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REVIEW ARTICLE

Pediatric Statin Administration: Navigating a Frontier with Limited Data

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Increasingly, children and adolescents with dyslipidemia qualify for pharmacologic intervention. As they are for adults, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) are the mainstay of pediatric dyslipidemia treatment when lifestyle modifications have failed. Despite the overall success of these drugs, the magnitude of variability in dose-exposure-response profiles contributes to adverse events and treatment failure. In children, the cause of treatment failures remains unclear. This review describes the updated guidelines for screening and management of pediatric dyslipidemia and statin disposition pathway to assist the provider in recognizing scenarios where alterations in dosage may be warranted to meet patients' specific needs.

INDEX TERMS atorvastatin, dyslipidemia, fluvastatin, lovastatin, pediatrics, pharmacogenomics, pharmacokinetics, pravastatin, rosuvastatin, simvastatin, statin

INTRODUCTION

Cardiovascular disease remains the number one cause of mortality in the United States.[1] Despite significant advances in medical and surgical management for heart disease and stroke, the burden of cardiovascular disease remains alarming. Coronary artery disease (CAD) alone accounts for 1 of every 7 deaths in the United States.[1] Although CAD has historically been perceived as a disease of middle to late adulthood, data now support onset at a much younger age. Clinically silent precursors to CAD, fatty streaks, have been observed in children as young as 3 years of age with coronary involvement identified at adolescence.[2] By the time individuals reach their 20s studies suggest that the incidence of coronary atherosclerosis can range from 45% to 75%.[3,4] Importantly, several studies confirm that the risk factors observed in adults (e.g., elevated low-density lipoprotein [LDL], obesity, hypertension, tobacco exposure, and diabetes) also contribute to atherosclerosis in children.[5,6] Collectively, these studies have illuminated the need for preventive cardiovascular services in children and young adults.

Trends in circulating lipid profiles support a role for screening in children as part of preventative care. The prevalence of total plasma cholesterol (TC) concentrations in excess of 200 mg/dL has risen to 10% in adolescents,[7,8] a far cry from the estimated 0.2% of the population that can attribute this laboratory finding to familial hypercholesterolemia.[9,10] This may be explained, in part, by the rate of overweight/obesity in children, which as in adults, can be associated with elevated cholesterol levels.[11] Importantly, most adolescents with elevated TC will continue to have elevated TC into adulthood, and those who are overweight have a 2-fold higher relative risk of CAD mortality, independent of adult weight.[12,13] When pediatric weight and lipid profiles are considered together, the prevalence of symptomatic CAD in young to middle-aged adults is expected to increase by 5% to 16% over the next 2 decades.[14] This will likely contribute to an additional 100,000 cases of early coronary heart disease that are specifically due to childhood obesity.

SCREENING AND MANAGEMENT GUIDELINES

Since the last comprehensive review of 3-hy-droxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) by Eiland et al,[15] the pediatric screening and management guidelines have changed, prompting this update for pediatric providers who make recommendations related to prescribing statins.

In 1992, the National Cholesterol Education Program (NCEP) began recommending targeted lipid screening in pediatric patients with risk factors for premature atherosclerotic cardiovascular disease.[16] This strategy exposed numerous cases of asymptomatic dyslipidemia that previously would have been neglected for decades. However, additional evidence suggests that simply relying on family history alone will miss at least 30% of pediatric patients with moderate dyslipidemia.[17] These previous NCEP guidelines also focused on LDL screening, essentially ignoring the combined dyslipidemic patterns that are observed in obese pediatric patients (i.e., increased triglycerides, increased LDL, decreased high-density lipoprotein [HDL]).

Realizing that a large proportion of at-risk children would remain unidentified, the National Heart, Lung, and Blood Institute convened an expert panel on Cardiovascular Health and Risk Reduction in Children and Adolescents to update the pediatric preventive cardiovascular guidelines, including modifications to lipid screening and management in childhood and adolescence.[18] The most striking modification in the updated NCEP guidelines resides in the domain on lipid screening where the panel now recommends universal lipid screening for all children between the ages 9 and 11 years and again between 17 and 21 years of age.[18] These age groups were targeted specifically to screen patients prior to and after puberty, when it is observed that TC and LDL can fluctuate with growth and sexual maturity.[19,20] The updated guidelines also suggest that lipid profiles can be obtained in either the fasting or non-fasting state given the reliability with either method.[21] This offers the benefit of facilitating screening in busy clinic settings where non-fasting lipid profiles may be easier to obtain.

Treatment guidelines were also clarified in the new guidelines with the goal of minimizing the burden of CAD in young adults. As expected,

Table 1. Treatment Cutpoints for Statin Therapy*

LDL	Presence of Concurrent Factors
≥190 mg/dL	None
160-189 mg/dL	Positive family history of early CVD or 1 high-level RF for early CVD or 2 moderate-level RF for early CVD
130-159 mg/dL	2 high-level RF for early CVD or 1 high-level and 2 moderate-level RF for early CVD

CVD, cardiovascular disease; LDL, low-density lipoprotein; RF, risk factor

* Decisions regarding pharmacologic treatment of dyslipidemia were based on the average results of 2 lipid profiles obtained at least 2 weeks apart but no more than 3 months apart.

diet and exercise are the first steps in which a provider managing children with lipid abnormalities should implement a change. When lifestyle modifications fail to improve lipid profiles over a 6-month period, pharmacologic therapy may be warranted to reverse lipid abnormalities. In children older than 10 years of age, use of pharmacologic management should be based on the average results of 2 lipid profiles obtained at least 2 weeks apart but no more than 3 months apart. The thresholds used to determine when drug therapy should be initiated are mirrored from the 1992 NCEP guidelines outlined in Table 1. The treatment algorithm is based on a combination of LDL level, family history, and/or associated risk factors and/or risk conditions (Table 2).

Contrasted with the adult guidelines which establish a threshold for treatment at ≥190 mg/dL, the implications of expanded drug use in children below this threshold are self-evident. A recent publication quantified this impact in just the adolescent population (17-21 years of age), which effectively spans both pediatric and adult criteria. Applying the pediatric recommendations to this population would result in 6-fold more patients qualifying for statin therapy than would be eligible based on the adult guidelines (2.5% vs. 0.4%, respectively). This equates to approximately 400,000 adolescents.[22] This discrepancy illustrates the challenge faced by providers who care for adolescents who are transitioning into adulthood; specifically, whether the risk of exposing significantly more children to chronic lipid-

Table 2. Risk Factor Definitions for Dyslipidemia Guidelines[18]

Positive Family History	myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death in parent, grandparent, aunt, uncle at <55 yr for males, < 65yr for females
High level risk	Hypertension that requires drug therapy (BP ≥ 99th percentile + 5 mm Hg), current cigarette smoker, BMI at the ≥ 97th percentile, presence of special high-risk conditions
Moderate level risk	Hypertension that does not require drug therapy, BMI ≥ 95th percentile, <97th percentile, HDL cholesterol < 40 mg/dL, presence of moderate risk conditions
Special high-risk conditions	Type 1 or 2 diabetes mellitus, chronic kidney disease/end-stage renal disease/post-transplantation, post-orthotopic heart transplantation, Kawasaki disease with current aneurysms
Special moderate-risk conditions	Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis), HIV infection, nephritic syndrome

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; RF, risk factor

lowering medications is offset by the anticipated reduction in morbidity and mortality from CAD. The risk of this chronic extrahepatic exposure of statins in the developing child is described briefly in *Distribution* below. Undoubtedly, additional investigations will be needed to clarify future guideline updates and risk of statin exposure in a developing child.

OVERVIEW OF THE STATINS

As shown by the guidelines, HMG-CoA reductase inhibitors are now the mainstay of pharmacologic treatment for dyslipidemia in both adults and children, due to their demonstrated efficacy in the primary and secondary prevention of CAD coupled with a relatively mild side effect profile.[15,23-28] The first 3 statins approved in the United States (lovastatin in 1987, simvastatin in 1991, and pravastatin in 1991) are fungus-derived (Tables 3-5) semisynthetic agents, whereas the remaining U.S. Food and Drug Administration-approved compounds (fluvastatin in 1993, atorvastatin in 1996, rosuvastatin in 2003, and pitavastatin in 2009) are synthetic agents (Table 6).[29]

Pharmacology
Statins decrease the hepatic synthesis of cholesterol by blocking the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol synthesis. In response to a subsequent decrease in intracellular sterols, expression of the genes encoding the cell-surface LDL receptor is up-regulated. This, in turn, enhances the hepatic uptake of LDL and reduces the circulating levels of LDL in the serum.[30] However, statins appear to possess other effects including a decrease

in inflammatory mediators downstream from HMG-CoA reductase (see *Future Considerations* below).[31-33] Thus, it remains debated whether the reduction in CAD and plaque formation occurs as a result of the statins' lipid-lowering effects or other anti-inflammatory effects.

Efficacy in Children
Clinical trials of statins in children have included lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, atorvastatin, and pitavastatin and most of the studies focused on lipid-lowering and safety (Tables 3-6). With few exceptions, exposure to the statins conferred no added safety risk compared with placebo. However, the trials described in Tables 3 to 6 ranged from 1 month to 2 years and thus, a paucity of data describing the safety of chronic exposure to statins initiated during childhood exists. Moreover, for nearly all agents, reductions in LDL exceeded 20%, and some agents achieved reductions in excess of 40% to 50%. There also appeared to be some degree of dose dependence in LDL response within this class of drugs. However, in many studies, the variability associated with mean response profiles was exceedingly large, almost equivalent in magnitude to the response itself (Tables 3-6). At present, the cause of this variability remains unknown.

With such a high degree of variability in LDL reduction at a given statin dose and the unknown long-term developmental consequences of regular pediatric statin use, identifying the dose that maximizes efficacy and minimizes the risk of toxicity (i.e., dose optimization) is of great clinical importance for a developing child. Notably, all studies presented used a "one-size-

Table 3. Lovastatin: Summary of Safety and LDL reduction in Pediatric Trials

Reference	Population	Lovastatin Dosing	LDL reduction (%)	Variance (%)	Safety
Clauss et al[34]	n = 54; 11-18 yr (females only) FH	20 mg/day × 4 wks 40 mg/day × 20 wks	23 at wk 4 27 at wk 24	SE 3.3 SE 3.4	no difference vs. placebo
Stein et al[35]	n = 132 (65 placebo); 13.3 ± 2.5 yr (males only) FH	10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 8 wks 40 mg/day × 24 wks	17 24 27 25	SE 2 SE 1 SE 2 SE 2	no difference vs. placebo
Lambert et al[36]	n = 69; 13.3 ± 2.7 yr (males only) FH	10 mg qd × 8 wks 20 mg/day × 8 wks 30 mg/day × 8 wks 40 mg/day × 24 wks	21 24 27 36	15 - 27 19 - 29 19 - 35 33 - 39	no SAE, increase in CK

CK, creatinine kinase; FH, familial hyperlipidemia; SAE, serious adverse events; SE, standard error

fits-all" dosage scheme, effectively ignoring the contributions of ontogeny and genetic variation in statin disposition that are assuredly present in pediatric patients.

Given that the use of statins will inevitably increase as a result of mandatory lipid screening programs and the observed difficulties with adherence to dietary/behavioral modifications, the pediatric community should proactively pursue a more comprehensive understanding of these agents in children and adolescents before their widespread use. The following section discusses developmental, physicochemical, and pharmacogenetic factors that influence the dose-exposure profile for the statins. Notably, the paucity of data for pediatric statin disposition requires extrapolation from *in vitro* and adult data.

DISPOSITION

Physiochemical Considerations

Despite sharing a common mechanism of action, the statins differ in their physicochemical properties (e.g., octanol-water partition coefficient, pH stability/solubility). These properties are incredibly important to the overall disposition of each agent and explain why the statins should be considered independently when tailoring dosage to individual patient populations. Two statin agents (lovastatin and simvastatin) are formulated as lactone prodrugs which require hydrolysis to become activated inhibitors of HMG-CoA reductase.[56,57] The remaining statins are administered in their active hydroxy acid forms.[31,58,59] Consequently, lovastatin and simvastatin are the most lipophilic as delivered

(simvastatin > lovastatin), readily translocating across membranes,[60,61] whereas pravastatin and rosuvastatin are the most hydrophilic agents, requiring transporter-mediated disposition.[58,60,61]

Another unique element of the statins lies with the pH-dependent chemical interconversion that can occur at any step in the disposition pathway and heavily influences the amount of active drug available at the target. For instance, formation of the inactive 3-alpha-hydroxy-pravastatin acid and lactone isomers in the acidic environment of the stomach prior to absorption can disrupt the amount of pravastatin acid delivered to the drug target (i.e., the liver).[62,63] Not surprisingly, isomer formation influences the pharmacodynamic effects of these drugs and is highly variable among healthy human subjects.[63,64] Although these data require replication in a larger cohort before changes can be made to the drug label, the extent of chemical interconversion should be taken into consideration in populations where statin response is highly variable.

Absorption

All statins are administered orally, thus, the extent of their systemic availability is determined by the aforementioned physicochemical properties of the drug, the physicochemical milieu of the patient's gastrointestinal environment, and the functional status of their intestinal transporters, which can be influenced by ontogeny and genetics.

Pravastatin preferentially undergoes transporter-mediated absorption, conferring a relatively robust absorption rate despite its hydrophilic properties.[65] *In vitro*, pravastatin appears to be

Table 4. Pravastatin: Summary of Safety and LDL Reduction in Pediatric Trials

Reference	Population	Pravastatin Dosing	% LDL Reduction	% Variance	Safety
Hedman et al[43]	n = 20; 4.9-15.6 yr FH	10 mg/day × 8 wk	21	Not reported	No SAE
Hedman et al[44]	n = 19; 4.4 - 18.9 yr cardiac transplant	10 mg/day × 8 wk	27	SD 27	No SAE, mild increase in CK
Hedman et al[45]	n = 35; 4.1 - 18.5 yr FH n = 35	10 mg/day Titration by 10 mg at 8, 16, 24, 52, 104 wk per LDL goal	25 at wk 8 27 at wk 16 29 at wk 24 33 at wk 52 32 at wk 104	SD 11 SD 13 SD 13 SD 14 SD 13	No SAE
Hedman et al[46]	n = 20; 4.9 - 15.6 yr FH	10 mg/day × 8 wk	20 (TT) 23 (TC)	SD 10 SD 12	No SAE
Hedman et al[46]	n = 12; 4.4 - 18.7 yr cardiac transplant	10 mg/day × 8 wk	34 (TT) 8 (TC)	SD 21 SD 8	No SAE
Knipscheer et al[47]	n = 72; 8 - 16 yr FH	5 mg/day × 12 wk 10 mg/day × 12 wk 20 mg/day × 12 wk	23 24 33	18-28 19-29 29-37	No difference between groups
Wiegman et al[48]	n = 214; 13 ± 3 yr FH	20 or 40 mg/day (< 14 vs. ≥ 14yr) × 104 wk	24	SD 17	No difference vs. placebo

CK, creatinine kinase; FH, familial hyperlipidemia; LDL, low-density lipoprotein; SAE, serious adverse events; SD, standard deviation; TC, SLCO1B1 521TC heterozygote genotypes; TT, SLCO1B1 521TT wild-type genotypes.

a substrate for the influx transporters OATP1A2 and OATP2B1. Notably, OATP2B1 uptake appears to be pH-sensitive, diminishing greatly as the pH increases from 5.0 to 7.4.[66-68] This observation suggests that the primary impact of OATP2B1 translocation occurs at the level of the enterocyte, where it is exposed to lower pH values, as opposed to the hepatocyte, where the systemic pH is higher and less uptake is expected. Pravastatin is not a substrate for the efflux transporters MDR1 and BCRP but, *in vitro*, appears to be a substrate for the efflux transporter MRP2, which is located on the apical surface of the enterocyte and liver.[68-71] *In vivo*, increased expression of MRP2 conferred by a 'gain of function' sequence variation (*ABCC2* c.1446C>G), increases presystemic clearance and reduces the bioavailability of pravastatin at the level of the enterocyte.[72]

Rosuvastatin similarly undergoes transporter-mediated absorption and, although not fully characterized, also appears be a substrate for OATP2B1 and BCRP.[73,74] However, rosuvastatin does not display the same pH sensitivity suggesting that OATP2B1 may be relevant to rosuvastatin disposition at the level of both the intestine and liver.[73] *In vivo*, a genetic variation in the gene encoding BCRP (*ABCG2* c.421C>A) contributes to an increase in rosuvastatin exposure by way of diminished export back into the intestinal lumen and into the biliary canaliculus.[75,76]

Fluvastatin, moderately more lipophilic than pravastatin or rosuvastatin, undergoes passive diffusion but *in vitro* is a substrate of OATP2B1.[73] Similarly, *in vitro* data reveal that atorvastatin is an OATP2B1 substrate at acidic and neutral pH; however, the high passive diffusion rates that are observed and lack of disruption in absorption by known inhibitors of OATP2B1 suggest that this transporter plays a very minor role in the absorption of atorvastatin.[73] Pitavastatin, also moderately lipophilic, undergoes passive diffusion and there is no evidence that transporter-mediated influx significantly influences the

Table 5. Simvastatin Summary of Safety and LDL Reduction in Pediatric Trials

Reference	Population	Simvastatin Dosage	% LDL Reduction	% Variance	Safety
de Jongh et al[37]	n = 173; 14.4 ± 2.1 yr FH	10 mg/day × 8 wk 20 mg/day × 8 wk 40 mg/day × 8 wk 40 mg/day × 24 wk	31 at wk 8 35 at wk 16 38 at wk 24 41 at wk 48	SD 11 SD 12 SD 16 SD 39	No SAE, Slight decrease in DHEA-S
Ferreira et al[38]	n = 36; 10.3 ± 4 yr HC	10 mg mg/day × 4 wk	37	SD 12	No difference vs. placebo
Dirisamer et al[39]	n = 20; 13 ± 2.4 yr FH	5 or 10 mg/day (LDL < 220 vs. ≥ 220) step-wise titration up to 20 mg × 52 wk	25 (5 mg) 30 (10 mg) 36 (20 mg)	Not reported	No differences between groups
de Jongh et al[40]	n = 50; 14.2 ± 3.1 yr FH	10 mg/day × 8 wk 20 mg/day × 8 wk 40 mg/day × 12 wk	40	19%	No differences vs. placebo
Stefanutti et al[41]	n = 16; 4 - 12 yr FH	10 mg/day × 52 wk	29	Not reported	No difference vs. placebo
Garcia-de-la-Puente et al[42]	n = 25; 4 - 17 yr renal disease	5 or 10 mg/day (≤30 vs. >30 kg) × 4 wk 10 mg or 20 mg titration (at wk 4) × 8 wk	34	Not reported	No difference vs. placebo

DHEA-S, dehydroepiandrosterone-sulfate; FH, familial hyperlipidemia; HC, hypercholesterolemia; LDL, low-density lipoprotein; SAE, serious adverse events; SD, standard deviation.

disposition of this drug. However, pitavastatin absorption can be attenuated presystemically by P-glycoprotein (P-gp).[77,78] Finally, there is no reported transporter-mediated absorption influencing the simvastatin or lovastatin lactones.

Another factor for consideration with respect to the absorption of statins is the impact of coadministered meals. Regardless of whether the drug is delivered by solution or capsule, concurrent administration of fluvastatin with food markedly reduces exposure and delays absorption (area under the curve [AUC], −17% to −24%; C_{max}, −60% to −73%; T_{max}, +56%).[79] This was also observed with pravastatin (AUC, −30%; C_{max}, −49%; T_{max}, +50%)[80] and rosuvastatin (AUC, −93%; C_{max}, −93%; T_{max}, +10%).[81] However, meals markedly slow the rate of absorption for atorvastatin (T_{max}, +124%) and pitavastatin (T_{max}, +143%). In fed states, atorvastatin C_{max} (−48%) and pitavastatin C_{max} (−55%) are reduced, although the impact on the extent of exposure for atorvastatin (AUC, −13%) and pitavastatin (AUC, −15%) is less pronounced.[82,83] In contrast, lovastatin concentrations drop when administered under fasting conditions (~33%),[84] whereas simvastatin can be taken without regard to meals.[85]

A final observation is the differential effect of morning versus evening dosage for the statin agents. When pravastatin is given in the evening, the C_{max} and AUC are reduced by approximately 60% compared with those for morning dosage.[86] Similarly, the C_{max} and AUC of atorvastatin are reduced by roughly 30% when administered in the evening.[87] Fluvastatin concentrations are reported to be higher following evening dosage,[88] while no significant differences were observed for rosuvastatin.[89] These differences in drug exposure relative to the timing of dosage could be secondary to physiologic patterns of gastric emptying. Circadian changes in drug absorption have been observed in response to increased gastric emptying times in the evening.[90] Additionally, the diurnal pattern of cholesterol biosynthesis (peak, 12:00 midnight to 4:00 AM) in relation to an evening dose could increase amount of statin used by the hepatocyte and thereby affect the plasma exposure of a statin.[91,92] Whether these differences definitely arise as a result of changes

Table 6. Synthetic Statins: Summary of Safety and LDL Reduction in Pediatric Trials

Agent (reference)	Population	Dosage	% LDL Reduction	% Variance	Safety
Fluvastatin (van der Graaf et al[49])	n = 84; 12.6 ± 2.1 yr FH	20 mg/day for 6 wk Titration to 40- or 80-mg intervals per LDL × 96 wk	34	29 - 39	N/A, no placebo arm
Atorvastatin (McCrindle et al[50])	n = 187; 14.1 ± 2.0 yr FH or severe HC	10 mg/day titration to 20 mg at wk 4 based on LDL continuing over 26 wk	40	SE 1	No difference vs. placebo
Atorvastatin (Gandelman et al[51])	n = 39; 6 to <18 yr FH	5 or 10 mg/day × 8 wk (< 10 vs ≥ 10yr) Titration per LDL at wk 4	37 (5 mg) 43 (5 mg to 10 mg) 38 (10 mg) 41 (10 mg to 20 mg)	SD 11 SD 6 SD 8 SD 12	No difference between groups
Atorvastatin (Argent et al[52])	n = 18; 13 ± 4 renal transplant	5 or 10 mg/day (< 40 kg vs. ≥ 40 kg) × 36 wk	57	SD 7	No difference vs. untreated
Rosuvastatin (Avis et al[53])	n = 176; 13.8 ± 1.7 FH	5, 10, 20 mg/day titration at wk 12 per LDL × 40 wk	38 45 50	SD 13 SD 17 SD 14	No difference vs. placebo
Rosuvastatin (Marais et al[54])	n = 44; 8 - 63 yr hoFH	20 mg/day × 6 wk 40 mg/day × 6 wk 80 mg/day × 6 wk	19 23 21.4	SD 16 SD 15 SD 21	No SAE
Pitavastatin (Braamskamp et al[55])	n = 106; 6 - 17 yr FH	1 mg/day × 12 wk 2 mg/day × 12wk 4 mg/day × 12wk	23.5 30.1 39.3	SE 2.1 SE 2.1 SE 2.2	DHEA-S significantly decreased (4 mg group)

DHEA-S, dehydroepiandrosterone-sulfate; FH, familial hyperlipidemia; HC, hypercholesterolemia; hoFH, homozygous familial hyperlipidemia; LDL, low-density lipoprotein; SAE, serious adverse events; SD, standard deviation; SE, standard error.

in absorption, distribution or elimination or intrinsic cholesterol production patterns remains unclear; however the observation that these patterns do not appreciably alter lipid-lowering properties of the affected statins limits the clinical relevance of these findings.

Concurrent with and subsequent to oral absorption, the statins (with the exception of pitavastatin) are subject to extensive first-pass extraction, effectively reducing their bioavailability.[29,59,93-96] Because drug-metabolizing enzymes mediate statin metabolism, these reactions are reviewed in *Metabolism* below. However, we point out here that when first-pass occurs at the level of the intestinal enterocyte, the absolute bioavailability of these agents is reduced, influencing both efficacy and toxicity. In contrast, when hepatocytes are the principal mediators of first pass, a more favorable scenario is set where concentrations at the target organ (i.e., the liver)

increase while peripheral exposure decreases, thereby leading to enhanced efficacy and fewer side effects (e.g., myalgias).[97]

Distribution

Hepatic uptake for the highly lipophilic statin lactones occurs by passive diffusion,[60] but for most of the statins, it is facilitated by transporter-mediated processes. OATP1B1, encoded by the solute-carrier organic anion transporter gene *SLCO1B1*, is the principle transporting protein into the hepatocyte for most statins and has been reviewed extensively.[60,98-100] Among the transporters with a minor role in statin disposition, pitavastatin, rosuvastatin, and fluvastatin are substrates for OATP1B3 (*SLCO1B3*),[60,101,102] rosuvastatin and fluvastatin appear to be substrates for OATP2B1 (*SLCO2B1*),[73,103,104] and rosuvastatin also appears to be a substrate for the sodium-dependent cotransporting polypeptide

(NTCP) which may account for as much as 35% of its hepatic uptake.[103] Fluvastatin also appears to enter the hepatocyte by passive diffusion.[105-107] As above, cellular uptake of the simvastatin and lovastatin lactones relies primarily on passive diffusion; however, simvastatin and lovastatin acid are substrates of OATP1B1 *in vitro* and *in vivo*.[108,109] Notably, the simvastatin and lovastatin lactones appear to inhibit OATP1B1-mediated transport.[110,111]

The clinical relevance of OATP-mediated statin disposition has been demonstrated in a number of drug-drug interaction studies. A 7-fold increase in the AUCs of atorvastatin acid and 2-hydroxy atorvastatin acid and a 3-fold increase in AUC of 4-hydroxy atorvastatin acid were observed when this statin was coadministered with rifampin (a known inhibitor of OATP1B1 and OATP1B3).[112-114] In the presence of cyclosporine (a potent inhibitor of OATP1B1 and CYP3A4) atorvastatin AUCs were 6- to 15-fold increased,[115-117] fluvastatin AUC was 3-fold increased,[118] lovastatin AUC was 20-fold increased,[119] pitavastatin AUC was 5-fold increased,[99] pravastatin AUC was 5- to 10-fold increased,[44,119,120] rosuvastatin AUC was 7-fold increased,[121] and simvastatin AUC was 3- to 8-fold increased.[122,123] Certainly, CYP3A4 inhibition from cyclosporine can contribute to the overall increases observed in statin exposure; however, this can be concluded to play a minor role given that rosuvastatin, pravastatin, and pitavastatin are not significantly metabolized by CYP3A4.[124-128] In fact, pravastatin, the most hydrophilic compound, had a 10-fold increase in AUC when administered to children and adolescents who were taking triple immunosuppressive therapy containing cyclosporine and no other CYP substrates.[44] Gemfibrozil, also an inhibitor of OATP1B1 and CYP2C8, produced a 2-fold increase in AUCs of atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.[99,129-133]

Cumulatively, the data from the above-described studies provide compelling evidence that OATP1B1 is a critically important determinant of drug disposition for most of the statins. Consequently, functional polymorphisms in the *SLCO* gene families are also expected to influence statin disposition and, thus, have been the subject of considerable interest.[99,134] Much of this work stems from a study of pravastatin pharmacokinetics, where extreme outliers were attributed to 2 single-nucleotide variants in *SLCO1B1*.[135] These mutations were observed in the promoter region (−11187G>A) and in exon 5 (c.521T>C) and were associated with a 50% reduction in non-renal clearance.[136] This finding was independently confirmed in heterozygous carriers of *SLCO1B1*15* (containing the 388A>G and 521T>C variants) who demonstrated mean pravastatin exposures (AUC_{0-12}) that were 93% higher and heterozygous carriers of the *17 haplotype (containing the −11187G>A, 388A>G, and 521T>C variants) who had exposures that were 130% higher than non-carriers.[137]

Ultimately, the functional consequence of *SLCO1B1* sequence variations on statin exposure are reflected by the dependence of the individual statin on OATP1B1 for cellular uptake. Heterozygosity for SLCO1B1*5 and *15 haplotypes is associated with a 3-fold, 2.5-fold, and 2-fold increase in exposure for simvastatin acid, atorvastatin and pravastatin, respectively, with very little effect on fluvastatin.[99] *SLCO1B1* genotype also influences the effect of rifampin on atorvastatin exposure wherein a 9-fold increase in AUC is observed in patients with a fully functional 521TT genotype versus a 5-fold increase in AUC observed for the 521CC genotype.[138] We would be remiss not to allude to the *in vitro* data which suggest that the C800T variant of NTCP may confer enhanced uptake of rosuvastatin, but there are no clinical data to support a role for this mutation *in vivo*.[103]

These studies underscore the critical role of OATP1B1 in statin disposition. By extension, this has important implications for drug safety, where an increase in systemic exposure mediated by reduced OATP1B1 activity can increase the risk of myopathy in statin-treated patients. The Statin Response Examined by Genetic Haplotype Markers (STRENGTH) trial demonstrated this with the observation that patients who were heterozygous for a non-coding sequence variation in linkage disequilibrium with c.521T>C experienced a 4.5-fold increase in risk of myopathy. Patients who were homozygous for this mutation experienced a 16.9 increase in risk of myopathy.[139]

All statins, except for pravastatin, are extensively protein bound.[56,57,65,95,96,125,140,141] Therefore, the circulating concentration of free drug is relatively low for most agents in this class. However, the extent of distribution into peripheral tissues in humans is not well characterized. In theory, the statins with reduced lipid solubility (e.g.,

pravastatin) should demonstrate less extensive tissue distribution, which would ostensibly provide a safer alternative in children, where brain and gonadal tissues are still maturing. *In vitro* and *in vivo* data support this supposition, demonstrating that lower exposures are observed for pravastatin than for lovastatin and simvastatin in the central nervous system,[142,143] and pravastatin also manifests a lower risk of myopathy than simvastatin and atorvastatin do.[144-149] However, there are contradictory data which suggest that pravastatin can influence gene expression in the central nervous system to the same extent as some of the other statins.[143] Until the active transporters responsible for tissue distribution of the statins and their ontogeny in children are more fully elucidated, practitioners will need to rely on the adverse event profiles reported from clinical studies.

Metabolism

Although *in vitro* reaction phenotyping studies suggest that cytochromes P450 (CYP) 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5 are all capable of metabolizing the statins, current data suggest that CYP3A4 is a major contributor to simvastatin, lovastatin, and atorvastatin metabolism.[95,150-152] In the presence of the CYP3A4/5 inhibitor troleandomycin, simvastatin acid metabolism is decreased by 90%.[150] When administered concurrently with the CYP3A4 inhibitor itraconazole, 15- to 19-fold increases are observed in simvastatin and lovastatin AUCs.[98,126-128] The impact of itraconazole on the AUC of atorvastatin is more modest (+47%),[151] and the coadministration of CYP3A4 inhibitors has no significant effect on clearance of pravastatin, fluvastatin, rosuvastatin, or pitavastatin, consistent with the limited role of CYP3A4 in the metabolism of these compounds.[153] *In vitro* and *in vivo* data suggest that fluvastatin is a substrate for CYP2C9,[154-156] whereas pravastatin, pitavastatin, and rosuvastatin do not undergo appreciable CYP-mediated metabolism.

Despite the fact that CYP3A4 activity is highly variable, mutations driving this variability have not been fully elucidated.[157] However, a sequence variation in intron 6 of this gene associated with reduced CYP3A4 expression and activity (rs35599367 C>T, designated CYP3A4*22) has also been associated with the need for 0.2- to 0.6-fold lower doses of atorvastatin, lovastatin,

and simvastatin to adequately manage lipid profiles.[158,159] With fluvastatin, patients homozygous for the *3 allele of CYP2C9 (which confers reduced activity in this enzyme) demonstrate 3-fold lower clearance values of the active fluvastatin enantiomer. Notably, the resultant lipid profiles were not correlated with CYP2C9 genotype.[160] Collectively, these studies support a role for allelic variations in drug-metabolizing enzymes influencing the pharmacokinetics and, in some cases, pharmacodynamics of the statins that rely on these pathways for clearance.

UDP-glucuronosyl transferase (UGT)-catalyzed conjugation is the primary route by which statins and their metabolites are further biotransformed in hepatocytes.[161,162] The open acids are conjugated by UGT to form an acyl glucuronide that subsequently cyclizes to form a lactone ring (i.e., lactonization). This process results in a loss of pharmacologic activity and is common to all statins present in the open acid form. Notably, carboxyl esterase can reverse the lactonization process thereby regenerating the open acids. Alternatively, the lactones can be directly metabolized by the CYPs in a process that appears to occur more rapidly than is observed for open acids.[60,163] Although important in the disposition of statins, the overall contribution of UGTs is quantitatively less substantial than that of the CYPs.[163] As above, pravastatin, rosuvastatin, and pitavastatin do not undergo extensive UGT-mediated conjugation.

Although conjugation plays a more limited role in statin disposition, recent data suggest that allelic variants of UGT may have a modest effect of statin activity. The UGT1A3*2 allele has been associated with increased lactonization activity for atorvastatin.[164] Homozygosity of the UGT1A3*2 allele was accompanied by a 1.7- and 2.7-fold increase in AUC of the parent and 2-hydroxyatorvastatin lactones, respectively, compared to that in patients who are homozygous for UGT1A3*1. Furthermore, this increase in lactone formation correlated with a reduction in the maximal effect of atorvastatin on total and LDL cholesterol-lowering from baseline.[165]

Excretion

Biliary excretion of the UGT-conjugated statins occurs through several transporters, including multidrug resistance 1 (MDR1; *ABCB1*), multidrug resistance-associated protein 2 (MRP2;

ABCC2), breast cancer resistance protein (BCRP; *ABCG2*), and bile salt exporting pump (BSEP; *ABCB11*). However, the quantitative importance of these efflux transporters in the overall disposition profile of the statins has yet to be fully elucidated. Nonetheless, the consequences of genetic variations in the efflux transporters relevant to the statins have also recently been examined. *In vitro*, there is no consensus regarding MDR1 expression or activity in the common allelic variants of *ABCB1* (c.1236C>T, c.2677G>T/A, c.3435C>T).[166] *In vivo*, these allelic variants do not appear to significantly influence the interindividual variability in fluvastatin, pravastatin, lovastatin, and rosuvastatin pharmacokinetics,[167] but significantly increase the exposure of simvastatin and atorvastatin acid by 60% and 55%, respectively.[168]

Conversely, the *ABCG2* c.421C>A variant, which has been associated with transport activity *in vitro*,[169] appears to increase the exposure of atorvastatin, fluvastatin, simvastatin lactone, and rosuvastatin by 72%, 72%, 111%, and 144%, respectively, in subjects with the AA genotype compared to those in patients with the wild-type CC genotype.[75,170] Note that this genotype does not appreciably impact the pharmacokinetics of simvastatin acid or pravastatin.[170] As discussed in *Absorption* above, pravastatin is subject to MRP2-mediated transport *in vitro* at the level of the enterocyte and hepatocyte.[69-71] *In vivo*, the *ABCC2* c.1446C>G variant decreases the exposure of pravastatin (AUC, −68%) compared to wild-type controls secondary to a "gain of function" mutation.[72] It remains unknown whether this decrease in exposure is due to enhanced presystemic and/or hepatic clearance. Conversely, Mrp2-deficient rats have significantly diminished biliary clearance of pravastatin,[71] and *in vitro* data suggest that BSEP may be an alternative mechanism by which pravastatin is cleared from the hepatocyte.[171]

Renal clearance is far less pronounced than biliary excretion. Most of the statin agents have minimal renal clearance (< 10%) after an orally administered dose,[56,57,59,79,124,172] except for pravastatin in which 20% is renally cleared.[62] The exposure of pravastatin acid is not impacted by diminished renal function; however, exposure of the 3-alpha-hydroxy-pravastatin metabolite was significantly increased (AUC, +48%) compared to that in subjects with normal renal function.[173]

Halstenson et al[173] suggest that this increased interconversion occurs secondary to decreased gastric pH, which is a direct result of kidney-related metabolic changes. Hepatic conversion to 3-alpha-5-beta, 6-beta-trihydroxy isomeric metabolite occurs more frequently in severe renal impairment, suggesting that more pravastatin acid is cleared hepatically. Although renal impairment does not appear to alter the exposure of pravastatin acid, the impact of both metabolites on statin disposition and response require further investigation. *In vitro*, pravastatin is a substrate of organic anion transporter 3 (OAT3), a transporter located on basolateral membrane of the proximal tubule, and it is responsible for its uptake in the kidney.[174,175] *In vitro*, gemfibrozil inhibits pravastatin uptake in OAT3-expressing cells.[176] *In vivo,* coadministration of pravastatin and gemfibrozil lead to an increase in pravastatin exposure (AUC, +202%) and decreased renal clearance (−40%).[131] This 40% reduction in renal clearance does not solely explain the increase in pravastatin exposure, but it could serve as a contribution to pravastatin disposition. Further investigation by Nishizato et al[136] found that several OAT3 single-nucleotide polymorphisms did not affect pravastatin pharmacokinetics.[136] However, the single-nucleotide polymorphisms included in this analysis have not been associated with decreased transporter function. Overall, patients with renal impairment do not require dose adjustments, but the impact of renal clearance with pravastatin administration requires further elucidation.

Given the current state of our knowledge of the disposition pathways for the available statins (most of which mature prior to adolescence) and the relative absence of data on the ontogeny of transporter expression which could influence recommendations for statin dosage in children, considerations for the selection of statin agents in the pediatric population will largely reflect the same considerations used with adult patients. To maximize the dose-exposure profile, considerations include whether the patient is receiving gastric acid-modifying therapy and whether greater adherence is anticipated to a regimen that requires medication administration with or without meals. To influence the exposure-response profile, one should consider the genetic constitution of the patient, the concurrent administration of drugs that

Table 7. Statin Studies Under Non-Hyperlipidemic Conditions

Condition	Investigated Mechanism(s)
Autoimmune myocarditis[181,182]	Inhibit expression of inflammatory cytokines Reduce infiltration of T cells Improve myocardial repolarization
Cardiac allograft vasculopathy[183-190]	Improve prognosis post-transplant Reduce expression of cell adhesion molecules Reduce graft rejection Reduce circulating monocytes Improve survival
Cancer[191-195]	Stimulate antiproliferation Promote apoptosis Inhibit angiogenesis Inhibit cell migration
Chronic kidney disease[196-198]	Decrease decline in GFR Prevent contrast induced acute kidney injury Decrease risk of stroke
Fracture injuries, bone healing, & osteoporosis[199-204]	Promote mesenchymal cell differentiation to osteoblasts Protect osteoblasts from apoptosis Reduce osteoclast activity and bone resorption
HIV[205-211]	Slow progression of vascular disease on ART Improve flow-mediated vasodilation Implement immunomodulation Reduce all-cause mortality
Immunomodulation[212-214]	Inhibit interferon production Decrease T cell activation
Infection[215-218]	Reduce risk of mortality from bacterial and viral infection
Lupus[219-222]	Reduce C-reactive protein Reduce circulating chemokines Improve endothelial function
Polycystic ovary syndrome[223-225]	Reduce markers of inflammation Reduce androgenic steroid concentrations
Rheumatoid arthritis[226-231]	Reduce risk of mortality Reduce joint pain/swelling Reduce markers of inflammation
Rotator cuff injury[232,233]	Stimulate migration and adhesion of tenocytes Protect against hyperlipidemia-associated RC injury
Sickle cell disease[178,234-236]	Reduce thrombin generation/lower circulating procoagulants Improve endothelial dysfunction

ART, antiretroviral therapy; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; RC, rotator cuff

compete as substrates for transport pathways, and comorbidities that may alter circulating protein stores of the presence of protein-binding displacers in the circulation. Future studies on the pharmacokinetics of statins in the pediatric population, and an expansion of our knowledge on the developmental patterns of transport expression, will permit clinicians to further individualize the selection and dosage of statins in this population.

FUTURE CONSIDERATIONS

Owing to their pleiotropic effects, the statins have been extensively evaluated for non-hyperlipidemic conditions, a few of which are detailed in Table 7, and many of which can impact children. For example, patients with sickle cell disease can develop oxidative stress and chronic inflammation to their distal vasculature as a result of transient vaso-occlusion and subsequent

reperfusion injury.[177] Hoppe et al[178] found that biomarkers of vascular dysfunction, including C-reactive protein and interleukin 6, were decreased in adolescents with sickle cell disease from 50% to 70% after a 3-week trial of low (20 mg) or moderate (40 mg) doses of simvastatin.

Additionally, statins have been used after cardiac transplantation to prevent coronary allograft vasculopathy (CAV). In pediatric cardiac transplantation, the prevalence of CAV has been reported to be as high as 17% in one retrospective analysis.[179] Greater-than-optimal LDL concentrations (>100 mg/dL) post transplantation have been reported in 39% of pediatric patients 1 year after transplantation,[180] which can be secondary to post-transplantation steroid and immunosuppressive therapy. The addition of pravastatin therapy in pediatric cardiac transplant recipients yielded a lower incidence of CAV.[179]

Most of the remaining conditions for which statins have been explored exploit the anti-inflammatory and antiproliferative effects of these drugs (Table 7). Thus, it would not be unexpected to see statin coadministration in the presence of infections, fractures, and malignancies in children. However, it should be appreciated that there are an equally large number of publications that refute a role for statins in these same conditions (Table 7). In the absence of sufficient prospective clinical trials to inform the role of these agents for indications other than hyperlipidemia, the practitioner must carefully weigh the risk-benefit ratio of these agents and thoughtfully examine the *in vitro* concentration-effect profiles to inform whether and at what dose these agents should be used in pediatric patients.

CONCLUSIONS

With precursors of CAD appearing in childhood, the establishment of pediatric preventive cardiology services is rapidly emerging. However, the most appropriate management of those children and adolescents, where lifestyle changes fail, remains challenging. Despite the overall success of statins, variability in drug response in the pediatric cohort remains concerning. Although not discussed above, genes involved with drug response may contribute to some of the variability in LDL reduction among children and

adults receiving statin therapy.[237-241] However, it remains unknown whether a consistent statin concentration (i.e., exposure) at the drug target was achieved in these studies. Therefore, future investigations must be designed to characterize these dose-exposure relationships in the developing child so that exposure can be controlled when attempting to determine response in this population. Once the covariates that influence statin disposition in children are validated, future clinical trials will be better informed to fully characterize the entire dose-exposure-response relationship. With these data, dosage will be optimized to maximize efficacy while minimizing toxicity in the individual pediatric patient. In the interim, understanding the statin disposition pathway will assist pediatric providers who make recommendations related to statin prescribing where alteration of drug delivery and dosage may be appropriately tailored to meet their specific patient needs.

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