ABSTRACT
There is a wealth of evidence suggesting an association between Dyslipidemia and Heart Failure. Statins are the treatment of choice for the management of Dyslipidemia because of their proven efficacy and safety profile. They also have an increasing role in managing cardiovascular risk in patients with relatively normal levels of plasma cholesterol. The article reviews the role of Statins in the treatment of Dyslipidemia. Although all statins act by blocking the HMG-CoA reductase enzyme, which catalyzes the rate-limiting step in de novo cholesterol synthesis, they differ in terms of their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy. Lovastatin, Pravastatin and Simvastatin are derived from fungal metabolites and have elimination half-lives of 1–3 h. Atorvastatin, Cerivastatin (withdrawn from clinical use in 2001), Fluvastatin, Pitavastatin and Rosuvastatin are fully synthetic compounds, with elimination half-lives ranging from 1 h for Fluvastatin to 19 h for Rosuvastatin. As a class, statins are generally well tolerated and serious adverse events, including muscle toxicity leading to rhabdomyolysis, are rare. Consideration of the differences between the statins helps to provide a rational basis for their use in clinical practice.

Keywords: Dyslipidemia, Statins, HMG-CoA reductase enzyme, adverse events.

INTRODUCTION
Cardiovascular diseases (CVD) are the most prevalent cause of death and disability in both developed and developing countries. South Asians around the globe have the highest rates of Coronary Artery Disease (CAD). According to National Commission on Macroeconomics and Health (NCMH), a government of India undertaking, there would be around 62 million patients with CAD by 2015 in India and of these, 23 million would be patients younger than 40 years of age. CAD is usually due to atherosclerosis of large and medium sized arteries and Dyslipidemia has been found to be one of the most important contributing factors. As it has long been known that lipid abnormalities are major risk factors for premature CAD. The process of atherosclerosis starts with early lesions consisting of subendothelial accumulation of cholesterol-engorged macrophages (foam cells). In fact, low-density lipoprotein cholesterol (LDL-C) levels submitted to oxidation (oxLDL) are captured from scavenger cells and, as early as childhood, the oxidative process takes place actively, demonstrated by the evidence that the antibodies against oxLDL are easily detectable in children. The initial lesions, known as 'fatty streaks', are clinically silent but are the precursors of fibrous lesions characterized by the accumulation of lipid-rich debris and smooth muscle cells. Lipid abnormalities may also result from one or more environmental factors (e.g., high saturated fat/cholesterol diet, obesity, caloric excess, stress and subclinical hypothyroidism) interacting with a predisposing genetic factor or susceptibility gene (multifactorial hypercholesterolemia). In fact, apart from genetic causes, which remain the most common cause of dyslipidemia in childhood, the prevalence of lipid abnormalities in children is increasing, primarily in association with the concomitant epidemic of obesity and subsequent metabolic syndrome, insulin resistance and Type 2 diabetes mellitus. Other possible secondary dyslipidemias include diabetes mellitus, chronic renal insufficiency and/or failure, hypothyroidism, primary biliary cirrhosis and other cholestatic liver diseases and drugs (e.g., glucocorticoids, b-blockers and antiretroviral agents).

Large-scale, prospective, randomized trials have demonstrated that intensive statin therapy significantly reduces lipid levels and the incidence of coronary events in individuals with low or average cholesterol levels. The article reviews the role of Statins in the treatment of Dyslipemias.

3-hydroxy-3-methylglutaryl-coA Reductase Inhibitor (statins)
Mevastatin was the first HMG-CoA reductase inhibitor and was isolated from Penicillium citrinum. Other statins Simvastatin, Lovastatin and Pravastatin are also fungal
derivatives, while Atorvastatin, Cerivastatin, Fluvastatin, Pitavastatin and Rosuvastatin are fully synthetic compounds. The use of statins (Simvastatin, Pravastatin, Lovastatin, Fluvastatin, Rosuvastatin and Atorvastatin) has become the preferred method for treating elevated LDL-C levels in children and adolescents who meet the criteria for drug therapy. In fact, their use is generally safe and well tolerated. However, it must be remembered that cholesterol is an essential structural component of cells, a precursor for steroid hormones, vitamin D metabolites and bile acids, and an important factor in neural myelinization and brain growth. Concerns of possible side effects of statins on growth, pubertal development and endocrinologic functions have restricted their use in children during the prepubertal stage. Furthermore, since fat-soluble vitamins are transported by lipoproteins, their reduction by statins has been suspected to lead to vitamin deficiencies.

The chemical structures of the different statins are shown below. These structures can be broadly divided into three parts: an analogue of the target enzyme substrate, HMG-CoA; a complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme; side groups on the rings that define the solubility properties of the drugs and therefore many of their pharmacokinetic properties. Atorvastatin, Fluvastatin, Lovastatin and Simvastatin are relatively lipophilic compounds, while Pravastatin and Rosuvastatin are more hydrophilic as a result of a polar hydroxyl group and methane sulphonamide group, respectively.

MECHANISM OF ACTION
3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) act by blocking the HMG-CoA reductase enzyme, which catalyzes the rate-limiting step in de novo cholesterol synthesis. All statins are competitive inhibitors of HMG-CoA reductase with respect to the binding of the substrate, HMG-CoA, but not for that of the co-enzyme NADPH, suggesting that their HMG-CoA-like moieties bind to the HMG-CoA-binding portion of the enzyme active site. Comparison of the six statin–enzyme complexes revealed subtle differences in their modes of binding. An additional hydrogen bond was demonstrated in the Atorvastatin– and Rosuvastatin–enzyme complexes along with a polar interaction unique to Rosuvastatin, such that Rosuvastatin has the most binding interactions with HMG-CoA reductase of all the statins.
Table 1: Pharmacokinetic Profile of Statins

<table>
<thead>
<tr>
<th>Contents</th>
<th>Atorvastatin</th>
<th>Cerivastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Rosuvastatin</th>
<th>Pitavastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal time of dosing</td>
<td>Any time of day</td>
<td>Evening</td>
<td>Bedtime</td>
<td>With meals morning and evening</td>
<td>Bedtime</td>
<td>Evening</td>
<td>Any time of day</td>
<td>Na</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>12</td>
<td>60</td>
<td>24</td>
<td>5</td>
<td>18</td>
<td>5</td>
<td>20</td>
<td>~80</td>
</tr>
<tr>
<td>Solubility</td>
<td>Lipophilic</td>
<td>Lipophilic</td>
<td>Lipophilic</td>
<td>Lipophilic</td>
<td>Hydrophilic</td>
<td>Lipophilic</td>
<td>Hydrophilic</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Effect of food</td>
<td>Bioavailability increased</td>
<td>No effect</td>
<td>Bioavailability decreased</td>
<td>Bioavailability increased</td>
<td>Bioavailability decreased</td>
<td>No effect</td>
<td>No effect</td>
<td>Na</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>98</td>
<td>&gt;99</td>
<td>&gt;98</td>
<td>&gt;95</td>
<td>~50</td>
<td>95–98</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Minor</td>
<td>Minor</td>
</tr>
<tr>
<td>Elimination half-life (h) CYP450 metabolism and isoenzyme</td>
<td>14</td>
<td>2.5</td>
<td>1.2</td>
<td>3</td>
<td>1.8</td>
<td>2</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>&lt;5</td>
<td>30</td>
<td>6</td>
<td>10</td>
<td>20</td>
<td>13</td>
<td>10</td>
<td>Na</td>
</tr>
</tbody>
</table>

Food intake has a variable effect on statin absorption; Lovastatin is more effectively absorbed when taken along with food, \(^{25}\) whereas the bioavailability of Atorvastatin, Fluvastatin and Pravastatin is decreased. \(^{26-28}\) No such effect is apparent for Simvastatin or Rosuvastatin. \(^{18, 29}\)

Statins are predominantly metabolized by the cytochrome P\(_{450}\) (CYP450) family of enzymes, composed of over 30 isoenzymes. \(^{10}\) The CYP3A4 isoenzyme metabolizes the greatest number of drugs in humans, \(^{31}\) including Lovastatin, simvastatin and Atorvastatin. \(^{10}\) A proportion of the circulating inhibitory activity of these three agents for HMG-CoA reductase is attributable to active metabolites. For Atorvastatin, the major active metabolites are 2-hydroxy- and 4-hydroxy-atorvastatin acid \(^{32}\) while for simvastatin the \(\beta\)-hydroxy acid and its 6\(^{\prime}\)-hydroxy, 6\(^{\prime}\)-hydroxymethyl and 6\(^{\prime}\)-exomethylene derivatives are the major active metabolites. \(^{33-34}\) Fluvastatin is chiefly metabolized by the CYP2C9 isoenzyme, while Pravastatin, Pitavastatin and Rosuvastatin do not undergo substantial metabolism by CYP450 pathways. \(^{30, 35-36}\) Lipophilic drugs are known to be much more susceptible to oxidative metabolism by the CYP450 system. \(^{37}\) It is now recognized that the statins metabolized by the CYP450 system are more likely to produce muscle toxicity because of the risk of drug interactions with many drugs that inhibit CYP450, notably the CYP3A4 isofom \(^{38-39}\); drug interactions may increase plasma levels of statins, with a consequent increased risk of toxic effects.

The predominant route of elimination for the majority of statins is via the bile after metabolism by the liver. \(^{40}\) Consequently, hepatic dysfunction is a risk factor for statin-induced myopathy. \(^{41}\) and all manufacturers recommend caution when prescribing statins to patients with a history of liver disease. Pravastatin is eliminated by both the kidney and liver, mostly as unchanged drug. \(^{42-43}\) However, as with some of the other currently available statins, its pharmacokinetics are altered in patients with hepatic. \(^{25}\) Rosuvastatin is also eliminated, largely unchanged, by both the kidney and liver \(^{44, 45}\) and its pharmacokinetic properties are not altered in patients with mild to moderate hepatic impairment. \(^{46}\)

PHARMACODYNAMICS
Statins are highly efficacious at lowering LDL-C, although there are differences in the extent of LDL-C lowering at therapeutic doses and in the maximal reduction achieved with
each agent. Of the statins currently available, Rosuvastatin is the most effective at lowering LDL-C, with reductions of up to 63% reported with a daily dose of 40 mg. Data from comparative trials confirm that on a milligram basis, Rosuvastatin is the most efficacious statin for lowering LDL-C, followed by Atorvastatin, simvastatin and Pravastatin. In general, statins are well tolerated and serious adverse events are rare. The most serious adverse effect associated with statin therapy is myopathy, which may progress to fatal or nonfatal rhabdomyolysis. The withdrawal of Cerivastatin from clinical use in 2001 heightened scrutiny of these effects, although all available data indicate that the increased incidence of rhabdomyolysis reported for Cerivastatin appears to be specific to this agent. The incidence of myopathy is low (approximately one in 1000 patients treated), is dose-related, and is increased when statins are used in combination with agents that share common metabolic pathways. There are few reports of statin-induced thrombocytopenia, the miscellaneous pathophysiologic mechanisms of drug-induced thrombocytopenia can be divided into two major categories (1): decreased platelet production via marrow suppression and (2) peripheral platelet clearance, usually by one of several possible immune mechanisms. Two previous analyses of the FDA database of the Adverse Events Reporting System (AERS) have questioned the safety of Rosuvastatin. Allegations were made that patients taking low doses of Rosuvastatin were at greater risk of developing serious kidney damage, kidney failure, and rhabdomyolysis than those taking other statins. Daniel M Keller, intervened results of 2 related trials investigating the effects of statins on urinary protein excretion and kidney function found Atorvastatin (ATV) protective and Rosuvastatin (RSV) unprotective, and possibly harmful, in diabetic and nondiabetic patients. Buyukhatipoglu et al. reported an unusual case of acute renal failure (ARF) in a patient who had been prescribed both a statin (Rosuvastatin) and a fibrate (Fenofibrate). Larry Husten, arbitrated adverse events associated with Rosuvastatin appear to be higher than with the other available statins, according to a post marketing analysis of adverse events reported to the FDA. In the primary analysis of the study, for the period in which data were available for all the agents (October 1, 2003 through September 30, 2004), the composite rate of adverse events, which included rhabdomyolysis, proteinuria/nephropathy, or renal failure, was significantly higher (p<0.001) for Rosuvastatin than the rates for Simvastatin, Pravastatin, and Atorvastatin. In a secondary analysis, the rate of adverse events during the first year of marketing for each drug was also found to be significantly higher for Rosuvastatin than for Pravastatin or Atorvastatin, although the difference with simvastatin did not achieve significance (p=0.02). However, the rate of adverse events for Rosuvastatin in this analysis was significantly lower than the rate for Cerivastatin (p=0.001), which was subsequently withdrawn from the market. Prajapati et al. reported Atorvastatin induced pancreatitis. In this case, the patients improved on dechallenge (withdrawal of the drug) and there were no other confounding factors that could have caused this Adverse Drug Event (ADE). Hence, the ADE was probably caused by Atorvastatin (WHO-UMC criteria: Probable; Naranjo's Score: 7, probable). Singh et al. reported Rosuvastatin to be the probable cause of pancreatitis in a patient. Acute pancreatitis has been previously reported with Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Lovastatin. Pancreatitis might be a class effect of statin drugs and the newest statin; Rosuvastatin is as likely to be associated with pancreatitis as the other statins. Shechter et al. inferred from a Medline search up to June 2005 on all prospective, double-blind, randomized clinical trials evaluating the impact of intensive statin therapy (any statin dose >40 mg/daily) on clinical outcomes after a 1 year follow-up revealed only eight trials. In all the eight trials, with a follow-up period of 12-60 months, intensive statin therapy was significantly more effective than and at least as safe as placebo or other standard statin regimens. Thus, based on the evidence-based medicine, intensive statin therapy enables more patients with Dyslipidemia to achieve the current National Cholesterol Education Program goal for low density lipoprotein, while ensuring a relatively high safety profile. Roberta Ara, affirmed intensive lipid-lowering strategy is a cost-effective alternative to a standard-dose generic statin. While Rosuvastatin 40 mg/day has been shown to be the optimal treatment using current prices for statins, when Atorvastatin 80 mg/day is available in generic form, this may be the optimal treatment for this patient group. Simvastatin 80 mg/day should not be considered an alternative owing to the adverse safety profile and limited additional benefits. McKenney et al. conducted STELLAR trial which is the largest trial of its kind to compare dose-related effects of statins on lipid goal achievement in patients with Dyslipidemia. Trial results indicated that Rosuvastatin 10 to 40 mg has greater efficacy than Atorvastatin 10 to 80 mg, Simvastatin 10 to 80 mg, and Pravastatin 10 to 40mg for achievement of ATP III LDL-C and non-HDL-C goals, European LDL-C goals, and Canadian LDL-C. Rosuvastatin 10 mg reduced LDL-C by 46%, which was significantly greater (p < 0.002) than the 37% reduction achieved with Atorvastatin 10 mg, the 28% to 39% reductions achieved with simvastatin 10 to 40 mg, and the 20% to 30% reductions achieved with Pravastatin 10 to 40 mg. In the Rosuvastatin 40-mg group, LDL-C was reduced by 55%, compared with 48% for Atorvastatin 40 mg (p < 0.002), 51% for Atorvastatin 80 mg (p = 0.006, NS), 39% for simvastatin 40 mg (p < 0.002), 46% for Simvastatin 80mg (p < 0.002), and 30% for Pravastatin 40 mg (p < 0.002). Statins are highly effective cholesterol-lowering agents, and have been shown to reduce cardiovascular morbidity and mortality in patients with and without CVD. Consequently, statins have become the therapy of choice for the treatment of many dyslipemias. Seven statins are currently approved for clinical use in treating effectively and rapidly in patients with a broad spectrum of dyslipemias. Although they share a common mechanism of action, there are differences in their relative efficacy for improving the lipid profile, as well as in their chemistry, Pharmacodynamics and Pharmacokinetics. Consideration of these differences should help to provide a rational basis for the safe and effective use of the current and emerging statins in clinical practice. More studies are needed to confirm the cost-effectiveness of statins to make any decision for health policy.
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