Coronary artery disease is one of the leading causes of death worldwide and dyslipidemia remains the most important and treatable risk factor. The recent NCEP ATP III guidelines suggest LDL lowering as the primary target and reducing triglycerides and increasing HDL cholesterol as the next line of lipid modification. Several clinical trials have very clearly shown that statins, which primarily reduce cholesterol and fibrates that improve triglyceride levels effectively decrease the cardiovascular mortality. In these studies, subjects with combined dyslipidemia benefited the most compared to those with individual lipid abnormalities. Niacin and ezetimibe are the newly introduced drugs, have been shown to be effective in reducing cholesterol and triglyceride levels. However, both these drugs seem to be more efficient in ameliorating serum lipids when combined with a statin. To achieve the NCEP targets and to improve the cardiovascular risk profile especially in those with severe or combined dyslipidemia, combination of drugs appear to be the best therapeutic approach. In addition, if targets in failures are not achieved with statin or fibrate, a combination would be a good alternative. However, side effects have been the main limitation in combination therapy. More clinical trials are required to demonstrate the safety of combination therapy.

SCOPE OF THE PROBLEM
Coronary artery disease [CAD] is the leading cause of morbidity and mortality worldwide, with the heaviest toll in developing countries. Though a plethora of risk factors have been established by various epidemiological, observational and case-control studies for CAD, dyslipidemia remains the most important risk factor for CAD and even more significant perhaps the most treatable risk factor. Combined dyslipidemia is characterized by the concomitant metabolic abnormalities of lipid metabolism, which are elevated LDL cholesterol and triglycerides and decreased HDL cholesterol levels. The recent INTERHEART study identified smoking and abnormal lipids as the two most important risk factors among the nine, which explained about 90% of the myocardial infarction. The abnormal lipid in this case control study was increased ApoB/ApoA1 ratio, which indicates combined dyslipidemia. Several epidemiological studies have highlighted the importance of serum cholesterol and LDL cholesterol levels with CAD. These studies have consistently reported a direct and dose dependent relationship between LDL cholesterol and CAD. Both fasting as well as postprandial triglycerides have been shown to be associated with CAD in several prospective and case control studies. The Framingham study was the first to demonstrate the association of low HDL levels with CAD. Studies have shown that for every 1 mg decrease in HDL the risk for heart disease increases by 2% in men and 3% in women. All the above-mentioned studies have delineated the individual contribution of these risk factors. However, combined dyslipidemia, which is common among a wide variety of conditions, [genetic disorders: familial combined hyperlipidemia, familial dysbetalipoproteinemia, acquired disorders: metabolic syndrome, diabetes or drug associated] increases the risk for CAD by 2 to 5 fold. The Helsinki Heart study, Quebec Cardiovascular Study and the PROCAM study showed a definite high risk among subjects with combined dyslipidemia compared to those with individual abnormalities. Among the variety of conditions that causes combined dyslipidemia, diabetes and metabolic syndrome are perhaps the most common and in the latter conditions insulin resistance appears to be the common denominator.

Prevalence of various lipid abnormalities in the Chennai Urban Population Study [CUPS] is given in Table 1. The prevalence of all the lipid abnormalities was higher among the diabetic subjects compared to subjects with normal glucose tolerance. Combined dyslipidemia was observed in 28.9% of the diabetic population in this study. In a another clinic-based study carried out on 17, 855 type 2 diabetic subjects, we found that the prevalence of myocardial infarction was significantly higher in subjects with combined hyperlipidemia compared to other lipid abnormalities.
Extrapolating the prevalence of combined dyslipidemia observed in diabetic subjects in the CUPS study to the whole of the India, the numbers are quite staggering. Presently there are over 31.7 million diabetic individuals in India and if 28.9% have combined dyslipidemia, this would translate to 9.2 million subjects with combined dyslipidemia. Furthermore, as the prevalence of diabetes is expected to increase to 79.4 million by the year 2030, this means there would be 22.9 million subjects with combined dyslipidemia. All these could translate into heavy economic burden and loss of quality of life due to the high prevalence of coronary artery disease among these subjects. Lipid control targeting definite goals should therefore be aggressively advocated to prevent coronary artery disease in these subjects.

**GOALS FOR TREATMENT**

The recent NCEP ATP III guidelines suggest LDL lowering as the primary target for modification of lipid. Subjects with either known CAD or CAD risk equivalent like diabetes are considered to be at high risk and the target for LDL is 70 mg/dl. Successful treatment of combined dyslipidemia also involves targeting non-HDL cholesterol as elevated non-HDL cholesterol indicates decreased HDL cholesterol and increased triglycerides levels. Non-HDL cholesterol is a cost effective and easily detectable marker of coronary artery disease. In addition to LDL levels, NCEP ATP III also recommends for non-HDL cholesterol target <130 mg/dl and a triglycerides target <150 mg/dl.

**CURRENT DRUG THERAPIES FOR ACHIEVING TARGETS**

Landmark studies in the past decades have confirmed that reducing low-density lipoprotein and triglycerides reduce the risk of CAD endpoints. Therapeutic life style changes[TLC] as suggested by NCEP is the primary step for ameliorating lipids. When TLC fails, drugs should be started. Statins, fibrates and niacin are the available drugs for ameliorating serum lipid levels favorably.

**CHOLESTEROL LOWERING AGENTS**

**Statins**

The proposed mechanism of action of statins is that, it competitively inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase and thus hinders endogenous cholesterol synthesis. Reduction in intracellular cholesterol levels in hepatocytes upregulate expression of the LDL receptor, resulting in increased clearance of LDL in the blood stream. Other effects of statins include improving endothelial function, modulate inflammation, plaque stability and prevention of thrombus formation. Several randomized clinical trials have shown that statins are highly effective for both primary and secondary prevention of CAD events. Some of the trials, which have shown concrete evidence for reduction in incidence of CAD, are shown in Table 2.

### Table 1: Association of Risk Factors with Glucose Intolerance

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normalglucosetolerance (n=1036)</th>
<th>Diabetic subjects (n=152)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypercholesterolemia (%)</strong></td>
<td>19.0%</td>
<td>42.8%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(Serum cholesterol : ≥ 200 mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia (%)</strong></td>
<td>17.6%</td>
<td>47.0%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(Serum triglycerides : ≥ 150 mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High LDL levels (%)</strong></td>
<td>53.3%</td>
<td>79.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(LDL cholesterol : ≥ 100 mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low HDL levels (%)</strong></td>
<td>75.1%</td>
<td>76.3%</td>
<td>0.74</td>
</tr>
<tr>
<td>(HDL cholesterol : Males &lt; 40 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females &lt; 50 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High LDL levels + Hypertriglyceridemia (%)</strong></td>
<td>10.9%</td>
<td>34.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(LDL cholesterol : ≥ 100 mg/dl + Serum triglycerides : ≥ 150 mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low HDL levels + High LDL levels + Hypertriglyceridemia (%)</strong></td>
<td>9.2%</td>
<td>28.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(HDL cholesterol : Males &lt; 40 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females &lt; 50 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL cholesterol : ≥ 100 mg/dl + Serum triglycerides : ≥ 150 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Effect of Statins on CAD Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).</td>
<td>Lovastatin</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Cholesterol and Recurrent Events (CARE) trial</td>
<td>Pravastatin</td>
<td>24%</td>
</tr>
<tr>
<td>The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study</td>
<td>Pravastatin</td>
<td>24%</td>
</tr>
<tr>
<td>The Scandinavian Simvastatin Survival Study (4S).</td>
<td>Simvastatin</td>
<td>34%</td>
</tr>
</tbody>
</table>

Extrapolating the prevalence of combined dyslipidemia observed in diabetic subjects in the CUPS study to the whole of the India, the numbers are quite staggering. Presently there are over 31.7 million diabetic individuals in India and if 28.9% have combined dyslipidemia, this would translate to 9.2 million subjects with combined dyslipidemia. Furthermore, as the prevalence of diabetes is expected to increase to 79.4 million by the year 2030, this means there would be 22.9 million subjects with combined dyslipidemia. All these could translate into heavy economic burden and loss of quality of life due to the high prevalence of coronary artery disease among these subjects. Lipid control targeting definite goals should therefore be aggressively advocated to prevent coronary artery disease in these subjects.
with statins compared to those with individual abnormalities. In the 4S study, simvastatin produced the best results, 52% risk reduction in CAD events in patients with increased LDL cholesterol, highest quartile for triglycerides and lowest quartile of HDL cholesterol.34

Six different types of statins [Rosuvastatin, atorvastatin, fluvastatin, lovastatin and simvastatin] are available in the market and the efficacy of these in reducing LDL levels and triglycerides varies considerably. Five of these [except rosuvastatin] were compared in the Atorvastatin Comparative Cholesterol Efficacy and Safety Study. Atorvastatin reduced LDL cholesterol by 42% in 54 weeks followed by lovastatin [36%], simvastatin [36%]. Similarly, atorvastatin had the maximum effect on triglycerides as it reduced triglycerides level by 19% followed by simvastatin [13%] and lovastatin [12%].33 Further, a very recent study suggested that atorvastatin at 40 mg/day decreased small dense LDL more compared to other statins.34

A comparative study on the efficacy of simvastatin with pravastatin suggested that simvastatin produced significantly greater mean percent reductions from baseline in total cholesterol (28% versus 21%), LDL cholesterol (38% versus 29%), and apolipoprotein B concentrations (25% versus 17%) compared to pravastatin, while there was not much difference in the mean reduction in triglyceride levels35 and increase in HDL cholesterol. The Simvastatin Pravastatin European Study Group showed that 5 mg simvastatin showed a significant reduction in plasma total (16% vs 12%) and LDL cholesterol(23% vs 18%) compared to 10 mg pravastatin.36 Atorvastatin and simvastatin are considered to be more beneficial than the other statins. However, studies are required comparing the recently introduced rosuvastatin with other statins.

**Ezetimibe**

This class of drugs inhibits cholesterol absorption and is considered to safer as it has a lower side effect profile, unlike statins it does not affect hepatocytes.37 This drug received US FDA approval in 2002 for treatment of primary hypercholesterolemia and familial hypercholesterolemia and homozygous sitosterolemia.37 The mechanism of action is yet not very clear. It inhibits a yet not identified sterol transporter that transports cholesterol in small intestine.38 This reduction in cholesterol absorption results in the cholesterol content of chylomicrons which in turn reduces the amount of the cholesterol, which is transported to liver. Reduction in hepatic cholesterol enhances LDL receptor expression as a compensation, which results in increased clearance of LDL particles. A very recent study suggests that a 145 kDa integral membrane protein is the molecular target of ezetimibe which blocks intestinal cholesterol absorption.39 Monotherapy with ezetimibe to results in minimal increase in HDL cholesterol, and decrease in triglycerides. Ten mg once daily reduces LDL levels by 17%.40

### TRIGLYCERIDE REDUCING DRUGS

**Fibrates**

Another class of drugs, the fibrates has been extensively used for reduction of triglycerides. The proposed mechanism of action of fibrates is: stimulation of lipoprotein lipase and reverse cholesterol transport, decrease the substrate availability for triglyceride synthesis in the liver, and modulation of low-density lipoprotein (LDL) receptor/ligand interaction.41 Recent studies confirm its action on inflammation and other cardiovascular risk factors and markers. The clinical trials, which have showed beneficial effect on coronary artery disease using fibrates, have been provided in Table 3.29-32 As fibrates stimulate reverse cholesterol transport it increased HDL cholesterol. In the Veterans Affairs HDL Intervention Trial [VA-HIT] study gemfibrozil significantly increased HDL levels resulting in remarkable decrease in myocardial infarction.33 Similar to statins, fibrates also had a more marked effect in subjects with combined dyslipidemia. In the Helsinki Heart Study, gemfibrozil, reduced the risk for coronary artery disease events by 71% in subjects with both elevated triglycerides and LDL to HDL ratio compared to the overall reduction of 31%.30 Similar results were seen for bezafibrate in the BIP trial.29

**Niacin**

Niacin was used for lipid lowering right from the 1950’s as a rapid release formulation.42,43 Recent studies have shown that niacin an effective drug which ameliorates lipoprotein(a) levels also favourably alters triglycerides and HDL levels.44 The mechanism of action of niacin is that it inhibits transport of free fatty acids from the peripherals tissues to the liver, preventing hepatic synthesis of triglycerides, it also decreases the apo A-I catabolism thereby increases HDL levels. Niacin is available in three formulations: immediate release, extended and sustained formulations. The major side effects are flushing and increase in blood sugar. Extended release formulation of niacin had better safety compared to the sustained release formulation. 3g of niacin per day reduced recurrent nonfatal myocardial infarction by 27% in the Coronary Drug Project.44

### COMBINATION THERAPY

The recently modified NCEP ATPIII guideline emphasizes more aggressive therapy for LDL lowering as the primary target and recommends levels of below 70 mg/dl in subjects with cardiovascular risk, and lowering non-HDL cholesterol and triglycerides as the next target.23 Hence, to improve the cardiovascular risk profile combination of drugs may be the best therapeutic approach. In addition there are failures to achieve the LDL target due to inadequate titration of statin dose. It has been shown that nearly 20% of coronary artery disease patients do not reach the LDL target with the potent statin therapies available.45 Hence combinations either with bile acid binding resins, fibrates or niacin could be used. Infact the American
Diabetes Association suggests combination therapy may be necessary to achieve lipid targets. However, lacuna in clinic trials to support safety of combination therapy limits its use.46

**Ezetimibe in combination with statin and fibrate**

Ezetimibe has been shown to be very effective in combination with statin in lowering LDL levels, the primary target suggested by NCEP guidelines.23 As monotherapy ezetimibe reduced 17% LDL levels this increased to 25% when combined with statin.47 It also increases HDL levels by 3% and reduces triglycerides by 14% in combination with statin.48 This drug seems to be more beneficial to fill the treatment gap of statins, as maximum doses of statins cannot be tolerated due to hepatotoxicity, addition of ezetimibe is considered to be effective.51,48 Further ezetimibe being safer could be titrated in combination with stains to achieve LDL target. In combination with fibrates, also recently this drug has been shown to be beneficial.50 One of the limitations of adding ezetimibe is that is expensive. More clinical trials are required to substantiate the role of ezetimibe in cholesterol lowering.

**Statin - fibrate combination**

More than 35 drug trials have studied the effect of statin and fibrate combination on lipid lowering.33 Gemfibrozil with lovastatin has been reported to be very effective in lowering both triglycerides and LDL cholesterol.50,51 A long-term efficacy study on fenofibrate and statin suggested that the decrease in the total cholesterol / HDL ratio was 24% in fenofibrate monotherapy, 29% with statin and 40% with combination.52 Similarly fluvastatin and bezafibrate combination decreased LDL cholesterol by 24%, triglycerides 38% and 22% increase in HDL cholesterol.53 Atorvastatin with micronized fenofibrate reduced LDL cholesterol by 46% and triglycerides by 50% and increased HDL by 22%.54

A comparative study on different statins and fibrates indicated that pravastatin and gemfibrozil combination decreased LDL cholesterol by 35%, increased triglycerides by 48% and increased HDL cholesterol by 14%, while simvastatin and gemfibrozil resulted in 39% decrease in LDL cholesterol, 54% decrease in triglycerides and 25% increase in HDL cholesterol, simvastatin and ciprofibrate combination resulted in 42% decrease in LDL cholesterol, 57% decrease in triglycerides and 17% increase in HDL cholesterol.55 All these studies indicate that combination of statin and fibrate produces more benefit than the respective monotherapies.

**Obstacles for statin- fibrate combination**

The tolerability and possible side effects of stain and fibrate combination has been a concern after the withdrawal of cerivistatin due to myopathy. More than 20 case reports have been published on the side effects of combination of statins and fibrates. Most of them have report rhabdomyolysis with acute renal failure and myopathy with elevated levels of CK as the major adverse effects. Myopathy occurs when statins are used in conjunction with drugs that inhibit cytochrome p450 3s 4 pathway.56 Interaction of fibrates with statin differs with the different formulations. Fenofibrate and statin combination seems to be favourable while gemfibrozil appears to affect the pharmacokinetics of all stains except fluvastatin.56-59 However, the frequency of myopathy seems to be extremely low. A review on 36 clinical trials suggested that none of the patients developed rhabdomyolysis or acute renal failure and only 0.12% developed myopathy with elevated CK levels. Less than 1.5% of the study subjects discontinued the combination due to myalgia or CK elevation. The US Food and Drug Administration [FDA] Adverse Event Reporting System [AERS] based on the prescriptions and cases reported provided the following rates on myopathy in various

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**Fig. 1 : Algorithm for Lipid Management**

Characterize dyslipidaemia

↑ Chol (LDL-c) ↔ TGL

↑ TGL, ↑ Chol

↑ TGL, ↔ Chol

↓ HDL-c

Lifestyle changes ± Statins ± Fibrates / Niacin

Lifestyle changes ± Statins ± Ezetimibe

Lifestyle changes ± Fibrates

Monitor
Liver / Renal function
Symptoms for myopathy / CK levels

Lifestyle changes ± Fibrates

? Specific HDL elevations (in future)
statins: 3.16 with cerivastatin to 0.19 with lovastatin, 0.12 with simvastatin, 0.04 with atorvastatin or pravastatin and 0 for fluvastatin per million prescriptions.

These reports however suggest that careful monitoring is required for combination therapy of statins with fibrates. The various risk factors which predispose an individual to develop myopathy includes old age, female gender, renal failure, hypothyroidism, alcohol intake heavy exercise and surgery. Patient counseling regarding the various risk is required, and they should be requested to report if there are any symptoms like muscular pain. Myopathy should then be confirmed with laboratory reports of CK.

**Statin-fibrate combination: Indian experience**

A recent nation-wide multicentric study on the effect of atorvastatin [10 mg] and fenofibrate [160 mg] combination on over 65 patients showed beneficial effect of this combination in lowering LDL cholesterol and triglycerides and increased HDL cholesterol. The adverse effects seen were very mild with 8.9% reporting pain in the legs, without elevated CK levels [Unpublished results]. In another study in progress at our centre, the Fenofibrate and Atorvastatin In Treating Hyperlipidaemia [FAITH] trial, combination therapy of atorvastatin and fenofibrate was found to be quite effective and safe (unpublished observation).

**Statin-niacin combination therapy**

This has been an attractive option as niacin reduces lipoprotein (a), the genetic determinant for coronary artery disease. A review of 9 clinical trials, on combination of niacin with statin revealed that this combination reduced LDL by 25% to 57% and increased HDL cholesterol from 13% to 36%. Further, studies have also shown that this combination reduces lipoprotein (a) and small dense LDL levels. Of the three formulations, immediate release and sustained release have been reported to cause myopathy. While extended release once daily niacin formulation (Niaspan) seems to be effective in decreasing LDL, triglycerides, lipoprotein (a) and CRP levels and increasing HDL cholesterol. Simvastatin plus niacin combination also reduced the risk for composite cardiovascular end point by 90% compared to placebo and resulted in regression of atherosclerosis as measured by angiography.

Other combination therapies include stain with bile acid resins, omega 3 fatty acids. Newer compounds like ezetimibe and avasimibe may be the preferred drugs in the future.

**ALGORITHM FOR LIPID THERAPY**

To achieve the lipid targets recommended by NCEP, we propose that the following algorithm may be used [Figure 1]. In subjects with predominant cholesterol and LDL elevation, statins are the drug of choice while for those with isolated hypertriglyceridemia, fibrates would be the drug of choice. In subjects with combined dyslipidemia, combination of statins and fibrates and/or niacin or other drugs should be considered. However, care should be taken to look for side effects by monitoring renal and liver functions and also check for symptoms of myopathy and CK levels.

**CONCLUSIONS**

Due to increased need for multi-drug therapy to achieve thereafter targets, poly pharmacy has become popular. The task of the pharmaceutical industry is to bring these polypills into the market, which can target combined dyslipidemia without adverse effects. Some formulations have already completed clinical trials and should soon become available. These combinations can help subjects with combined dyslipidemia achieve recommended NCEP ATP III targets. However, careful studies of side effects are also required before introducing into routine practice, as the risk of side effects also increase when combination therapy is used.

**REFERENCES**


56. Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. Am J Cardiol 2002;90:50K-60K.


