 mg/dl (optional if LDL level less than 160 mg/dl for primary prevention of CHD and stroke in low risk patients). Pharmacologic treatment, to date, is not advocated for healthy individuals with LDL level less than 160 mg/dl, unless 2 or more CVD risk factors are present. For secondary prevention initiation of statin therapy is recommended to achieve a goal of LDL level less than 100 mg/dl and to achieve a 30 to 40% reduction in LDL levels in high-risk individuals. Goal of less than 70 mg/dl using high-dose statin treatment is considered desirable. In patients with acute coronary syndrome, it is strongly advocated that statin therapy be started regardless of baseline LDL levels.

Current recommendation (Table 1)

American Heart Association/American College of Cardiology, American Diabetes Association, and National Kidney Foundation1 all advocate an aggressive secondary prevention approach to lipid-lowering therapy in diabetics, patients with peripheral vascular disease (PVD) and chronic kidney disease (CKD) recommending the use of statins to achieve a target LDL level of at least 100 mg/dl, similar to that of patients with established CHD (Table 2). There has been continuous attempt to promote more and more use of statins considering its vast potential to alter the atherosclerotic process, however, side effects and financial constraints have been the limitations. In the latest European Society of Cardiology (ESC) recommendation consideration for drug therapy has been recommended if LDL-C levels more than 190 mg/dl in low risk, more than 100 mg/dl in moderate risk and more than 70 mg/dl in high risk very high risk individuals. In very high risk patients (established CVD, type 2 diabetes mellitus, type 1 diabetes mellitus with end organ damage, moderate to severe CKD) target serum LDL-C level less than 70 mg/dl or more than or equal to 50% reduction has been advocated (Table 3).
atorvastatin 80 mg or pravastatin 40 mg. Over 18 months, atorvastatin lowered LDL-C greater (to 2.04 mmol/l) than pravastatin (to 2.84 mmol/l) and atheroma volume progressed with pravastatin by 2.7% whilst remaining stable in atorvastatin group (-0.4%). The first study which actually demonstrated regression of plaque size was the ASTEROID study which showed that rosuvastatin therapy with 40 mg/day for 24 months resulted in LDL lowering to 60 mg/dl, was associated with a reduction of PAV (79%) and TAV (6.8%) thereby promoting coronary atherosclerosis regression.

Simvastatin was tried in Heart Protection Study (HPS) in patients with established CHD, non-coronary atherosclerosis or diabetes and significant reduction in total mortality was seen. Similarly, PROSPER study showed significant reduction in CHD death, nonfatal MI or stroke where pravastatin was tried in elderly for primary and secondary prevention strategy. ALLHAT-LLT was conducted to determine whether pravastatin compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor. It was found that pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study, high-dose extended-release niacin was given in addition to simvastatin therapy in patients with a history of cardiovascular disease, high triglycerides (TG), and low levels of HDL cholesterol. This study has been terminated prematurely. 18 months of enrolment schedule, because combination of niacin and simvastatin did not show any additional benefit over and above simvastatin alone. Moreover, there was also a small, unexplained increase in ischemic stroke in the niacin group.

Observational studies have suggested that statins may lower the risk of periprocedural myocardial injury. ARMYDA trials have shown the beneficial effects of atorvastatin in patients undergoing PCI both in the setting of ACS and stable CAD. The results of ARMYDA trials may support the indication of “upstream” administration of high dose statins in patients with acute coronary syndromes treated with early invasive strategy.

The most recent tool which has been employed to study the effect of statins on the dynamics of atherosclerosis is optical coherence tomography (OCT) where pilot studies have shown increase in the thickness of fibrous cap in patients treated with early invasive strategy.

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- Risk categories: CHD or CHD risk equivalents, 2 or more risk factors (10 year risk >20%), and 0-1 risk factor. Risk factors include: cigarette smoking, hypertension, family history of premature CHD, age (men >45 years, women >55 years) and low HDL-C level (HDL-C count as a negative risk factor).

Table 2:ESC: Intervention strategy as a function of total CV risk and LDL-C level

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<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C level</th>
<th>&lt;70</th>
<th>70 to &gt;100</th>
<th>100 to &lt;155</th>
<th>155 to &gt;190</th>
<th>&gt;190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class/Level</td>
<td>I/C</td>
<td>I/C</td>
<td>I/C</td>
<td>I/C</td>
<td>I/C</td>
<td>I/C</td>
</tr>
<tr>
<td>(&lt;1)</td>
<td>No lipid intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>consider drug if uncontrolled</td>
</tr>
<tr>
<td>(&gt;1 to &lt;5)</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>consider drug if uncontrolled</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>consider drug if uncontrolled</td>
</tr>
<tr>
<td>(&gt;5 to &lt;10)</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>consider drug if uncontrolled</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>immediate drug intervention</td>
</tr>
<tr>
<td>(&gt;10)</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>and immediate drug intervention</td>
<td>Lifestyle intervention</td>
<td>Lifestyle intervention</td>
<td>and immediate drug intervention</td>
</tr>
</tbody>
</table>

Panel III (NCEP-ATP III) guidelines recommend initiation of lipid-lowering drug therapy if LDL level is more than 190 mg/dl (optional if LDL more than 160 mg/dl) for primary prevention of CHD and stroke in low risk patients. Pharmacologic treatment, to date, is not advocated for healthy individuals with LDL level less than 160 mg/dl, unless 2 or more CVD risk factors are present. For secondary prevention initiation of statin therapy is recommended to achieve a goal of LDL level less than 100 mg/dl and to achieve a 30% to 40% reduction in LDL levels in high-risk individuals. Goal of less than 70 mg/dl using high-dose statin treatment is considered desirable. In patients with acute coronary syndrome, it is strongly advocated that statin therapy be started regardless of baseline LDL levels.

American Heart Association/ American College of Cardiology, American Diabetes Association and National Kidney Foundation guideline advocate an aggressive secondary prevention approach to lipid-lowering therapy in diabetics, patients with peripheral vascular disease (PVD) and chronic kidney disease (CKD) recommending the use of statins to achieve a target LDL level of at least less than 100 mg/dl, similar to that of patients with established CHD (Table 2). There has been continuous attempt to promote more and more use of statins considering its vast potential to alter the atherosclerotic process, however, side effects and financial constraints have been the limitations.

In the latest European Society of Cardiology (ESC) recommendation for drug therapy has been recommended if LDL-C levels more than 190 mg/dl in low risk, more than 100 mg/dl in moderate risk and more than 70 mg/dl in very high risk individuals. In very high risk patients (established CVD, type 2 diabetes mellitus, type 1 diabetes mellitus with end organ damage, moderate to severe CKD) target serum LDL-C level less than 70 mg/dl or more than or equal to 50% reduction has been advocated (Table 3). In a recent consensus statement by American Diabetic Association (ADA)/American College of Cardiology (ACCORD) trial investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease. The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.

Table 3: ESC: Recommendation for treatment targets for LDL-C

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level &gt;10%) the LDL-C goal is less than 70 mg/dl and/or &gt;50% LDL-C reduction when target level cannot be reached</td>
<td>Ia/A</td>
<td>A</td>
</tr>
<tr>
<td>In patients at HIGH CV risk (immediately elevated single risk factors, a SCORE level &gt;5 to &lt;10%) an LRC-C goal less than 100 mg/dl should be considered</td>
<td>Ia/C</td>
<td>C</td>
</tr>
<tr>
<td>In subjects at MODERATE CV risk (SCORE level &gt;1 to 5%) an LDL-C goal less than 115 mg/dl should be considered</td>
<td>Ia/B</td>
<td>I</td>
</tr>
</tbody>
</table>

<ref>Table 1: The NECP-ATP III goals for LDL cholesterol and cutpoints for therapeutic lifestyle changes (TLCs) and drug therapy in different risk categories</ref>
Table 4: ADA and ACC consensus statement on lipoprotein management

<table>
<thead>
<tr>
<th>Treatment Goals</th>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>Non-HDL-C (mg/dl)</th>
<th>Apo-B (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-risk patients</td>
<td>&lt; 100</td>
<td>&gt; 60</td>
<td>&gt; 130</td>
<td>&lt; 300</td>
</tr>
<tr>
<td>High-risk patients</td>
<td>&lt; 130</td>
<td>&gt; 40</td>
<td>&gt; 160</td>
<td>&lt; 400</td>
</tr>
<tr>
<td>All others</td>
<td>&lt; 160</td>
<td>&gt; 50</td>
<td>&gt; 190</td>
<td>&lt; 500</td>
</tr>
</tbody>
</table>

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There have always been propositions for an expanded use of statins in a greater proportion of the general population, since the publication of the earliest evidence of the beneficial effects of lipid lowering therapy. The present consensus statement updates the current preventive management guidelines for the use of statins to healthy, normocholesterolemic, intermediate- to high-risk individuals.

**References**

Treatment Goals

<table>
<thead>
<tr>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>Ape-B (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>&gt; 40</td>
<td>&lt; 20</td>
</tr>
</tbody>
</table>

High-risk patients including those with (1) known CVD or (2) Diabetes plus or more additional CVD risk factors

High-risk patients, including those with (1) no diabetes and known CVD but 2 or more additional major CVD risk factors or (2) Diabetes but no other CVD risk factors

Atherosclerotic plaque.

There have always been propositions for an expanded use of statins in a greater proportion of the general population, since the publication of the earliest evidence of the beneficial effects of lipid lowering on major cardiac events. A meta-analysis of primary prevention setting. Future updates to the current clinical preventive management guidelines may extend the use of statins to healthy middle-aged men, intermediate- to high-risk individuals.


Coronary Heart Disease has emerged as a paradigm of non-communicable disease throughout the world, and more so in countries like India. Relentless efforts in the field of medical research over the last few decades, had unveiled the robust role of LDL cholesterol in the pathogenesis of atherosclerosis. It contributes to endothelial dysfunction, plaque formation and growth, plaque instability, disruption and thrombosis leading to the ultimate fate of CHD. Statins have proved their efficacy in terminating this pathological chain of events, slowing progression and even inducing regression of atherosclerotic plaque. They have emerged as a mandatory therapy in secondary prophylaxis of CHD. However, the role of statins is probably much wider than what we have yet been able to establish. Advocating statins for normo-cholesterolemic, intermediate- to high-risk individuals, or beyond LDL level to other treatment strategy would probably save more lives than expected. So the proposition for an expanded use of statins in a greater proportion of at-risk population needs careful evaluation. However, routine combination of statins with drugs for lowering triglycerides/raising HDL should be done with caution. We look forward to updates of the current clinical preventive management guidelines.

References


Summary

As with many other countries throughout the world, India, where CHD follow a more aggressive course, is experiencing a pandemic of cardiovascular diseases. Understanding the role of elevated LDL cholesterol as a primary risk factor in the pathogenesis of atherosclerosis has continuously evolved during the last five decades, and has led to the advances in the field of medical science. Beyond mere deposition of cholesterol within the arterial wall, its contribution to chronic inflammation, plaque formation and growth, plaque instability and disruption, and thrombosis have been realized.

Reducing cholesterol to prevent CHD related mortality and morbidity has been tried for decades using dietary, pharmacological and even surgical interventions. Before the era of statins, cholesterol lowering resulted in reduction of cardiovascular mortality and morbidity. After the era of statins, cholesterol lowering resulted in reduction of heart disease, stroke and other cardiovascular events. However, the role of statins is probably much wider than what we have yet been able to establish. Advocating statins for normo-cholesterolemic, intermediate- to high-risk individuals, or beyond LDL level to other treatment strategy would probably save more lives than expected. There have always been propositions for an expanded use of statins in a greater proportion of the general population, since the publication of the earliest evidence of the beneficial effects of lipid lowering on major cardiac events. A meta-analysis of primary prevention setting. Future updates to the current clinical preventive management guidelines may extend the use of statins to healthy middle-aged men, intermediate- to high-risk individuals.

There have always been propositions for an expanded use of statins in a greater proportion of the general population, since the publication of the earliest evidence of the beneficial effects of lipid lowering on major cardiac events. A meta-analysis of primary prevention setting. Future updates to the current clinical preventive management guidelines may extend the use of statins to healthy middle-aged men, intermediate- to high-risk individuals.
Profiles in Preventive Cardiology

Michael S. Brown

Michael Stuart Brown was born on April 13, 1941, in Brooklyn, New York. In 1962, Brown graduated from the College of Arts and Sciences of the University of Pennsylvania. In 1966, he received his M.D. degree from the University of Pennsylvania School of Medicine. For the next two years, he worked as an intern and resident in Internal Medicine at the Massachusetts General Hospital in Boston.

From 1968 to 1971, Brown worked at the National Institutes of Health as a special assistant to the Director. In 1971, he joined Southwestern Medical School at the University of Texas. The following year, he teamed up with Goldstein, who joined Southwestern’s staff in 1972. They began researching cholesterol metabolism, focusing on familial hypercholesterolemia, a genetic condition that affects 1 in 500 people. Sufferers of this condition have abnormally high levels of cholesterol in their blood, and fall victim at an early age to heart attacks and strokes.

54. Brown and his wife, Alice, have two daughters: Elizabeth and Sara.