INTRODUCTION

Cholesterol was first postulated to be related to atherosclerosis when it was found to be a major component of advanced atherosclerotic plaques. The first association was reported in 1930s subsequent large epidemiologic studies such as Seven Countries Study\(^1\) (1) and Framingham Heart Study\(^2\) confirmed the strong relationship between serum cholesterol and CAD. In the MRFIT trial\(^3\), the relationship between serum cholesterol and CAD was found to be continuous, graded and strong. Many prospective studies including Lipid Research Clinics Prevalence Study\(^4\) and Johns Hopkins Precursors Study\(^5\) confirmed the “cholesterol hypothesis” that the relationship between serum cholesterol and atherosclerosis is causal and that reduction of serum cholesterol would reduce atherosclerotic disease. Subsequently for the reduction of lipids various pharmacological, non-pharmacological strategies were used, but till the discovery of statins, no significant decrease in lipids could be achieved. The hypolipidemic therapy could be divided into three eras: pre-statin era, statin era and high-dose statin/pleiotropic era.

(A) Pre-statin era

Meta-analysis of randomized trials evaluating the efficacy of cholesterol lowering prior to the WOSCOPS and 4S statin trials demonstrated clear reductions in coronary mortality and events, but equivocal impaction all-cause mortality\(^6\). Clinical trials of cholesterol reduction with clinical events as the primary end point are summarised in table 1 below:

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>End-point</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary drug project(^7)</td>
<td>Niacin</td>
<td>Total mortality</td>
<td>11%</td>
</tr>
<tr>
<td>POSCH(^8)</td>
<td>Ileal bypass</td>
<td>Fatal CAD/nonfatal MI</td>
<td>35%*</td>
</tr>
<tr>
<td><strong>Primary prevention:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO(^9)</td>
<td>Clofibrate</td>
<td>Nonfatal MI</td>
<td>25%*</td>
</tr>
<tr>
<td>Lipid research clinics(^10)</td>
<td>Cholestyramine</td>
<td>Fatal CAD/nonfatal MI</td>
<td>19%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total mortality</td>
<td>7%</td>
</tr>
<tr>
<td>Helsinki heart study(^11)</td>
<td>Gemfibrozil</td>
<td>Fatal CAD/nonfatal MI</td>
<td>34%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total mortality</td>
<td>(−5.8%)</td>
</tr>
</tbody>
</table>

\(*p< 0.05.\)
Table 2: Statin era trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>End point</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S(^{12})</td>
<td>Simvastatin</td>
<td>Total mortality</td>
<td>30%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatal CAD/nonfatal MI</td>
<td>44%*</td>
</tr>
<tr>
<td>CARE(^{13})</td>
<td>Pravastatin</td>
<td>Fatal CAD/nonfatal MI</td>
<td>24%*</td>
</tr>
<tr>
<td>LIPID(^{14})</td>
<td>Pravastatin</td>
<td>CAD mortality/MI</td>
<td>26%*</td>
</tr>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOSCOPS(^{15})</td>
<td>Pravastatin</td>
<td>Fatal CAD/nonfatal MI</td>
<td>31%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total mortality</td>
<td>22%*</td>
</tr>
<tr>
<td>AFCAPS(^{16})</td>
<td>Lovastatin</td>
<td>Acute coronary events &amp;</td>
<td>37%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudden cardiac death</td>
<td></td>
</tr>
</tbody>
</table>

*p< 0.05

Table 3: High dose statin era trials

<table>
<thead>
<tr>
<th></th>
<th>PROVE IT-TIMI-22</th>
<th>A-to-Z</th>
<th>TNT</th>
<th>IDEAL</th>
<th>MIRACL</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4162</td>
<td>4497</td>
<td>10001</td>
<td>8888</td>
<td>3086</td>
</tr>
<tr>
<td>Population</td>
<td>Post-ACS</td>
<td>Post-ACS</td>
<td>Stable CAD</td>
<td>Stable CAD</td>
<td>Non-STE ACS</td>
</tr>
<tr>
<td>Treatment</td>
<td>40 mg pravastatin vs 80 mg atorvastatin</td>
<td>Placebo(4 mo) then 20 mg Simvastatin vs 40 mg simvastatin(1mo) then 80 mg simvastatin</td>
<td>10 mg atorvastatin vs 80 mg atorvastatin</td>
<td>20 mg Simvastatin vs 80 mg atorvastatin</td>
<td>80 mg of atorvastatin vs placebo</td>
</tr>
<tr>
<td>Duration</td>
<td>24 months</td>
<td>721 days</td>
<td>4.9 years</td>
<td>4.8 years</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Death,MI,UA, stroke</td>
<td>CV death, MI, stroke</td>
<td>CHD death, MI, stroke</td>
<td>CHD death, MI</td>
<td>Death, nonfetal MI, recurrent ischemia</td>
</tr>
</tbody>
</table>

(B) Statin era

The era started with the publication of 4S trial, and various studies of primary and secondary prevention trials had shown beneficial effects with statins, with consistent risk reduction and mortality benefit (Table 2).

(C) High dose statin / pleiotropic era

There is ample evidence of high dose statins being highly effective in reducing the event rates and mortality in the coronary artery disease which is higher than that which can be attributable to lipid lowering (Fig. 1). The landmark trials that have shown the superior efficacy of higher doses of statin include MIRACL\(^{17}\), PROVE IT-TIMI-22\(^{18}\), TNT\(^{19}\), A to Z\(^{20}\), IDEAL\(^{21}\) (Table 3).

The meta-analysis of these large trials\(^{22}\), which gives information of more than 1,00,000 patient years, has shown that there is 16% additional reduction in coronary death or MI (p < 0.00001) with high dose statins as compared to conventional doses of statins. The drugs were well tolerated without any major adverse events.

The benefit of high dose statins were apparent within 14 days of starting therapy in some clinical trials. The benefits of high dose statins are because of “pleiotropic effects” of statins.

In addition to the lipid lowering effects, statins are associated with a number of potentially antiatherogenic mechanisms, the so-called “pleiotropic effects” (pleiotropy: from Greek word for “more”) which may play a significant supplementary role to LDL-C reduction in lowering the risk for cardiac events with statin treatment.

Lipophilic statins, such as atorvastatin and Simvastatin, are more likely to enter endothelial cells by passive diffusion than are hydrophilic statins, such as Pravastatin and rosuvastatin, which are primarily targeted to the liver. However, because lipophilic activity does not entirely predict the ability of statins to exert extrahepatic effects in animal models and human studies, it is likely that other unidentified factors may play a role. Until recently, all cholesterol-independent or “pleiotropic” effects of statins were believed to be mediated by inhibition of mevalonate synthesis. However, recent research shows that many other mechanisms play a role.
Potential mechanisms

- **Inflammation**
  - Reduce CRP
  - Reduce inflammatory cytokine gene expression
  - Reduce inflammatory signaling pathway
  - Cytokine switching from pro to anti-inflammatory

- **Endothelial dysfunction**
  - Improve arterial blood flow
  - Increase endothelial progenitor cells
  - Reduce endothelial cell activation

- **Increased coagulation**
  - Increased thrombomodulin expression
  - Reduced tissue factor expression

1. Effects Based on the Mevalonate Pathway:

Mevalonate, the product of HMG-CoA Reductase, is a precursor in the synthesis of not only cholesterol but also a range of other important molecules involved in functions as varied as cellular respiration, signal transduction and NO production (Fig. 2).

- Decreased isoprenylation of GTP-binding proteins from farnesyli-PP and geranylgeranyl-PP; consequently FPP and GGPP production can potentially influence cell signaling, growth, differentiation and motility as well as gene expression and the intracellular movement of the cell structural components.

2. Effects Independent of the Mevalonate Pathway:

- Decreased protein glycosylation from dolichyl-P; HMG-CoA reductase inhibition decreases the synthesis of a homologus series of a-saturated polyisoprenoid alcohols containing 14-24 isoprene units that are products of a terminal branch of the mevalonate pathway. Dolichyl phosphate appears to act as a regulator of cell growth through limiting N-linked glycosylation of IGF-1 receptor.

- Ubiquinone (Coenzyme Q): A product of the mevalonate pathway, is an electron carrier in the oxidation-reduction reactions. Ubiquinone depletion may be the basis for some of the pleiotropic effects of statins.

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**Fig. 1:** Risk of coronary death or MI in a meta-analysis of major high-dose statin trials
Proposed ancillary effects of statins in atherosclerosis

Effects on plaque composition and stability:
- Macrophage function
  - Macrophage proliferation inhibition
  - Macrophage migration inhibition
  - Macrophage scavenger receptors decreased
  - Matrix metalloproteinase secretion inhibition
- Neovascularization
  - Low-dose statins promote angiogenesis
  - High doses inhibit angiogenesis
- Smooth muscle function (lipophilic statins)
  - Apoptosis promoted
  - Proliferation inhibited
  - Migration inhibited
- Thrombosis
  - Platelet activation decreased
  - PAI-1 expression decreased
  - Tissue factor production decreased
  - Thrombolysis increased
- Endothelial function
  - Decreased endothelin-1 synthesis
  - Increased eNOS synthesis
  - Increased NO synthesis

The future: Expanding indications of statin therapy

The statin therapy is established in the management of CAD, irrespective of lipid profile readings. In patients with abnormal lipid profile and other complications of atherosclerosis, it is established for definitive management. With the better understanding of mechanism of actions and long term follow-up data with various trials, there are newer expanding indications of statin therapy:

1. **Osteoporosis**

   Simvastatin and lovastatin—enhance new bone formation with increased expression of BMP-2 gene in bone cells, thus they are helpful in the management of osteoporosis.\(^{30,31}\)

2. **Malignancy: Antiproliferative action**

   There are many reports of inhibition of cancer growth and induction of apoptosis by statins in human and animal cell lines in vitro and also in vivo in animals. These are usually attributed to effects on GTP-binding proteins. There is no evidence, however, for a consistent effect of statin therapy on cancer incidence in the many participants in large outcome trials.\(^{32-34}\)

3. **Renal disease**

   Apart from reducing CAD related mortality, the effect of statins on inflammation may be relevant to the treatment of progression of renal disease. In addition, their effect on fibrogenesis may influence the development of not only glomerulosclerosis but also interstitial fibrosis.\(^{35}\)

4. **Hypertension**

   Statins improve vasodilatation and endothelial dysfunction that frequently accompany hypertension and hypercholesterolemia, possibly through their effects on NO synthesis. Furthermore, the combination of a statin with an ACEI or CCB appeared to have a greater antihypertensive effect compared with ACEI or CCB alone. Statins improve the elasticity of arterial wall and thereby helps in reducing the vascular stiffness.

5. **Inflammatory diseases**

   Recently, there are some pilot studies of the use of simvastatin in patients with inflammatory arthritis.\(^{37}\)

   The pleiotropic effects of statins appear to be dose-dependent and rapid, and may improve inflammation, endothelial function and coagulation, while the longer-term effects of intensive statin therapy may be more related to both pleiotropic and lower lipid levels which in turn reduce cardiovascular events, by impacting on disease progression and atheroma burden. At present it is difficult to quantify the relative contribution that is made by the lipid versus the non-lipid lowering effects of statins to the overall cardiovascular risk reduction. What is certain now is that intensive statin therapy is
associated with the greatest pleiotropic effect in vitro, the greatest LDL reduction and the greatest clinical benefit in patients.

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REFERENCES


