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Statin Use: Reduction of Cardiovascular Risk in Individuals with Familial Hypercholesterolemia

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by

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Abstract

Familial hypercholesterolemia is an autosomal dominant disorder that contributes to premature onset of cardiovascular disease. As a result of this genetic mutation, individuals with familial hypercholesterolemia are exposed to high levels of LDL cholesterol early in life. Numerous clinical studies have illustrated the beneficial effect of statins on LDL cholesterol levels, as well as the role they play in reducing atherosclerosis. It is for these reasons that statins remain the first drug of choice for familial hypercholesterolemia. This document will feature a case report of a young adult male presenting with suspected familial hypercholesterolemia, including the diagnostic workup and treatment plan for this individual. The literature review will discuss the use of statin medications in the treatment of familial hypercholesterolemia to reduce cardiovascular risk in this population. Cardiovascular disease remains the number one killer in the United States. Early recognition of this disorder, in addition to prompt treatment of these individuals, could have a substantial impact on the disease burden of cardiovascular disease in the United States each year.

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Background

In the case that an individual presents to the clinic with a family history significant for premature cardiovascular disease, when should the clinician raise suspicion for familial hypercholesterolemia? What type of diagnostic findings might indicate that familial hypercholesterolemia should be considered in the differential diagnosis? If familial hypercholesterolemia is suspected, what is the best course of treatment?

In practice, familial hypercholesterolemia is frequently under-recognized and unfortunately, at times, the diagnosis is not made until the patient presents with late-stage atherosclerotic cardiovascular disease. As clinicians, we must conduct thorough family histories of our patients, inquiring about premature cardiovascular events in first-degree relatives. Upon diagnosis of familial hypercholesterolemia, the clinician's first priority should be cardiovascular risk reduction for these patients. Individuals with untreated heterozygous familial hypercholesterolemia, the much more common form of this disease, typically develop coronary heart disease as early as the third to fourth decade of life. The use of statin medications remains the first-line therapy for these patients. Statins have been proven to reduce the incidence of coronary and other vascular events in these patients.

Case Report

The following clinical presentation will set the stage for the ensuing discussion regarding the use of statin drug therapy in patients with familial hypercholesterolemia in an effort to reduce their cardiovascular risk.

A 24-year-old well-appearing male presents to the outpatient clinic requesting to have his cholesterol checked, owing his concern to his family history. Upon further investigation, the

patient reveals that his father recently passed away suddenly due to a heart attack at age 46. The patient is unsure of his father's past medical history, but he reports that his 30-year-old brother has high cholesterol and is taking some type of medication for this, though he is unsure which medication this is. The patient denies any family history of diabetes, hypertension, kidney disease or thyroid disease. He reports that his mother is healthy and without any medical conditions.

The patient's past medical history is benign, revealing a history of allergic rhinitis for which he takes Zyrtec as needed. Surgical history includes a tonsillectomy and adenoidectomy at the age of 4 years old.

The patient's social history reveals he is a full-time college student and also working as an EMT on weekends. He reports he is insured through his employment. He does not use tobacco. He does admit to drinking alcohol, drinking 1-2 drinks up to 5 times a week, with heavier consumption (up to ten drinks) on the weekends on occasion. He is active, exercising 4-5 times a week. He reports he enjoys running.

The patient denies any cardiovascular complaints today; denies any chest pain, palpitations, or shortness of breath. He denies any extreme fatigue or lower extremity edema. He reports good exercise capacity. He does briefly note that his left elbow and right knee have been "sore", but he attributes this to working out.

Physical examination of the patient reveals an alert, oriented male that does not appear to be in any acute distress, very pleasant. Vital signs are as follows: blood pressure 110/54, heart rate 62, temperature 37.1 Celsius, height 6'1", weight 200 lbs. (BMI 26.4). His thyroid is palpable without enlargement or nodules. His respiratory effort is easy, even, and regular. Lungs are clear throughout, no wheezing or crackles. Heart rate is regular. Normal S1 and S2 heart

sounds. Moderate pulses are noted bilaterally in both upper and lower extremities. The lower extremities are negative for any peripheral edema. The left elbow is observed and is without redness or swelling, no signs of cellulitis or effusion. The right knee is also observed and is without redness or swelling, no signs of cellulitis or effusion.

At this point, a seemingly healthy and asymptomatic male with a family history significant for early onset cardiovascular disease is presenting to the clinic with concerns of elevated blood cholesterol levels. It is reasonable to proceed with the following diagnostic labs: lipid profile, comprehensive metabolic panel (CMP) for inclusion of liver function tests and total serum glucose, and thyroid stimulating hormone (TSH). Our differential diagnosis is familial hypercholesterolemia versus potential secondary hypercholesterolemia. With familial hypercholesterolemia in the differential, it is prudent to screen for any other potential comorbid conditions that may further contribute to cardiovascular risk in this patient, such as impaired fasting glucose, type 2 diabetes mellitus or thyroid disease.

Our lab results reveal the following: total cholesterol 310 mg/dl, triglycerides 140 mg/dl, high density lipoprotein (HDL) 60 mg/dl, and low density lipoprotein (LDL) 209 mg/dl. CMP reveals serum glucose 86, aspartate aminotransferase (AST) 20 U/L, alanine transaminase (ALT) 22 U/L. TSH is within normal limits.

Upon interpretation of the lipid panel, in addition to the family history of premature cardiovascular death, it is safe to assume that there is a high likelihood that this patient does in fact have familial hypercholesterolemia. Therefore, the patient is started on atorvastatin 40 mg daily and is instructed to continue with rigorous diet and exercise efforts. He is to return to the office in 4 weeks for a recheck of his lipid panel and liver function panel. The subsequent section will highlight the literature review and the supporting evidence for the chosen treatment plan for

this patient, as well as the implications of this treatment plan in the reduction of cardiovascular risk for this patient.

Literature Search

In order to compile a solid evidence foundation for this topic, the following search strategies were implemented. CINAHL, a research tool for nursing and health professionals, was accessed via the University of North Dakota Harley French Library website. The "CINAHL Headings" tool was used to search the following term: "familial hypercholesterolemia". This search yielded a broad range of 593 results. Therefore, the following limits were placed: publication beyond 2010, and academic journals only (exclude magazines, dissertations). This narrowed the search to 199 results. The publication by Safeer (2015) provided sound information in regard to the background of familial hypercholesterolemia. This publication also referenced two important and credible resources that were added to the literature review: a cohort study looking at the efficacy of statins in familial hypercholesterolemia (Vermissen et al., 2008) and the *Consensus Statement from the European Atherosclerosis Society* by Nordestgaard et al., 2013. Finally, *The Agenda for Familial Hypercholesterolemia: A Scientific Statement* from the American Heart Association (AHA), by Gidding et al. (2015) was reviewed and will be referenced throughout the literature review portion of this document.

The literature search was narrowed further by using the following CINAHL headings: "familial hypercholesterolemia" and "cardiovascular risk". The same limits as the prior search, searching for publications dated 2010 and beyond, and academic journals only, were implemented for this search as well. This CINAHL search yielded 34 results. Raal et al. (2011) implemented a large retrospective cohort study to better evaluate the impact of advances in lipid-

lowering (particularly statin) therapy on cardiovascular disease in patients with homozygous familial hypercholesterolemia. These results will be summarized in the following section.

This search also yielded the following important resource: *2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults* (Stone et al., 2013). This guideline focuses on atherosclerotic cardiovascular disease (ASCVD) risk reduction, as well as LDL-C treatment goals, global risk assessment for men and women in terms of cardiovascular disease, and safety recommendations regarding pharmacologic treatment (including the use of statins) for hypercholesterolemia. This guideline will be referenced throughout the literature review section of this document.

Additionally, the following useful resources were collected: a case study evaluating heterozygous familial hypercholesterolemia (Friedrich, 2010), a clinical review of familial hypercholesterolemia (Turgeon, Barry, & Pearson, 2016), a prospective cohort study analyzing the effects of hypercholesterolemia on left ventricular function in children with familial hypercholesterolemia (Di Salvo et al., 2012), and two commentary articles regarding the management of familial hypercholesterolemia and drug therapy of hypercholesterolemia in children and adults (Robinson, 2013; Braamskamp, Wijburg, & Wiegman, 2012).

Literature Review

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetically transmitted disorder that remains a common cause of premature coronary heart disease. FH is one of the most common serious genetic disorders, affecting an estimated 620,000 individuals in the United States alone (Robinson, 2013). First described over 125 years ago, FH was initially classified as a dermatological disorder due to the characteristic features, both xanthomas and xanthelasmas, that

would commonly manifest in patients (Gidding et al., 2015). Eventually, increased low-density lipoprotein cholesterol (LDL or LDL-C) became the hallmark of FH. Further observation led to the discovery of a receptor for LDL particles and it was later established that patients with FH possessed a mutation in the gene that coded for this LDL receptor protein (Gidding et al., 2015). Thus, increased levels of LDL found in patients with FH are a consequence of a failed production of LDL receptor protein, leading to a reduction in overall LDL receptor activity.

To summarize the pathological consequence of this matter, recall that cholesterol is packaged into apolipoprotein B-containing very low-density lipoproteins (VLDL) (Nordestgaard et al., 2013). VLDL is the precursor of LDL. LDL accounts for 75% of the cholesterol transport in the body, transporting the cholesterol from the liver to peripheral tissues (Gidding et al., 2015). "Regulated endocytosis of LDL via apolipoprotein B by peripheral cells and hepatocytes occurs through the LDL receptor and adaptor protein" (Nordestgaard et al., 2013, p. 3480). Nearly 70% of LDL is cleared from the plasma by LDL receptors located on the cellular membranes of liver cells (Gidding et al., 2015). The mutations of the LDL receptor can be differentiated into either LDL receptor-deficient mutations or LDL receptor-defective mutations. "The major effect of the type of LDL receptor mutation relates to the contribution of the defect to the LDL-C level" (Gidding et al., 2015, p. 2170). Mutations of the LDL receptor (LDLR) gene lead to defective uptake of LDL from the blood, resulting in massive amounts of LDL remaining in the bloodstream (Robinson, 2013).

Inherited in an autosomal dominant fashion, FH can be further delineated into two groups: the more common heterozygous FH, as well as homozygous FH. Heterozygous FH (HeFH) is the most common form of the disease, affecting approximately 1 in 300 to 500 persons worldwide (Robinson, 2013). "When left untreated, patients with HeFH typically have

2- to 3- fold higher levels of plasma LDL-C compared with healthy individuals" (Robinson, 2013, p. 140).

In contrast, homozygous FH (HoFH) is a rare form of the disease, with a prevalence of 1 in 1 million persons. HoFH is a more severe and aggressive form of FH that is often unresponsive to traditional treatment of hypercholesterolemia (Robinson, 2013). Patients with HoFH have levels of LDL-C that are 6- to 10-fold higher than normal individuals (Robinson, 2013).

From an epidemiologic standpoint, "the prevalence of FH is as high as one in 100 among certain groups, including French Canadians, Christian Lebanese, and 3 populations in South Africa (Ashkenazi Jews, Dutch Afrikaners, and Asian Indians)" (Safeer, 2015, p. 465). Prior to the release of the International Classification of Diseases 10th revision, FH was not designated an independent code, and therefore made reliable estimates of the number of individuals with FH difficult.

Cardiovascular Risk in Patients with Familial Hypercholesterolemia

Due to the subtle, if any, physical manifestations of FH, the disease is difficult to diagnose. Unfortunately, the disease goes undiagnosed in approximately 80% of individuals who have it (Safeer, 2015). Long-term exposure to elevated LDL levels leads to an increased risk for cardiovascular events; patients with FH have a much higher risk of dying from a coronary event than those in the general population. Men with FH have more than a 50% risk of coronary heart disease by age 50 and women with FH have a 30% risk of coronary heart disease by age 60 (Safeer, 2015).

Though the focus of this document is to discuss intervention, it is reasonable to first discuss the screening process for FH briefly. FH should be suspected in all patients who have a

family history of premature heart disease. If suspicion of FH is high, additional screening in the form of a lipid profile can be pursued for any patient older than age 2 (Safeer, 2015). FH should be included in the differential diagnosis for any encounter in which a patient is found to have very high LDL levels (Safeer, 2015). FH should be suspected in the presence of LDL levels greater than or equal to 190 mg/dl in patients aged 20 years and older (Safeer, 2015). For patients younger than 20 years old, suspect FH with LDL levels greater than or equal to 160 mg/dl (Safeer, 2015).

In addition to serum LDL levels, the diagnosis of familial hypercholesterolemia can be determined by referring to several different validated criteria sets, such as the MEDPED Criteria or the Simon Broome Criteria (As cited in Safeer, 2015 by Fahed & Nemer, 2011). These criteria sets look at not only the LDL level, but also varying degrees of family history as well as physical findings. Physical findings that would prompt concern for FH include tendon xanthomas at any age, tuberous xanthomas or xanthelasmas in patients under age 20-25, and arcus corneae in patients younger than age 45 (Safeer, 2015).

Once the diagnosis of familial hypercholesterolemia is established, a multifaceted approach to treatment interventions must be initiated to protect the patient from adverse cardiovascular events. Upon the diagnosis of homozygous FH in particular, the clinician should assume atherosclerosis is present at the time of diagnosis (Gidding et al., 2015). In terms of determining cardiovascular risk for these patients, it must be noted that risk calculators such as the Framingham Risk Score are *not* appropriate for patients with FH, as these patients' risk for cardiovascular events is much higher due to lifelong exposure to elevated LDL levels (Robinson, 2013). Despite the great risk of atherosclerotic cardiovascular disease associated with familial hypercholesterolemia, up to 50% of patients that achieve a proper diagnosis of familial

hypercholesterolemia fail to receive an adequately aggressive treatment regimen (Turgeon, Barry, & Pearson, 2016).

To better appreciate the concept of cumulative LDL burden, Figure 1 in Appendix A demonstrates the direct relationship between LDL and the age in which an individual with FH may reach the threshold for coronary heart disease. As the figure depicts, the coronary heart disease threshold is much lower in an individual with heterozygous FH in comparison to the general population, as the LDL cholesterol burden is reached as early as age 35 (Nordestgaard et al., 2013). This threshold is even lower in the individual with homozygous FH, as a patient with homozygous FH may reach this threshold as early as age 12.5. The graph also visualizes the effect of statin therapy on this threshold, a topic that will be covered in the following section.

In addition to the coronary artery disease risk associated with FH, a prospective cohort study by Di Salvo et al. (2012) also examined the link between left ventricular morphology and functional cardiac alterations occurring during childhood as a result of FH. The authors of this study evaluated 90 children, 45 with FH and 45 controls, all with a mean age of 11 +/- 3 years. Inclusion criteria for the study included: presence of one parent with a definite clinical or molecular diagnosis of FH, age between 6 and 16 years, use of a low-fat diet for greater than 3 months, fasting plasma LDL cholesterol levels above the 90th percentile and triglyceride levels <4.0 mmol/L on 2 separate occasions, fasting glucose levels in the normal range, adequate contraception (for sexually active girls), and finally no treatment for hypercholesterolemia (including plant sterol or stanol) (Di Salvo et al., 2012). The control group of healthy children was matched 1:1 for age and were comparable for gender. There were not any cardiovascular structural or functional abnormalities present in the control individuals, and none of the control individuals received any medications.

Left ventricular (LV) measurements were taken from two-dimensional guided M-mode tracings (Di Salvo et al., 2012). LV was indexed for height and for body surface area. In the children with FH, the left ventricular walls appeared thicker and there was also a significantly higher LV mass present in these patients. It was also found that children with FH have mild diastolic and systolic abnormalities, thereby increasing their cardiovascular risk. This study incorporated office and ambulatory blood pressure monitoring, thus excluding the possibility that these structural abnormalities were related to established or marked hypertension. The study's findings are significant and, again, emphasize the crucial importance of early intervention in these patients.

Statin Therapy and Risk Reduction in Patients with Familial Hypercholesterolemia

As discussed above, reducing the risk of cardiovascular events in patients with FH remains the top priority in the treatment plan. For reduction of cardiovascular risk, treatment with a statin medication is the first drug of choice, as the efficacy and safety of this LDL lowering class of medication, as well as its effectiveness in preventing cardiovascular disease, has been amply demonstrated in both primary and secondary prevention trials (Friedrich, 2010).

Statin medications, scientifically and structurally referred to as 3-Hydroxy-3-methylglutaryl-coenzymeA (HMG-CoA) reductase inhibitors, exert their effects by inhibiting the HMG-CoA enzyme, which is the enzyme required for endogenous synthesis of cholesterol (Braamskamp, Wijburg, & Wiegman, 2012). "Decreased cholesterol levels in hepatocytes trigger a feedback mechanism that leads to an increased presence of LDL receptors on the cell surface of the hepatocyte, thus increasing LDL-C clearance from the circulation" (Braamskamp, Wijburg, & Wiegman, 2012, p. 766).

The American College of Cardiology (ACC) and the American Heart Association (AHA) released the *Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults* in 2013 with the goal of preventing cardiovascular disease and improving the management of patients with cardiovascular disease. The authors of this guideline used data from randomized controlled trials (RCTs), systematic reviews, and meta-analyses of RCTs to effectively update the clinical practice recommendations for this topic. The authors of this guideline found extensive and consistent evidence supporting the use of statins for the *primary* prevention of atherosclerotic cardiovascular disease (ASCVD) in individuals with primary elevations of LDL above 190 mg/dl, a grade "B" recommendation (Stone et al., 2013).

Due to the fact that placebo controlled trials are not ethical in patients with FH, there is lacking estimates of the true efficacy of statin treatment in patients with FH (Vermissen et al., 2008). Vermissen et al. (2008) instead conducted a cohort study to determine the efficacy of statin treatment on the risk of coronary heart disease in patients with FH. This study recruited a cohort of 2,400 patients with FH from 27 different lipid clinics, with a "start date" of January 1st, 1990, which was just after the first statin (simvastatin) became available in the Netherlands. Patients who already had coronary heart disease were excluded, thus "mimicking" a controlled primary prevention trial starting at the introduction of the first statin (Vermissen et al., 2008). For the comparison group, a group of patients were selected from the large Rotterdam study, which was a large population-based, prospective follow-up study that assessed the disease burden in elderly people. Specifically, patients with familial hypercholesterolemia who were older than 55 years at the time of January 1st, 1990 were the ones selected from the Rotterdam study. The analysis and comparison groups were matched for age and sex.

The major outcome for this study was myocardial infarction. The Cox proportional hazard model was used to estimate the risk of coronary heart disease among statin treated patients, compared with the untreated patients from the comparison Rotterdam group. In familial hypercholesterolemia, the absolute risk of first onset coronary heart disease was 11/1000 person years in the statin treated patients, compared with 119/1000 person years in the untreated group (Vermissen et al., 2008). Incident coronary heart disease also occurred at a younger age in the untreated patients, with age of onset at 48.6 years versus 50.9 years in the statin treated group (Vermissen et al., 2008). In conclusion, the statin treated group had a *76%* reduction in risk of coronary heart disease compared with the untreated patients (adjusted for year of birth and sex; hazard ratio 0.24 with 95% confidence interval 0.18 to 0.30, $P < 0.001$) (Vermissen et al., 2008).

A retrospective cohort study conducted by Raal and colleagues sought to evaluate the impact of advances in lipid-lowering therapy on cardiovascular disease in patients with homozygous FH. This study reviewed data from July 1972, which was also the time of inception of the first specialized lipid clinics in South Africa, through March 2009. The medical records of homozygous FH subjects were reviewed. Similar to the study by Vermissen and colleagues, January 1, 1990 was selected as the delineation for modern lipid-lowering therapy, as this was the date in which the first statin was available in South Africa (Raal et al., 2011).

A major adverse cardiovascular event (MACE), defined as death due to a cardiovascular cause or nonfatal myocardial infarction, stroke, or need for arterial revascularization, was the endpoint for this study. All-cause mortality and time to first MACE were compared before and after the introduction of the modern lipid-lowering therapy. “Despite not achieving LDL-C target and only achieving a mean reduction in LDL-C of 26%, patients who had received modern lipid-lowering therapy, particularly statin therapy, showed a significant reduction in mortality” (Raal et

al., 2011, p. 2205). The authors conclude this study by stating that advances in statin therapy are associated with delayed cardiovascular events, as well as prolonged survival rates, in patients with homozygous FH.

The *Scientific Statement* document from the AHA (Gidding et al., 2015) provides clinicians with recommendations for treatment of FH. For adult heterozygotes, the approach to treatment begins with an initial goal of reducing LDL by at least 50%, and this is predominantly achieved by use of a statin. This goal can be followed by achieving an LDL of < 100 mg/dl (in the absence of CAD or other major risk factors), or < 70 mg/dl (in the presence of CAD or other major risk factors) (Gidding et al., 2015). The maximal LDL reduction that can be tolerated with therapy is preferred; when the statin-induced side effects are disabling but a response to the statin is present, treatment with a lower dose of the statin given daily or even on alternating days should be encouraged (Gidding et al., 2015). For homozygotes, lipid-lowering therapy (usually statins) should be initiated *at* diagnosis and as early as possible (Gidding et al., 2015). Despite reducing LDL only modestly in this group, "statin therapy has been shown to reduce cardiovascular and all-cause mortality" (Gidding et al., 2015, p. 2180).

Specific dosing recommendations of various statin medications are provided in the report by Gidding et al., 2015. These recommendations can be found in Table 1 of Appendix A of this document. Statins are as effective in children as they are in adults, with LDL reductions of 21-39% achieved, depending on the dose and type of statin that is being prescribed (Braamskamp, Wijburg, & Wiegman, 2012). "The NLA Expert Panel on Familial Hypercholesterolemia recommends initial treatment for pediatric patients with statin therapy beginning at age 8 years, although patients with homozygous FH may require treatment at an earlier age" (Robinson, 2013, p. 145). Treatment goals for pediatric patients with FH are similar to those of adults; a

reduction in LDL levels of at least 50% or an LDL level less than 130 mg/dl should be the target (Robinson, 2013). The safety efficacy of statins in pediatric patients remains high; to date, no significant adverse effects of statins have been identified in pediatric patients (Robinson, 2013).

In terms of the management and monitoring of statin therapy in these patients, "a high level of RCT evidence supports the use of an initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and calculated LDL-C), followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy, to determine a patient's adherence" (Stone et al., 2013, p. S21). Adverse effects of statin medications include headache, dyspepsia, myositis, and potential elevation in hepatic transaminase levels (Gidding et al., 2015). Therefore, upon initiation of statin therapy, Gidding and colleagues recommend obtaining a liver function panel at baseline, again at 3 months, and periodically thereafter. A CPK should be obtained at baseline only if the patient has symptoms of myalgia.

Learning Points

1. Familial hypercholesterolemia is an autosomal dominant disorder that results in a genetic mutation that contributes to extreme elevations in LDL cholesterol.
2. Familial hypercholesterolemia should be suspected in the presence of LDL levels greater than or equal to 190 mg/dl in patients age 20 and older, and in the presence of LDL levels greater than or equal to 160 mg/dl in patients under the age of 20.
3. Long-term exposure to elevated LDL levels puts patients with familial hypercholesterolemia at significant risk for cardiovascular events; men with familial hypercholesterolemia have more than a 50% risk of coronary heart disease by age 50 and women have a 30% risk of coronary heart disease by age 60.

4. The efficacy and safety of statins have been amply demonstrated in both primary and secondary prevention trials; for this reason, statins remain the drug of choice in patients with familial hypercholesterolemia.
5. The use of modern statin therapy in patients with familial hypercholesterolemia is associated with delayed cardiovascular events, as well as prolonged survival rates in these individuals.

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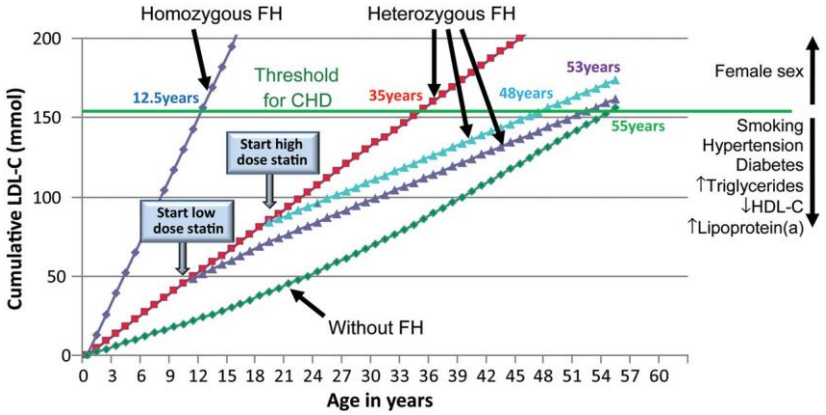
Appendix A

Figure 1. LDL Cholesterol Burden in Individuals with or without Familial Hypercholesterolemia



(Nordestgaard et al., 2013)

Table 1. Dosages of Lipid-Lowering Drugs

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Atorvastatin, adult	10–20 mg every day	10–40 mg every day	80 mg every day	Administer any time of day. Dose adjustment in patients with renal dysfunction is not necessary.
Atorvastatin, pediatric	10 mg every day (10–17 y for HeFH)	10–20 mg every day	20 mg every day	…
	10–20 mg every day (>6 y for HoFH)	10-80 mg every day	80 mg every day	
Fluvastatin, adult	20 mg QHS	20–80 mg divided every day bid	40 mg bid 80 mg XL every day	Dose adjustments for mild to moderate renal impairment are not necessary.
Fluvastatin, pediatric	20 mg QHS	20–80 mg divided every day bid	40 mg bid	…
	80 mg XL every day (10–16 y for HeFH)	Same	80 mg XL every day	

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Lovastatin, adult	20 mg with dinner	20–40 mg with dinner	40 mg bid	Administration with food increases bioavailability. Twice-daily dosing provides greater LDL-C–lowering efficacy than every-day dosing. In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dose increases >20 mg/d should be carefully considered and, if deemed necessary, implemented cautiously.
Lovastatin, pediatric	20 mg with dinner (10-17 y for HeFH)	10–40 mg with dinner	40 mg daily	…
Pitavastatin, adult	1–2 mg every day	1–2 mg every day	4 mg every day	Administer any time of the day with or without food. Moderate renal impairment (glomerular filtration rate, 30<60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) and end-stage renal disease on hemodialysis: starting dose of 1 mg once daily and maximum dose of 2 mg.
Pitavastatin, pediatric	Not currently available	Same	Same	…
Pravastatin, adult	10–40 mg every day	10–40 mg every day	80 mg every day	Administer with food to reduce dyspepsia. In patients with a significant history of renal or hepatic dysfunction, a starting dose of 10 mg is recommended.
Pravastatin, pediatric	20 mg every day (8–13 y for HeFH)	Same	Same	…
	40 mg every day (14–18 y for HeFH)	Same	Same	
Rosuvastatin, adult	10–20 mg every day	10–20 mg every day	40 mg every day	Administer any time of the day. Consider 5-mg starting dose in Asians. In patients with creatinine clearance <30 mL/min who are not on hemodialysis, start with 5 mg with a maximum dose of 10 mg.
Rosuvastatin, pediatric	5–10 mg every day (10–17 y for HeFH)	5–20 mg every day	20 mg every day	…
Simvastatin, adult	20–40 mg QPM	20–40 mg QPM	40 mg QPM	Administer with food to reduce dyspepsia. Simvastatin 80 mg should be used only in patients who have been taking this dose for ≥12 mo without evidence of muscle injury (myopathy). In patients with severe renal impairment, start with 5 mg QPM.
Simvastatin, pediatric	10 mg QPM (10–	10–40 mg QPM	40 mg QPM	…

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
	17 y for HeFH)			
	40 mg QPM (>13 y for HoFH)	Same	Same	

Adapted from Gidding et al., 2015, p. 2179-2181