Published in final edited form as:

Curr Diab Rep. 2014 July ; 14(7): 499. doi:10.1007/s11892-014-0499-8.

Risks and benefits of statin use in young people with type 1 diabetes

Petter Bjornstad, M.D.¹, R. Paul Wadwa, M.D.^{1,2}

¹Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

²Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, CO

Abstract

Cardiovascular disease (CVD) is the primary cause of mortality in patients with type 1 diabetes (T1D). Despite advances in the management of microvascular complications of T1D there is a lack of similar progress in reduction of macrovascular complications. Dyslipidemia is one of the major contributory factors for macrovascular complications in T1D, but the literature suggests significant under-treatment of this risk factor in children and adolescents with diabetes. Statins have shown to be both effective and safe in young people with familial hypercholesterolemia and adults with diabetes mellitus, but the role for statins in children and adolescent with T1D remains unclear and controversial. In this review, we will summarize the risks and benefits of statin use in young people with T1D.

Keywords

Dyslipidemia; type 1 diabetes; statins; lipid-lowering medications; macrovascular complications; microvascular complications

Introduction

The incidence of type 1 diabetes (T1D) is increasing worldwide and particularly in children under the age of 5 years of age, with one quarter of patients being diagnosed between 5 and 10 years of age (1). Cardiovascular disease (CVD) is the primary cause of mortality in patients with T1D (2) with studies demonstrating a 10–30 fold increased risk of CVD (3, 4) in this at risk population. The major contributory factors for CVD in T1D include dyslipidemia, hypertension, hyperglycemia, insulin resistance and obesity (5, 6). Despite advances in the management of microvascular complications of T1D (7, 8) there is a lack of similar progress in reduction of macrovascular complications (8).

Dyslipidemia is an important and potentially modifiable CVD risk factor in children and adolescents with T1D. It is increasingly recognized that atherosclerosis begins early in life

Address all correspondence to: R. Paul Wadwa, M.D., Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, 1775 Aurora Court, Aurora, CO 80045, Phone: 303.724.2323, Fax: 303.724.6779, Paul.Wadwa@ucdenver.edu.

Author Contributions

PB wrote, contributed to discussion, and reviewed/edited the manuscript; RPW wrote, contributed to the discussion, and reviewed/edited the manuscript.

in association with dyslipidemia and tracks into adulthood in people without diabetes (9, 10). For adults with T1D, statin therapy is considered critical both in primary and secondary prevention of CVD (11). A recent meta-analysis in adults with T1D showed that 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C was associated with 21% reduction in major vascular events (12). Despite the encouraging findings in adults there is evidence of under-treatment of dyslipidemia in children and adolescents with T1D (5, 6, 13), as illustrated by Diabetes-Patienten-Verlaufsdokumentation (DPV)-data where only 0.4% of 27,358 children with T1D received lipid-lowering medical treatment, despite 28.6% meeting criteria for dyslipidemia (5).

In this review, recent data and current recommendations on statin therapy in youth with T1D will be reviewed. We will also review the risks and benefits of statin therapy in young people with T1D, and thereby explore whether pediatric providers are justified in their cautious approach to stating statins in this age group.

Dyslipidemia in children and adolescents with T1D

Diabetic dyslipidemia, Fredrickson phenotype V, is classically characterized by elevated chylomicrons, VLDL, total cholesterol and triglycerides (14). Children and adolescents with T1D demonstrate a significant amount of dyslipidemia. Schwab et al reported dyslipidemia in 28.6% in young subjects with T1D (<26 years olds) (5). Similarly, Maahs et al. demonstrated sustained abnormalities of total cholesterol, HDL-C and LDL-C over 10 years in children and adolescents with T1D, with 28% and 11% having LDL-C levels 160 and 190 mg/dL respectively (15). They also reported that 40–63% of children with abnormal lipids remain abnormal, thereby showing that the lipid abnormalities track from childhood to adulthood (15).

Clinically apparent vascular complications are rarely diagnosed in children and adolescents with T1D. Although vascular complications of T1D rarely manifest prior to puberty (16), it is recognized that atherosclerosis begins in childhood in association with dyslipidemia, as evident by landmark studies such as the Bogalusa Heart Study (10), the Muscatine Study (17), the Young Finns Study (18), and the Pathobiologic Determinants of Atherosclerosis in Youth (PDAY) (9).

The PDAY Study demonstrates that dyslipidemia is associated with arterial fatty streaks and fibrous plaques in youth (9). Furthermore, the Bogalusa Heart Study reported agreement between fatty streaks and LDL-C, and that evidence of atherosclerosis was seen during childhood in up to 50% of cases (10). In the Young Finns Study, Raitakari et al. showed that exposure to CVD risk factors, like dyslipidemia, early in life may induce changes in arteries that lead to progression of atherosclerosis (18). The Muscatine Study demonstrated that risk factors including dyslipidemia in childhood is associated with higher carotid intimal-media thickness (IMT), a proxy for CVD, in young and middle-aged adults (17). These studies show that dyslipidemia track from childhood to adulthood and lend support for the notion that efforts to reduce CVD risk factors in children and adolescent may reduce the risk of atherosclerosis and clinical CVD later in life (19), but similar studies are lacking in the T1D population.

Recommended screening and treatment

The American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) have formulated guidelines for dyslipidemia screening and treatment in T1D primarily based on expert opinions and data extrapolated from adult studies.

The ADA recommends screening for dyslipidemia in the form of a fasting lipid profile on children with T1D > 2 years of age soon after diagnosis (after glucose control has been established) if there is a family history of hypercholesterolemia or a cardiovascular event before age 55 years, or if family history is unknown. If family history is not of concern, ADA recommends the first lipid screening at puberty (12 years of age). For children diagnosed with diabetes at or after puberty, they recommend obtaining a fasting lipid profile soon after the diagnosis. For both age-groups, if lipids are abnormal, annual monitoring is advised, and if LDL-C values are within the accepted risk levels (<100 mg/dL [2.6 mmol/L]), a lipid profile should be repeated every 5 years (20). With regard to treatment, ADA also sets the goal of therapy to LDL-C value of 100 mg/dL (2.6 mmol/L), and recommends the addition of a statin to glycemic control and dietary modification if the child is older than 10 years, has LDL-C >160 mg/dL (4.1 mmol/L), or LDL-C >130 mg/dL (3.4 mmol/L) with one or more CVD risk factors (20).

The ISPAD Clinical Practice Consensus Guidelines 2009 recommends statin therapy for LDL-C > 130 mg/dL (3.4 mmol/L) and one or more CVD risk factors, or with lower LDL-C levels if metabolic control and dietary changes fail to lower to target of <100 mg/dL (2.6 mmol/L) (21). Jolliffe et al. formulated age and gender-specific thresholds for total cholesterol, LDL-C, HDL-C and triglycerides for adolescents aged 12 – 19, and also suggested different treatment approaches for these thresholds (22). The National Heart, Lung, and Blood Institute (NHLBI) provided in 2011 a cardiovascular risk reduction guideline for children and adolescents, which included nonHDL-C (acceptable <120 mg/dL [3.1 mmol/L], borderline 120–144 mg/dL [3.1–3.7 mmol/L] and high 145 mg/dL [3.8 mmol/L]) as part of screening, which can be accurately calculated in non-fasting state and is particularly useful in T1D (23).

Furthermore, timing of pharmacologic interventions remains controversial and complex, and is influenced by several factors including background risk of CVD, safety of pharmacologic agents and degree of long-term benefit to be gained from intervention (Figure 1A and 1B).

Lipid-lowering therapies

Lipid lowering medications in youth include statins, ezetimibe, bile acid sequestrants (resins), niacins and fibrates. Statins will be reviewed separately in the paragraphs below. Ezetimibe selectively inhibits intestinal cholesterol absorption, and is approved for children with familial hypercholesterolemia (FH). In adults – ezetimibe has demonstrated additive effects in lowering LDL-C when combined with statin therapy (24). However, the ENHANCE trial reported no additional effects of ezetimibe with simvastatin compared to simvastatin alone in improving carotid IMT (25). Moreover, treatment with ezetimibe in the

Simvastatin and Ezetimibe in Aortic Stenosis trial demonstrated higher cancer incidence and associated mortality in adults than those treated with simvastatin (26). Bile acid sequestrants act preventing the reabsorption and recirculation of intestinal bile acids and thereby promote the conversion of cholesterol to bile salts and consequently deplete the overall cholesterol pool. Treatment with cholestyramine has shown to reduce cholesterol by 8.5% compared to placebo (27). However, due to the frequency and severity of adverse effects, including abdominal pain and nausea, this therapy is poorly tolerated. A new bile acid sequestrant, colesevelam, holds promise for people with T1D, as it has shown to reduce LDL-C with few adverse effects, and is also approved for lowering HbA1c in type 2 diabetes (T2D) (28). The proposed insulin sensitizing properties of colesevelam (29) could be beneficial in T1D as insulin resistance is increasingly recognized as an important component of the disease (30). Niacin is a vitamin which increases HDL-C levels by inhibiting production of VLDL-C by the liver. It is rarely prescribed in pediatrics, due to the common adverse effects of flushing, impaired glucose tolerance, liver failure and myopathy (31). Fibrates activate peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and influence the metabolism of triglycerides and HDL-C. Fibrates have been shown to be both safe and effective in reducing triglycerides in children (32), but is limited in its ability to reduce LDL-C and studies also demonstrate a limited ability to reduce triglycerides sufficient (33). Statins remain the recommended first-line pharmacological therapy for dyslipidemia in T1D.

Statins

In 2007, the American Heart Association (AHA) published a statement on drug therapy for dyslipidemias in high-risk children and adolescents, including those with T1D and T2D (34). The most significant change in this statement was the recommendation of statin therapy for children and adolescents (34). One year later, in 2008, the American Academy of Pediatrics (AAP) also changed their recommendations for hypercholesterolemia to include statins among potential first-line agents, with 8 years of age as the minimum age to commence pharmacotherapy and LDL-C treatment cutoff point of 130 mg/dL for youth with diabetes (35). In contrast to AHA, the AAP did not specifically define diabetes mellitus as a high-risk condition in line with hypercholesterolemia.

Statins, or HMG-CoA reductase inhibitors, work by competitively inhibiting the rate limiting step of endogenous synthesis of cholesterol, HMG-CoA reductase, resulting in lower LDL-C levels. In addition, statins have additional effects including plaque stabilization, anti-inflammation, anti-thrombosis and inhibition of arterial smooth muscle cell proliferation (36). Statins have been shown to be effective in reducing CVD-associated morbidity and mortality in adults (37). The primary aim of pharmacotherapy in children and adolescent with T1D is to lower significantly elevated LDL-C with successful treatment considered as LDL-C levels lowered to less than 100 mg/dL.

This stands in contrast to the current recommendations for adults, where the recently published guidelines by the American College of Cardiology and American Heart Association no longer recommend level-driven goals and rather guide treatment based on risk factor profiles (38). The guideline, which is limited to adults (> 21 years of age), is not without controversy and has been criticized for making follow-up LDL-C monitoring

irrelevant, not allowing gradation in residual risk and tailoring of therapy to the individual (39). Level-driven goals for lipid indices remain the recommendations for therapy for children and adolescents (23).

Most data on the efficacy and safety of statins in children and adolescents are from studies in those with FH. Of note, children with T1D have similar lipid profiles as those with FH with elevated LDL-C, and moreover LDL-C is what most treatment recommendations are based on. Numerous randomized controlled trials have demonstrated the efficacy of statins in lowering LDL-C and apoB with no increase in adverse effects compared to placebo in children and adolescents with FH (40–44). McCrindle et al. demonstrated that atorvastatin reduced LDL-C by 40% compared to placebo in 187 adolescents with FH (42). This is noteworthy as youth with T1D at high risk for CVD demonstrate increased carotid intima media thickness (IMT) (18, 45). Rodenburg et al. demonstrated that younger age at statin initiation was an independent predictor of effect of treatment on carotid IMT (46). Moreover, it has been shown that early statin therapy restored endothelial function in children with FH (47). Early intervention with statins also appears likely to reduce future atherosclerosis in children with T1D, but evidence is still lacking. The Pediatric Atorvastatin in Diabetes Trial (PADIT) demonstrated that atorvastatin significantly lowered LDL-C and also confirmed an excellent short-term safety profile in adolescents with T1D (48). Atorvastatin's LDL-C lowering capabilities were more recently confirmed by a small randomized control study on statin therapy in children with T1D (49). Statins may also have additional effects which may be beneficial in preventing vascular complications in T1D. Tehrani et al. showed that statins also have antithrombotic effects in adult patients with T1D and dyslipidemia (50).

Statins and macrovascular complications

Large interventional trials have demonstrated reduced coronary artery disease and mortality with statin use in adults (51). Cholesterol Treatment Trialists' Collaborators meta-analysis of 14 randomized trials of statins in over 18,000 subject with diabetes demonstrated 21% reduction in major vascular events per 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C, and similar results for both T1D and T2D (52). Statins have also been shown to significantly reduce all-cause mortality for adults at risk for CVD (53). Cohen et al. demonstrated that moderate reduction in LDL-C sustained over a life-time could markedly reduce CVD (54).

Poor glycemic control vs. dyslipidemia – refining macrovascular risk

Data from epidemiological studies suggest that the risk of CVD in T1D is driven more by poor glycemic control, hypertension and nephropathy than by lipids (55). Schwab et al. have demonstrated that lipid profiles in children and adolescents with T1D are influenced primarily by 4 factors; age, gender, BMI and HbA1c levels (56). Therefore some clinicians who feel the role of statin therapy is secondary to glycemic control and weight management and should be limited to patients with more than 10 years' duration of disease and evidence of target organ damage or additional cardiovascular risk factors (e.g. smoking) (31, 56). Although glycemic control may play an important role in dyslipidemia, evidence from SEARCH and CACTI studies demonstrate that lowering of HbA1c is associated with only a very small decrease in LDL-C (decrease in LDL-C by 4mg/dL per 1% decrease in HbA1c)

(57, 58). Furthermore, the Dietary Intervention Study in Children (DISC) showed that a fat reduced diet only modestly lowers LDL-C (<5 mg/dL reduction of LDL-C in intervention group compared to control) (59). Moreover, the SEARCH study reported that only 15% of adolescents met the ADA and AHA recommendations for total and saturated fat intake (60), indicating that these goals may be unattainable for adolescents with T1D. For these reason, dietary changes and optimal glycemic control alone are unlikely to achieve the lipid levels recommended for high-risk individuals.

Statins and microvascular complications

Diabetic nephropathy is one of the leading causes of mortality in T1D, diabetic retinopathy is the most common cause of vision loss in developed countries (61) and diabetic neuropathy affects up to 57% of children and adolescents with T1D (62).

Experimental and clinical studies have demonstrated the deleterious effects of dyslipidemia on the microvasculature and progression of diabetic nephropathy, retinopathy and neuropathy (63–65). Although statin therapy has been shown to be effective in reducing development of CVD and associated mortality in T1D, their effects on diabetic microvascular complications are less clear due to the lack of prospective randomized interventional trials. There are, however, some data in adults indicating that statins may reduce the rate of progression of microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy (66–68). In addition, diabetic rodent models have demonstrated improved nerve conduction with statins, but this has not yet been shown in humans (69).

Safety

The efficacy and safety profile of statins for children and adolescents appear similar to that for adults. There are now trial data indicating efficacy and safety in the use of statins in children and adolescents (70, 71). Most of these data are derived from short-term trials conducted in children with FH that show treatment to be safe (44). The longest follow-up in studies of statins in children is however only 2 years (43).

Several statins are FDA approved for use in adolescents with FH, including atorvastatin, lovastatin, pravastatin, and simvastatin, after trials confirmed their efficacy and safety in children and adolescents (44). There are now several systematic reviews in addition to a Cochrane Database meta-analysis on the effects on statins in children and adolescents with FH (44, 72). No significant side effects were observed in terms of growth, pubertal development, testicular volume, menarche, endocrine function parameters, or liver or muscle enzymes (44). Adverse effects that were reported were mild and included primarily headache, gastrointestinal distress and myalgia. Moreover, in a meta-analysis the prevalence of significantly elevated alanine amino transferase was reported to be only 0.7% in childrenreceiving statins (44). Furthermore, there has been no cases of rhabdomyolysis reported in adolescents (40–44), but asymptomatic increase in creatine kinase has been reported infrequently in adolescents receiving statin therapy (44). Some authors have raised concern about validity of the adverse effect reporting in the systematic reviews due to non-

uniform monitoring and reporting of adverse effects, including interference with growth, nutrition and puberty (31). Recently, one meta-analysis reported that the risk of cataracts was increased by 29% among statin users compared with non-users (73). Statins also now carry a US Food and Drug Administration warning stating that they may increase risk of new onset diabetes and impair glycemic control in those with diabetes. In a large meta-analysis, statins were associated with an absolute difference of risk of 0.4% of new onset diabetes compared to placebo (74). Data from the Incremental Decrease in Endpoints Through Aggressive Lipid Lower (IDEAL) trial suggest that the prevention of cardiovascular events outweigh the higher risks of new onset diabetes and poorer glycemic control (75). There is little data on the effects of statin use on glycemic control in children and adolescents with type 1 diabetes.

In general, statins are effective and safe in adolescent girls, with no documented adverse effect on growth and development or on adrenal and gonadal hormones (43). Statins are, however, contraindicated during pregnancy due to teratogenic effects, for which reason birth control is a necessity for females who are sexually active (76). Because adolescence can be a period of poor compliance for patients with T1D, some authors believe statins should not be used to treat adolescent females, whereas others feel that as long as the adolescent is adequately counseled on the risks and contraception is considered, statin therapy is safe (31). Another issue to consider with regard to statin use in adolescents is transition of care. Adolescents transitioning from pediatric to adult care are more likely to be started on statin therapy by their adult provider. While there are important differences between children and adults, the differences between post-pubertal adolescents and young adults are less clear.

In summary, although short-term studies on statin use in children and adolescent with FH report minimal adverse effects (42, 43), long-term safety of statin use, and especially their effect on glycemic control, has not been established in children and adolescents with T1D. Therefore, further studies are needed to document the long-term safety of statins and to determine their effects on glycemic control and CVD in children and adolescents with T1D.

Conclusions

T1D is associated with a number of factors that drive progression of atherosclerosis, including dyslipidemia, hyperglycemia, insulin resistance, hypertension and diabetic nephropathy (77). Atherosclerosis begins in childhood in T1D in association with dyslipidemia and the formation of arterial fatty streaks and increased carotid intima media thickness (IMT) (9, 78), with subsequent risk of early-onset CVD (77). In adults statins are effective in the primary and secondary prevention of CVD in patients with diabetes (79). Despite advances in the management of T1D, dyslipidemia in children and adolescents remains inadequately treated. Wood et al. recently reported that only 65% of participants of the T1D Exchange study met the ADA targets for LDL-C, suggesting a large proportion of children and adolescent with T1D with significant vascular risk factors (80). Moreover, encouraging findings from short-term clinical trials in children and adolescents indicate statins are both effective and safe as lipid-lowering medication in this age group (44).

There are discrepancies across clinical guidelines as to the role of statin use in children and adolescents with T1D or at which age it should be initiated, due to the paucity of clinical trials on statin use in children and adolescents with T1D. Arguments against statin therapy in children with T1D include: lack of sufficient data on safety and efficacy (including concerns for teratogenicity in girls of child-bearing age), medication cost, potential life-time treatment duration, and data that early vascular lesions can regress with treatment as adults (Table 1). Conversely, arguments for statin therapy are numerous and include data showing CVD and mortality risk reduction with statins in adults, safety documented in adults and children and adolescents with FH, large studies showing early atherosclerosis in children with progression into adulthood, tracking of lipids from childhood to adulthood and significant increased risk of CVD in children and adolescent with T1D compared with non-diabetics (Table 1). Furthermore, there is evidence from studies in children and adolescents with familial hypercholesterolemia that early statin therapy can ameliorate lipid associated endothelial dysfunction (47).

Dyslipidemia in children and adolescents with T1D may be secondary to poor glycemic control and weight management, but still plays an important role in the development of atherosclerosis deserving of greater recognition as a therapeutic target of its own. Encouraging results from small clinical trials hold promise for statin to become a safe and effective therapy in preventing vascular complications in children with T1D in the future (48, 49). Before that time, however, large scale longitudinal trials in children and adolescents with T1D are urgently needed to address both efficacy and safety. We have previously described difficulties in recruiting adolescents with T1D for such trials (81). Future studies will require multiple centers to work together to recruit a sufficient number of participants and provide adequate data. A large multicenter randomized clinical trial on statin use in young people with T1D, Adolescent T1D Cardio-renal Intervention Trial (AdDIT), is ongoing and will hopefully provide helpful data regarding the risks and benefits of statin therapy in children and adolescents with T1D (82, 83). In the interim, clinicians who consider prescribing statins to children and adolescents should carefully weigh risks and benefits, and monitor closely for potential adverse effects.

In conclusion, the current literature suggests that dyslipidemia plays an important role in the development of vascular complications in T1D. There are encouraging data on safety and efficacy of statin therapy in children and adolescents, but large scale longitudinal trials on statin therapy in children and adolescents with T1D are needed to properly address statin use for treatment of dyslipidemia in young people with T1D.

Acknowledgements

Drs. Bjornstad and Wadwa have no conflict of interest to disclose.

References

1. Soltesz G, Patterson CC, Dahlquist G 2007 Worldwide childhood type 1 diabetes incidence--what can we learn from epidemiology? *Pediatric diabetes* 8 Suppl 6:6–14 [PubMed: 17727380]
2. Federation ID 2007 Diabetes Atlas.

3. Libby P, Nathan DM, Abraham K, Brunzell JD, Fradkin JE, Haffner SM, Hsueh W, Rewers M, Roberts BT, Savage PJ, Skarlatos S, Wassef M, Rabadan-Diehl C 2005 Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. *Circulation* 111:3489–3493 [PubMed: 15983263]
4. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC 2003 Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 46:760–765 [PubMed: 12774166]
5. Schwab KO, Doerfer J, Hecker W, Grulich-Henn J, Wiemann D, Kordonouri O, Beyer P, Holl RW 2006 Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes: cross-sectional data from the German diabetes documentation and quality management system (DPV). *Diabetes Care* 29:218–225 [PubMed: 16443863]
6. Margeisdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jorgensen K 2008 High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. *Diabetologia* 51:554–561 [PubMed: 18196217]
7. Maahs DM, Rewers M 2006 Editorial: Mortality and renal disease in type 1 diabetes mellitus--progress made, more to be done. *The Journal of clinical endocrinology and metabolism* 91:3757–3759 [PubMed: 17028289]
8. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ 2006 The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes* 55:1463–1469 [PubMed: 16644706]
9. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP 3rd, Herderick EE, Cornhill JF 1999 Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA : the journal of the American Medical Association* 281:727–735 [PubMed: 10052443]
10. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA 1998 Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *The New England journal of medicine* 338:1650–1656 [PubMed: 9614255]
11. Reiner Z 2013 Statins in the primary prevention of cardiovascular disease. *Nature reviews. Cardiology* 10:453–464 [PubMed: 23736519]
12. Collins R, Armitage J, Parish S, Sleight P, Peto R 2003 MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–2016 [PubMed: 12814710]
13. Kershner AK, Daniels SR, Imperatore G, Palla SL, Pettitt DB, Marcovina S, Dolan LM, Hamman RF, Liese AD, Pihoker C, Rodriguez BL 2006 Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. *The Journal of pediatrics* 149:314–319 [PubMed: 16939739]
14. Beaumont JL, Carlson LA, Cooper GR, Fejfar Z, Fredrickson DS, Strasser T 1970 Classification of hyperlipidaemias and hyperlipoproteinaemias. *Bulletin of the World Health Organization* 43:891–915 [PubMed: 4930042]
15. Maahs DM, Wadwa RP, McFann K, Nadeau K, Williams MR, Eckel RH, Klingensmith GJ 2007 Longitudinal lipid screening and use of lipid-lowering medications in pediatric type 1 diabetes. *The Journal of pediatrics* 150:146–150, 150 e141–142 [PubMed: 17236891]
16. Daneman D 2005 Early diabetes-related complications in adolescents: risk factors and screening. *Hormone research* 63:75–85 [PubMed: 15677872]
17. Davis PH, Dawson JD, Riley WA, Lauer RM 2001 Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation* 104:2815–2819 [PubMed: 11733400]
18. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnema T, Akerblom HK, Viikari JS 2003 Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA : the journal of the American Medical Association* 290:2277–2283 [PubMed: 14600186]

19. McGill HC Jr., McMahan CA 2003 Starting earlier to prevent heart disease. *JAMA : the journal of the American Medical Association* 290:2320–2322 [PubMed: 14600192]
20. 2013 Standards of medical care in diabetes--2013. *Diabetes Care* 36 Suppl 1:S11–66 [PubMed: 23264422]
21. Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K 2009 Microvascular and macrovascular complications associated with diabetes in children and adolescents. *Pediatric diabetes* 10 Suppl 12:195–203 [PubMed: 19754630]
22. Jolliffe CJ, Janssen I 2006 Distribution of lipoproteins by age and gender in adolescents. *Circulation* 114:1056–1062 [PubMed: 16940191]
23. Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I 2011 Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 128 Suppl 5:S213–256 [PubMed: 22084329]
24. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, Suresh R, Sun S, Veltri EP 2002 Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *Journal of the American College of Cardiology* 40:2125–2134 [PubMed: 12505224]
25. Kastelein JJ, Akdim F, Stroes ES, Zwiderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E 2008 Simvastatin with or without ezetimibe in familial hypercholesterolemia. *The New England journal of medicine* 358:1431–1443 [PubMed: 18376000]
26. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerds E, Gohlke-Barwolf C, Holme I, Kesaniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R 2008 Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *The New England journal of medicine* 359:1343–1356 [PubMed: 18765433]
27. 1984 The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA : the journal of the American Medical Association* 251:351–364 [PubMed: 6361299]
28. Stein EA, Marais AD, Szamosi T, Raal FJ, Schurr D, Urbina EM, Hopkins PN, Karki S, Xu J, Misir S, Melino M 2010 Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. *The Journal of pediatrics* 156:231–236 e231–233 [PubMed: 19879596]
29. Fonseca VA, Handelsman Y, Staels B 2010 Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes, obesity & metabolism* 12:384–392
30. Nadeau KJ, Regensteiner JG, Bauer TA, Brown MS, Dorosz JL, Hull A, Zeitler P, Draznin B, Reusch JEB 2010 Insulin Resistance in Adolescents with Type 1 Diabetes and Its Relationship to Cardiovascular Function. *Journal of Clinical Endocrinology & Metabolism* 95:513–521 [PubMed: 19915016]
31. O’Gorman CS, O’Neill MB, Conwell LS 2011 Considering statins for cholesterol-reduction in children if lifestyle and diet changes do not improve their health: a review of the risks and benefits. *Vascular health and risk management* 7:1–14
32. Wheeler KA, West RJ, Lloyd JK, Barley J 1985 Double blind trial of bezafibrate in familial hypercholesterolaemia. *Archives of disease in childhood* 60:34–37 [PubMed: 3882058]
33. Ginsberg HN 2001 Hypertriglyceridemia: new insights and new approaches to pharmacologic therapy. *The American journal of cardiology* 87:1174–1180; A1174 [PubMed: 11356393]
34. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, Daniels SR 2007 Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 115:1948–1967 [PubMed: 17377073]
35. Daniels SR, Greer FR 2008 Lipid screening and cardiovascular health in childhood. *Pediatrics* 122:198–208 [PubMed: 18596007]
36. Campese VM, Park J 2007 HMG-CoA reductase inhibitors and the kidney. *Kidney international* 71:1215–1222 [PubMed: 17495867]

37. Belay B, Belamarich PF, Tom-Revzon C 2007 The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics* 119:370–380 [PubMed: 17272627]
38. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr., Watson K, Wilson PW 2013 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*
39. Raymond C, Cho L, Rocco M, Hazen SL 2014 New cholesterol guidelines: Worth the wait? *Cleveland Clinic journal of medicine* 81:11–19 [PubMed: 24391101]
40. Lambert M, Lupien PJ, Gagne C, Levy E, Blauchman S, Langlois S, Hayden M, Rose V, Clarke JT, Wolfe BM, Clarson C, Parsons H, Stephure DK, Potvin D, Lambert J 1996 Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Canadian Lovastatin in Children Study Group. Pediatrics* 97:619–628 [PubMed: 8628597]
41. Knipscheer HC, Boelen CC, Kastelein JJ, van Diermen DE, Groenemeijer BE, van den Ende A, Buller HR, Bakker HD 1996 Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatric research* 39:867–871 [PubMed: 8726243]
42. McCrindle BW, Ose L, Marais AD 2003 Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *The Journal of pediatrics* 143:74–80 [PubMed: 12915827]
43. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ 2004 Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA : the journal of the American Medical Association* 292:331–337 [PubMed: 15265847]
44. Avis HJ, Vissers MN, Stein EA, Wijburg FA, Trip MD, Kastelein JJ, Hutten BA 2007 A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arteriosclerosis, thrombosis, and vascular biology* 27:1803–1810
45. Jarvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Ronnema T, Raitakari OT 2002 Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes* 51:493–498 [PubMed: 11812760]
46. Rodenburg J, Vissers MN, Wiegman A, van Trotsenburg AS, van der Graaf A, de Groot E, Wijburg FA, Kastelein JJ, Hutten BA 2007 Statin treatment in children with familial hypercholesterolemia: the younger, the better. *Circulation* 116:664–668 [PubMed: 17664376]
47. de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ 2002 Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *Journal of the American College of Cardiology* 40:2117–2121 [PubMed: 12505222]
48. Haller MJ, Stein JM, Shuster JJ, Theriaque D, Samyn MM, Pepine C, Silverstein JH 2009 Pediatric Atorvastatin in Diabetes Trial (PADIT): a pilot study to determine the effect of atorvastatin on arterial stiffness and endothelial function in children with type 1 diabetes mellitus. *Journal of pediatric endocrinology & metabolism : JPEM* 22:65–68 [PubMed: 19344076]
49. Canas JA 2013 Atorvastatin Safely Reduced Non-HDL Cholesterol in Children with Type 1 Diabetes (T1DM) and High LDL-C: Preliminary Results. *Endocrine reviews* 34
50. Tehrani S, Mobarrez F, Antovic A, Santesson P, Lins PE, Adamson U, Henriksson P, Wallen NH, Jorreskog G 2010 Atorvastatin has antithrombotic effects in patients with type 1 diabetes and dyslipidemia. *Thrombosis research* 126:e225–231 [PubMed: 20637495]
51. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R 2005 Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267–1278 [PubMed: 16214597]
52. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C 2008 Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 371:117–125 [PubMed: 18191683]
53. Kwiterovich PO Jr., 1998 State-of-the-art update and review: clinical trials of lipid-lowering agents. *The American journal of cardiology* 82:3U–17U; discussion 39U–41U

54. Cohen JC, Boerwinkle E, Mosley TH Jr., Hobbs HH 2006 Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *The New England journal of medicine* 354:1264–1272 [PubMed: 16554528]
55. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B 2005 Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *The New England journal of medicine* 353:2643–2653 [PubMed: 16371630]
56. Schwab KO, Doerfer J, Marg W, Schober E, Holl RW 2010 Characterization of 33 488 children and adolescents with type 1 diabetes based on the gender-specific increase of cardiovascular risk factors. *Pediatric diabetes* 11:357–363 [PubMed: 20624248]
57. Maahs DM, Ogden LG, Dabelea D, Snell-Bergeon JK, Daniels SR, Hamman RF, Rewers M 2010 Association of glycaemia with lipids in adults with type 1 diabetes: modification by dyslipidaemia medication. *Diabetologia* 53:2518–2525 [PubMed: 20820753]
58. Guy J, Ogden L, Wadwa RP, Hamman RF, Mayer-Davis EJ, Liese AD, D'Agostino R Jr., Marcovina S, Dabelea D 2009 Lipid and lipoprotein profiles in youth with and without type 1 diabetes: the SEARCH for Diabetes in Youth case-control study. *Diabetes Care* 32:416–420 [PubMed: 19092167]
59. Lauer RM, Obarzanek E, Hunsberger SA, Van Horn L, Hartmuller VW, Barton BA, Stevens VJ, Kwiterovich PO Jr., Franklin FA Jr., Kimm SY, Lasser NL, Simons-Morton DG 2000 Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: the Dietary Intervention Study in Children. *Am J Clin Nutr* 72:1332S–1342S [PubMed: 11063475]
60. Mayer-Davis EJ, Nichols M, Liese AD, Bell RA, Dabelea DM, Johansen JM, Pihoker C, Rodriguez BL, Thomas J, Williams D 2006 Dietary intake among youth with diabetes: the SEARCH for Diabetes in Youth Study. *Journal of the American Dietetic Association* 106:689–697 [PubMed: 16647326]
61. Ciulla TA, Amador AG, Zinman B 2003 Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 26:2653–2664 [PubMed: 12941734]
62. Trotta D, Verrotti A, Salladini C, Chiarelli F 2004 Diabetic neuropathy in children and adolescents. *Pediatric diabetes* 5:44–57 [PubMed: 15043690]
63. Bonnet F, Cooper ME 2000 Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. *Diabetes & metabolism* 26:254–264 [PubMed: 11011217]
64. Klein BE, Moss SE, Klein R, Surawicz TS 1991 The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. *Ophthalmology* 98:1261–1265 [PubMed: 1923364]
65. Elliott J, Tesfaye S, Chaturvedi N, Gandhi RA, Stevens LK, Emery C, Fuller JH 2009 Large-fiber dysfunction in diabetic peripheral neuropathy is predicted by cardiovascular risk factors. *Diabetes Care* 32:1896–1900 [PubMed: 19587366]
66. Sen K, Misra A, Kumar A, Pandey RM 2002 Simvastatin retards progression of retinopathy in diabetic patients with hypercholesterolemia. *Diabetes Res Clin Pract* 56:1–11 [PubMed: 11879715]
67. Elisaf M, Mikhailidis DP 2002 Statins and renal function. *Angiology* 53:493–502 [PubMed: 12365855]
68. Fried LF, Forrest KY, Ellis D, Chang Y, Silvers N, Orchard TJ 2001 Lipid modulation in insulin-dependent diabetes mellitus: effect on microvascular outcomes. *Journal of diabetes and its complications* 15:113–119 [PubMed: 11358679]
69. Leiter LA 2005 The prevention of diabetic microvascular complications of diabetes: is there a role for lipid lowering? *Diabetes Res Clin Pract* 68 Suppl 2:S3–14 [PubMed: 15953505]
70. de Jongh S, Ose L, Szamosi T, Gagne C, Lambert M, Scott R, Perron P, Dobbelaere D, Saborio M, Tuohy MB, Stepanavage M, Sapre A, Gumbiner B, Mercuri M, van Trotsenburg AS, Bakker HD, Kastelein JJ 2002 Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation* 106:2231–2237 [PubMed: 12390953]

71. Stein EA, Illingworth DR, Kwiterovich PO Jr., Liacouras CA, Siimes MA, Jacobson MS, Brewster TG, Hopkins P, Davidson M, Graham K, Arensman F, Knopp RH, DuJovne C, Williams CL, Isaacsohn JL, Jacobsen CA, Laskarzewski PM, Ames S, Gormley GJ 1999 Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA : the journal of the American Medical Association* 281:137–144 [PubMed: 9917116]
72. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H 2010 Statins for children with familial hypercholesterolemia. *The Cochrane database of systematic reviews*:CD006401
73. Leuschen J, Mortensen EM, Frei CR, Mansi EA, Panday V, Mansi I 2013 Association of Statin Use With Cataracts: A Propensity Score-Matched Analysis. *JAMA ophthalmology*
74. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I 2010 Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375:735–742 [PubMed: 20167359]
75. Waters DD, Ho JE, Boekholdt SM, DeMicco DA, Kastelein JJ, Messig M, Breazna A, Pedersen TR 2013 Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *Journal of the American College of Cardiology* 61:148–152 [PubMed: 23219296]
76. Kusters DM, Homsma SJ, Hutten BA, Twickler MT, Avis HJ, van der Post JA, Strokes ES 2010 Dilemmas in treatment of women with familial hypercholesterolaemia during pregnancy. *The Netherlands journal of medicine* 68:299–303 [PubMed: 20739726]
77. Krantz JS, Mack WJ, Hodis HN, Liu CR, Liu CH, Kaufman FR 2004 Early onset of subclinical atherosclerosis in young persons with type 1 diabetes. *The Journal of pediatrics* 145:452–457 [PubMed: 15480366]
78. McGill HC Jr., McMahan CA, Zieske AW, Malcom GT, Tracy RE, Strong JP 2001 Effects of nonlipid risk factors on atherosclerosis in youth with a favorable lipoprotein profile. *Circulation* 103:1546–1550 [PubMed: 11257083]
79. Tunstall-Pedoe H 2013 Starting statins for primary prevention of cardiovascular disease. *Heart*
80. Wood JR, Miller KM, Maahs DM, Beck RW, Dimeglio LA, Libman IM, Quinn M, Tamborlane WV, Woerner SE 2013 Most Youth With Type 1 Diabetes in the T1D Exchange Clinic Registry Do Not Meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes Clinical Guidelines. *Diabetes Care* 36:2035–2037 [PubMed: 23340893]
81. Bishop FK, Wadwa RP, Ellis S, Rewers M, Maahs DM 2012 Lessons learned from a lipid lowering trial in adolescents with type 1 diabetes. *International journal of pediatric endocrinology* 2012:24 [PubMed: 22846167]
82. 2009 Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AdDIT). *BMC pediatrics* 9:79 [PubMed: 20017932]
83. Marcovecchio ML, Woodside J, Jones T, Daneman D, Neil A, Prevost T, Dalton RN, Deanfield J, Dunger D 2013 Adolescent Type 1 Diabetes cardio-renal Intervention Trial (AdDIT): Urinary screening and baseline biochemical and cardiovascular assessments. *Diabetes Care*

Figure 1A and 1B. Hypothetical Relationship of LDL-C, LDL-C-lowering and Future CVD in Youth with T1D

Figure 1A represents possible long-term risk reduction assuming high background CVD risk and benefit from LDL-C lowering, and Figure 1B represents lower background CVD risk and less benefit from LDL-C lowering. Reproduced with permission of the copyright owner: Maahs et al. *Dyslipidemia in Youth with Diabetes: To Treat or Not to Treat?* *J Pediatr.* 2008 October;153(4):458–465.

Table 1

Arguments for and against statin therapy in youth with T1D

Arguments <i>for</i> statin therapy	Arguments <i>against</i> statin therapy
Dyslipidemia track into adulthood	Lack of sufficient data on safety
Atherosclerosis associated with dyslipidemia in childhood	Lack of sufficient data on efficacy
Dyslipidemia involved in micro- and macrovascular complications	Potential life-time treatment duration
Data showing CVD and mortality risk reduction with statins in adults	Data that early vascular lesions can regress with treatment as adults
Safety documented in adults and children and adolescents with FH	

Adapted from Maahs et al. *Dyslipidemia in Youth with Diabetes: To Treat or Not to Treat?* *J Pediatr*. 2008 October;153(4):458–465.