Clinical Experience of Combination Lipid Lowering Therapy

V Mohan[†], R Deepa[‡]

[†]Diabetiologist & Director, [‡]Research Specialist, Madras Diabetes Research Foundation & Dr. Mohans' M.V. Diabetes Specialities Centre, Gopalapuram, Chennai, India.

53

ABSTRACT

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.[1,2] 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.[3,4] 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.[5] 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.[6,7] These studies have consistently reported a direct and dose dependant 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.[8,9] The Framingham study was the first to demonstrate the association of low HDL levels with CAD.[10] 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.[11,12] 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.[13] The Helsinki Heart study,[14] Quebec Cardiovascular Study[15] and the PROCAM study[13] 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.[16]

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.[17-19] 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.[20]

Table 1 : Association of Risk Factors with Glucose Intolerance[19]

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

Table 2 : Effect of Statins on CAD Events[24 - 27]

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

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[21] 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.[22] 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.[23] 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.[24-32] Therapeutic life style changes[TLC] as suggested by NCEP is the primary step for ameliorating lipids.[22] 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.[24-27] The Heart Protection Study (HPS) provided the most convincing results on the benefits of LDL lowering and concluded that cholesterol lowering with 40mg/day of simvastatin has a profound impact on the CAD event rates not only in subjects with prior CAD but also in subjects with high risk and low to average cholesterol levels.[28]

A very interesting point brought out in some of these clinical trials is that subjects with combined dyslipidemia benefited the most

Table 3 : Effect of Fibrates on CAD Death[29 - 32]

Study	Drug	Risk reduction
Primary prevention		
Helsinki Heart Study	Gemfibrozil	34%
Secondary prevention		
Bezafibrate Infarction Prevention Study	Bezafibrate	9%
Veterans Affairs High-Density Lipoprotein Intervention Trial.	Gemfibrozil	22%
Diabetes Atherosclerosis Intervention Study	Fenofibrate	23%

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.[24]

Six different types of statins [Rosuvastatin, atorvastatin, fluvastatin, lovastatin, pravastatin 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 40mg/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 levels[35] 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 sistosterolemia.[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.[31] 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.[41,42] Recent studies have shown that niacin an effective drug which ameliorates lipoprotein(a) levels also favourably alters triglycerides and HDL levels.[43] 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 0titration 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 bee 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.[41,48] 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.[49] 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.[43] 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 trails 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

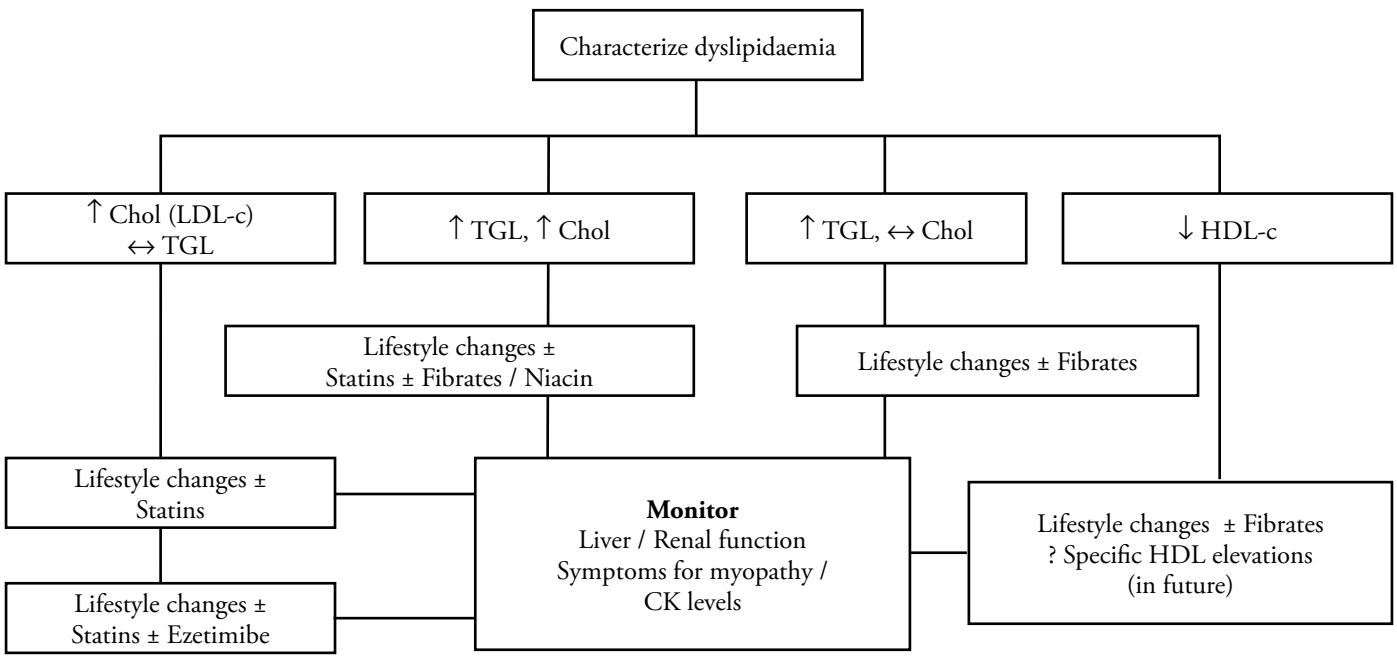

Fig. 1 : Algorithm for Lipid Management

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.[43]

These reports however suggest that careful monitoring is required for combination therapy of statins with fibrates. The various risk factors which predisposes 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%.[60] Further, studies have also shown that this combination reduces lipoprotein (a) and small dense LDL levels.[61,62] Of the three formulations, immediate release and sustained release have been reported to cause myopathy.[63-65] 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 [66-68]. 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 [69].

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.[70,71]

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

1. Murray CJ, Lopez AD. Alternative projection of mortality and disability by cause 1990-2020; Global Burden of Disease Study. *Lancet* 1997; 349:1498-1504.
2. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998; 97: 596 – 601.
3. Kannel WB. Range of serum cholesterol values in the population developing coronary artery disease. *Am J Cardiol* 1995;76:69C - 77C.
4. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256: 2823-2828.
5. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-952.
6. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989;320:904 - 910.
7. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251: 351-364.
8. Gotto AM Jr. Hypertriglyceridemia: risks and perspectives. *Am J Cardiol* 1992;70:19H - 25H.
9. Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK, et al. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. *Arterioscler Thromb* 1992;12: 1336-1345.
10. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986;256:2835 - 2838.
11. Kwiterovich PO Jr. The antiatherogenic role of high-density lipoprotein cholesterol. *Am J Cardiol* 1998;82:13Q – 21Q.
12. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79:8 - 15.
13. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Prospective Cardiovascular Munster study. *Am J Cardiol* 1992;70:733 - 737.
14. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation* 1992;85: 37-45.
15. Lamarche B, Moorjani S, Lupien PJ, Cantin B, Bernard PM, Dagenais GR, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. *Circulation* 1996;94:273 - 278.

16. Reaven GM. A syndrome of resistance to insulin stimulated uptake (Syndrome X). Definitions and implications. *Cardiovasc Risk Factors* 1993; 3: 2 – 11.
17. Deepa R, Arvind K, Mohan V. Diabetes and risk factors for coronary artery disease. *Current Science* 2002; 83; 1497-1505.
18. Mohan V, Deepa R, Shanthi Rani S, Premalatha G. Prevalence of coronary artery disease and its relationship to lipids in a selected population in south India. *JACC* 2001; 38; 682-687.
19. Mohan V, Shanthirani CS, Deepa R. Glucose intolerance (diabetes and IGT) in a selected south Indian population with special reference to family history, obesity and life style factors – The Chennai Urban Population Study (CUPS 14). *JAPI* 2003; 51; 771-777.
20. Rajmohan L, Deepa R, Anjana Mohan, Mohan V. Association between Isolated hypercholesterolemia, isolated hypertriglyceridemia and coronary artery disease in south Indian Type 2 diabetic patients. *Indian Heart J* 2000; 52: 400-406.
21. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. *Diabetes care* 2004: 27: 1047 – 53.
22. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *J Am Med Assoc* 2001;285:2486-2497.
23. Grundy SM, Cleeman JI, Merz CNB, Jr. Brewer HB, Clark LT, Hunninghake DB, et al. For the Coordinating Committee of the National Cholesterol Education Program, Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines**.** *Circulation* 2004 110: 227 – 239.
24. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;344: 1383-1389.
25. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG et al. For the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335: 1001–1009.
26. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349 – 1357.
27. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beeree PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615 - 1622.
28. Goldberg RB. Statin treatment in diabetic subjects: what the heart protection study shows - Landmark Study. *Clinical Diabetes* 2003,21: 151-152.
29. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* 2000; 102:21 - 27.
30. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation* 1992; 85:37-45.
31. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, 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* 2001; 285:1585 - 1591.
32. Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes - the Diabetes Atherosclerosis Intervention Study, a randomized study. *Lancet* 2001; 357: 905 – 910.
33. Andrews TC, Ballantyne CM, Hsia JA, Kramer JH. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *Am J Med* 2001;111: 185-191.
34. Schaefer EJ, McNamara JR, Tayler T, Daly JA, Gleason JL, Seman LJ, et al. Comparisons of effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects. *Am J Cardiol* 2004;93:31 - 39.
35. Lambrecht LJ, Malini PL. Efficacy and tolerability of simvastatin 20 mg vs pravastatin 20 mg in patients with primary hypercholesterolemia. European Study Group. *Acta Cardiol* 1993;48:541 - 554.
36. Steinhagen-Thiessen E. Comparative efficacy and tolerability of 5 and 10 mg simvastatin and 10 mg pravastatin in moderate primary hypercholesterolemia. Simvastatin Pravastatin European Study Group. *Cardiology* 1994;85:244 - 254.
37. Neal RC, Jones PH. Lipid lowering: Can ezetimibe help close the treatment gap? *Cleveland Clin J Med* 2003;70:777-783
38. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001:23:1209-1230.
39. Kramer W, Girbig F, Corsiero D, Pfenninger A, Frick W, Rhein M, et al. Aminopeptidase N (CD13) is a molecular target of the cholesterol absorption inhibitor Ezetimibe in the enterocyte brush border membrane. *J Biol Chem* 2004 [in press)
40. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002; 90:1092-1097
41. Shepherd J. Mechanism of action of fibrates. *Postgrad Med J* 1993; 69 Suppl 1:S34-41.
42. Stein EA. Management of dyslipidemia in the high-risk patient. *Am Heart J* 2002;144:S43-S50.
43. Xydakis AM, Ballantyne CM. Combination therapy for combined dyslipidemia. *Am J Cardiol* 2002;90:21K-29K.
44. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360 - 381.
45. Brown AS, Bakker-Arkema RG, Yellen L, Henley RW Jr, Guthrie R, Campbell CF, et al. Treating patients with documented atherosclerosis to National Cholesterol Education Program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin. *J Am Coll Cardiol* 1998;32:665 - 72.
46. American Diabetes Association. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004; 27 (suppl 1): S68 – S71.
47. Gagne C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1084-1091
48. Patel SB. Ezetimibe. A Novel Cholesterol-lowering Agent that Highlights Novel Physiologic Pathways. *Curr Cardiol Rep* 2004;6:439 - 442.
49. Reyderman L, Kosoglou T, Statkevich P, Pember L, Boutros T, Maxwell SE, et al. Assessment of a multiple-dose drug interaction between ezetimibe, a novel selective cholesterol absorption inhibitor and gemfibrozil. *Int J Clin Pharmacol Ther* 2004;42:512 - 518.
50. Lipid and Lipoprotein analysis. In : Lipid research clinics manual of laboratory operation, Vol. 1. Washington DC: US Government printing office; 1974. HEW publication. NIH 75 – 628.
51. Krauss RM, Blanche PJ. Detection and quantitation of LDL subfractions. *Curr Opin Lipodology* 1992; 3: 377 – 383.
52. Ellen RLB, Mcpherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 1998;81:60B - 65B.
53. Pauciullo P, Borgnino C, Paoletti R, Mariani M, Mancini M. Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidaemia (FACT study). *Atherosclerosis* 2000;150:429-436.
54. Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Kontopoulos AG. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. *Diabetes Care* 2002;25:1198 - 1202.

55. Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, Didangelos TP, Carina MV, Kranitsas DF, et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. *Am J Cardiol* 1997;80:608 - 613.
56. Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. *Am J Cardiol* 2002;90:50K-60K.
57. Backman JT, Kyrklund C, Kivisto KT, Wang JS, Neuvonen PJ. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000;68:122 - 129.
58. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther* 1999;84:413 - 428.
59. Pravastatin. Physician's Desk Reference. MontVale, NJ: Medical Economics Company, 2002.
60. Guyton JR, Capuzzi DM. Treatment of hyperlipidemia with combined niacin statin regimens. *Am J Cardiol* 1998;82:82U–84U.
61. Jacobson TA, Chin MM, Fromell GJ, Jokubaitis LA, Amorosa LF. Fluvastatin with and without niacin for hypercholesterolemia. *Am J Cardiol* 1994;74: 149–154.
62. O'Keefe JH Jr, Harris WS, Nelson J, Windsor SL. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. *Am J Cardiol* 1995;76:480–484.
63. Rader JI, Calvert RJ, Hathcock JN. Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992;92:77–81.
64. Norman DJ, Illingworth DR, Munson J, Hosenpud H. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin [letter]. *N Engl J Med* 1988;318:46–47.
65. Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis [letter]. *Ann Intern Med* 1988;109:597–598.
66. Kashyap ML, McGovern ME, Berra K, Guyton JR, Kwiterovich PO Jr, Harper WL, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol* 2002;89:672–678.
67. Insull W, Adams M, Evans R, McGovern M, Simmons P, Thompson E, et al. Dose-response effects on high-density lipoprotein cholesterol and multiple other lipoproteins of a new, once-daily formulation of lovastatin and niacin in patients with primary hypercholesterolemia [abstract]. Presented at the 14th Drugs Affecting Lipid Disorder Meeting; New York, New York; September 9–12, 2001.
68. Hunninghake DB, McGovern ME, Simmons PD, Evans R, Batcheller AB, Cefali EA. Dose-ranging and dose-sparing effects of a once-daily formulation of lovastatin and extended release niacin in patients with hyperlipidemia [abstract]. Presented at the 14th Drugs Affecting Lipid Disorder Meeting; New York, New York; September 9–12, 2001.
69. Brown BG, Zhao X-Q, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–1592.
70. Davidson MH, McGarry T, Bettis R, Melani L, Lipka L, LeBeaut A, et al. For the Ezetimibe Study Group. Ezetimibe co-administered with simvastatin in 668 patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;39:226A. Poster session abstract 1084-90.
71. Raal FJ, Marais AD, Klepack E, Lovalvo J, McLain R, Heinonen T. Avasimibe, an ACAT inhibitor, enhances the lipid lowering effect of atorvastatin in subjects with homozygous familial hypercholesterolemia. *Atherosclerosis* 2003 ;171:273 - 279.