Harms of treatment with cholesterol-lowering drugs in children: A systematic review of the published literature

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July 23rd, 2010

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ABSTRACT

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Background: Some clinical guidelines recommend pharmacologic treatment for children with hyperlipidemia. These medications decrease cholesterol levels, but their side effects or potential harms in children are not well understood.

Objective: To systematically review published trials of cholesterol-lowering medications in children and quantify their harms.

Design/Methods: A comprehensive search was used to identify prospective studies evaluating the use of cholesterol-lowering drugs compared to controls in children with hyperlipidemia. Titles and abstracts were independently reviewed by authors and appropriate articles were fully evaluated. Blinded investigators completed quality assessments of included studies, followed by data extraction of all reported side effects or other harms using a standardized form.

Results: A systematic search of the published literature identified 1070 titles and abstracts for potential inclusion. The 17 articles that met final inclusion criteria varied widely in quality, were generally not powered to detect adverse effects, and more than half disclosed pharmaceutical company sponsorship. None followed subjects for > 6 years. All included subjects (N=1604) with a probable diagnosis of heterozygous familial hyperlipidemia Studies evaluated the following therapies: HMG CoA reductase inhibitors (statins) versus placebo (10 studies), bile acid sequestrants (4 studies), bile acid sequestrants as add-on therapy to statins (1 study), statins as add-on therapy to bile acid sequestrants (1 study), and ezetemibe (1 study). Statins generally had similar harms to placebo, except in 7 of the 11 studies there was an increase in muscle symptoms or abnormal muscle enzyme laboratory values. Additionally, 3 of 5 statin studies evaluating dihydroepiandrosterone (DHEAS) reported significant changes in hormone levels. Two of 5 studies that evaluated bile acid sequestrants reported an increase in gastrointestinal symptoms. Ezetimibe therapy added to statin therapy increased myalgias (5.6% combined therapy vs. 0.8% placebo, p=0.03).

Conclusions: Published studies of pharmacotherapy for hyperlipidemia in children are limited by small numbers, short follow-up periods, and a unique population. The available studies suggest that statins, bile acid sequestrants, and cholesterol absorption blockers all have associated side effects. Unfortunately, currently available studies have not fully assessed longer term harms, complicating treatment decisions.

INTRODUCTION

In adults, cardiovascular disease is the leading cause of death and morbidity in the United States[1]. Evidence has shown that high levels of total cholesterol and low density lipoprotein cholesterol can lead to the formation of atherosclerotic plaques and is one of the leading risk factors for coronary heart disease[2]. Lipid measurements in adults have been proven to be effective in identifying those at risk, and early treatment has been shown to decrease the incidence of coronary heart disease in persons with abnormal lipids[2].

Children are not immune from high cholesterol either, as elevated cholesterol levels in children have gradually become more common with the growing obesity epidemic, especially here in the United States. Evidence has shown that atherosclerotic plaques can form at a young age[3]. However, it is unclear if this leads to increased cardiac related mortality once these children become adults. This lack of evidence creates difficult questions that care providers for children must face: "Should I treat this child with high cholesterol? And, "If I use medication to treat this child, could I be causing more harm than good?"

In an effort to help answer one of these questions, we performed a systematic review of available research to look at the harms associated with the medications used to treat high cholesterol in children.

BACKGROUND

Dyslipidemia – What is It?

Lipids are fat soluble compounds that naturally occur in the human body, and serve a wide array of biological functions, including energy storage, molecular signaling, and manufacture of cell membranes. When lipid levels are abnormally high however, they can play a key role in accelerating human disease processes, especially in helping to form plaques in arterial blood vessels, a syndrome commonly known as atherosclerosis. These elevations of lipids and subsequent atherosclerosis are one of the leading risk factors and a predictor of cardiac related mortality in adults. These abnormal levels of total cholesterol, low-density lipoprotein cholesterol (LDL), triglycerides, or deficiency of high-density lipoprotein cholesterol (HDL) are all caused by disorders of lipoprotein metabolism that can be termed "dyslipidemias", and can be either acquired or familial[4]. Risk factors for dyslipidemia include established family history, diabetes, nephritic syndrome, and hypothyroidism[5].

Why are dyslipidemias medically relevant?

In light of this basic background information, it is important to consider why dyslipidemias are considered relevant to the medical field. Numerous studies have demonstrated that the most consistent and strongest risk factors for cardiovascular disease in adults include elevated LDL, low HDL, hypertension, diabetes mellitus, cigarette use, obesity, and especially increasing age[1,6]. The most notable of these studies, the Framingham Study, was a large scale, long-term follow-up study that helped identify the

risk factors for heart disease and has recently been adapted to help calculate a patient's risk of dying within ten years from heart disease based on their individual risk factors[7].

Obviously, a person's age or family history cannot be altered; however several of the other risk factors mentioned are amenable to some degree of change. As cardiovascular disease is the leading cause of death among adults in the United States, it is important to recognize and attempt to treat/correct any of these other risk factors that can be altered[4,8].

Lipid disorders are one of the modifiable risk factors that can be altered through medical treatment and lifestyle changes. Early detection and treatment of abnormal lipid levels in adults has been proven to help decrease cardiovascular related deaths[5]. This has resulted in the National Cholesterol Education Program's (NCEP's) recommendation to screen once every 5 years starting at 20 years of age, with increasing frequency as a person grows older or if they have abnormal cholesterol levels[7].

How is dyslipidemia defined?

As mentioned above, dyslipidemias come in four basic categories: elevated total cholesterol levels, elevated LDL cholesterol levels, elevated triglyceride levels, and low HDL cholesterol. Cholesterol levels are obtained by measurements in blood samples. Total cholesterol, triglycerides, and HDL are measured directly, while LDL levels can be measured directly or calculated via the Friedewald equation, which uses measurements of total cholesterol, HDL, and triglycerides to estimate LDL concentrations[8].

In general, the definitions of dyslipidemia are based on previously studied population norms for serum cholesterol levels, and serum levels falling outside the 95th percentile are often considered "abnormal" or dyslipidemic. For example, the American Association of Clinical Endocrinologists considers a person to have a dyslipidemia if his/her serum total cholesterol level is greater than or equal to 240mg/dL[8]. A person can also be said to have a dyslipidemia if his/her serum HDL cholesterol is less than 35mg/dL, serum LDL cholesterol is greater than or equal to 160mg/dL, or their serum triglycerides are greater than 200mg/dL[8]. These specific numbers may vary slightly between various professional organizations.

It is important to note that while these specific number cutoffs may give the appearance that dyslipidemias are dichotomous (either normal or abnormal), this is actually not the case. It is more appropriate to view them in combination with the other previously mentioned risk factors as continuous risk factors for cardiac related death, with serum concentrations at these levels or worse only increasing an individual's risk of heart disease death. This point is further illustrated by the National Cholesterol Education Program's newest classification method, which can be found in **Table 1** below[7].

Table 1

NCEP ATIII Classification of LDL, Total, and HDL Cholesterol Levels			
LDL Cholesterol			
	<100		Optimal
	100-129		Near Optimal/above optimal
	130-159		Borderline High
	160-189		High
	>/= 190		Very High
Total Cholesterol			
	<200		Desirable
	200-239		Borderline High
	>/= 240		High
HDL Cholesterol			
	<40		Low
	>/=60		High

What are the current recommendations for treating dyslipidemias?

As previously mentioned, elevated lipids act as a continuous risk factor and a predictor of cardiac related mortality. With this in mind, treating elevated lipid levels has become a major priority of primary care providers and specialists across the US. In general, treatment of dyslipidemia is aimed at lowering lipid levels, with the idea being that cardiac related mortality will be subsequently reduced. Treatment can be either through pharmacological or therapeutic life-style changes.

Often, before pharmacologic interventions are necessary, many guidelines recommend therapeutic lifestyle changes as a first line approach to treat high cholesterol. Therapeutic lifestyle changes include the use of exercise in combination with a low-fat, low-cholesterol diet, such as the American Heart Association Step I diet, as the first step in treating most pediatric dyslipidemia[4]. Dietary changes, especially in conjunction with exercise, are often used as first line therapies in helping to battle against dyslipidemia. For this reason, the NCEP also recommends dietary changes, increased physical activity, and weight reduction prior to initiating pharmacological therapy in their newest set of guidelines[7].

Should therapeutic lifestyle changes alone not be effective and a physician deem in necessary to use medications to treat dyslipidemias, numerous pharmacologic treatment options exist. The most commonly prescribed medication for treating dyslipidemias in the United States are 3-Hydroxy-3-methyl-glutaryl Coenzyme A Reductase Inhibitors, which are more commonly known as "**statins"**. These medications decrease LDL concentrations by decreasing intracellular cholesterol levels and up-regulating LDL receptors, which in turn clears more LDL from circulation, and can

reduce LDL levels by 20-50%[1,9]. In addition, they are the one intervention that evidence has shown to not only reduce LDL levels, but are also effective in cholesterol plaque stabilization and been found to reduce cardiac risk[10].

Other cholesterol-lowering medications commonly used include: 1)**bile acid-binding resins,** which work by binding cholesterol in bile acids in the intestinal lumen, preventing their re-uptake into circulation and lowering cholesterol levels by 10-20% when used alone or in combination with other medications[1,11]; 2) **Niacin** (nicotinic acid) lowers both LDL and triglycerides while at the same time increasing HDL by decreasing hepatic production of very low-density lipoprotein (VLDL), however its use is limited by its harsh side effects, which have been found to be excessively common[1,12]; 3) **Cholesterol absorption blockers** are an emerging treatment for dyslipidemias and act by reducing absorption in the small intestine [1]. and 4) **fibrates** reduce triglyceride levels by acting on VLDL [1].

<u>When is treatment of dyslipidemias recommended?</u>

The National Cholesterol Education Program's (NCEP) executive panel recommends treatment modalities on the basis of a combination of cholesterol levels and a patient's risk factors[7]. Their recommendations are also the same as those used by the American Association of Clinical Endocrinologists (AACE)[8]. Both of these organizations' recommendations focus primarily on LDL cholesterol levels, as extensive research has shown that elevated LDL levels are a major risk factor for heart disease[7,8]. Both organizations provide basic LDL goals on a scale that varies in accordance with a patient's of number cardiac-related of risk factors. The higher the number of patient's risk

factors, the lower their target LDL goal should be, as risk greatly increases with multiple risk factors and even moderately increased LDL levels[7,8].

Table 2 shows the current clinical guidelines for treatment as described by both the NCEP and the AACE[7,8]. These clinical guidelines stress the importance of adjusting treatment modalities and LDL target levels on the basis each individual patient's risk factors, including current LDL level. This personalized approach targets each individual patient and incorporates all the patient's risk factors, helping simplify a physician's treatment decisions.

TABLE 2. AACE and NCEP treatment Recommendations.

	LDL level and intervention recommended						
Coronary Artery Disease Risk Factors	**Therapeutic Lifestyle changes**	**Pharmacologic Therapy**	**Goal LDL**				
<2	>/= 160	>/= 190	< 160				
>/= 2	>/= 130	>/= 160	< 130				
With Atherosclerotic Disease	>/= 100	>/= 130	< 100				
With Type 2 Diabetes	>/= 100	>/= 130	< 100				
Risk Factors: Smoking, Hypertension, HDL <40, Family History of CAD, Age (men >45, women >55)							

What are the harms of the drugs used to treat dyslipidemias?

As with nearly any medical therapy, there are harms associated with pharmacologic treatments used to lower lipids. They have been studied extensively with the same substantial safety monitoring and experimentation that any drug must go through to be FDA approved. The side effects associated with these medications can vary in both frequency and severity depending on drug class. For example, bile acid-binding resins are known to often cause gastrointestinal issues such as abdominal pain, flatulence, diarrhea, nausea, and vomiting[1]. Cholesterol absorption blockers like ezetimibe are also known to cause similar GI complaints[1]. Fibrates are known to cause myopathies leading to muscle breakdown and rhabdomyolysis, especially when combined with other cholesterol lowering medications such as statins[1]. Statins have been shown to increase hepatic transaminase levels, which are often used as surrogate markers for liver damage[1]. Statins are also known to cause muscle aches, cramps, creatinine kinase elevations, and rhabdomyolysis[1]. Niacin is known to have a high incidence of side effects, and is often not recommended to patients for that very reason. Its side effects can include but are not limited to flushing, liver failure, myopathies, glucose intolerance, and hyperuricemia[1]. These are just a few of the side effects commonly seen with lipid lowering medications.

Dyslipidemia in Children/Adolescents

The majority of the clinical burden of dyslipidemias occurs in adulthood; however recent research increasingly indicates that the processes of atherosclerotic cardiovascular disease may begin much earlier in life and progresses through one's life span[1,3]. In children, total cholesterol levels increase from birth, stabilize around two years of age, peak before puberty, and show a slight decline during adolescence[5].

Currently, no specific evidence exists that supports a particular level of childhood cholesterol is predictive of adult cardiovascular disease, rendering evidence-based recommendations for cholesterol screening in childhood elusive. However, research in children and adolescents demonstrates that risk factors for adult cardiovascular disease may be present as early as childhood, especially given the increasing prevalence of obesity[1]. Current estimates by the Centers for Disease Control based on data collected by the National Health and Nutrition Examination Survey (NHANES) from 1999–2006 show that up to 20.3% of children between the ages of 12 and 19 have abnormal lipid levels, including 42.9% of children that were obese[13,14].

Research has also shown that atherosclerotic lesions begin in childhood. Specifically, the Bogalusa Heart Study found atherosclerotic lesions at autopsy with increased frequency in children with increased lipid levels[1,15]. In this study, data on thousands of children and young adults was collected through cross-sectional studies to evaluate cardiovascular risk factors dating back as far as 1973[3]. Following any deaths of study subjects for any reason (mostly trauma), researchers requested permission from family members to perform autopsies on the deceased, looking for evidence of atherosclerosis in the aorta and coronary arteries[3]. The study showed that fatty streaks

of atherosclerosis could be found in the abdominal aorta at 3 years of age and coronary arteries at 10 years of age[3,4]. However, this evidence merely shows that fatty streaks can form in childhood. It fails to directly link childhood lipid levels to health outcomes in adulthood, leaving the adult coronary heart disease risk attributable specifically to dyslipidemia during childhood unknown[5].

While it is increasingly clear that cholesterol concentrations can be elevated during childhood and adolescence, no long-term studies have been able to demonstrate a direct relationship between lipid levels measured in childhood and coronary heart disease and cardiovascular related death in adults[4]. Parts of the Bogalusa studies followed their patients for up to 17 years[3], but this would still put the oldest patients in the study in their mid-30s at last follow-up, at least a decade short of when the majority of cardiac related deaths would start to occur. Further, many of the drug trials in children demonstrate through serum cholesterol measurements that the medications being used are effective at lowering serum cholesterol levels. However, these studies do not follow their subjects into adulthood to determine whether this reduction in serum cholesterol levels actually reduces heart disease deaths.

A recent cohort study performed by Dr Paul Franks and his colleagues followed over 4,800 children from an Indian reservation through the age of 55 in an effort to link causes of death to obesity and metabolic syndromes such as dyslipidemia and hypertension in childhood[16]. The study did show that premature death from all "endogenous" causes (cause was disease or self-inflicted injury) was 73% more common in the highest BMI group than the lowest BMI group, however there was no correlation when they looked at cholesterol levels[16]. Also, no specific comparisons were made for

cardiac related deaths only. This lack of evidence further increases questions on whether treating cholesterol in childhood has any effect on reducing cardiac related deaths in adulthood.

For now, we are left to speculate on the relationship between lipid levels in childhood and the ultimate outcome of interest, cardiovascular related mortality in adulthood. It is logical to assume that children with cholesterol problems would become adults with cholesterol problems, and some research has shown that between 40-55% of children with dyslipidemias go on to become adults with dyslipidemias[4]. Given that adults with cholesterol problems are at higher risk for heart disease, one could speculate that these children would be at higher risk in adulthood. However, it is also important to consider the other side of that same argument. As approximately 50% of children with dyslipidemias go on *not* to have dyslipidemias in adulthood, is it necessary to treat *all* children with dyslipidemias, especially given the lack of evidence that this intervention reduces cardiac related deaths in adulthood?

With all of these arguments in mind, the potential relationship between childhood and adult dyslipidemias has been deemed enough evidence by some children's healthcare organizations place an emphasis on primary prevention of dyslipidemias via screening in childhood[1,4]. Optimal screening programs would identify persons with progressive atherosclerosis that are most at risk of cardiovascular disease in adulthood. However, we currently lack noninvasive, inexpensive clinical tools to look for atherosclerosis, leaving serum cholesterol levels as a surrogate marker to calculate long-term risk[1]. This lack of direct evidence continues to be a point of contention, further clouding the picture. The lack of direct evidence also results in different opinions on whether or not screening in

childhood should be conducted, as demonstrated by the varying recommendations given by medical agencies that can be found below.

How do experts define dyslipidemia in children?

The currently available definitions for dyslipidemia in children do not vary greatly from those definitions in adults, and are also constructed to identify patients who would theoretically be at higher risk for cardiovascular related morbidity and mortality. The parameters currently used for dyslipidemias in children were created following the Lipid Research Clinics Prevalence Study conducted in the 1970s, which studied population distributions of lipid levels in children and adolescents[5,17]. In pediatric patients, dyslipidemia is commonly defined as a total cholesterol level of >200mg/dL and LDL >130mg/dL, as these values correspond to the 95th percentile as observed in the Lipid Research Clinics Prevalence Study[5,17]. The American Heart Association has gone on to define triglyceride concentrations of >150mg/dL and HDL concentrations of <35mg/dL to also be considered abnormal in children and adolescents[1]. Like adults, screening is performed by measuring total cholesterol and HDL concentrations via fasting or non-fasting blood sample; however it is important to note that triglyceride and LDL levels can only be calculated or measured accurately if a fasting sample is taken[5].

What methods are used for treating dyslipidemias specifically in children?

The current treatment modalities used for the treatment of dyslipidemias in children do not vary greatly from those used in adults found on page 6 above. Many recommend therapeutic lifestyle changes including diet and exercise as the first line approach, followed by pharmacologic intervention[1,4,18]. However, evidence has shown that therapeutic lifestyle changes have minimal effectiveness in children, leaving many providers instead to opt for the pharmacological approach[5]. The lipid-lowering medications currently used in children include statins, fibrates, cholesterol absorption blockers, niacin, and bile acid-binding resins. The most commonly used medication class is the statins, while the least commonly used medications are the fibrates and niacin due to their side effect profiles as noted in adults[1]. The side effect profiles for all of these medications in adults and children are thought to be similar, however current research is limited. Using available research studies where these medications were used in children, we conducted a systematic review to better look at these effects. Results can be found below.

Current Recommendations for Screening in Children/Adolescents

In light of this background information, the current recommendations for screening and treating children for dyslipidemias put out by varying organizations can be found below.

American Academy of Pediatrics (AAP)

The newest set of recommendations for pediatricians, released in 2008, requests that pediatricians initiate a "lifelong approach" to cardiovascular disease prevention in their patients by tracking lipid levels and the progression of atherosclerosis into adulthood[1]. While the AAP readily admits that firm evidence-based recommendations for cholesterol screening in children are not currently available, they also think that increased cholesterol concentration in childhood increases the risk of later cardiovascular disease[1]. The AAP's newest recommendations suggest cholesterol screening for all overweight children, as targeted screening only towards persons with a positive family history missed somewhere from 30% to 60% of the population that needed screening[1]. The specific recommendations of the AAP, as taken from *Pediatrics*, the official journal of the AAP, states the following[1]:

1. The population approach to a healthful diet should be recommended to all children older than 2 years according to Dietary Guidelines for Americans. This approach includes the use of low-fat dairy products. For children between 12 months and 2 years of age for whom overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or CVD, the use of reduced-fat milk would be appropriate.

2. The individual approach for children and adolescents at higher risk for CVD and with a high concentration of LDL includes recommended changes in diet with nutritional counseling and other lifestyle interventions such as increased physical activity.

3. The most current recommendation is to screen children and adolescents with a positive family history of dyslipidemia or premature (</=55 years of age for men and

</=65 years of age for women) CVD or dyslipidemia. It is also recommended that pediatric patients for whom family history is not known or those with other CVD risk factors, such as overweight (BMI >/=85th percentile, <95th percentile), obesity (BMI >/=95th percentile), hypertension (blood pressure >/=95th percentile), cigarette smoking, or diabetes mellitus, be screened with a fasting lipid profile.

4. For these children, the first screening should take place after 2 years of age but no later than 10 years of age. Screening before 2 years of age is not recommended.

5. A fasting lipid profile is the recommended approach to screening, because there is no currently available noninvasive method to assess atherosclerotic CVD in children. This screening should occur in the context of well-child and health maintenance visits. If values are within the reference range on initial screening, the patient should be retested in 3 to 5 years.

6. For pediatric patients who are overweight or obese and have a high triglyceride concentration or low HDL concentration, weight management is the primary treatment, which includes improvement of diet with nutritional counseling and increased physical activity to produce improved energy balance.

7. For patients 8 years and older with an LDL concentration of >/=190 mg/dL (or >/=160 mg/dL with a family history of early heart disease or >/=2 additional risk factors present or >/=130 mg/dL if diabetes mellitus is present), pharmacologic intervention should be considered. The initial goal is to lower LDL concentration to <160 mg/dL. However, targets as low as 130 mg/dL or even 110 mg/dL may be warranted when there is a strong family history of CVD, especially with other risk factors including obesity, diabetes mellitus, the metabolic syndrome, and other higher-risk situations.

US Preventive Services Task Force

The US Preventive Services Task Force (USPSTF) determined that there was good evidence that children with lipid disorders are at higher risk for becoming adults with lipid disorders, with some studies showing that up to 45-60% of children with dyslipidemias on to become adults with dyslipidemias[4]. However, the Task Force also concluded that there are critical research gaps with respect to benefits of screening and treatment on long term reduction of cardiovascular disease, harms of potential pharmacologic interventions, or that diet or exercise interventions in childhood lead to

improved lipid levels or better outcomes in adulthood[5]. The Task Force agreed that children with familial dyslipidemias would be most likely to benefit from screening, but also determined that information acquired through family history could be unreliable and failed to detect somewhere between 30% and 60% of children with elevated lipid levels[4,5]. Further, drug treatment of dyslipidemias in childhood has only been shown to be effective specifically in familial monogenic dyslipidemias, and intensive diet therapy and counseling were shown to only be effective up until cessation of counseling[4].

With all of this in mind, the Task Force failed to find sufficient evidence to recommend for or against screening, and gave lipid screening in children/adolescents less than age 20 an "I" (insufficient) ranking[5], and concluded overall that the effect of screening and treatment of childhood dyslipidemia with respect to prevention of cardiovascular disease and death in adulthood could not be addressed because of lack of evidence and long term studies[4].

American Heart Association

The American Heart Association revised its most recent set of guidelines with respect to dyslipidemia screening and treatment in children and adolescents in 2007. Their initial recommendations, made in 2003, suggested that screening occur only in patients with a positive family history[1]. Specifically, children greater than two years of age with a family history of early heart disease (<55 years) should receive a fasting lipid screening, while those whose parents had a total cholesterol level of >/=240 mg/dL should receive a total cholesterol screen[19]. In 2007, the recommendations were updated to recommend screening to all children who were overweight or obese, regardless of

family history[5]. The guidelines also lay out an ideal diet consisting of fruits, vegetables, whole grains, fish, low-fat dairy products, reduced intake of fruit juice and sugar-sweetened drinks, and reduced salt in combination with increased physical activity in order to help reduce lipid levels and fight obesity in childhood[1].

American Academy of Family Physicians

When treating children, it is also important to consider the opinions and guidelines of family practitioners, as they also treat a large portion of the pediatric population. One of the most recent articles published with respect to lipid screening and treatment in the American Family Physician[19], the journal of the American Academy of Family Physicians, did not lay out any specific recommendations for their practitioners. Instead, the article presented the recommendations of the American Heart Association, the American Academy of Pediatrics, and the US Preventive Services Task Force[19]. However, the articles does state that it is likely that the number needed to treat to prevent one premature death from this condition would be extremely high and involve years of treatment for many persons who would not benefit[19], a key point that is overlooked by the AAP in their most recent recommendations. According to the Framingham study, the risk for having a heart attack greatly increases at 55 years of age in men and 65 in women[7], meaning that treatment would have to occur for decades in order to help reduce the risk. Further, as it is unknown what percentage of children with dyslipidemias would actually suffer from heart disease related death if untreated, it is impossible to know what percentage of children would receive unnecessary treatment and suffer any possible harms the treatments may cause.

The article goes on to present numerous resources to be used by providers on the subject, and stresses the importance of physical activity and healthy lifestyle in helping fight the obesity epidemic in the United States, saying: "Family physicians should be advocates in their communities for changes that promote building physical activity into daily life. Such changes include programs that encourage children to walk and bike to school; efforts to build sidewalks, greenways, and bike paths; planning for healthy, walk-able neighborhoods; and support for the development of parks and playgrounds" [19].

Focused Clinical Question

In light of this background information, it is apparent that there is some evidence to suggest that abnormal lipid levels do develop in childhood and may continue into adulthood. However, it is unclear as to whether screening and treating these disorders in childhood will result in any changes in our most important outcomes measure: reduction in cardiovascular related mortality in adulthood. Even though no intervention in childhood has been proven to be beneficial in reducing cardiac mortality in adulthood, there is a logical basis for why it could be beneficial and should be considered if there is no harm caused by the treatment itself. With that in mind, we found and applied the available evidence in an effort to answer a related question that may help in making the decision as to whether we should treat lipid disorders in childhood. Specifically, in children/adolescents with dyslipidemia, what are the harms associated with pharmacological therapy when compared to control groups that use no intervention, therapeutic lifestyle changes, or placebo?

METHODS

Population

To properly study the harms associated with pharmacological treatment in children vs. placebo or non-pharmacologic therapy, we chose to study a population comprised of children ages 0 to 18 years. We selected this age group because current treatment recommendations are unclear, varying from one professional group to the other. We focused our study on this population in an effort to compile these studies and create a result with much more power.

Following review of the papers pulled for full article review, we limited the population to those persons in which the lipid disorder was the primary medical condition. We did not include studies in which the majority of the patients had other debilitating illnesses, as these disturbances would be more likely to contribute to adverse events when compared to the pharmacologic interventions themselves, which is the goal of our study. For example, illnesses resulting in kidney or liver failure were specifically not considered, as these disturbances would most likely be responsible for multiple other morbidities and increase the likelihood for complications with any pharmacologic intervention as they are the major organs responsible for drug metabolism.

Intervention

We focused our literature review on pharmacologic therapy with lipid-lowering or altering agents. Specifically, drug classes to be included are: statins (HMG co-A Reductase Inhibitors), fibrates, niacin, bile acid sequestrants, and cholesterol absorption blockers. We did not consider procedural interventions such as plasma exchange,

apheresis, and liver transplantation that have been previously tried. The pharmacologic interventions mentioned will be compared to individuals managed conservatively with therapeutic lifestyle changes such as diet and exercise, individuals taking a placebo, or individuals to whom no intervention is given.

Outcomes

The outcomes we examined were adverse events related to treatment with these agents in our population. The term "adverse events" can be very broad and encompass numerous different outcomes, so we chose to focus on those events that most directly related to treatment or were common side effects of the medications as demonstrated in adults. Outcomes we considered included allergic reactions, muscle myopathies/myalgias, liver or renal failure, excessive flushing, other skin rashes, GI distress requiring hospitalization or medical treatment, anxiety or depression requiring psycho-social therapy or medical treatment, adverse drug interactions, or any other serious side effect associated with the pharmacologic interventions being studied. Any laboratory anomalies reported were also included. Side effects included could be reported by the patient, researcher, or treating physician.

Time Frame

Though many of the pharmacologic agents currently used to treat lipid disorders have been available for decades, the statin class was not introduced to the United States' market until 1987[20]. Given that statins are currently the most commonly prescribed agents for lipid disorders in the United States, we chose to focus our search for studies

that have been published within the statin era. Additionally, each study included had to have participants enrolled, on treatment, and followed for at least one month during the intervention.

Publication Types

To maximize the usefulness of this review to the medical field, only primary research studies were considered. No editorials, reviews, or letters were evaluated or included in our review. Specific study types that were included were randomized controlled trials and cohort studies as they employ control groups to help lower potential for confounding and various other biases, thus allowing them to show associations in the relationship between intervention and outcome. Cross-sectional and open label studies were also considered, but their inclusion was dependent on having sufficient control groups and meeting all other inclusion criteria. Case control studies were also considered. Only published studies were considered due to availability.

Inclusion/Exclusion Criteria

Table 3 lists the inclusion and exclusion criteria, which were based on the population, intervention, outcomes, timeframe, and publication types previously discussed. Studies included in the systematic review were published since 1987 and available in English. Each study had to give results as to adverse events in persons eighteen years of age and younger, and were not accepted if they did not specifically give adverse events for this age group separately from those occurring in older individuals. Studies focusing on those persons affected by other major medical complications that

would be likely to increase the rate of adverse events were also not considered. Only studies that included one of the pharmacologic interventions previously mentioned were included. Lastly, study types considered were randomized controlled trials, cohort studies, cross-sectional studies, and case control studies.

Table 3. Inclusion/Exclusion Criteria applied to each study.

Category	Include	Exclude
Research Designs	*Randomized controlled trial *Prospective/retrospective cohort *Cross-sectional *Case control studies	*Reviews *Letters *Editorials
Population	*Children ages 0 – 18 *Patients with dyslipidemia as primary problem	*Persons Older than 18 *Patients with homozygous familial dyslipidemias *Patients with other primary disorders
Study Characteristics	*Published Studies *Available in English *Concomitant control group *Must discuss adverse events	*Unpublished studies *Studies not available in English *Studies without concomitant control group *No discussion of adverse events
Date	*Studies published since 1987#	*Studies performed before 1987
Interventions	*Pharmacologic treatment for hyperlipidemia or dyslipidemia	*Studies without pharmacologic intervention *non-pharmacologic interventions such as plasma exchange, apheresis, or liver transplant

Note – Statins first introduced to US market in 1987

Search Strategy

NOTE: Exact search terms and limits used can be found in **Table 4**.

Databases

To fully search all the available publications and material on the topic, three separate databases were used. The decision was made to search both the Medline and EMBASE databases due to their comprehensive nature, and the International Pharmaceutical Abstracts database as the intervention we desired was pharmacologic.

Search Terms

The search terms used were targeted at achieving the desired population (age 0-18), medical affliction (some lipid disorder), and the intervention. To find the population, the terms chosen were "child" OR "adolescent" OR "pediatric". The terms aimed at capturing lipid disorders were "hyperlipidemia" OR "hypercholesterolemia" OR "dyslipidemia". Finally, multiple terms were used to include the multiple possible pharmacologic interventions for these disorders: "atorvastatin" OR "pravastatin" OR "lovastatin" OR "rosuvastatin" OR "fluvastatin" OR "simvastatin" OR "hmg CoA reductase inhibitors" OR "bile acid sequestrant" OR "cholestyramine" OR "colestipol" OR "colesevelam" OR "fibrate" OR "fenofibrate" OR "clofibrate" OR "niacin" OR "drug therapy" OR "anticholesterolemic agents" OR "antilipemic agents". This list of pharmacologic terms includes drug names, drug classes, and just drug therapies in general to be fully comprehensive. Each of the terms was separated by "OR" as

indicated, with the categories of population, disorder, and intervention all separated by "AND" in an effort to ensure that each result found included each of the three parts.

Limits

Limits were applied on the search to capture the proper time frame and ensure its availability in English. The time frame was set to include all studies PUBLISHED since January 1, 1987 up until the time of the first abstracts were reviewed on April 1, 2009.

Table 4. Exact Search Terms and Limits used.

Search Terms and Limits				
Age Terms	**Disability/Illness Terms**	**Intervention Terms**	**Limits**	
Child	hyperlipidemia	atorvastatin	Available in English	
Adolescent	hypercholesterolemia	pravastatin	Published date after January 1, 1987	
Pediatric	dyslipidemia	lovastatin		
		rosuvastatin		
		fluvastatin		
		simvastatin		
		hmg coa reductase inhibitors		
		bile acid sequestrant		
		cholestyramine		
		colestipol		
		colesevelam		
		fibrate		
		fenofibrate		
		clofibrate		
		niacin		
		drug therapy		
		anticholesterolemic agents		
		antilipemic agents		
Note: Terms in each column were separated by "OR", while the columns were separated from each other by "AND"				

Quality Criteria

The quality of each study considered for inclusion was also evaluated and graded by two reviewers per study. The decision was made to grade the quality of these studies according to Downs/Black Criteria as originally seen in the Journal of Epidemiology and Community Health in 1998 (checklist available in **Appendix 1**)[21], due to their comprehensiveness and ability to accommodate heterogeneous study types. Each study was reviewed separately by two masked individuals, who applied the Downs/Black Criteria and recorded the quality grades accordingly. The two scores assigned for each study were then averaged to give the final score. Both Pearson Pairwise Correlations and weighted Kappa values were calculated in order to help ensure there was high inter-rater agreement in quality grading.

According to the Downs/Black system, points are rewarded on the basis of parameters such as reporting of basic study demographics, disclosure of possible biases and confounders, internal and external validity measures, and up to five total points on the basis of study size/power. A total of 32 points are possible, with a higher point total indicating higher quality. Point values in the single digits would indicate studies of poor quality that contained major flaws, while studies with point totals in the mid to upper twenties and lower thirties would indicate good quality studies which have no major flaws or errors.

Article Selection

Following completion of the search of the aforementioned databases using the search strategy described, two separate researchers each read all of the titles and abstracts. Any article that could be relevant was noted and later reviewed in full. Abstracts that were not related or did not fit Inclusion/Exclusion Criteria were discarded. An article did not need to be pulled by both researchers to be reviewed, meaning that any article selected by either researcher was pulled for full text review.

Each article pulled was then reviewed independently by two separate authors or investigators, who applied the inclusion/exclusion criteria to it in order to determine whether or not it could be included in the review. If an article was deemed to pass the inclusion and exclusion criteria by both persons, it was then considered for the review. The quality criteria previously discussed were applied to these articles, and each article was given an overall numerical grade based on the results of the Down's questionnaire previously described and available in **Appendix 1**. We then abstracted results and evidence from the articles and put it into evidence tables to quantify the results and present them in a clear and concise manner. The evidence table used with results included can be found in **Appendix 2**. Following this process, each of the articles selected and evidence abstracted underwent a secondary review by two different researchers than those who originally performed the reviews to verify the appropriateness of the articles selected, ensure the quality of the articles selected, and verify that the information was properly quantified into the evidence tables. Each of the separate reviewers then met to help draw final conclusions on the data collected and determined its significance in the medical field.

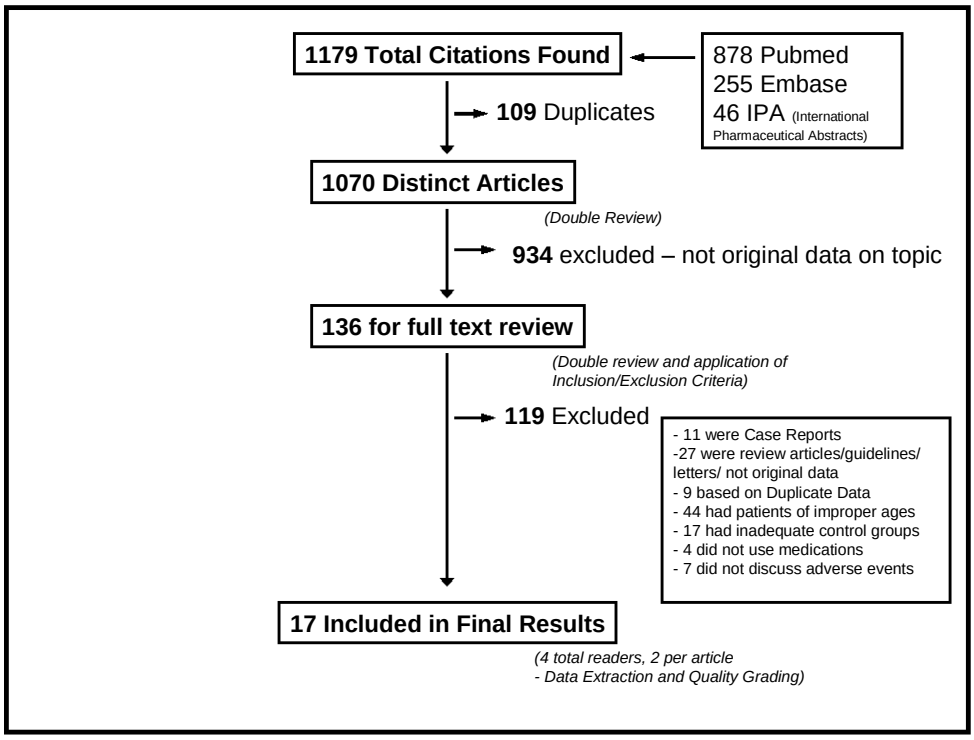
RESULTS

Search Results NOTE: Search results can be found summarized in **Figure 1**.

Using the search terms, criteria, and databases mentioned above, the initial search was performed and returned 1179 titles; 878 of those were from Pubmed, 255 from Embase, and 46 from the International Pharmaceuticals Abstracts database. A brief initial review of the title and abstracts found 109 duplicate titles, leaving 1070 unique articles for further review and application of inclusion/exclusion criteria. Each of these titles and abstracts were read by two individuals, and as previously stated, any article suggested by either reviewer that could be relevant was pulled for full text review. Of these 1070 articles, 934 were excluded for various reasons or they were not original data on the topic, leaving 136 articles that were pulled for full text review.

Each of these 136 articles was individually reviewed, and the Inclusion/Exclusion Criteria previously discussed (**Table 3**) were applied. An agreement by both researchers on each article was reached for whether or not to include each article and a reason for its exclusion. Of the 136 articles, 17 were selected for final inclusion into the systematic review. Eleven of the 109 excluded articles were excluded because they were case reports, 27 were excluded because they were review articles or guidelines not containing original data, 9 articles were based on duplicate data from already included primary studies, 44 did not fit the proper age range, 17 had inadequate control groups, four did not treat with medications, and seven had no mention of any adverse events.

Figure 1. Search Results.



Article Details and Demographics

The articles found are briefly discussed below. Full details are available in the data extraction table (**Appendix 2**).

Study Types

Of the 17 articles that met all inclusion criteria and included in the final systematic review, 9 were blinded randomized controlled trials[22-30], one was a double-armed study with randomized controlled trial and case control arms[31], one was a double-armed randomized controlled trial with blinded and open label arms[32], three were randomized controlled trials that were open label studies[33-35], one was a case control study[36], one was a prospective cohort study[37], and one was a crossover trial.[11]

Medication Class

In the 17 included articles, medication classes studied included HMG CoA reductase inhibitors (statins), bile acid sequestrants, and cholesterol absorption blockers. Eleven of the 17 articles studied statins; 10 versus placebo or diet therapy[22-27,30,31,35,36] and one as an add-on therapy to bile acid sequestrant.[11] Of the other 6 included studies, 5 explored bile acid sequestrants (4 as monotherapy[23,32-34] and one as add-on therapy to a statin[37]), and only one studied the cholesterol absorption blocker ezetimibe, which was studied as add-on therapy to a statin.[29]

Length of Follow-up

Following administration of the intervention, patients were followed for varying lengths of time. Follow-up varied from 1 month[35] up to 70 months.[34] Eight of the studies had a follow-up period of at least one year[26-28,30,32-34,36], while only three had a follow-up of three months or less.[24,25,35]

Patient Demographics

A total of 1,604 study subjects participated in the studies that were included in the final results, 897 subjects were members of the intervention group, while 707 were part of the control groups. The subjects' ages ranged from one year in one study[33] to eighteen years in four studies.[11,30,31,35] Each of the 17 studies included patients of at least ten years of age, while only three studies included patients younger than six.[33,34,36] There was a slightly higher percentage of males that participated in studies (~60% male vs. ~40% female). It should be noted however, that one study did not report sex[34], one study had only female participants[22], and two studies had only male participants.[25,27]

Study Sponsorship

Of the 17 included studies, 10 disclosed pharmaceutical sponsorship. Five studies were funded in part by contributions from Merck[22,23,25,27,29], 3 by Bristol-Myers Squibb[24,28,30], one by Pfizer[26], and one by Upjohn[32]. One of the studies sponsored by Merck was also co-sponsored by Schering-Plough Pharmaceuticals[29]. Each of the studies sponsored by Merck included a statin as either the intervention or as part of the control group, while studies funded by Bristol-Myers Squibb included both statins and

bile acid sequestrants. The study funded by Pfizer used atorvastatin as the intervention, and Upjohn funded a study on the bile acid sequestrant Colestipol.

Quality Grading

Quality grading was performed by two separate individuals according to the Downs/Black criteria (**Appendix 1**) as described in the Methods section. Scores are reported individually and as a mean in the Data Extraction form, **Appendix 2**, with a higher score indicating stronger quality of the work. Out of a possible 32, the highest average score was 26, which was the grade given to two studies[25], and ten of the seventeen studies had an average score of at least 20[11, 22-28,30,32]. The lowest average score for any study was determined to be 8[37], while no other study had a quality grade worse than 12.5. Also of note, none of the studies received additional quality points for power based on sample size according to the Downs/Black Criteria, indicating that none of the studies had adequate sample sizes to measure small differences between intervention and control groups.

To measure inter-observer reliability between quality graders, a weighted kappa value was measured and calculated. This value was found to be 0.48 ($p=0.0002$), indicating a moderate degree of agreement between observers[38]. The Pearsons Correlations were also calculated to look at inter-observer agreement between graders. All of the correlations were found to be between +0.77 and +0.95, indicating a high degree of positive relationships between the values. Ten of the 17 articles graded had a Downs/Black score difference of 2 or less (out of the possible 32) from the 2 evaluators

per study[22,25-30,35-37], while the largest single difference seen by the separate reviewers was 6 points and occurred only on one occasion[33].

Study Size

The final studies included varied greatly with respect to sample size; however, they were all smaller studies. Only six of the seventeen studies had more than 100 total subjects enrolled when you combined the control and intervention groups[25-27,29-31], and 6 of the seventeen studies had less than 50 total subjects[11,33-37]. Only 2 of the 17 studies had more than 200 total subjects[29,30], with the largest study having 248 total subjects[29]. Conversely, the smallest study had only 13 total subjects [37]. With respect to the intervention group sizes, the largest study had 140 subjects[26], while the smallest had only 4 in the intervention group[37]. Control group sizes varied from 122 subjects[29] to 8[36].

Harms Data

All safety parameters monitored for and harms found are available in Appendix 2. In total, intervention groups had 418 side effects noted as compared to 317 side effects noted in control groups (a 31.86% increase).

Statins

As previously mentioned, eleven of the seventeen studies in the final results used statins in the intervention group; ten as monotherapy[22-27,30,31,35,36] and one as an add-on therapy to a bile-acid sequestrant.[11]

The majority of these studies had extensive monitoring for harms and laboratory anomalies. All of the studies monitored subjects by physical examination and vital signs, and 10 of the eleven had some type of laboratory testing. For example, all of the studies except for two[11,36], also monitored liver function via AST and ALT and the muscle enzyme CK. Six of the studies monitored hemoglobin and hematocrit[11,22-26], three monitored thyroid function via TSH[24,25,27], five measured the androgen precursor DHEAS[22,23,25,27,30], five monitored cortisol [22-25,30], and four monitored LH/FSH[22,23,27,30]. Other studies monitored routine serum chemistries[11,23-25], bilirubin levels[24,25], urinalysis[23,25], measured menstrual cycle lengths[22,30], or paid special attention to sexual maturation[27,30].

It is important to note however, that not all of the studies indicated that they regularly questioned patients for adverse events/side effects. Two of the studies[30,31] make no mention of patient reported harms, and three additional studies reported the harms only as reported through the physician[24,27,35,36], though there is indication that the

physicians in these studies were asking patients about possible side effects. The remaining five studies specifically mentioned harms as reported directly from the patients[11,23,25,26].

Overall, the side effects in statins were very similar to those found in the control groups. In total, there were 283 recorded adverse events in the intervention groups where statins were used vs. 191 in the control groups (NOTE – there were 561 total patients in intervention groups vs. 387 in control groups). Two of the statin studies found no side effects[31,36], another found only two cases of elevated AST and ALT[35], and a fourth study found only four elevations in CK that were not accompanied by muscle pain or myalgias[30]. Seven of the eleven total studies investigating statins showed elevations in either AST/ALT or CK[23-27,30,35], while only two of the nine studies that measured AST, ALT, and CK did not find any elevations. Elevations in AST/ALT ranged from 3 times the upper limit of the normal value[23] to 10 times the upper limit of the normal value[35]. Subjects in four of these studies experienced cramps or muscle pains[11,23,25,27], three of which were accompanied by CK elevations more than 2 times the upper limit of normal[23,25,27]. The fourth study did not measure CK as part of their safety parameters.[11] Subjects receiving statins experienced GI complaints such as 2 total incidences of flatulence and bloating[11,23], 4 experienced nausea and vomiting[22,24], 4 experienced diarrhea[22,27], one subject had constipation[11], and one subject had heartburn[25]. However, the incidences of these harms were relatively similar to their control groups, with 5 patients experiencing flatulence, 3 persons experienced nausea and vomiting, 2 experienced diarrhea, 8 experienced constipation, and one experienced heartburn. In addition, twenty total subjects in both the intervention and control groups of six of studies

experienced incidences of abdominal pain[11,22-24,26,27,]. It is also worth noting that of the side effects in control groups, all five of the patients with flatulence, 7 of the eight with constipation, and 8 of the 20 with abdominal pain were subjects in the dual therapy study, where the control group was taking colestipol monotherapy.[11] Studies also reported that patients experienced many generalized complaints including headache, fever, fatigue, sleep disorders, and skeletal pains, all of which are listed and quantified in Appendix 2.

It is important to note however, that while these finding were all noted and were found at slightly increased rates when compared to control groups, almost none of them were found to be statistically significant, due largely to the small study sizes. However, there were several studies that found side effects of statins that were statistically significant when compared to control groups. The study conducted by Lambert et al. showed statistically significant increases in both AST and CK in the intervention group, as well as statistically significant increases in the androgen precursor dehydroepiandrosterone sulfate (DHEAS) [25]. AST and CK were 17% elevated in the intervention group, with a P value of p=0.0008, while DHEAS level was decreased in the 10mg dosing group (p=0.0165) [25]. This study also found statistically significant changes in cortisol; it increased cortisol levels in the intervention group at lower doses (p=0.0099) and decreased it at higher dosages (p=0.0206) [25]. Two other studies also showed statistically significant changes in DHEAS, both showing statistically significant decreases when compared to control groups, both with P values less than 0.05[23,27]. In total, five of the studies that used statins as the intervention group measured DHEAS[22,23,25,27,30], three of which showed statistically significant alterations in levels in the intervention group[23,25,27].

There was one additional study that demonstrated statistically significant differences between intervention and control groups[22]. This study showed statistically significant decreases in systolic blood pressure and LH (Leutinizing Hormone) in the placebo group as opposed to the intervention group. These decreases in the control group created statistically significant differences between control and intervention group, but there were no changes at all noted in these parameters in the intervention group.

With respect to the absolute number of physical complaints, studies did demonstrate increased numbers of patient complaints in the intervention groups when compared to their controls. There were 216 total physical complaints in the intervention group, compared to 152 in the control group. This increased number of complaints was not statistically significant, but they were found to be higher in all but two of the seven studies that reported finding physical complaints[11,30], leaving their clinical significance uncertain.

Bile Acid Sequestrants

Five of the seventeen studies included in the final results used a bile acid sequestrant as the intervention; four as monotherapy vs. placebo or diet control[28,32-34,], and one in combination with a statin vs. statin monotherapy as the control group[37]. Two of the five studies used the bile acid sequestrant colestipol[32,33], while the other three used the bile acid sequestrant cholestyramine [28,34,37].

Each of these studies looked at various harms. One study looked only at height and weight measurements[33], while others were much more extensive, looking at serum levels of Vitamins A, B12, D, and E, liver function tests (AST/ALT), sexual maturation

and hormones, hematology, thyroid studies, bone age, iron studies, folate, zinc, and carotenoids. Only two of the five studies made note of patient reported physical complaints[28,32].

Safety monitoring revealed that two of the five studies showed increased occurrences of multiple GI side effects, side effects which included: three cases of abdominal pain, one case of flatulence, two cases of constipation, three cases of diarrhea, four instances of nausea, one episode of vomiting, one case of heartburn, one case of loss of appetite, and even one case of intestinal obstruction, though this was not thought to be secondary to the intervention[28,32]. Patients in control groups only experienced 1 episode of vomiting and two episodes of abdominal pain[28]. Two of the studies also showed minor changes in weight when compared to the control group[32,34], and both of the studies that monitored folate levels showed increases in folate[28,32]. One study noted a statistically significant increases in homocysteine, with P value <0.05[28]. Two of these studies reported no adverse events[33,37].

Cholesterol Absorption Blockers

Only one study included in the final results used a cholesterol absorption blocker (ezetimibe) as the intervention, and it used ezetimibe 10mg in combination with a statin as the intervention, while placebo in combination with a statin was used as the control[29]. With respect to harms, researchers monitored physical exam findings such as height, weight, menstrual cycle or menstrual changes, and any physical complaints[29]. They also monitored laboratory tests such as CBC, serum chemistries (BMP/CMP), thyroid function, sex hormone levels, protein, albumin, electrolytes such as calcium and

phosphorus, liver function tests (AST/ALT), CK levels, and monitored kidney and urinary changes via routine urinalysis[29].

This strict monitoring found increased levels of side effects and differences in laboratory tests in the intervention group when compared to the control group. Specifically, there were increased levels of GI side effects such as abdominal pain (6 vs. 3), nausea (8 vs. 4), and diarrhea (9 vs. 3) [29]. The intervention group also showed increased CK levels on laboratory testing and increases in ALT levels (6 vs. 3) [29]. There were also various episodes of other physical complaints such as headache, acne, flu-like symptoms, sinusitis and pharyngitis, which were found in comparable numbers in both intervention and control groups[29].

With that in mind, there was one statistically significant harm found when comparing ezetimibe and statin combination therapy to the control group of statin monotherapy: myalgias[29]. In the intervention group, 5.6% of patients experienced myalgias, compared to only 0.8% of the control group ($p = 0.03$) [29].

CONCLUSIONS/DISCUSSION

When considering the problem of dyslipidemias in children, there are two major factors that should be considered; whether screening should be performed routinely for lipid abnormalities in childhood and whether treatment should be initiated if a dyslipidemia is found.

When determining to what degree screening for dyslipidemias in children should be performed, there seems to be two different schools of thought. As found and detailed in pages 18-19 above, the AAP favors a wider-scaled screening approach. The AAP's recommendations are somewhat supported by the evidence, however the evidence is not strong enough to recommend the wide-scale screening that the AAP indicates. For example, in their recommendations #3 and #4, the AAP recommends that all overweight children should be screened between the ages of 2 and 10. They make these recommendations on the evidence from the Bogalusa Heart Study[3], which as previously discussed found atherosclerotic lesions in children at autopsy developing at a young age. However, it should be noted that no reliable screening mechanism currently exists that can look directly for atherosclerosis in large or small vessels, leaving serum cholesterol levels as our only screening tool.

The AAP also made their recommendations on the basis of evidence found in studies by Dr Tamir et al[39] and Dr Hickman et al[14]. Dr Tamir's work in the Lipid Research Clinics Program Prevalence Study showed that serum lipid levels increase in childhood until the age of 2, at which point they reach "similar" levels to those seen in young adults[39]. Dr Hickman's work as part of the Third National Health and Nutrition

Examination Survey (NHANES) showed that total cholesterol levels usually peaked between 9 and 11 years of age at approximately 171mg/dL[14].

Further research performed by Dr Hickman and colleagues as part of NHANES showed that cholesterol levels decrease from these levels during pubertal development by approximately 10mg/dL on average and slowly increase into adulthood[14]. Given that these levels often decrease without intervention, with some studies showing that approximately half of dyslipidemic children will not be dyslipidemic as adults[4], testing during this time period is likely not necessary on the wide-scale basis that the AAP recommends. Further, while some of the studies used by the AAP in creating their guidelines did find a correlation between serum lipid levels in childhood and adulthood[40], none of these studies, nor any other cited by the AAP demonstrate a correlation between serum lipid concentrations in childhood and cardiac-related death in adulthood. Also, no study to date has demonstrated that treatment of children with dyslipidemias reduces cardiac-related death in adulthood**.** These sentiments are shared by the USPSTF, who also concluded that currently available evidence is insufficient to recommend screening on a wide-scale basis[5].

With respect to treatment of lipid abnormalities in childhood, the evidence found in available studies suggests that children using lipid-lowering medications have increased absolute numbers of side effects compared to children using placebo, therapeutic lifestyle changes, or no intervention (418 events/laboratory anomalies vs. 317). The studies also demonstrate that the side effect profiles in children of each medication subclass are comparable to those found in adults, however the overall lack of data is a major issue and makes this a difficult conclusion to make. As expected given

their side effect profiles in adults, statins gave increased muscle symptoms such as pain, cramping, and myopathies, and showed elevations of the liver enzymes AST and ALT on serum testing. Bile acid sequestrants such as colestipol and cholestyramine showed increased numbers of gastrointestinal symptoms such as abdominal pain, diarrhea, constipation, nausea, vomiting, bloating, and flatulence. The one study using the cholesterol absorption blocker ezetimibe showed increased incidence of myalgias.

As previously noted however, only five of the seventeen total studies found statistically different numbers of side effects, despite the consistent trends in that direction. There are many reasons that could explain a lack of statistically significant findings in these studies. The first and most obvious explanation would be because there truly are no differences between control and intervention groups, and that the side effects experienced would have occurred even without medical treatment. However, given the limited number of available studies, the limited number of study participants, and shorten length of both intervention and follow-up, it is possible that differences do indeed exist but are not readily apparent due to these study limitations.

Though the studies showed increased numbers of side effects in the intervention groups, the limited size and duration of these studies also make it difficult to determine whether these studies have any true clinical significance that would affect treatment decisions made by practicing clinicians. A clinician may look at these studies, see a higher number of absolute events, and decide not to use a medication in a child. However, the percentage of events occurring in intervention group vs. control groups was similar, which could lead another physician to assume the medications were safe in children and prescribe them for treatment. The combined lack of statistical significance

and unknown clinical experience makes treatment decisions that clinicians make on a regular basis challenging.

Another issue that may explain the lack of differences may be the lack of standardized reporting and measuring of harms. As mentioned above, some of the studies went through extensive protocols to monitor patients for laboratory anomalies and physical complaints, while others checked only height and weight. The studies that regularly asked patients about physical complaints and had more extensive laboratory monitoring reported more adverse events, while those that undertook less strenuous monitoring reported less harms and or no harms at all. More strenuous monitoring and following of patient reported harms should be used in safety studies in the future to fully gauge the number of side effects these medications could be causing.

Another key issue with available research is the short length of medication usage and follow-up. Subjects in the included studies received at most 5 years of treatment while they were being followed, while in fact these interventions would likely need to be continued for decades in order to reduce cardiac events. For example, 3 of the 5 studies that looked for it found statistically significant alterations of dehydroepiandrosterone sulfate (DHEAS) with statin usage. It currently remains uncertain as to whether these were solely laboratory abnormalities or whether there is actually potential for morbidity such as stunted growth and maturation or precocious puberty over longer time periods. To determine this, patients taking statins would need to be monitored until they had finished growth, development, and sexual maturation. This would take longer than the 5 years or less over which all seventeen of these studies were conducted.

In short, the debate about whether treatment of lipid disorders is appropriate in children continues to be complicated. The research found shows that there are inherent risks in pharmacologic therapies for these lipid disorders; however the degree of these risks is still uncertain, especially over long periods of use. On top of all of this, the decision of whether treatment should be initiated continues to remain complicated by the lack of long term data and proof that treatment in childhood actually reduces morbidity and mortality further down the road. The studies show that these drugs are effective in lowering cholesterol in children; however it is unclear if they lower the incidence of or have any effect at all at preventing death and heart disease once these children reach adulthood. Medication usage would need to be used for decades in order to determine if there is truly any reduction of cardiac mortality. No study available comes close to following patients for that duration of time for efficacy or safety, making the decision to initiate therapy a difficult one to make based on current research.

Unfortunately, we are currently left wondering if these drugs truly reduce cardiac-related mortality, and if the benefits actually outweigh the harms. Ideally, pediatric patients being treated with lipid-lowering medications would be followed from initiation of therapy until death with regular physician monitoring for side effects, measurements of lipid levels, and autopsy to determine cause of death, and would be matched to control patients undergoing similar monitoring. Obviously, this would be difficult to do from a monetary and feasibility standpoint, and has not been done to date. Given the feasibility and difficulty of any prospective studies, harms data and longer term follow-up data may be more easily attainable and studied through retrospective review of large databases, such as an HMO database, that would likely contain millions of children and their

medical records. A retrospective study like this would help reduce cost and be less time consuming, however retrospective reviews entail their own problems, especially with respect to limiting possible biases and capturing clinically relevant variables that are often missed.

The overall lack of current evidence for or against the use of these medications raises a larger point: How much evidence is needed before any new intervention should be used and incorporated into everyday practice? Are short term studies for safety and efficacy sufficient to support the use of an intervention needed for a much longer time period? What size studies are sufficient to allow for implementation of interventions that will be used on a wide-scale basis? What type of studies must be done in order to prove an intervention is both safe and effective? Randomized controlled trials are often thought to be the "gold standard", but are other study types acceptable? How "sure" must we be before we start and intervention?

These are all very relevant questions across all fields of medicine, and all are difficult to answer. Many would immediately point to the meteoric rise and fall of the use of COX-2 inhibitors as a prime example of the need for more extensive research before incorporating an intervention into everyday practice. However, others could point to the use of penicillin or various vaccines as interventions that saved thousands of lives and are still used, despite their incorporation into "everyday" usage without extensive long-term research prior to their incorporation into routine care. These examples are just a couple of the many that could be used to argue either side of this challenging issue, an issue that currently lacks a clear solution or immediate answers.

Obviously, more research is preferred whenever possible before an intervention is initiated. However, this research takes time, money, and effort that may not be readily available, especially when the intervention in question would be used over an extended period of time. When the intervention in question could potentially save lives on a wide-scale basis, the pressure to implement the intervention in question will continue to mount, even if research is not readily available.

In the face of the ongoing obesity epidemic and the millions of cardiac-related deaths annually, this is the case with screening for and treatment of dyslipidemias in children. For the time being, decisions on whether to treat and screen for dyslipidemias continue to remain a complex but necessary decision that physicians face. Given the lack of current evidence to the contrary and the recent recommendations by the AAP, the medications used to treat dyslipidemias will likely continue to be used. However, should a physician decide to treat a child with abnormal serum lipid levels with medications, monitoring should be performed in order to assure that the medications are not causing otherwise avoidable harms. Physicians should continue to check with both children and their parents for new physical complaints at routine visits. Lastly, children currently on these medications should continue to be followed, if possible into adulthood, to examine whether cardiac related morbidity and mortality are reduced in an effort to help shed further light on the subject.

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APPENDIX I

The Downs/Black Checklist for measuring study quality[21].

Reporting
1. *Is the hypothesis/aim/objective of the study clearly described?*

yes 1
no 0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*
If the main outcomes are first mentioned in the Results section, the question should be answered no.

yes 1
no 0

3. *Are the characteristics of the patients included in the study clearly described?*
In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

yes 1
no 0

4. *Are the interventions of interest clearly described?*
Treatments and placebo (where relevant) that are to be compared should be clearly described.

yes 1
no 0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*
A list of principal confounders is provided.

yes 2
partially 1
no 0

6. *Are the main findings of the study clearly described?*
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

yes 1
no 0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*
In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes 1
no 0

8. *Have all important adverse events that may be a consequence of the intervention been reported?*
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

yes 1
no 0

9. *Have the characteristics of patients lost to follow-up been described?*
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

yes 1
no 0

10. *Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

yes 1
no 0

External validity
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*
The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

yes 1
no 0
unable to determine 0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*
The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

yes 1
no 0
unable to determine 0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*
For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

yes 1
no 0
unable to determine 0

Internal validity - bias
14. *Was an attempt made to blind study subjects to the intervention they have received?*
For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

yes 1
no 0
unable to determine 0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

yes 1
no 0
unable to determine 0

16. *If any of the results of the study were based on "data dredging", was this made clear?*
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

yes 1
no 0
unable to determine 0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?*
Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

yes 1
no 0
unable to determine 0

18. *Were the statistical tests used to assess the main outcomes appropriate?*
The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

yes 1
no 0
unable to determine 0

19. *Was compliance with the intervention/s reliable?*
Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

yes 1
no 0
unable to determine 0

20. *Were the main outcome measures used accurate (valid and reliable)?*
For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

yes 1
no 0
unable to determine 0

Internal validity - confounding (selection bias)
21. *Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?*
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.

yes 1
no 0
unable to determine 0

22. *Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?*
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

yes 1
no 0
unable to determine 0

23. *Were study subjects randomized to intervention groups?*
Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.

yes 1
no 0
unable to determine 0

24. *Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*
All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

yes 1
no 0
unable to determine 0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*
This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

yes 1
no 0
unable to determine 0

26. *Were losses of patients to follow-up taken into account?*
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

yes 1
no 0
unable to determine 0

Power

27. *Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*
Sample sizes have been calculated to detect a difference of x% and y%.

Size of *smallest* intervention group
A <n1
0
B n1–n2 1
C n3–n4 2
D n5–n6 3
E n7–n8 4
F n8+ 5

APPENDIX 2