Dyslipidemic drugs in metabolic syndrome

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ABSTRACT

Introduction: Metabolic syndrome predisposes to diabetes and atherosclerotic vascular disease. Statins reduce cardiovascular events, so all metabolic syndrome patients should be evaluated for dyslipidemia. Many patients fail to achieve lipid goals with statin monotherapy. Co-administration of ezetimibe (EZE) and atorvastatin (ATV) may enable more patients to achieve low-density lipoproteincholesterol (LDL-C) goal while avoiding risks of high-dose statin monotherapy. Materials and Methods: The present study compares rosuvastatin (Rsv) with a combination of (Atv) and (Eze). Metabolic syndrome patients, 30-70 years with LDL-C ≥ 130 mg/dl and a 10-year CHD risk score of 10% were randomized to double-blind treatment with (Rsv) 5 mg (n = 67) or (Atv) 10 mg+(Eze) 10 mg (n = 68) for 12 weeks. Results: LDL-C reduced significantly; (32.3% and 30.3%, P < 0.001) in (Atv)+(Eze) and (Rsv), respectively, but there was no significant difference between two arms. More patients achieved LDL-C goal of ≤ 100 mg/dl with (Atv)+(Eze) compared to (Rsv) (65% vs. 58%, P < 0.05). Triglycerides (TG) were reduced more with (Atv)+(Eze) compared to (Rsv) (28.1% and 21.4%, P < 0.001). Greater increase in high-density lipoprotein cholesterol (HDL-C) was observed with (Atv)+(Eze). Both treatments were well tolerated. Conclusion: This study shows that the combination of (Atv)+(Eze) has more efficacy and comparable safety to that of (Rsv).

Key words: 3-hydroxy-3-methylglutaryl-CoA, reductase, insulin resistance syndrome, low-density lipoproteincholesterol, statins

INTRODUCTION

The expert panel on detection, evaluation, and treatment of high blood cholesterol defined the metabolic syndrome as a constellation of metabolic derangements that includes insulin resistance, hypertension, dyslipidemia, central or visceral obesity, impaired glucose tolerance/impaired fasting glucose that is associated with increased risk for development of type 2 diabetes and atherosclerotic vascular disease.1-3

Metabolic syndrome is not limited to a particular region, it has engulfed wide regions of the world and the problem is increasing at a rapid pace due to sedentary lifestyle, rapid urbanization, abnormal eating habits and behavioral changes. So it is imperative to search for the best therapy to reduce the burden of the disease.

South Asians are more predisposed to develop type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD).4,5 Clustering of cardiovascular risk factors in South Asians was initially reported from UK.6,7 Since then, a number of investigators have reported a high prevalence of the metabolic syndrome in South Asian populations settled in other countries. Prevalence of the metabolic syndrome as defined by National Cholesterol Education Program, adult treatment panel III (NCEP, ATP III)8 and other criteria ranges from about 11% to 41% in different regions of India.9-13

The atherogenic dyslipidemia associated with the metabolic syndrome is characterized by low concentrations of high-density lipoprotein cholesterol (HDL-C), increased levels of triglyceride (TG); and preponderance of small low-density lipoprotein cholesterol (LDL-C) particles.14 Many patients may also have raised LDL-C, which increases the risk of cardiovascular events.15

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Statins are the most effective and best-tolerated agents for treating dyslipidemia and they are recognized as first-line therapy for lowering of cholesterol levels.\(^\text{[14,16-19]}\) By reducing LDL cholesterol and triglyceride levels and increasing HDL cholesterol,\(^\text{[29]}\) they have shown to reduce cardiovascular morbidity and mortality in large outcome trials in various populations.\(^\text{[31-26]}\) Moreover, statins have ‘pleiotropic’ effects, such as reducing oxidative stress and modulating inflammatory responses,\(^\text{[27]}\) and these effects may improve other risk factors associated with the metabolic syndrome. Evidence suggests that High sensitive C-reactive protein, an inflammatory biomarker is a strong, independent predictor and associated with an increased risk of cardiovascular events.\(^\text{[28-37]}\) Recently conducted Justification for the use of Statins in Primary Prevention and Intervention Trial Evaluating Rosuvastatin Trial, trial has shown that rosuvastatin (Rsv) significantly reduced the incidence of major cardiovascular events even in apparently healthy population with LDL \(<130\) mg/dl by reducing hs-CRP. Since metabolic syndrome is a pro-inflammatory state, the patients should be evaluated for statin therapy.

A large international, prospective, randomized trial, the Comparative study with Rosuvastatin in Subjects with Metabolic Syndrome study\(^\text{[38]}\) and some other studies have shown that statins can improve lipid levels in patients with the metabolic syndrome.\(^\text{[39-42]}\) Because of the increased Cardiovascular Disease (CVD) risk associated with the metabolic syndrome and extensive clinical trial evidence documenting reduction of CVD risk with statin treatment, all patients with the metabolic syndrome should be evaluated as candidates for statin treatment as part of a multidisciplinary approach to reduce CVD risk.\(^\text{[43]}\)

Despite the proven benefits of statin therapy, many patients fail to achieve lipid goals in clinical practice.\(^\text{[44-46]}\) This may be due to inappropriate dosing of statins, increased risk of adverse effects (myopathy and hepatotoxicity) with high-dose statin monotherapy, and insufficient LDL-C-lowering efficacy of current drugs.\(^\text{[49,51]}\) With recent focus on more aggressive treatment guidelines and inability of the high-risk patients to reach their target LDL-C goals with currently available lipid-lowering agents, a search for new therapies or combination therapies with improved efficacy and safety is imperative.

Co-administration of ezetimibe (EZE) with atorvastatin (ATV) may enable more patients to achieve LDL-C goals while avoiding the risks associated with high-dose statin monotherapy through dual inhibition of intestinal cholesterol absorption (EZE) and cholesterol biosynthesis (statin). In previous studies, EZE+ATV co-administration therapy was shown to produce significant incremental reductions in LDL-C with no increased risk of adverse effects compared with LDL-C in patients with raised cholesterol.\(^\text{[52-54]}\)

The present study is the first study designed to evaluate the lipid-lowering effect of a newer statin, Rsv versus a combination of ATV and EZE in patients with metabolic syndrome in the Indian population. Rsv has shown to be more efficacious than ATV in the previous studies, however, the combination of ATV and EZE has also shown to produce significant reduction in LDL-C when compared to ATV alone, with no increased risk of adverse effects, enabling more patients to achieve LDL-C goals, while avoiding the risks associated with high-dose statin monotherapy. This study is designed keeping in mind the search for a better alternative in the patients with metabolic syndrome and dyslipidemia.

**Materials and Methods**

**Study design**

This is a randomized, double-blind, parallel group study comparing the efficacy and safety of Rsv versus a combination of ATV and EZE in the patients with metabolic syndrome, conducted at an Indian tertiary care government teaching hospital. After institutional ethics committee approval and written informed consent, patients meeting the inclusion and exclusion criteria at enrolment entered a 6-week dietary run-in period, in which they were recommended the NCEP ATP III therapeutic life-style-change diet and all lipid-lowering therapy was withdrawn at least 14 days before the end of this period. Eligible patients were then randomized to receive Rsv 5 mg or ATV+EZE (10/10 mg) for 12 weeks [Figure 1].

**Figure 1: The study of population flowchart**
Concomitant medications like erythromycin, azole antifungals, vitamin K antagonists, immunosuppressives, glitazones, systemic steroids or any medication interacting with the statin metabolism was not permitted during the study. The patient was discontinued from the trial, if the patient took lipid-lowering medication (other than the medication understudy).

**Study population**
Patients (male or female) ≥18 years were eligible for the study if they had metabolic syndrome as defined by the presence of at least three of the following: Abdominal obesity (waist circumference >102 cm for men and >88 cm for women); TG ≥1.70 mmol/L (150 mg/dL); HDL-C <1.04 mmol/L (40 mg/dL) for men and <1.30 mmol/L (50 mg/dL) for women; Blood Pressure ≥130/85 mmHg or receiving antihypertensive treatment; and Fasting blood glucose ≥6.11 mmol/L (110 mg/dL).[10] Patients were also required to have LDL-C ≥3.36 mmol/L (130 mg/dL) and additional multiple risk factors conferring a 10-year CHD risk score of >10%. The exclusion criteria included the following: Use of lipid-lowering agents within the past 6 months; TG ≥5.65 mmol/L (500 mg/dL); LDL-C ≥6.48 mmol/L (250 mg/dL); Documented history of CHD or other atherosclerotic disease; A history of known familial hypercholesterolemia; A history of serious or hypersensitivity reactions to other statins; Uncontrolled hypothyroidism; Uncontrolled hypertension; Acute liver disease or hepatic dysfunction [hepatic transaminases or bilirubin ≥1.5× the upper limit of normal (ULN)]; unexplained serum creatine kinase (CK)>3× ULN; and use of prohibited concomitant medications.

**Endpoint assessments**

**Efficacy**
Blood samples were collected at 6 weeks (beginning of the dietary lead-in period), 0 weeks (randomization) and 12 weeks. The primary efficacy variable was percentage change in LDL-C from baseline levels to 12 weeks of treatment (Rsv 10 mg; ATV+EZE 10/10 mg). Secondary endpoints included: Percentage of patients achieving the LDL-C goal of <2.59 mmol/L (100 mg/dL) at 12 weeks; percentage change in total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) from baseline to 12 weeks.

**Safety and tolerability**
Adverse events reported spontaneously by the patients, revealed by observation or elicited in response to an open question, were recorded. Laboratory safety variables included: Hemoglobin, platelet count, leucocyte count, serum aspartate aminotransferase (ASAT), serum alanine aminotransferase (ALAT), serum alkaline phosphatase, serum bilirubin, CK and serum creatinine. Pre-specified safety variables included the incidence of ALT and AST elevations ≥3 times ULN and CK elevations of 5-10 with muscle symptoms or ≥10 times ULN with or without muscle symptoms. Myopathy was prospectively defined as CK elevations ≥10 times ULN associated with muscle symptoms with no other plausible etiology such as exercise or trauma. Causality assessment of all the adverse events was done according to Naranjo scale.[55]

**Laboratory methods**
Lipids in total serum were measured using automated enzymatic methods. TC was measured by CHOD-PAP method[60] by a commercially available kit. HDL-C was measured by PEG-PAP method[5] by a commercially available kit. TG was measured by enzymatic Glycerol Phosphate Oxidase-Phenol+Aminophenazone (GPO-PAP) method[50] by a commercially available kit from Pointe Scientific Inc, USA. LDL-C is calculated using Friedewald’s equation.[99] All other analyses were performed at the central laboratory.

**Statistical analysis**
To detect a clinically significant difference of 6% in the primary endpoint, i.e., mean percentage change in LDL-C from baseline to 12 weeks between ATV+EZE (10/10) mg and ATV (5) mg; with a power of 90%, significance level of 5%, and a standard deviation of 10, a total of 59 patients per active treatment arm were required. Assuming a withdrawal rate of 10%, approximately 65 patients per treatment arm would need to be randomized using a ratio of 1:1. Efficacy data was evaluated on the basis of the intention-to-treat (ITT) populations, which consisted of all patients with at least one dose of study medication, a baseline reading, and at least one post-baseline assessment for one or more lipid variables in the randomized treatment period. Last observation carried forward (LOCF) was used on the ITT population for patients with missing data. Efficacy endpoint analysis was done by Students’ independent t-test. The proportion of patients reaching the LDL-C goal of ≤100 mg/dl was analyzed using a Mantel-Haenszel test. Safety data were evaluated for all patients who received at least one dose of study medication.

**RESULTS**

**Patient demographics**
A total of 507 patients were screened; of which 183 met the eligibility criteria and were enrolled for the dietary lead-in period. Out of this, 48 patients discontinued before randomization for various reasons like consent withdrawal, protocol violation, lost to follow-up etc., so the ITT population consisted of 135 patients [Figure 2]. Three patients from the ATV+EZE group and 4 from
Rsv discontinued after randomization, so 128 patients completed the study. Table 1 shows the demographics and baseline characteristics of the population. Both the groups were well matched.

Efficacy

Table 2 shows the mean reduction in lipids at the end of 12 weeks; there was no significant difference in the percentage of LDL-C reduction between the two arms (32.3% vs. 30.3%, P > 0.05). There was also no significant difference (−3.5%, P > 0.05) regarding the percentage of TC reduction between the two arms. Both treatments increased the HDL-C level; with Atv+Eze more than Rsv group (8% vs. 3.9%) but the difference between them was not significant. Atv+Eze combination arm was significantly better than Rsv arm with reference to triglyceride and VLDL reduction (−6.7%, P < 0.05). The total percentage of patients reaching the LDL-C goal of ≤100 mg/dl was 61.7%. More patients in the Atv+Eze combination group reached the goal (65% vs. 58.3%), but this was not statistically significant. Moreover, the overall percentage of females reaching the goal was greater than males (66% vs. 56%).

Safety

Table 3 shows the adverse events in the treatment groups. Both the treatments were well tolerated. A total of 19.1% of the patients from Atv+Eze combination arm and 16.4% from Rsv arm experienced the events. There was no significant difference between the two arms. All the adverse events except one were in the “doubtful” or “probable” (Naranjo 0 to +2) category based on Naranjo scale. Severity was also 0 (no disability) to 1 (minor temporary) The Adverse Drug Reaction profile of both the groups was similar. The Liver Function Test (LFT), Renal Function Test (RFT), hemogram and platelet counts were within the normal limits in both the groups after 12 weeks. The most frequent adverse events were headache and loose stools which were unrelated to the medication under study. No patient in the Atv+Eze arm experienced any Side effect related to treatment but one patient in the Rsv arm experienced serious adverse event (myalgia) related to treatment causing withdrawal from the study. In this case also, there was no clinically important elevation of CK >5× ULN or any associated muscle symptoms.

Discussion

The problem of metabolic syndrome is increasing day by day in India; the South Asian population is more prone to develop diabetes and CHD.4,5 India especially is becoming the diabetes capital of the world. The statins are the most effective and best-tolerated agents for treating dyslipidemia and they are recognized as first-line therapy.
for lowering cholesterol levels.[14,16-19] Moreover, they also have pleiotropic effects which are beneficial in metabolic syndrome pathophysiology. Recent guidelines call for a more aggressive lipid lowering but still, many patients on statin monotherapy fail to achieve the optimum lipid goals. Further, the statins demonstrate only an additional 6% reduction in LDL-C for every doubling of the dose, while side-effects increase linearly with dose. This is the first study evaluating the efficacy and safety of Rsv versus a combination of ATV and EZE in patients with metabolic syndrome in the Indian population.

Results of this study show that there is no significant difference in LDL-C reduction between the two treatment arms. Many previous studies have shown a superiority of Rsv over ATV[42,60-69] but when EZE is combined with ATV, we found no significant difference (32.3% vs. 30.3%, P > 0.05). This finding is consistent with the previous studies where EZE+ATV co-administration therapy was shown to produce significant incremental reductions in LDL-C with no increased risk of adverse effects when compared with ATV alone in patients with raised cholesterol.[52-54,70-72]

This may be due to dual inhibition of intestinal cholesterol absorption by EZE and cholesterol biosynthesis by ATV. High levels of HDL-C are considered to be good for CHD; in this study, both the treatment arms increased the HDL-C level but there was no significant difference between both the arms. As seen in the table, there is a significant difference in Triglyceride reduction between the two arms with Atv+Eze combination decreasing more than Rsv. EZE interferes with absorption of dietary cholesterol/TG at the intestinal brush border (exogenous pathway), thus decreasing their level. Other parameters like TC are reduced by both treatments but with no significant difference. In previous studies, patients on Rsv have consistently shown more patients in the combination arm reached the goal. Reason is the same as explained previously. Moreover, the overall percentage of females reaching the goal is higher which is consistent with previous studies but there was no subgroup-by -treatment interaction when data were stratified by age-group, baseline LDL-C levels and BMI (body mass index).

Both the therapies were well tolerated in this high-risk population. Major concerns with statin therapy include the rare occurrence of serious muscle-related adverse events (myopathy and rhabdomyolysis) and the potential for elevating serum transaminases.[53,74] There were no clinically significant differences between EZE+ATV combination therapy and Rsv with regard to the incidence of any clinical or laboratory adverse event. Safety of both the regimens has been established previously.[54,71,75-77]

We have chosen the minimal dose recommended for Asian population which might be the reason for absence of any serious event. Compliance of both regimens was good as the both were given once daily.

**Conclusion**

Co-administration of EZE with statin is a treatment strategy that targets both the synthesis and intestinal absorption of cholesterol. It has been shown to produce significant incremental reductions in LDL-C beyond that achieved by either agent alone.[50-72,78] This treatment regimen may be especially advantageous for CHD patients who frequently fail to attain optimal LDL-C levels with the highest doses of the most effective statins on one hand and minimizing adverse events on the other. In our study, the combination therapy is found to be equally safe and compliant, reducing the TG more than Rsv, and enabling more patients to reach the lipid goal.

**References**

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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). JAMA 2001;285: 2486-97.
2. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
3. Ginsberg HN, Stalenhoef AF. The metabolic syndrome: Targeting dyslipidaemia to reduce coronary risk. J Cardiovasc Risk 2003;10:121-8.
4. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414-31.
5. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998;97:596-601.
6. McKeigue PM, Pierpoint T, Ferrie JE, Marmot MG. Relationship of glucose intolerance and hyperinsulinaemia to body fat pattern in south Asians and Europeans. Diabetologia 1992;35:785-91.
7. McKeigue PM, Marmot MG, Syndercombe Court YD, Cottier DE,
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Rahman S, Riemersma RA. Diabetes, hyperinsulinaemia, and coronary risk factors in Bangladeshis in east London. Br Heart J 1988;60:390-6.
8. Mohan V, Shanthisri S, Deepa R, Premalatha G, Sastry NG, Saroja R, et al. Intra-urban differences in the prevalence of the metabolic syndrome in southern India - the Chennai Urban Population Study (CUPS No. 4). Diabet Med 2001;18:280-7.
9. Gupta A, Gupta R, Sarna M, Rastogi S, Gupta VP, Kothari K. Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. Diabetes Res Clin Pract 2003;61:69-76.
10. Deepa R, Shanthisri CS, Premalatha G, Sastry NG, Mohan V. Prevalence of insulin resistance syndrome in a selected south Indian population - the Chennai urban population study-7 (CUPS-7). Indian J Med Res2002;115:118-27.
11. Ramachandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay J. Metabolic syndrome in urban Asian Indian adults—a population study using modified ATP III criteria. Diabetes Res Clin Pract 2003;60:199-204.
12. Misra A, Pandey RM, Devi JR, Sharma R, Vilem NK, Khanna N. High prevalence of diabetes, obesity and dyslipidaemia in urban slum population in northern India. Int J Obes Relat Metab Disord 2001;25:1722-9.
13. Misra A, Vikram NK, Arya S, Pandey RM, Dhingra V, Chatterjee A, et al. High prevalence of insulin resistance in postpubertal Asian Indian children is associated with adverse truncal body fat patterning, abdominal adiposity and excess body fat. Int J Obes Relat Metab Disord 2004;28:1217-26.
14. Grundy SM. Hypertriglyceridaemia, insulin resistance, and the metabolic syndrome. Am J Cardiol 1999;83:25F-9F.
15. LaRoso JC, Hunninghake D, Bush D, Criqui MH, Getz GS, Gotto AM Jr, et al. The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. The Task Force on Cholesterol Issues, American Heart Association. Circulation 1990;81:1721-33.
16. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. Eur Heart J 1998;19:1434-503.
17. A desktop guide to Type 2 diabetes mellitus. European Diabetes Policy Group 1999. Diabet Med 1999;16:716-30.
18. De Backer G, Ambrosioni E, Borsh-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2003;10:S1-10.
19. American Diabetes Association: Management of Dyslipidemia in Adults With Diabetes. Diabetes Care 2002;25:s74-7.
20. Sowers JR. Effects of statins on the vasculature: Implications for aggressive lipid management in the cardiovascular metabolic syndrome. Am J Cardiol 2003;91:14B-22B.
21. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S) Lancet 1994;344:1383-9.
22. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med1995;333:1301-7.
23. Sacks FM, Pfeiffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001-9.
24. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349-57.
25. Downs JR, Czeizel AM, Weis S, Whitney E, Shapiro DR, Beere 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;279:1615-22.
26. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beavers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): A multicenter randomised controlled trial. Lancet 2003;361:1149-58.
27. Liao JK. Beyond lipid lowering: The role of statins in vascular protection. Int J Cardiol 2002;86:5-18.
28. Ridker PM. Clinical application of C‑reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363-9.
29. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.
30. Ridker PM, Hennekens CH, Buring JE, Rifai N. C‑reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
31. Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, et al. C‑reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: Results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999;99:237-42.
32. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C‑reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.
33. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: A comparison of C‑reactive protein, fibrinogen, homocysteine, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285:2481-5.
34. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. BMJ 2000;321:199-204.
35. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C‑reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol 1997;17:1121-7.
36. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C‑reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation 2002;105:2595-9.
37. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C‑reactive protein and coronary heart disease in the MRFFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;144:537-47.
38. Stalenhoef AF, Ballantyne CM, Sarti C, Munir J, Tonstad S, Rose H, et al. A comparative study with rosuvastatin in subjects with metabolic syndrome: Results of the COMETS study. Eur Heart J 2005;26:2664-72.
39. Hunninghake DB, Ballantyne CM, Maccubbin DL, Shah AK, Gumbiner B, Mitchell YB. Comparative effects of simvastatin and atorvastatin in hypercholesterolemic patients with characteristics of metabolic syndrome. ClinTher 2003;25:1670-86.
58. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

59. Brown WV, Chitra RR, Zedler HE, Bays HE, Hassman HA. Long term efficacy and safety of rosvastatin: Results of a 52 week comparator-controlled trial versus pravastatin and simvastatin [abstract]. Eur Heart J 2001;22:270.

60. Olsson AG, Southworth H, Wilpshaar JW. Long term efficacy and safety of rosvastatin: Results of a 52 week comparator-controlled trial versus Atorvastatin [abstract] Eur Heart J 2001;22:253.

61. Davidson M, Ma P, Stein EA, Gotto AM Jr, Raza A, Chitra R, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. Am J Cardiol 2002;89:678-75.

62. Berne C, Siewert-Delle A, URANUS study investigators. Comparison of rosvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: Results from the URANUS study. Cardiovasc Diabetol 2003;4:7.

63. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR® Trial). Am J Cardiol 2003;92:152-60.

64. Schuster B, Schuster P, Schauer EC, Sartori J, Schusser J, et al. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. Am Heart J 2004;147:705-13.

65. Birdwell PC, Djuvone CA. Drug interactions of lipid-altering drugs. Drug Saf 1998;19:355-71.

66. Ballantyne CM, Stein EA, Bays HE, Djuvone CA, McBride PE, Battisti WP, Brady WE. Efficacy and safety of 10 mg and 20 mg simvastatin with atorvastatin therapy in patients with type 2 diabetes mellitus. Clin Ther 2004;26:1821-33.

67. Ballantyne CM, Stein EA, Bays HE, Djuvone CA, McBride PE, Battisti WP, Brady WE. Efficacy and safety of 10 mg and 20 mg atorvastatin with atorvastatin therapy in patients at risk of coronary heart disease (from the URANUS Trial). Am J Cardiol 2007;99:1538-43.

68. Saito Y, Yamada N, Shinai K, Sasaki J, Ebihara Y, Yanase T, et al. Effect of rosvastatin 5-20mg on triglycerides and other lipid parameters in Japanese patients with hypertriglyceridemia. Atherosclerosis 2001;149:505-11.

69. Strandberg TE, Feely J, Sigurdsson EL, DISCOVERY study group. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: A discovery study. Clin Ther 2004;26:1821-33.

70. Jeppesen J, Andersen JL, Tapanen H, Uusitalo S, Sandros J, et al. Effect of ezetimibe coadministered with atorvastatin in patients with primary hypercholesterolemia. A prospective, randomized, double-blind trial. Circulation 2003;107:2409-15.

71. Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol 2004;93:1487-94.

72. Gagne C, Gaudet E. Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;105:2469-75.

73. Naranjo CA, Busto U, Sellers EM, Sandoz P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

74. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470-5.

75. Izzo C, Grillo F, Murador E. Improved method for determination of high-density-lipoprotein cholesterol I. Isolation of high-density lipoproteins by use of polyethylene glycol 6000. Clin Chem 1981;27:371-4.
et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. Curr Med Res Opin 2004;20:1437-45.
76. Bernini F, Poli A, Paoletti R. Safety of HMG-CoA reductase inhibitors: Focus on atorvastatin. Cardiovasc Drugs Ther 2001;15:211-8.
77. Shepherd J, Hunninghake DB, Stein EA, Kastelein JJ, Harris S, Pears J, et al. Safety of rosuvastatin. Am J Cardiol 2004;94:882-8.
78. Ballantyne CM, Lipka LJ, Sager PT, Strony J, Alizadeh J, Suresh R, et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. Int J ClinPract 2004;58:653-8.