REVIEW ARTICLE

Rosuvastatin: Role in Secondary Prevention of Cardiovascular Disease

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Abstract

Cardiovascular (CV) diseases are a major cause of premature death and disability. Non-communicable diseases (NCD) are responsible for 52% of mortality amongst Indians, of these CV diseases are responsible for 66% of NCD mortality in India. We not only need widespread primary preventive strategy but also need effective secondary prevention protocols to reduce this.

Secondary prevention in patients who already had myocardial infarction (MI) or revascularization is of utmost importance to reduce mortality, cardiac events and improve quality of life. Lifestyle changes and medical therapy have a very important role in secondary prevention of CVD.

Optimal control of hypertension, diabetes mellitus and dyslipidemia plays a critical role in secondary prevention. Statins are one of the most commonly used drugs in secondary prevention as a part of medical therapy. Effective LDL reduction, more patients achieving LDL goals, reduction in intima thickness, improvement in endothelial dysfunction, reduction in inflammatory markers are considered to be surrogate markers of reduced risk with statins.

Rosuvastatin is one of the two most commonly used statins. It is a potent, effective and safe HMG-COA reductase inhibitor. Data related to secondary prevention is limited with rosuvastatin. Most of the clinical evidences with rosuvastatin have shown more effective LDL reduction than other statins. More number of patients achieve LDL goals and reduction in intima thickness. This article attempts to explore data on role of rosuvastatin for secondary prevention.

Introduction

Cardiovascular diseases are the major cause of premature death and disability in Western countries. This trend is becoming more common in developing countries.[1] In developing countries like India,[2] CV events are associated with huge economic burden and health problems, so efforts are being put to reduce the incidence of CV events. CV disease occurs a decade earlier in Indians when compared to Europeans.[3] In India, almost 66% of NCD mortality is attributed to CVD related condition.[4]

3-hydroxy-3-methyl-glutaryl-coenzymeAreductase (HMG-CoA reductase) inhibitors i.e. Statins, lower cholesterol effectively and are used to prevent CV events. It has been shown in several large clinical trials that use of statins has reduced cardiovascular event rates.

Given the fact that low density lipoprotein-cholesterol (LDL-C) levels have been used to monitor the lipid-lowering response to treatments in almost all trials, it remains the primary target in the management of dyslipidemias.[1] The benefits with statins can be seen across LDL cholesterol range. There is no exact lower value of LDL for the benefits. The ability to reduce LDL levels and raise high density lipoproteins (HDL) levels differs with different statins.[5] The aim of this paper is to evaluate evidence base that exists on the role of rosuvastatin in secondary prevention of CVD.

Secondary Prevention

Lifestyle measures and drug therapy for optimal control of hypertension, diabetes mellitus and dyslipidemia plays a critical role in secondary prevention.[6] Many studies have shown that reduction of cholesterol levels decreases recurrence of coronary events at all levels of baseline cholesterol.[7] The Adult Treatment Panel III (ATP III) and American Heart Association (AHA) recommended the LDL goals of < 70 mg/dL for secondary prevention. The recent ACC/AHA guidelines recommend high intensity statin therapy for secondary prevention of all patients with atherosclerotic cardiovascular disease (ASCVD) irrespective of the baseline LDL levels.[8] Statins are the initial choice of drugs for lowering LDL levels and one can consider additional agents if LDL goals are not reached. [7]

Many studies have now shown that as compared to standard therapy, intensive statin therapy helps in reducing all cause mortality in patients with acute coronary syndrome (ACS).[8] With statin therapy for every 2 mg/dL LDL cholesterol reduction it has shown to reduce stroke, coronary events and coronary revascularization by one percent.[9] Different statins are used routinely which help in reducing LDL, triglycerides (TGs) and increase HDL levels (Table 1).

Rosuvastatin

Rosuvastatin is a HMG-CoA

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Table 1: Comparative effectiveness of routinely used statins[10-12]

Statin and dose	Rosuvastatin 10 mg	Atorvastatin 10 mg	Simvastatin 10 mg	Fluvastatin 20 mg	Pravastatin 10 mg	Lovastatin 20 mg
HDL increase %	8 %	6%	5%	1%	3%	7%
LDL reduction %	46%	37%	28%	17%	20%	29%
TG reduction%	20%	20%	12%	5%	8%	12%

Table 2: Comparative pharmacokinetics of statins[19]

Statin	Solubility	Bioavail-ability %	Protein binding %	Active metabolites	CYP 450 metabolism and iso enzyme	Elimination half-life (h)	Renal excretion %
Rosuvastatin	Hydrophilic	20	90	minor	limited	19	13
Atorvastatin	Lipophilic	12	98	Yes	Yes 3A4	14	<5
Simvastatin	Lipophilic	5	95-98	Yes	Yes 3A4	2	13
Fluvastatin	Lipophilic	24	>98	No	Yes 2C9	1.2	6
Pravastatin	Hydrophilic	18	50	No	No	1.8	20
Lovastatin	Lipophilic	5	>95	Yes	Yes 3A4	3	10

reductase inhibitor. It has an additional polar methane sulphonide group. This makes rosuvastatin less lipophilic and improves its ionic interaction with HMG-CoA reductase. The inhibition is selective and reversible. This inhibition leads to decreased sterol synthesis and hence decreased hepatocellular cholesterol, resulting in enhanced synthesis of LDL receptors and hence more LDL is being taken from circulation into liver. This leads to decrease in LDL-C and total cholesterol (TC) concentration in circulation.[13,14] Rosuvastatin also reduces production of very low density lipoprotein-cholesterol (VLDL-C) and triglycerides (TGs) by reducing synthesis of apolipoprotein B (APO B).[15] Rosuvastatin has high hepatocyte concentration and low systemic concentration and this is because of high affinity of rosuvastatin to organic anion transporting polypeptide-1B1 (OATP-1B1) present in basolateral membrane of hepatocyte. It also has pleiotropic effects. It has shown to improve endothelial dysfunction by increasing production of nitric oxide. It has also shown anti-inflammatory effects which is due to reduction in high sensitivity C reactive protein. The antithrombotic effects of rosuvastatin are because of its ability to reduce platelet aggregation.[16]

Clinical Pharmacokinetics[17]

Absorption

Rosuvastatin has oral bioavailability of 20% with peak plasma levels achieved in 5 hours.

Food does not affect absorption and can be taken with or without food.

Distribution

Rosuvastatin is 88% plasma protein bound with volume of distribution being 134 litres.

The ability of statins to passively diffuse into extrahepatic tissues depends on their lipophilicity. This can have implications on their extrahepatic side effects. The more lipophilic the statin the more chance it has to diffuse into extrahepatic tissues. When compared to other statins like atorvastatin and simvastatin, rosuvastatin is less lipophilic[18] (Table 2).

Metabolism

Rosuvastatin is a poor substrate for metabolism by hepatic cytochrome P-450 (CYP3A4) enzymes. It is mainly metabolised by CYP 2C9 to a less potent metabolite N-desmethyl rosuvastatin. It shows minimal drug-drug interactions and plasma half life of rosuvastatin is 19 hours.

Elimination

Approximately 90% of rosuvastatin is eliminated in faeces with 10% being eliminated in urine.

Markers of atherosclerosis

Many efforts are being made to identify markers of atherosclerosis.

Biomarkers: It has been shown that there is a relation between increased risk and increased levels of cytokines, the cell adhesion molecules P-selectin and E-selectin; and acute-phase reactants such as high sensitive C-reactive protein (hsCRP), serum amyloid A and fibrinogen. Many efforts are also towards identifying factors which affect plaque stability and CAD which is not stable like myeloperoxidase, soluble CD40 ligand, placental growth factor, free fatty acids and pregnancy-associated plasma protein A. There are also markers to identify endothelial dysfunction.[20]

Intima media thickness: There is a strong co-relation between carotid intima media thickness (IMT) and atherosclerosis extent and end-organ damage. Determination of markers of preclinical atherosclerosis could influence clinician's decision to intervene with medication and to use more aggressive treatment of risk factors in primary prevention and in patients with atherosclerotic disease. Measuring IMT in large superficial arteries using ultrasonography helps to assess the deterioration in arterial wall and also to assess cardiovascular risk. Carotid IMT is influenced by age, lifestyle, cholesterol level, hypertension, smoking and lipoprotein-a. Carotid IMT mirrors burden of atherosclerosis and help predict subsequent events. Now there is growing interest to use carotid IMT clinically and identify atherosclerosis and subjects at high risk.[21]

Rosuvastatin in Secondary Prevention

The 4S trial with simvastatin (Scandinavian Simvastatin Survival Study) was one of the first secondary prevention trial which showed significant reduction in overall mortality, major coronary events and coronary death in post MI patients or patients with ischaemic heart disease.[22] Similarly, the LIPID study (Long term intervention with pravastatin in ischemic disease) with pravastatin showed reduction in cardiovascular events and mortality in post MI patients or patients with unstable angina.[23] There are clinical evidences with rosuvastatin which shows improvement in surrogate markers.

Clinical Evidence with Rosuvastatin (Table 3)

We have many studies with use of rosuvastatin. The characteristics and salient findings of these trials are being analysed below (Table 3).

Statin therapies for elevated lipid levels compared across doses to Rosuvastatin trial (STELLAR) was a multicentre randomised trial. At the conclusion of the trial it was shown that rosuvastatin reduced non-HDL-C by 42.0% to 50.9% compared with

Table 3: Major Characteristics of the statin trials

Trial	Design	Sample size	Duration	Comparative therapies	Main outcome measures
Stellar	RCT	2431	6 weeks	Rosuvastatin 10,20,40 and 80 mg Vs Atorvastatin 10,20,40 and 80 mg, Simvastatin 10,20,40 and 80 mg and Pravastatin 10, 20, 40 mg	Primary outcome –Reduction of LDL cholesterol Secondary objective-Achieving NCEP III and JETF LDL goals
Pulsar	RCT	996	6 weeks	Rosuvastatin 10mg OD vs Atorvastatin 20 mg OD	Primary outcome –Reduction of LDL cholesterol Secondary objective-Achieving *NCEP III LDL goals < 100 mg/dL
Asteroid	RCT	349	24 months	Rosuvastatin 40 mg	Primary Outcome –Change in percent atheroma volume and change in nominal atheroma volume in the most diseased 10 mm subsegment Secondary endpoint – Change in normalised total atheroma volume in the entire artery
Orion	RCT	33	24 months	Rosuvastatin 40/80 mg vs Rosuvastatin 5 mg	Change in plaque volume and composition in carotid artery
Meteor	RCT	984	24 months	Rosuvastatin 40 mg vs placebo	Slow progression /cause regression in CIMT
Cosmos	RCT	126	78 weeks	Rosuvastatin 2.5 mg – 20mg (Dose is increase at 4 weeks interval upto 20 mg/day)	Effects on Coronary atheroma volume
Saturn	RCT	1039‡	24 months	Rosuvastatin 40mg vs Atorvastatin 80 mg	Assess progression of coronary atherosclerosis
Space rocket	RCT	1263	3 months	Rosuvastatin 10mg vs Simvastatin 40 mg	ESC-03 lipid targets of LDL-C and TC.
Centauras	RCT	478†	3 months	Rosuvastatin 20mg vs Atorvastatin 80 mg	Reduction apo B/apo A1
Lunar	RCT	825	12 weeks	Rosuvastatin 20mg,40 Vs Atorvastatin 80 mg	Lowering LDL cholesterol

*NCEP: National Cholesterol Education Program Adult Treatment Panel III; JETF: Joint European Task Force; ‡519 atorvastatin group and 520 Rosuvastatin group; †226 in rosuvastatin and 252 in atorvastatin group

34.4% to 48.1% with atorvastatin, 26.0% to 41.8% with simvastatin, and 18.6% to 27.4% with pravastatin. Adult Treatment Panel III LDL cholesterol goals were achieved by 82% to 89% of patients treated with rosuvastatin 10 to 40 mg compared with 69% to 85% of patients treated with atorvastatin 10 to 80 mg; rosuvastatin reduced apo B by 36.7% to 45.3% compared with 29.4% to 42.9% with atorvastatin, 22.2% to 34.7% with simvastatin, and 14.7% to 23.0% with pravastatin. Increase in apo A-I (8.8%) was highest in the rosuvastatin 20 mg group, and this increase was significantly greater than in the atorvastatin 40 mg and 80 mg groups. Rosuvastatin was well tolerated in the trial.[24]

Prospective study to evaluate the utility of low doses of the statins Atorvastatin and Rosuvastatin (PULSAR trial): 996 patients with LDL-C >130 and < 220 mg/dL and patients with atherosclerosis, coronary artery disease or coronary artery disease-risk equivalent were included in the study. At the conclusion of study it was found that LDL-C reduction by rosuvastatin 10 mg was 44.6% and with atorvastatin 20 mg it was 42.7% and the results were statistically significant ($p<0.05$). With 10 mg rosuvastatin 68% achieved NCEP ATP III and 2003 European LDL-C goals and with atorvastatin 20 mg 62.5% and 63.3% achieved NCEP ATP III and 2003 European LDL-C goals and the results were statistically significant ($p<0.05$). The increase in HDL-C levels with rosuvastatin 10 mg was 6.4% as compared with atorvastatin 20 mg which was 3.1% and the results were statistically significant ($p<0.001$). The improvement of lipid ratios and apolipoprotein A-1 levels was better with rosuvastatin 10 mg as compared to atorvastatin 20 mg. The study also found rosuvastatin to be cost effective and was well tolerated and there were no incidences of liver insufficiency, renal insufficiency or rhabdomyolysis.[25]

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID trial): It is a multicentric prospective, open label trial. 507 patients were randomised in the trial and 349 completed the trial.

The assessments were done by intravascular ultrasound (IVUS) imaging at baseline and at end of 24 months. At the end of trial it was found that the LDL-C reduction was 53.2% (statistically significant $p<0.001$) from the baseline, there was 14.7% (statistically significant $p<0.001$) increase in HDL levels.

There was also significant reduction in endpoints of regression of atherosclerosis which were measured by IVUS imaging. There was -0.98% mean change in percent atheroma volume (PAV) of entire vessel and -6.1 mm^3 mean change in atheroma volume in the 10 mm most diseased subsegment and -14.7 mm^3 mean change in total atheroma volume (TAV).[26]

Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation (ORION trial): It is a randomised double-blind trial. 43 patients were randomised in the trial and 33 completed the trial. The assessment was done by 1.5 Tesla MRI. At end of the trial both low dose and high dose rosuvastatin significantly reduced LDL levels (38.2% vs 59.9%), not much change was seen in plaque volume, but there was 41.4% reduction in lipid rich necrotic core.[27]

Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin (METEOR trial): It is a multicentric, randomised double blind placebo-controlled trial. The assessment was done by carotid ultrasound. Before Randomization Carotid ultrasound was performed twice, and once at 6, 12, and 18 months after randomization, and twice more at the end of 24 months. At the end of trial there was 49% reduction in the LDL levels from baseline, there was also significant reduction in endpoints of regression of atherosclerosis which were measured by IVUS imaging. Common carotid artery sites showed −0.0038 mm/y change in maximum carotid intima media thickness (CIMT). Carotid bulb sites showed – 0.0040 mm/y change in maximum CIMT and Internal carotid artery showed –0.0039 mm/y change in maximum CIMT.

Compared to placebo, rosuvastatin reduced rate of progression of maximum CIMT and the results were statistically significant. The study showed rosuvastatin caused very few adverse effects and it was well tolerated.[28]

Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in

Table 4: Discovery group of studies of statins in high risk cardiovascular patients[29-38]

Study	Study population	Type of patient	Comparator	Results[†]
Discovery Asia	1482	CV high risk	Rosuvastatin 10 mg vs Atorvastatin 10 mg	65.8%, 49.5%
Discovery Alfa	1506	CV high risk	Rosuvastatin 10 mg vs Atorvastatin 10 mg	57.5%, 39.2%
Discovery Belux	938	CV high risk	Rosuvastatin 10 mg vs Atorvastatin 10 mg	71.8%, 46.5%
Discovery Beta	504	CV high risk	Rosuvastatin 10 mg vs Simvastatin 20 mg	44.5%, 22.2%
Discovery Dutch	1215	CV high risk	Rosuvastatin 10 mg vs Atorvastatin 10 mg, Simvastatin 20 Vs Pravastatin 40 mg	50.2%, 24.9%, 26.3%, 18.5%
Discovery Penta	1124	50% CV high risk	Rosuvastatin 10 mg vs Atorvastatin 10 mg	71.2%, 61.4%
Discovery UK	1874	CV high risk	Rosuvastatin 10 mg vs Atorvastatin 10 mg	76%, 55%, 50%

[†]% of patients with LDL <100 mg/dl; All studies duration 12 weeks

Japanese Subjects (COSMOS trial): It is a multicentric open label trial. 214 patients were randomised and received treatment and 126 completed the trial. The assessment was done by IVUS imaging. At the end of trial there was 38% reduction in LDL-C levels and 19.8% increase in HDL-C levels. 60% of enrolled patients showed plaque regression. Rosuvastatin showed reduction in plaque volume of coronary artery and the results were statistically significant.[29]

The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN trial): It is a multicentric, randomised double blind trial. The assessment was done by IVUS imaging. At the end of trial rosuvastatin group had lower levels of LDL-C and higher levels of HDL-C levels. There was also significant reduction in endpoints of regression of atherosclerosis which was measured by IVUS imaging. It was found that decrease in percent atheroma volume (PAV) was – 1.22% with rosuvastatin as compared to atorvastatin which was - 0.99%. Reduction in normalised TAV was - 6.99 mm^3 with rosuvastatin as compared to atorvastatin which was -4.42 mm^3. Percentage of patients who showed regression for PAV was 68.5% with rosuvastatin and 63.2% with atorvastatin.[5]

The Secondary Prevention of Acute Coronary Events - Reduction of Cholesterol to Key European Targets (The SPACE ROCKET trial): It is a multicentre, randomized trial which compared 10 mg rosuvastatin with 40 mg simvastatin. At the end of the trial Rosuvastatin reduced LDL-C by 78 mg/dL and TC by 150 mg/dL as compared to simvastatin which reduced LDL-C by 75 mg/dL and TC by 145 mg/dL. The goals were achieved in 79.9% with rosuvastatin as compared to 77.6% with simvastatin. The study concluded that rosuvastatin 10 mg was more effective than simvastatin 40 mg in reducing LDL-C and achieving European Society of Cardiology-03 (ESC-03) goals.[30]

Comparison of the Effects Noted in The ApoB:ApoA-1 ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome (CENTAURUS trial): It is a randomised, double blind, parallel group trial. The study was done on patients with non-ST elevation MI. At the end of the trial it was seen that at 1 month rosuvastatin 20 mg reduced apolipoprotein B/ apolipoproteinA-1 (apo B/apo A-1) ratios to a greater extent than atorvastatin 40 mg (44.4% vs 42.9%) and the results were statistically significant. The trial showed that rosuvastatin 20 mg decreased apo B/apo A-1 to a greater extent than atorvastatin 40 mg at 1 month but no difference could be seen at the end of 3 months.[31]

Limiting Undertreatment of Lipids in Acute Coronary Syndrome with Rosuvastatin (LUNAR trial): It is a multicentre randomised trial in patients of acute coronary syndrome. At the conclusion of trial it was shown that rosuvastatin 40 mg reduced LDL-C by 46.8% compared to 42.7% with atorvastatin 80 mg. Reduction of LDL-C with rosuvastatin 20 mg was similar to atorvastatin 80 mg. Increase in HDL-C was 11.9%, 9.7% and 5.6% with rosuvastatin 40,20 mg and atorvastatin 80 mg respectively. The study concluded that rosuvastatin 40 mg more effectively reduced LDL-C and increased HDL-C as compared to atorvastatin 80 mg in patients with acute coronary syndrome and both treatments were effectively tolerated.[32]

As mentioned in Table 4 Direct Statin Comparision of LDL-C values: An evaluation of rosuvastatin therapy (Discovery) studies. These were done in different countries of the world to assess the efficacy of statins to achieve target lipid levels. These studies showed that rosuvastatin was significantly more effective than other statins in achieving LDL and total cholesterol goals in different population's worldwide.[33-42]

Safety of Rosuvastatin

Rosuvastatin has been studied in different ethnic groups and it is well tolerated. The risk of myopathy was comparable or slightly less than other available statins. The incidence of myopathy was 0.1% in placebo controlled trials with 40 mg rosuvastatin. Rosuvastatin does not have adverse effect on renal function.[43,44] 40,600 patients were analysed retrospectively and the results showed that rosuvastatin does not increase risk of renal failure or renal impairment. In all the studies of rosuvastatin in secondary prevention of CVD and discovery group of studies, it was well tolerated and found to be safe.

Conclusion

Rosuvastatin reduces LDL-C, increases HDL-C more effectively and helps more patients achieve lipid goals than other statins. In addition, rosuvastatin showed improvement in markers of atherosclerosis like reduction in lipid rich necrotic core, reduced rate of progression of maximum CIMT, reduction in plaque volume and decreasing apo B/apo A-1 ratio. These studies have shown that rosuvastatin has a role in regression of coronary atherosclerosis and is beneficial in patients for secondary prevention.

References

1. Catapano AL, Reiner Z, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis* 2011; 217 Suppl 1:S1-44.
2. Srinath Reddy K, Shah B, Varghese C, Ramadoss A. Responding to the threat of chronic diseases in India. *Lancet* 2005; 366:1744–49.
3. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *JAMA* 2007; 297:286–94.
4. Patel V, Chatterji S, Chisholm D, et al. Chronic diseases and injuries in India. *Lancet* 2011; 377:413–28.
5. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011; 365:2078-87.
6. Hall SL, Lorenc T. Secondary prevention of Coronary artery disease. *American Family Physician* 2010; 81:289-96.
7. 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.
8. Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA

Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation* 2014; 129:S1-S45.

9. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. *CMAJ* 2008; 178:576-84.
10. McTaggart F. Comparative pharmacology of Rosuvastatin. *Atheroscl Suppl* 2003; 4:9-14.
11. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E et al. For the STELLAR Study Group. Comparison of the efficacy and safety of Rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; 92:152-60.
12. Jones P, Kafonek S, Laurora I, Hunninghake D. For the CURVES Study Investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin and fluvastatin in patients with hypercholesterolemia (The CURVES study). *Am J Cardiol* 1998; 81:582-7.
13. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001; 11:1160–4.
14. Buckett L, Ballard P, Davidson R, et al. Selectivity of ZD4522 for inhibition of cholesterol synthesis in hepatic versus non-hepatic cells. *Atherosclerosis* 2000; 151:41.
15. Arad Y, Ramakrishnan R, Ginsberg HN. Effects of lovastatin therapy on very-low-density lipoprotein triglyceride metabolism in subjects with combined hyperlipidemia: evidence for reduced assembly and secretion of triglyceride-rich lipoproteins. *Metabolism* 1992; 41:487-93.
16. Grosser N, Erdmann K, Hemmerle A, et al. Rosuvastatin upregulates the antioxidant defense protein heme oxygenase-1. *Biochem Biophys Res Commun* 2004; 325:871-6.
17. Martin PD, Warwick MJ, Dane AL, et al. Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. *Clin Ther* 2003; 25:2822-35.
18. Martin PD, Mitchell PD, Schneck DW. Pharmacodynamic effects and pharmacokinetics of a new HMG-CoA reductase inhibitor, rosuvastatin, after morning or evening administration in healthy volunteers. *Br J Clin Pharmacol* 2002; 54:472-7.
19. Rosenson RS. Rosuvastatin: a new inhibitor of HMG-coA reductase for the treatment of dyslipidemia. *Expert Rev Cardiovasc Ther* 2003; 1:495-505.
20. Drexler H. Factors involved in the maintenance of endothelial function. *Am J Cardiol* 1998; 82:3S-4S.
21. Poredos P. Markers of Preclinical Atherosclerosis and their Clinical Relevance. *The Open Atherosclerosis and Thrombosis Journal* 2011; 4:1-10.
22. 4S group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994; 344:1383-9.
23. 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. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; 339:1349-57.
24. Jones PH, Davidson MH, Stein EA, et al; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; 92:152-60.
25. Clearfield MB, Amerena J, Bassand JP, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia--Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). *Trials* 2006; 7:35.
26. Nissen SE, Nicholls SJ, Sipahi I, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006; 295:1556-65.
27. Underhill HR, Yuan C, Zhao XQ, et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. *Am Heart J* 2008; 155:584.e1-8.
28. Crouse JR 3rd, Raichlen JS, Riley WA, et al. METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* 2007; 297:1344-53.
29. Takayama T, Hiro T, Yamagishi M, et al. COSMOS Investigators. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Circ J* 2009; 73:2110-7.
30. Hall AS, Jackson BM, Farrin AJ, et al; SPACE ROCKET Trial Group.. A randomized, controlled trial of simvastatin versus rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events--Reduction of Cholesterol to Key European Targets Trial. *Eur J Cardiovasc Prev Rehabil* 2009; 16:712-21.
31. Lablanche JM, Leone A, Merkely B, et al. Comparison of the efficacy of rosuvastatin versus atorvastatin in reducing apolipoprotein B/apolipoprotein A-1 ratio in patients with acute coronary syndrome: results of the CENTAURUS study. *Arch Cardiovasc Dis* 2010; 103:160-9.
32. Pitt B, Loscalzo J, Monyak J, Miller E, Raichlen J. Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study). *Am J Cardiol* 2012; 109:1239-46.
33. Alfonso JF.Rosuvastatin: Role in Cardiovascular High-risk Patient. *Rev Fac Med* 2013; 61:41-51.
34. Bots AFE, Kastelein JJP. Achieving lipid goals in real life: the Dutch DISCOVERY Study. *Int J Clin Pract* 2005; 59:1387–94.
35. Strandberg TE, Feely J, Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparison of the effects of Rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: A DISCOVERY study. *Clin Ther* 2004; 26:1821–33.
36. Zhu JR, Tomlinson B, Young MR, Sim KH, Lee LT, Sriratanasathavorn C. A randomised study comparing the efficacy and safety of Rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study). *Curr Med Res Opin* 2007; 23:3055–68.
37. Binbrek AS, Elis A, Al-Zaibag M, et al. For the DISCOVERY Alpha Study Group Rosuvastatin versus atorvastatin in achieving lipid goals in patients at high risk for cardiovascular disease in clinical practice: a randomized, open-label, parallel-group, multicenter study (DISCOVERY Alpha Study). *Curr Ther Res* 2006; 67:21–43.
38. Herregods MC, Daubresse JC, Michel G, Lamotte M, Vissers E, Vandenhoven G. DISCOVERY BELUX: comparison of Rosuvastatin with atorvastatin in hypercholesterolaemia. *Acta Cardiol* 2008; 64:493-9.
39. Laks T, Keba E, Leiner M, et al. Achieving lipids goals with Rosuvastatin compared with simvastatin in high risk patients in real clinical practice: a randomized, open label, parallel group, multicenter study: the DISCOVERY Beta study. *Vasc Health Risk Manag* 2008; 4:1407-16.
40. Gupta M, Constance C. Direct statin comparison of LDL-C values: an evaluation of Rosuvastatin therapy (DISCOVERY – Canada). [abstract] *Atheroscler Suppl* 2005; 6:108.
41. Fonseca FAH, Ruiz A, Silva JM, Fuenmayor M, Marotti M. For the DISCOVERY PENTA Investigators. The DISCOVERY PENTA study: a DIrect Statin Comparison of LDL-C Value – an Evaluation of Rosuvastatin therapY compared with atorvastatin. *Curr Med Res Opin* 2005; 21:1307–15.
42. Middleton A, Fuat A. Achieving lipid goals in real life: the DISCOVERY-UK study. *Br J Cardiol* 2006; 13:72–6.
43. Shepherd J, Vidt DG, Miller E, Harris S, Blasetto J. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology* 2007; 107:433-43.
44. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; 370:1781-90.