

THE USE OF STATINS IN CHILDHOOD

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Numerous studies have demonstrated the remarkable efficacy and safety of statins for the prevention of cardiovascular disease in high-risk adults. Currently statins are the most widely prescribed drug in the United States. Statins have been studied in randomized controlled trials in adolescents with severe Familial Hypercholesterolemia and short-term studies verify that they are effective at lowering LDL cholesterol and improve surrogate markers of atherosclerosis. They appear safe over the short term. Interest is growing in their use in adolescents at high risk of future cardiovascular disease however many questions remain unanswered regarding their use, including the optimal timing of their introduction, the safety of their long-term use and whether we should prescribe low doses of statins or escalate doses to achieve a target level of LDL-cholesterol. The purpose of the paper is to review what is known about statins and to highlight particular areas of uncertainty with respect to their use that I believe are often under appreciated and nonetheless important for pediatricians to know.

Descriptors: HYDROXYMETHYLGLUTARYL-CoA REDUCTASE INHIBITORS, FAMILIAL HYPERLIPOPROTEINEMIA TYPE II, PRIMARY PREVENTION

Introduction

The interest in prescribing statins beginning in childhood has intensified recently in the United States due to the obesity epidemic, the repeated demonstration of their benefits in high risk adults and due to the release of a recent American Academy of Pediatrics guideline that advocated their use in high-risk children, as young as 8-years of age (1-3). The evidence is compelling that statins markedly decrease cardiovascular (CV) morbidity and mortality as well as total mortality in adults who have established cardiovascular disease; see Table 1. This has been established in numerous well-known secondary prevention trials (4-8). Primary prevention studies of

middle-aged adults (those without any prior history of cardiovascular events) treated with statins also unequivocally demonstrates lower future CV risk; see Table 1 (9-11). However, whether statins prescribed in primary prevention studies have consistently decreased all cause mortality (particularly among women and subgroups of patients who initially are at lower risk of cardiovascular events) is debated (12). The above points are summarized in Table 2. To be fair many of the primary prevention studies are powered to detect a difference in the rate of both fatal and non-fatal CV events and would require a doubling of the study population size to properly address differences in total mortality.

The issue underlying this question is whether the observed decreases in cardiovascular mortality in primary prevention studies are offset by increases in other cause mortality. Two large meta-analyses of studies in adults have addressed whether statins increase cancer mortality and/or decrease non-illness mortality, (suicide, accidents, homicides) and neither found evidence of an increase in other cause mortality (13, 14). However, evidence

on statins and cancer-risk is mixed and clearly if there is a relationship between cumulative statin dose and cancer risk, adolescents begun on statins would be of higher risk than adults begun at middle-age. Furthermore, these analyses of non-cardiovascular mortality and statin use aggregate data from trials employing different statins and there may be important differences between the individual drugs.

While these points may seem academic to some this is precisely where pediatricians need to scrutinize the evidence most closely. Children and adolescents are at no appreciable risk of acute myocardial infarctions, and consequently the results of primary prevention studies are applicable. Furthermore, a focus on the effects of statin use on total mortality (not just cardiovascular morbidity and mortality) is the outcome that pediatricians should attend to. In general results of secondary prevention studies are so impressive and widely publicized that they have been over generalized in the minds of both the public and in many physicians.

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Table 1
Cardiovascular and Total Mortality in Adult Statin Trials

Tablica 1.
Kardiovaskularni i ukupni mortalitet u istraživanjima statina u odraslih

Study Name (Reference)	Number Enrolled	CDH Risk Reduction	Total Mortality Reduction
CARE (4)	4,000	24%	NS
4S (5)	4,000	42%	30%
LIPID (6)	9,000	24%	22%
GREACE (7)	1,600	47%	43%
ALLHAT-LLA (8)	10,000	17%	NS
WOSCOPS (9)	6,500	31%	22% P=0.051
AFCAPS-TEX CAPS (10)	6,600	37%	NS
JUPITER (11)	18,000	44%	20%

Pathobiology of Atherosclerosis Relevant to Statins

A brief review of atherosclerosis and the pathophysiology of myocardial infarction are warranted. The commonly held notion that myocardial infarctions occur as a result of a progressive critical narrowing of the coronary artery is erroneous. While this phenomenon can occur and is responsible for stable angina it is now appreciated that the majority of myocardial infarctions (MIs) do not occur at areas of narrowing. This is explained by a phenomenon known as the Glagov hypothesis (15). Glagov observed that as the atherosclerotic plaque develops there is radial growth in the coronary artery and preservation of the lumen. The majority of MIs occurs not at areas of flow restriction but where the surface of advanced atherosclerotic plaque has eroded, ruptured or hemorrhaged, and as a consequence has developed a thrombogenic surface capable of precipitating a clot (16). The concept that the surface properties of plaque and its propensity to erode or rupture has created the concept of atherosclerotic "plaque stability" as the critical determinant of acute MI risk. MI risk is

now viewed primarily as function of the burden of unstable plaque.

The reason why this is relevant to the use of statins in childhood is simply that imaging studies of atherosclerotic plaque have demonstrated that adults experience the established reduction of LDL-C and in CV risk without physical regression of plaque. Statins do not make advanced atherosclerotic plaque "go away" (17). How do they work then? While the answer is not entirely been established the most reasonable explanation is that a transformation from unstable to stable plaque occurs before any appreciable physical regression occurs. Both the LDL-C lowering effect and/or alternatively pleiotropic effects (that are independent of lipid-lowering) statins may be responsible. The point here is that when we are prescribing statins to adolescents, our expectation is that it will prevent the development of plaque. This is a reasonable expectation but it is not the mechanism by which statins appear to work in middle-aged adults.

Pharmacology/Safety

All statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway. In response to a decrease in intracellular cholesterol sterol response elements in the promoter region of LDL gene up-regulate the expression of LDL-C receptors on the cell surface that bind to and internalize LDL-C and consequently circulating levels of LDL-C decrease.

The statins are hepatoselective, meaning they inhibit cholesterol biosynthesis in hepatocytes to a much greater extent than in other cell types, and as a consequence statins exert their cholesterol-lowering effects by acting on the liver. The mechanism by which this hepatoselectivity is achieved (increased absorption and extraction from the portal circulation, selective intrahepatic conversion to an active form, and subsequent high first pass metabolism to inactive form varies greatly between the individual statins (18). As a consequence, the statins have a small but potentially important difference in the degree to which they inhibit cholesterol biosynthesis in non-hepatocytes (peripheral cells).

The statins all have a sigmoidal dose-response curve and consequently every doubling of the dose from the minimal dose lowers LDL-C by 6%. Statins do not lower triglyceride concentrations. Other pharmacological properties are summarized in Table 3. The statins vary greatly in their lipophilicity and as a consequence the degree to which they penetrate the blood-barrier. In addition they also vary to the degree to which they are metabolized by the cytochrome P450 (CYP450) system and a consequence are susceptible to drug interactions mediated by CYP450 inhibition as a cause of undesirable side effects. Commonly used drugs that should not be prescribed with

Table 2
A Summary of Mortality Data for Adult Statin Trials

Tablica 2.
Sažetak podataka o mortalitetu u istraživanjima statina u odraslih

	Cardiovascular Morbidity and Mortality	All-Cause Morbidity and Mortality
Secondary Prevention Trial	Strongest	Strong
Primary Prevention Trial	Strong	Moderate, Debated

Table 3
U.S. FDA Approved Statins for Pediatrics

Tablica 3.
Odobreni statini za djecu u SAD

Name	Age Range (Years)	(mg/Dose Range * day)	Metabolic pathway	Lipophilicity
Atorvastatin	10-17	10-20	CYP3A3/4 substrate; CYP2C8 inhibitor	+
Lovastatin	10-17	10-40	CYP3A3/4 substrate	++
Simvastatin	10-17	10-40	CYP3A3/4 substrate	+++
Pravastatin	8-13; 14-18	20; 40	CYP3A4, CYP2C8/9, CYP2D6 inhibitor	Hydrophilic

statins include macrolides, azole antifungals, protease inhibitors, and fibrates.

Pleiotropic effects of statins refer to effects that are not mediated directly by reductions in circulating LDL. In vitro experiments have shown that statins have numerous effects non-lipid lowering effects including effects on nitric oxide bioavailability, on cell growth, apoptosis, and cell to cell signaling, and while it is controversial it has been hypothesized that these effects are in part responsible for changes in atherosclerotic plaque stability or rupture-risk (19). Statins have an anti-inflammatory effect and have been consistently shown to lower CRP (11).

Based on a very large amount of data derived from randomized controlled trials in adults, statins have proven to be remarkably safe drugs (20). The predominant safety concerns related to hepatotoxicity and myopathy. It is widely recognized that statins frequently cause mild $<3\times$ upper limit of normal elevation of liver function tests, (LFT's) in 1-3% of treated patients. This phenomenon appears to be dose-related. These elevations are most often transient, reversible and not associated with histologic changes on biopsy. A persistent LFT elevation $>3\times$ ULN or symptomatic liver disease warrants discontinuation. Despite the wide spread recognition of their effects on liver enzymes acute liver failure occurs has been estimated to occur at a rate of 1 per million person years of use; the incidence of acute liver failure in surveillance studies of statin users is not different than the background rate for the population (21).

The predominant established safety concern is related to muscle toxicity. Statin related muscle effects varies from myalgia unassociated with elevation of the muscle enzyme creatinine phosphokinase (CPK) to statin-related myopathy associated with elevation of CPK, to frank rhabdomyolysis (CPK $>10-50\times$ the upper limit of normal associated with elevation of serum creatinine). In adults, surveillance studies have found that myopathy with CPK $\geq 10\times$ ULN occurs at a rate of approximately 1/23,000 patient's years of therapy with lower dose therapy. Increases are noted with higher doses. Death as a consequence of rhabdomyolysis-related multi organ failure has been reported with all currently available statins and has been reported to occur at a rate of 0.15 deaths per 1 million prescriptions (22). These large-scale surveillance studies have established that the risk of rhabdomyolysis is related to higher statin doses, CYP450 inhibiting drug-interactions, and pre-existing hepatic or renal disease. As a consequence, in the United States, the Food and Drug administration has only licensed the lower statin doses for use in children and adolescents.

Recently it was shown that mutations in the gene for a peptide organic anion transporter OATP1B1 that controls intracellular statin concentration was shown to be responsible for a large portion of the observed cases of myopathy in the SEARCH - trial a large randomized secondary prevention trial of simvastatin in adults (23). This study raises the possibility that pre-treatment pharmacogenetic profiles may be used to identify and tailor drug choice and dose. Statins are

potently teratogenic and should not be prescribed to women who may become pregnant intentionally or unintentionally (24).

For Pediatricians long-term safety is a concern and the available data derived from longer-term adult studies and the currently available short-term studies in children are unable to answer the question of whether statins have unique toxicities in developing organisms.

Familial Hypercholesterolemia

With few exceptions pediatric statin trials have been conducted in children and adolescents with heterozygous familial hypercholesterolemia (FH). Consequently, a brief review of this condition is warranted. Brown and Goldstein first described heterozygous Familial Hypercholesterolemia in 1974 as an autosomal co-dominant condition in which the LDL receptor is absent or dysfunctional. FH is found worldwide with a prevalence of roughly 1 in 500 individuals. Subsequently 1000 mutations in the LDL-receptor gene sequence have been identified and reported to the LDL-R mutation database (25). Adults and children with heterozygous FH have one half of the normal amount of LDL receptor function and their total and LDL-C concentrations 2-3 $\times$ above normal values from infancy on. Scavenger cells loaded with cholesterol invade the tendons and the cornea and patients develop Achilles' tendon thickening, Achilles' tendonitis, tendon xanthomata, and arcus senilis during adolescence or later.

Table 4
Historical rates of CAD in Familial Hypercholesterolemia

Tablica 4.
Učestalost koronarne i arterijske bolesti u obiteljskoj hiperkolesterolemiji

Age	Male	Female
30	5	0
40	20	5
50	50	12
60	85	58

In my experience the prevalence of these findings among affected adolescence is very low and varies by mutation. Children and adolescents so infrequently have findings that they are most often identified by targeted screening or by case finding based on parental history. Cascade screening of all the first degree relatives of identified affected individuals has been proposed as a means of identifying patients with FH and this is feasible in geographically stable populations but in the US it poses ethical issues regarding privacy and unauthorized dissemination of personal health information. The huge number of LDL receptor mutations that result in the FH phenotype (and the different admixtures of mutations present in different populations) has thwarted the development of an inexpensive genetic test for Familial Hypercholesterolemia as well as making it difficult to establish a "gold standard" from which a clinical phenotype can be developed. Nonetheless clinicians should suspect FH in children less than 16 with total cholesterol concentration that exceeds

6.7 mmol/l when secondary causes of hyperlipidemia have been excluded and family studies reveal a pattern of 50% of the first degree relatives are similarly affected i.e. one parent and grandparent.

Adults with FH in the pre-statin era had a greatly elevated risk of atherosclerotic heart and peripheral vascular disease; see Table 4 (26). Interestingly, they are not at increased risk of stroke (27). The delayed onset of symptomatic CV in females when compared to males is relevant to pediatricians deciding when to initiate treatment.

Familial Hypercholesterolemia the use of Statins and Mortality

Recently two studies have examined the historical decline in morbidity and mortality for adults with heterozygous Familial Hypercholesterolemia in relation to the introduction of statins. Investigators in the UK used a national registry of patients with heterozygous Familial Hypercholesterolemia (www.primarycare.ox.ac.uk/research/vascular/

research/simon_broome) to examine the difference on mortality rates in adults before and after 1992 and found that there was a 50% reduction in CHD mortality (without an increase in the non-coronary mortality) after the use of statins become routine (28). Vermissen et al. used historical data to compare the mortality data on 2146 adult patients with FH (mean age of 43) in the Netherlands who began on Simvastatin in 1990 with a comparison group who were not treated until 3-4 years later and demonstrated an 80% percent reduction in mortality-risk in the treated group; treatment reduced the mortality risk to a level that was equivalent to the general population (29). From a pediatric perspective this remarkable finding raises the fundamental question of whether we need to initiate treatment during adolescence.

Pediatric Studies

There are 6 randomized controlled trials of statins in adolescents summarized in Table 5 (30-36). The total number of children studied is 832 and consequently only 416 children have been carefully studied while taking statins in the context of a randomized controlled trial. This is a tiny fraction of the number of adults who have been studied. These studies demonstrate unequivocally that statins are effective at lowering LDL-C from 20-40%. Early concerns that statins, by inhibiting cholesterol biosynthesis, might interfere with steroidogenesis and pubertal development have been allayed by several studies in both males and females

Table 5
Pediatric Statin Studies

Tablica 5.
Istraživanja statina u djece

Statin-Year	Ref	Numbered Enrolled	LDL-C (% change)	Other Outcome
Atrovastatin 2003	30	187	-40	
Lovastatin 1999	31	132	-22	
Pravastatin 1996	32	72	-30	
Pravastatin 2004	33	214	-24	C-IMT
Lovastatin 2005	34	54	-32	
Simvastatin 2002	35	175	-40	
All Trials Pooled		834	-31%	

demonstrating normal concentrations of sex steroids and pubertal progression in treated subjects. These medications are extremely well tolerated. A meta-analysis of 6 existing pediatric statin studies that examined data from roughly 400 children in the active treatment arms of six randomized controlled trials confirmed that statins have a very low rate of adverse effects with no significant differences between treatment and placebo group. Very few withdrawals occurred among subjects receiving statins during these trials. Furthermore significant elevations of LFTs and CK occurred in less than 1% of treated subjects (36).

It is well known that atherosclerosis progresses sub-clinically from the second decade of life and there is great interest in the use of non-invasive surrogate markers coronary of atherosclerosis in adolescents both as a risk-indicator and as surrogate for "hard outcome data" such as coronary mortality and morbidity. Weigman demonstrated that children treated with pravastatin experienced regression of carotid intimal medial thickness in contrast to controls with Familial hypercholesterolemia who's C-IMT progressed during the study (33).

Conclusions/Future directions

Statins are remarkable drugs that are both highly effective and safe in adults. They have been demonstrated to be effective at lowering LDL-C and in one study at improving a surrogate marker of atherosclerosis progression among children and adolescents with FH. Preliminary safety data derived from pediatric studies and from adult studies are reassuring but our knowledge of the safety is limited in 3 fundamental ways. First, adult data cannot reassure us that statins are safe in developing organisms. Second, existing pediatric studies are all less than 2 years duration - the safety profile of their long term use remains an open question and third the currently available pediatric studies are significantly underpowered to detect rare adverse events that may be unique to children. Because pediatricians are treating risk factors rather than disease we have a special obligation to understand and maximize the

safe use of statins. While no data is currently available to justify this assertion, given the important differences in the pharmacology of individual statins, it seems unlikely that all statins will prove equally safe over the long-term. Recent developments in pharmacogenetics may help identify individuals at high risk for adverse effects.

The fundamental question of how to optimally time the introduction of statins to high-risk individuals with FH is remains unanswered and while current US recommendations suggest introduction as young as 8 and certainly during the second decade, practitioners in the United Kingdom are more conservative with only 23% reporting that they would prescribe statins to a hypothetical 10-15 year old boy with FH (3, 37). Recent data suggests that substantial benefit occurs among individuals with FH when statins are introduced even as late as the fifth decade of life (29).

Future directions for the use of statins include studies that examine statin-use in a range of other pediatric conditions that are associated with premature atherosclerosis such as diabetes, and chronic renal failure. Whether the anti-inflammatory properties of statins are beneficial in mitigating the progression of atherosclerosis in Lupus is the subject of an ongoing trial, the APPLE study. Ultimately the development and validation of non-invasive techniques to assess sub-clinical atherosclerosis will make major contributions to the use of statins for pediatric atherosclerosis prevention.

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Sažetak

UPORABA STATINA U DJETINJSTVU

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Brojne studije su pokazale znatnu učinkovitost i sigurnost statina za prevenciju kardiovaskularnih bolesti kod visokorizičnih osoba. Statini su trenutno najprepisivaniji lijek u Sjedinjenim državama. Statini se proučavaju nasumce kod adolescenata sa snažnom obiteljskom hiperkolesterolemijom i kratkoročne studije potvrđuju da su učinkovite u smanjenju LDL kolesterola te da poboljšavaju surogatne markere ateroskleroze. Čine se sigurnim u kraćem periodu. Raste interes za njihovo korištenje kod adolescenata sa velikim rizikom budućih kardiovaskularnih bolesti. Ipak, mnogo pitanja ostaje neodgovoreno glede njihove uporabe, optimalnog tempiranja njihovog uvođenja, sigurnosti dugoročnog korištenja te da li prepisati niske doze statina ili pojačati doze kako bi se postigla željena razina LDL kolesterola. Svrha ovog rada jest ponoviti ono poznato o statinima i naglasiti posebna područja nesigurnosti sa osvrtom na njihovu primjenu, koja se često podcjenjuje, ali je svejedno važna za pedijatre.

Deskriptori: HIDROKSIMETILGLUTARIL-CoA INHIBITORI REDUKTAZE, OBITELJSKA HIPERLIPOPROTEINEMIA TIP II, PRIMARNA PREVENCIJA