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Pharmacological Aspects of Statins Are Relevant to Their Structural and Physicochemical Properties

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ABSTRACT
Statins are group of hypolipidemic agents that are effective at lowering blood lipid levels subsequently improving ischemia associated pathology of atherosclerosis. This beneficial effect jointly linked to the members of statin and the miscellaneous effects they produce which is distinctly present with some statins but not others. These lipid lowering agents differ structurally and physically resulting in two group based on their hydrophobicity. Since, lipophilic penetrate readily across cell membrane, hydrophilic potentially needs a carrier and their volume of distribution is lower comparative to lipophilic statins. These structural and physicochemical variation ultimately result in variation in pharmacokinetic properties and could potentially carry an impact on their pharmacodynamics and the outcome of the therapeutic course. Moreover, variation in these properties could lead to repurposing of statin for new indications in the future.

Keywords: Statin, Hydrophilic, Lipophilic, Pharmacokinetic, Pharmacodynamic.

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INTRODUCTION
Lipid lowering drugs have shown to reduce the ischemic heart disease (IHD) both in patients with hyperlipidaemia and those with normal LDL-C levels. Therefore, it has been recommended to introduce some dietary changes to reduce the cholesterol level (particularly LDL-C)[1]. Various classes of medication have been introduced as hypolipidaemic agents including; bile acid-binding resins, nicotinic acid, fibrates, cholesterol-absorption inhibitors and more recently the statins, the latter are the most commonly prescribed lipid-reducing therapies[2]. The mechanism of action of statins is based on blocking the committed step in the synthesis of cholesterol; recently called the mevalonate pathway. Additionally, statins upregulate HDL-C and decrease triglyceride levels[3]. Moreover, statin exert its lipid-modifying effects through inhibition of apolipoprotein-B100 biosynthesis and reduction in biosynthesis of triglyceride-rich lipoproteins in liver[4].

Apart from their lipid-modifying effects, statins characterized by its pleiotropic effects through exerting a beneficial cardiovascular effects[5]. These newly discovered actions has been attributed to their inhibitory role in biosynthesis of non-steroidal isoprenoid compounds, an intermediary product of mevalonate pathway[6]. Statin pleiotropic effects include inhibition of inflammatory response, stimulation of repair endothelial cell injury and inhibition of smooth muscle cell proliferation[1,5]. Large clinical studies reported that statins reduced the morbidity and mortality rate in patients with or without IHD[7]. Moreover, statins have been shown to reduced progression and even encourage regression of coronary atherosclerosis, resulting in reduction in percentage of new ischemic injury and subsequently coronary occlusion in comparison to statin-untreated patients[8]. This effect has been attributed to the reduction in the core of atherosclerotic plaque resulting in prevention of plaque rupture that would initiate intramural hemorrhage/thrombosis[1].

This review article aimed at explaining the link between the differences between satins pharmacokinetics and pharmacodynamics and its correlation to structural and physicochemical properties.

Diversity of statin structures
Source of statins
fungal derived statins include; lovastatin, pravastatin, and simvastatin, while synthetic statin include; atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin[9].

Structure of statins
the chemical structure of each is outlined below (see Figure 2). The principle parts of structure are three basic units; the analogue of HMG-CoA which is the target enzyme substrate and a side chain ring structure that determines their physical properties especially their solubility and pharmacokinetic; and the third part is the complex ring structure which is involved in binding of statin molecule to the HMG-CoA reductase enzyme[10] (see Figure 1).

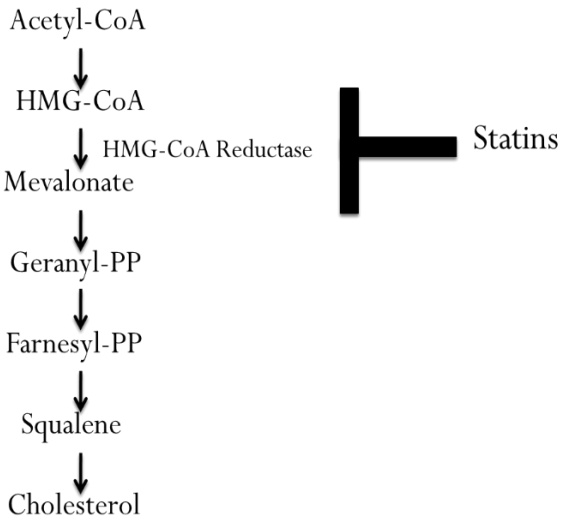

Figure 1. Cholesterol biosynthesis pathway showing potential effects of inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins, causing a decrease in prenylation of signalling molecules as well as derivatives from mevalonate and cholesterol.

Physicochemical properties of statins

some statins are lipophilic including, lovastatin, atorvastatin, simvastatin, and fluvastatin, while both rosuvastatin and pravastatin are hydrophilic because they carry a methane-sulphonamide-moiety and hydroxyl-moiety, respectively[11]. The mechanism of statins is based on binding of the molecules to the active site of the enzyme, thereby preventing the substrate from binding and therefore inhibiting the subsequent steps of cholesterol biosynthesis. The structural crystallography of statin-enzyme complex revealed that rosuvastatin has supra-binding through hydrogen bonding coupled with the polar interaction unique to the rosuvastatin; these variation could explain the dominant pleiotropic activities of certain statins in comparison to others[10].

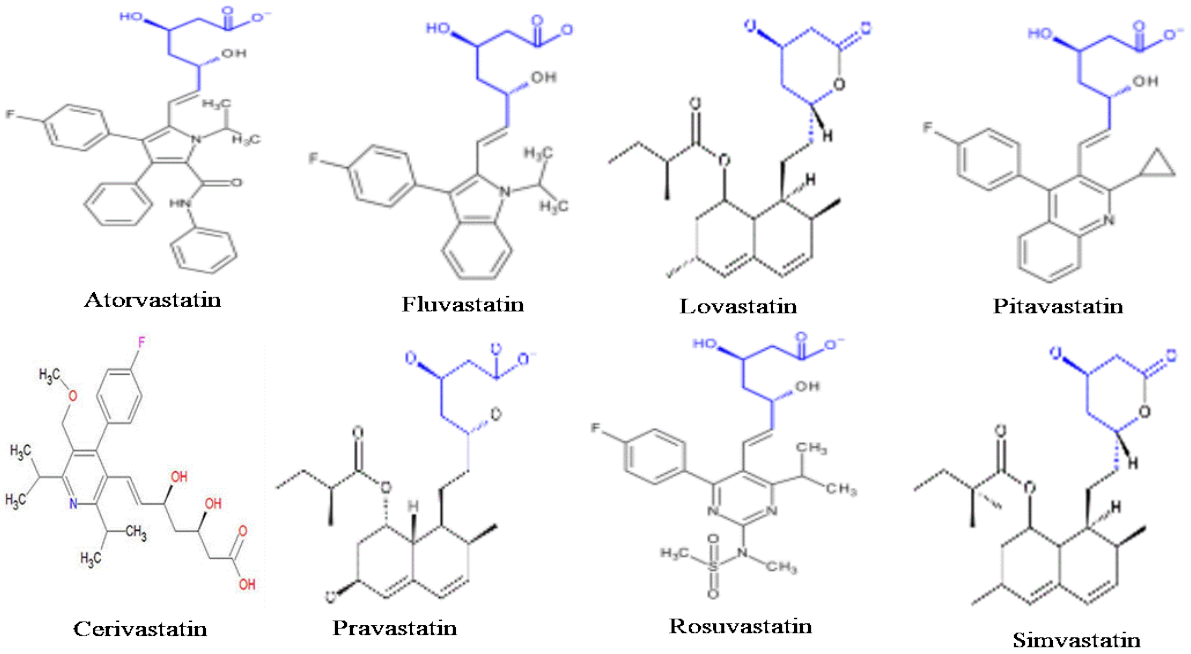

Figure 2. Chemical structure of the statins and HMG-CoA.

Diversity of statin pharmacokinetics

Administration and Absorption

Following oral administration of simvastatin and lovastatin as a lactone-prodrug; they undergo enzymatic hydrolysis into active form, hydroxyl acid active form[12], while other statins are administered as an active as such i.e. they are already hydroxyl acid active form[6,11,13]. Following administration, the absorption is rapid reaching peak plasma level (T_{max}) in approximately 4 hours[1,6]. The time of administration during the day of rosuvastatin have no effect on pharmacokinetic of rosuvastatin[1] whereas atorvastatin pharmacokinetics were affected accordingly[11], nevertheless, their pharmacodynamics is the same regardless to their administration time[6,11]. This variation could be explained by their longer duration of action than other statins (<3 hours)[14]; hence, they are favorably administered on evening to interfere with peak hepatic cholesterol synthesis.

Bioavailability and half-life

The clearance half-life of atorvastatin is up to 14 hours[6], this long elimination time is responsible about the extended lipid-lowering effects of atorvastatin compared to other statins[15]. Additionally, the lipid-lowering efficacy is further extended by atorvastatin active metabolite[16]. The elimination half-life is 19 hours for rosuvastatin[15] and 11 hours for pitavastatin[1]. The commercially available statins characterized by massive first-pass effect and thereby low bioavailability[16]. The bioavailability of pitavastatin is higher (up to 80%)[13] than cerivastatin (up to 60%)[6]. Liver: being the target organ for metabolism of statin, first-pass effects determine the effect of statins. Statin absorption affected by food at various degree, food

improves the absorption of lovastatin and impairs the absorption of is best absorbed with food atorvastatin, fluvastatin, and pravastatin[17] whereas food has no effects on simvastatin or rosuvastatin[6,18]; nevertheless, hypolipidaemic efficacy of statins are not affected by weather the drug were administered with the dinner or at bedtime[19]. Apart from pravastatin, the plasma protein binding capacity of statins is extensive resulting in low free form of the drug[6]. Despite of high circulating free form of pravastatins and rosuvastatin compared to other statins, its hydrophilic properties prevents widespread tissue distribution[20]. Conversely, other statins; particularly cerivastatin, are highly lipophilic[6,14]. The hepatoselectivity of statins contribute to their efficient pharmacodynamics activity given that cholesterol is synthesized in the liver; this hepatoselectivity is mainly attributed to their physicochemical properties; particularly, their solubility properties.

Distribution: The mechanism of transport of lipophilic statins is passive diffusion while hydrophilic statin transportation through membrane barriers is facilitated diffusion[1,21]. Statin lipophilic nature induce hepatic shunting and improve passage through extrahepatic cell membrane barriers, hence, hydrophilic satins characterized by higher hepatoselectivity compared to lipophilic; this low penetration could explain the lack of adverse muscular effect of pravastatin[9]. Conversely, rosuvastatin and pravastatin (hydrophilic statins) are highly extracted by liver[15].

Metabolism

Statins are mainly metabolized by cytochrome P450 enzyme[19] more precisely CYP3A4 isoenzyme play the greatest role in statin metabolism[6], the hypolipidaemic efficacy is partially related to the active metabolites; 2-hydroxyatorvastatin or 4-hydroxyatorvastatin for atorvastatin while for simvastatin the metabolites are hydoxysimvastatin, hydoxymethylsimvastatin, exomethylenesimvastatin[6,19]. Moreover, fluvastatin is metabolized by CYP2C9 isoenzyme, nevertheless, pravastatin, pitavastatin and rosuvastatin were only slightly metabolized by CYP450 isoenzyme[22]. Oxidative metabolism by CYP450 isoenzyme is the chief pathway for lipophilic statins[20], moreover, muscular toxicity is more prominent with those statins which undergo metabolism by CYP450 isoenzyme, which is most often related to drug interaction due to inhibition of CYP450 (notably the CYP3A4 system)[19].

Elimination

The major route of elimination of most statin metabolites is bile[8], therefore, liver failure is a contributing factor for statin induced adverse effects especially myopathy[3]. Pravastatin excreted unchanged by liver and kidney[6,14], and liver dysfunction have slight effect on pharmacokinetic properties[20]. Similarly, rosuvastatin mainly eliminated unchanged by liver and kidney[9], and liver dysfunction have no effects on its pharmacokinetic properties[1].

Table 1. Pharmacokinetics of statins.

	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Dosing Time[1]	Any time of day	Bedtime	With food morning and night	Any time of day	Bedtime	Any time of day	Evening
Prodrug[23]	No	No	Yes	No	No	No	Yes
Bioavailability[23]	12%	9-50%	5%	51%	18%	20%	5%
Half-Life[23]	14h	2.3h	3h	12h	2h	19h	3h
Vd[1]	381L	330L	----	148L	35L	134L	---
Lipophilicity[16]	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Metabolites[1]	Yes	No	Yes	Yes	Yes	Yes	Yes

Diversity of statin pharmacodynamics

Currently available statins have different hydrophilic/lipophilic properties, thereby, having different inhibition efficacy for extra-hepatic HMG-CoA reductase enzyme[22].

The lipid bilayer of the cellular membrane prevents hydrophilic statins from passage through the cellular membranes of extrahepatic cells. Conversely, lipophilic affinity of lipophilic statins encourages their penetration into hepatic and extrahepatic cells. This property of lipophilic statins determine the supratherapeutic effects achieved by some statins in extrahepatic organs[24]. These include, inhibition of synthesis of dolichol, ubiquinone (CoQ_{10}), farnesylated proteins, and heme A[25]. Lipophilic statins attenuate the myocardial ATP production further worsening the affected the ischemic region[26]. In contrast to pravastatin (hydrophilic statin), simvastatin (lipophilic statin) has increased the myocardial stunning and worsen reperfusion of the ischemic region[24]. Similarly, fluvastatin and atorvastatin attenuate myocardial reperfusion of affected segment and enhance myocardia staggering, however, similar effects were not reported in dogs treated by pravastatin (hydrophilic statins)[27]. Despite of greater tissue penetration of lipophilic statins compared to hydrophilic statins; the clinical studies have not reported a great difference between the members of statins[28,29,21]. Additionally, it has been demonstrated that hydrophilic and lipophilic statin increase NO production and isoprenylation by endothelial cells and[30,31,32]; reducing the infarct size and protecting the myocardium from ischemia-reperfusion injury; through lipid-lowering-independent mechanism[33, 34]. These findings have complicated the picture of selection of weather hydrophilic or lipophilic statins is better for patients with cardiovascular diseases. Moreover, Statins lower serum cholesterol level and inflammatory cell counts in plaques (e.g. macrophage); stabilising plaques from ruptures[30]. Nevertheless, when plaque rupture occurs, cardiac events in patients on lipophilic statin exacerbated leading to ischaemia[35]

Role in cardiovascular therapy

A study conducted by Maruyama T. et al, 2011[29]; comparing the effects of hydrophilic statins (pravastatin) versus lipophilic statin (atorvastatin and pitavastatin) versus control group (no statin). The results confirmed higher reduction in LDL-C level in in the atorvastatin and the pitavastatin group as compared to the pravastatin group. Another study conducted by Kim MC. et al, 2011[28];

comparing the effects of hydrophilic statins versus lipophilic statin; at various time-points, data confirmed that there were a non-significant difference between statins.

A study conducted by Sakamoto et al[36], 2007; comparing the effects of hydrophilic statins (rosuvastatin and pravastatin) versus lipophilic statin (atorvastatin and simvastatin). After 2 years of initiation of therapy, the results showed that the Lipophilic Statin group showed a 2-fold reduction of LDL-C as compared with that of hydrophilic statins. A study conducted by Jones et al, 2003[5]; using high doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin. The study has compared lipid profile parameters. The results indicated that LDL reduction were best with rosuvastatin and least with atorvastatin. Similarly, HDL elevation was best with rosuvastatin and worst with atorvastatin. In a different study, conducted by Nicholls et al.[38], 2010; using a sequential doses of hydrophilic versus lipophilic hypolipidemic agents. The study has compared lipid profile measurements of a range of different doses of the statins with each other and other hypolipidemic agents. The study concluded a remarkable efficacy of hydrophilic statin over lipophilic one.

Conclusions

It has been confirmed that hydrophilic and lipophilic statins are different in various molecular aspects, including structure, mode of action, pharmacokinetic and pharmacodynamic properties. The present systematic review has focused on the comparison between published studies on hydrophilic versus lipophilic statins to detect the differences between these drugs regarding their hypolipidaemic efficacy, if any. Collected studies; confirm that hydrophilic statins show much better effect on overall lipid profile.

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Conflict of interest

The authors declare no conflict of interest.

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