Chapter

15 Statins Beyond Lipid Control

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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 1: Pre-statin era clinical trials

Study	*Intervention*	*End-point*	*RRR*
Secondary prevention:			
Coronary drug project[7]	Niacin	Total mortality	11%
POSCH[8]	Ileal bypass	Fatal CAD/nonfatal MI	35%*
Primary prevention:			
WHO[9]	Clofibrate	Nonfatal MI	25%*
Lipid research clinics[10]	Cholestyramine	Fatal CAD/nonfatal MI	19%*
		Total mortality	7%
Helsinki heart study[11]	Gemfibrozil	Fatal CAD/nonfatal MI	34%*
		Total mortality	(–5.8%)

*p< 0.05.

Table 2: Statin era trials

Study	*Intervention*	*End point*	*RRR*
Secondary prevention			
4S[12]	Simvastatin	Total mortality	30%*
		Fatal CAD/nonfatal MI	44%*
CARE[13]	Pravastatin	Fatal CAD/nonfatal MI	24%*
LIPID[14]	Pravastatin	CAD mortality/MI	26%*
Primary prevention			
WOSCOPS[15]	Pravastatin	Fatal CAD/nonfatal MI	31%*
		Total mortality	22%*
AFCAPS[16]	Lovastatin	Acute coronary events & Sudden cardiac death	37%*

*p< 0.05

Table 3: High dose statin era trials

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

(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 trails that have shown the superior efficacy of higher doeses 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 lipophilicity 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.

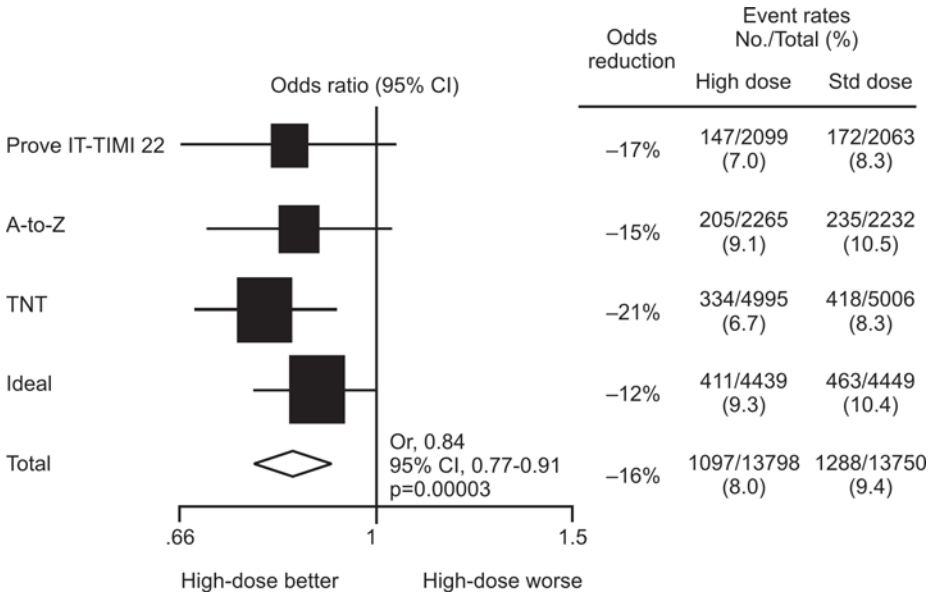

Fig. 1: Risk of coronary death or MI in a meta-analysis of major high-dose statin trials

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 farnesyi-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[23,24].
- 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[25].
- 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[26].

2. Effects Independent of the Mevalonate Pathway:

- Direct binding to leukocyte function antigen-1: Statins selectively block b2-integrin leucocyte function antigen-1(LFA-1), which has an important role in inflammation through mediating T-cell activation, leucocyte migration adhesion and co-stimulation of lymphocytes[27].
- Anti-oxidant effects: Atorvastatin has no apparent antioxidant effect *in vitro* but pharmacological concentrations of its metabolites substantially protect LDL,VLDL and HDL from oxidation in a concentration-dependent manner, probably by free-radical scavenging[28].

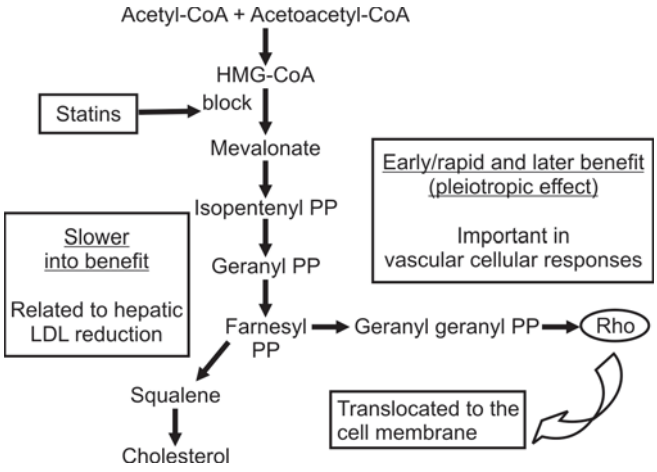

Fig. 2: Dose-dependent cellular effects of statin therapy, with simultaneous effects on cell signaling and cholesterol synthesis

Proposed ancillary effects of statins in atherosclerosis[29]

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: Antiproliferatine 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[36]. Statins improv e 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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