

# Statins for Primary Prevention



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### **Purpose and Overview**

This Internal Medicine Grand Rounds will review the evidence regarding statin use in the primary prevention setting, particularly data that concerns using LDL-C thresholds, and intermediate-term risk assessments to guide statin therapy in this population.

### **Learning Objectives**

At the conclusion of this lecture the listener should be able to

- 1) Understand the significance of the association of elevated serum levels of atherogenic lipoprotein species, including LDL-C, in determining ASCVD risk, independent of other risk factors.
- 2) Understand the importance of estimating 10 year absolute risks in determining an individual's eligibility for statins, and the strengths and weaknesses of the ACC/AHA Pooled Cohort Equations.
- 3) Be familiar with additional clinical tools, including life time risk estimates, coronary artery calcium, and C-reactive protein, that may help to better risk stratify individuals.

While atherosclerotic cardiovascular disease (ASCVD) rates have declined in recent years, CVD remains the leading cause of mortality in the United States. Elevated serum levels of total cholesterol and low density lipoprotein cholesterol (LDL-C) are considered a major risk factor for ASCVD. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are effective in reducing serum LDL-C and their development is considered a significant breakthrough in our efforts to reduce CVD morbidity and mortality.

As with any medication, the decision on who should be considered for statin therapy is based on balancing the benefits, risks, patient preferences, and costs of treatment. For statins, individuals who are at the highest absolute risk for ASCVD are expected to derive the greatest benefit, which outweighs the potential side effect and adverse event risks and the costs of treatment, adjusted for the quality of life years gained and expenditure avoided from ASCVD events averted. The benefits of treatment are defined by the absolute risk reduction which is proportional to the absolute baseline risk. Therefore, since the introduction of statins until recently, national and global organizations, including the National Cholesterol Education Program's Adult Treatment Program (ATP)-III group, which were the most established cholesterol guidelines in the United States from 2002 to 2013, recommended statin therapy using a combination of 10 year absolute risks and LDL-C thresholds, aiming for lower thresholds and targets in those at higher absolute risks.<sup>1</sup>

This preventive approach was significantly modified by the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, which places much more emphasis on 10 year absolute risk over LDL-C thresholds or targets.<sup>2</sup> This was done as an attempt to base the new guidelines as much as possible on evidence from clinical trials of statins that compared outcomes in patients at intermediate or high risk of cardiovascular events randomized to fixed doses of either statin versus placebo or high dose statin versus low dose statin. To date, there have not been any large randomized clinical trials assessing for improvement in ASCVD outcomes titrating statin doses to achieve a specific LDL-C goal. In addition, there was limited data assessing whether elevated cholesterol levels may lead to ASCVD morbidity and mortality in individuals who have little or no other ASCVD risk factors, and therefore are at low overall absolute risk. Based on these data, the 2013 ACC/AHA cholesterol guidelines recommended moderate or high dose statin to 4 groups of patients based almost entirely on their intermediate term absolute risk (Table 1), 3 of which involve primary prevention populations.

Table 1: Groups with Statin Benefit by the 2013 ACC/AHA Cholesterol Guidelines
1) Secondary Prevention in individuals with established CVD
2) Individuals with diabetes 40-75 years old with LDL-C 70-189 mg/dL
3) Primary Prevention in individuals with LDL-C $\geq$ 190 mg/dL
4) Primary Prevention in individuals 40-75 years old with 10 year estimated risk of ASCVD of $\geq$ 7.5% with LDL-C 70-189 mg/dL

## **Statins for Secondary Prevention of ASCVD**

Patients with a previous history of established ASCVD are at the highest absolute risks of having recurrent ASCVD events. Multiple randomized clinical trials in patients immediately after an acute coronary syndrome or with a remote history of ASCVD have demonstrated that allocation to the statin (versus placebo) or high dose statin (versus low dose statin) arm led to reduction of ASCVD events. An individual level meta-analysis of 26 statin clinical trials with 170,000 participants demonstrated for approximately every 40 mg/dL in LDL-C, there was a decrease in relative risk of ASCVD events by 20%.<sup>3</sup> Therefore, it is widely accepted that the benefits of statin therapy far outweigh the risks in the secondary prevention of ASCVD.

## **Statins for Primary Prevention of ASCVD in Patients with Diabetes Mellitus**

Patients with diabetes mellitus are at significantly increased risk of ASCVD events and some epidemiological data have suggested that having diabetes mellitus is equivalent to having established ASCVD in terms of risk. In the Collaborative Atorvastatin Diabetes Study (CARDS), 2838 patients without ASCVD were randomized to atorvastatin 20mg or placebo.<sup>4</sup> Atorvastatin reduced the composite end-point of acute coronary syndrome, coronary revascularization or stroke by 37%. It was estimated that 37 major cardiovascular events would be prevented per 1000 people treated for 4 years. A meta-analysis by the Cholesterol Treatment Trialists' Collaborators of 18,686 people with diabetes followed for 4.3 years showed that there was a 9% proportional reduction in all-cause mortality and 21% reduction in major vascular events, irrespective of whether they had a history of ASCVD and independent of baseline LDL-C levels.<sup>5</sup> Therefore, there is sufficient clinical trial data to recommend statins in patients with diabetes mellitus, and in addition to the ACC/AHA cholesterol guidelines, statin therapy was also recommended by the ATP-III guidelines when LDL-C > 70-100 mg/dL and is currently recommended by the American Diabetes Association in all patients.

## **Statins for Primary Prevention of ASCVD in Patients without Diabetes Mellitus**

While abundant data is present for treating patients with established ASCVD and diabetes mellitus with statins, there is significant disagreement on who should be targeted for statin therapy in the rest of the population. Although the individual absolute risk of ASCVD in this subgroup is lower than patients with established ASCVD and diabetes, greater overall events by a margin of 2:1 occur in those without a history of either due to their greater numbers.

### *Primary Prevention Statin Trials*

Several statin primary prevention trials have been conducted over the last 25 years (Table 2). The West of Scotland Coronary Prevention Study (WOSCOPS) screened for men with total cholesterol levels > 252 mg/dL, and if LDL-C remained > 155m/dL after 4 weeks of diet recommendations, randomized them to pravastatin 40mg or placebo.<sup>6</sup> After a median follow-up of 4.9 years, there was a 31% reduction in the composite outcome of non-fatal myocardial

infarction or death. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), 6605 patients with LDL-C between 130-190 and low HDL-C were randomized to lovastatin 20-40 mg.<sup>7</sup> After a median of 5.2 years, there was a 37% reduction in the primary outcome of coronary heart disease death, myocardial infarction, unstable angina and sudden cardiac death. In 2002 the Anti-Hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Component (ALLHAT-LLT) trial showed no significant difference in the primary outcome of all cause mortality in 10,355 patients with LDL-C 120-189 mg/dL, hypertension and 1 additional cardiovascular risk factor randomized to pravastatin 40mg.<sup>8</sup> However, up to 1/3 of the patients in the placebo began to take lipid lowering therapy during the study and the differences in on treatment LDL-C were less than expected, which may have led to a lack of difference in events between the groups. The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) trial randomized 10,305 patients with hypertension, total cholesterol <252 mg/dL and 3 additional cardiovascular disease risk factors to atorvastatin 10 mg or placebo.<sup>9</sup> The risk of the combined end-point of non-fatal myocardial infarction and coronary heart disease death was 36% lower in the atorvastatin arm. After a mean follow-up of 5.3 years in the MEGA trial, pravastatin 10-20 mg daily + diet decreased the risk of the combined outcome of coronary heart disease death, myocardial infarction, angina, sudden cardiac death and coronary revascularization by 33% in 3,966 patients with total cholesterol of 220-270 mg/dL compared to diet alone.<sup>10</sup> The recently completed Heart Outcomes Prevention Evaluation (HOPE)-3 study evaluated the effects of statin therapy in a lower risk group, randomizing 12,705 men older than 55 years old and women older than 65 years old with at least 1 additional cardiovascular disease risk factor to rosuvastatin 10mg or placebo.<sup>11</sup> After a follow-up of 5.6 years, there was a 24% decrease in the 1<sup>st</sup> primary outcome of cardiovascular disease death, nonfatal myocardial infarction, and non-fatal stroke, and a 25% decrease in the 2<sup>nd</sup> primary outcome which included components of the 1<sup>st</sup> primary outcome + revascularization, heart failure, and resuscitated cardiac arrest.

Trial	N	Statin	Inclusion Criteria	Baseline LDL-C	F/U	Outcomes
WOSCOPS (1995)	6595	Pravastatin 40mg	LDL-C > 155 after diet	192	4.9	↓31% MI + CHD death ↓28% CHD death ↓22% all cause mortality
AFCAPS/ TexCAPS (1998)	6605	Lovastatin 20-40mg	LDL-C 130-190 M: 45-73 yo, HDL < 45 W: 55-73 yo, HDL < 47	150	5.2	↓37% CHD death+ MI +US+SCD ↓40% MI ↓32%UA
ALLHAT-LLT (2002)	10355	Pravastatin 40mg	HTN + 1 additional CV risk factor	146	4.8	All cause mortality 14.9% prava vs 15.3% placebo (p=NS)
ASCOT-LLA (2003)	10305	Atorvastatin 10mg	HTN + 3 CV risk factors	133	3.3	↓36% MI + fatal CHD
MEGA (2006)	7832	Pravastatin 10-20 mg	Age: 40-70 yo Total Chol. 220-270	157	5.3	↓33% fatal CHD+MI+angina+SCD+coronary revascularization ↓48% MI
JUPITER (2008)	17802	Rosuvastatin 20mg	LDL < 130 hsCRP > 2	108	1.9	↓44% MI+CVA+CVD death+ revascularization + UA ↓54% MI ↓20% all cause mortality
HOPE-3 (2016)	12705	Rosuvastatin 10mg	Men > 55 yo, Women > 65 yo + 1 CV risk factor	128	5.6	↓24% CVD death+MI+CVA ↓25% CVD death+ MI+CVA+ revasc+CHF+resuscitated cardiac arrest

In reviewing these trials, a few conclusions can be drawn. In all trials except 1, significant reductions in ASCVD events were seen with a fixed dose statin compared to placebo. Some trials used baseline total cholesterol or LDL-C in their inclusion criteria, while others only had non-lipid cardiovascular disease risk factors in their inclusion criteria. None of the trials attempted to achieve on-treatment total cholesterol or LDL-C targets. The absolute reduction in risk was proportional to the intermediate-term predicted absolute risk at baseline.<sup>12</sup> While overall the patients in these primary prevention trials had intermediate to high intermediate-term risks via their risk factors, the more recent trials evaluated populations with lower short term risk (HOPE-3 population had a 10 year ASCVD risk of 8.7%).

Although there has not been a trial that evaluated statin therapy in an exclusively low risk group, subgroup analysis from the Cholesterol Treatment Trialists Collaborators meta-analysis of the individual data from 27 trials of individual data demonstrated that the relative risk reductions in ASCVD events with statins in the lowest risk groups, those at 5 year risks of <5% and 5-10%, were at least as robust, 31-38%, as seen in higher 5 year risk groups. This meta-analysis also reported a 15% relative reduction in vascular mortality and a 9% relative reduction in total mortality in those individuals without a history of vascular disease.

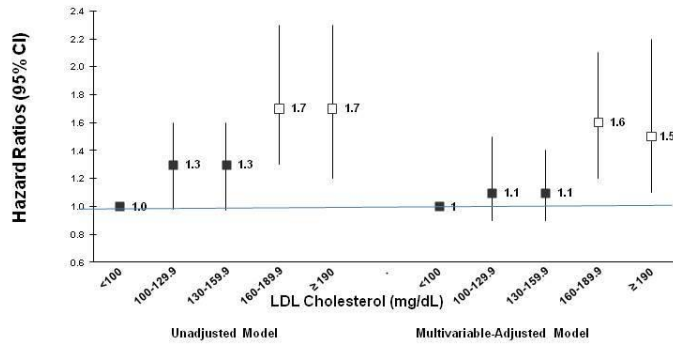
### **Statin treatment in patients with elevated LDL-C levels and at low 10 year risk of ASCVD**

The 2013 ACC/AHA guidelines recommend high dose statin therapy for serum LDL-C  $\geq$  190 mg/dL, with possible consideration given to LDL-C  $\geq$  160 mg/dL due to concerns of a hereditary cause of hyperlipidemia, such as familial hypercholesterolemia. However, LDL-C  $\geq$  190 mg/dL by itself is not specific for the diagnosis of familial hypercholesterolemia. In addition, it is unclear whether this threshold is appropriate for initiating statin therapy in a low risk population.

Several observations support the theory that LDL-C may lead to atherosclerosis independent of other ASCVD risk factors. The 'lipid hypothesis' proposes that serum cholesterol levels play a key causative role in the development of atherosclerosis. Autopsy data of 35 children and young adults aged 5-24 years old demonstrate that atherosclerosis, as evidenced by fatty streaks, is already present in the aorta and its extent correlates with serum total cholesterol and LDL-C.<sup>13</sup> Epidemiological and genetic studies also support the association of serum cholesterol levels in young adults to future ASCVD events. In a prospective study of 1,017 young men with lipids measured at a mean age of 22 years, increasing total cholesterol levels were associated with higher incident CVD mortality after a median follow-up of > 30 years.<sup>14</sup> Similarly, in 356,222 middle aged men of the MRFIT cohort, a continuous graded increase in the risk of coronary heart disease death was seen with increasing levels of total cholesterol, without a threshold level below which this risk was not present.<sup>15</sup> In a recent analysis of individuals of the Cooper Center Longitudinal Study (CCLS) with a 10 year ASCVD risk of < 7.5% and followed for > 20 years, a significant association was seen between LDL-C levels and CVD mortality, and an association independent of other risk factors seen for LDL-C  $\geq$  160 mg/dL, supporting this cut-off for even otherwise low risk individuals (Figure). These epidemiological data demonstrate that there is a

continuous, graded relationship between serum cholesterol and LDL-C levels and ASCVD risk, without a threshold level below which the risk is not present.

## CVD Death in the CCLS in those with 10 year estimated ASCVD < 7.5%



Studies evaluating mutations in genes that affect serum cholesterol levels also support the lipid hypothesis. Work by Drs. Jonathan Cohen and Helen Hobbs identified a loss of function mutation in the gene for proprotein convertase subtilisin/kexin type 9 (PCSK9) that results in low LDL-C and low ASCVD event rates. Interestingly, the effect of the lower LDL-C is greater than what is seen in statin trials.<sup>16</sup> For example, a nonsense mutation associated with a 28% decrease in LDL-C was associated with an 88% reduced risk of coronary heart disease, and another polymorphysm associated with a 15% decrease in LDL-C levels was associated with a 47% reduced risk of coronary heart disease. Mendelian randomization studies, in which polymorphysms associated with cholesterol levels are used to randomize individuals to either lower or higher levels of cholesterol during a course of their lifetimes, have also demonstrated a lower risk of ASCVD per unit of LDL-C decrease that seen in statin trials.<sup>17</sup> These data suggest that having lower LDL-C over a course of a lifetime, and delaying the initiation of the atherosclerotic process, lowers the risk of ASCVD events to a greater degree than lowering LDL-C later in life, when the atherosclerotic process has already advanced. A recent study from the Framingham Offspring Cohort with serial measures of LDL-C also confirms this, showing that in cohort participants with an estimated 10 year ASCVD risk < 7.5%, those who had LDL-C levels consistently > 130 mg/dL had higher event rates compared to those with LDL-C not consistently > 130 mg/dL throughout the course of the study.<sup>18</sup>

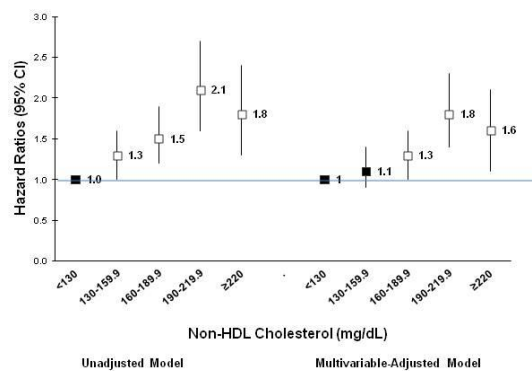
A 20 year follow-up report of WOSCOPS also supports treating patients earlier. Men who were assigned to pravastatin for the 5 year period of the trial had continued benefits seen in the following 15 years, including a 13% reduction in all cause mortality and 21% decrease in CVD death, supporting a legacy effect which may be due to the delay in development at the early stages of atherosclerosis.<sup>19</sup>

## Lipid Measures other than LDL-C

Several other lipid measures besides LDL-C may be considered for assessing risk of ASCVD including of non-HDL cholesterol levels, total cholesterol/HDL-C ratio, apolipoprotein B levels, LDL-C particle size and number. In addition to measuring LDL-C and intermediate density lipoprotein cholesterol which are measured by LDL-C calculated by the Friedwald equation, non-HDL-C measures very low density lipoprotein cholesterol, which is also thought to play a role in the development of atherosclerosis. One apolipoprotein B molecule is present on each of the atherosclerotic lipoproteins listed above, so it provides information on the total number of atherogenic lipid particles. Differences in sizes of LDL-C particles have been reported to confer different ASCVD risks, however this laboratory test is not widely available.

Of the alternatives to LDL-C, non-HDL-C appears appealing since it does not require additional lab testing, is less affected by the fasting state, evaluates a more complete profile of atherogenic lipids, and appears to outperform LDL-C. In most studies, non-HDL-C appears to have a stronger association with future ASCVD risk than LDL-C.<sup>20</sup> Similarly when non-HDL was assessed in low risk individuals of the CCLS, the associations with CVD mortality appeared more robust than for LDL-C (Figure). While the ATP-III guidelines had recommended non-HDL-C levels as secondary targets, the 2013 ACC/AHA do not recommend assessing this lipid measure.

### CVD Death in the CCLS in those with 10 year estimated ASCVD < 7.5%



## Statin Treatment Based on Intermediate-Term Absolute Risk

The most controversial aspect of the 2013 ACC/AHA cholesterol guidelines is the recommendation that the patient-physician discussion about statin therapy be initiated in all individuals with a 10 year ASCVD risk of  $\geq 7.5\%$  by the Pooled Cohort Equations (PCE),



irrespective of LDL-C levels. The previous ATP-III guidelines recognized near optimal LDL-C was < 130mg/dL in low risk individuals, but had higher LDL-C targets as predicted absolute 10 year risks, using a combination of number of risk factors and the Framingham Risk Score for hard coronary heart disease events, decreased.<sup>1</sup> Similar to the current guidelines, lipid lowering therapy was not recommended in low risk individuals unless LDL-C levels also exceeded 160-190 mg/dL, however lower thresholds were used for those with risk estimated to be in the 10-20% range.

### *Pooled Cohort Equations*

Another major debated issue with the ACC/AHA guidelines was the use to the PCE to estimate 10 year risk. The guidelines committee members moved away from a variation of the Framingham Risk Score used by the ATP-III guidelines to estimate 10 year risks due to its exclusion of stroke and stroke mortality and its derivation from a mostly Caucasian population, not representative of the overall US population. The PCE were derived from African-American and Caucasian men and women 40-79 years old and free of CVD at baseline from the Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study, Coronary Artery Risk Development in Young Adults (CARDIA), Framingham, and Framingham Offspring cohorts. Age and sex specific equations using the risk factors of age, total cholesterol, HDL-C, systolic blood pressure, diabetes, and smoking status for ASCVD events including myocardial infarction, coronary heart disease mortality, stroke and stroke mortality were developed and internally validated.<sup>21</sup> Online versions of the risk calculator can be found at [tools.acc.org/ASCVD-Risk-Estimator](https://tools.acc.org/ASCVD-Risk-Estimator).

When applied to the National Health and Nutrition Examination Survey (NHANES), a representative sample of the US population, the estimated number of adults who would be eligible for statin therapy increased from 43.2 million Americans by the ATP-III criteria to 56 million by the ACC/AHA criteria, with 10.4 million of the increase occurring in individuals for the purposes of primary prevention. Increased statin eligibility was especially more marked among older individuals with the ACC/AHA criteria.<sup>22</sup>

When compared to the ATP-III recommendations for statin eligibility, application of the ACC/AHA guidelines appears to improve discrimination, or the ability to accurately classify those individuals who will have an event as being at risk, and to classify those individuals who will not have an event as being not at risk. In the Dallas Heart Study, 1 ASCVD event prevented for each additional 14 patients treated with high dose statin and 21 patients treated with moderate dose statin.<sup>23</sup> It was estimated that the new guidelines would result in an additional 4479 to 4771 patients with ASCVD event prevented in Dallas County. Similarly, in a primary prevention population in the Framingham Offspring and 3<sup>rd</sup> Generation cohorts, hazard ratio for ASCVD events was higher in those who were statin eligible by the ACC/AHA criteria, 6.8 (95% CI 3.8-11.9), than they were by ATP-III criteria, 3.1 (95% CI 1.9-5.0).

Multiple studies have also assessed the calibration, or the accuracy of the risk estimates to predict observed ASCVD events of the ACC/AHA PCE. In 10,997 adults in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, estimated risks and observed risks at 5 years per 1000 person-years for individuals by 10 year PCE estimates of <5%, 5-7.5%, and  $\geq 7.5\%$  were 1.9 and 1.9 (95% CI 1.3-2.7), 4.8 and 4.8 (95% CI 3.4-6.7), and 6.9 and 6.1 (95% CI 4.4-8.6), respectively.<sup>24</sup> However, most other studies have not reported the ACC/AHA PCE to be as well calibrated. Soon after they were released, Ridker and Cook raised concerns that the 2013 ACC/AHA PCE overestimated observed risks by 75-150% in 3 well characterized cohorts, the Women's Health Study, the Physician's Health Study, and the Women's Health Initiative Observational study. The authors estimated that this may cause 13-16 million individuals whose true 10 year risk of ASCVD is <7.5% to become statin eligible.<sup>25</sup> Another study looking at 'real world' multi-ethnic population of 307,591 men and women of the Kaiser Permanente Northern California System demonstrated a similar overestimation, which was more pronounced in individuals without diabetes. There have been several reasons that have been proposed for the poor calibration between the ACC/AHA PCE and observed events in several cohorts. It is possible that statin use was underdocumented or ASCVD events under-ascertained in the cohorts. The PCE were derived in cohorts several decades old when the prevalences of several ASCVD risk factors and rates of ASCVD events were different than what they are now, and these equations may not be able to predict ASCVD events as accurately in more contemporary cohorts and populations. Finally, PCE were derived from cohorts consisting of African-Americans and Caucasian individuals, and may not perform as well in other races.

Another criticism of the ACC/AHA PCE is the large influence of age in determining the 10 year risk for ASCVD. For example, a 66 year old Caucasian man, 72 year old Caucasian woman, 69 year old African-American man, and 73 year old African-American woman would all have a 10 year ASCVD risk  $\geq 7.5\%$  even if they do not have any additional risk factors. Certainly, age is the major risk factor that drives most of the risk prediction calculators, but the proportion of men and women > 60 years old that would meet eligibility for statin treatment is higher with the ACC/AHA PCE compared with other calculators. Similarly, younger individuals may not meet eligibility criteria for statin therapy due to low 10 year risk even though they may significantly benefit from treatment. The following 3 cases illustrate some of the shortcomings of the ACC/AHA PCE.

Patient A: 55 year old Caucasian man, smoker, systolic blood pressure 145 mmHg, total cholesterol 150 mg/dL (LDL-C 70 mg/dL), HDL-C 50 mg/dL: PCE 10 year risk of ASCVD 8.8%.

Patient B: 59 year old Caucasian woman, non-smoker, systolic blood pressure 115 mm Hg, total cholesterol 260 mg/dL (LDL-C 180 mg/dL), HDL-C 50 mg/dL: PCE 10 year risk of ASCVD 3.2%.

Patient C: 59 year old Caucasian woman, non-smoker, systolic blood pressure 115 mmHg, total cholesterol 150 mg/dL (LDL-C 70 mg/dL), HDL-C 50 mg/dL: PCE 10 year risk of ASCVD 2.0%.

Patient A may benefit from being on a high dose statin, but much greater benefit would be gained from concentrating on tobacco cessation and treatment of his blood pressure. Similarly, patient B would likely derive a much greater benefit from statins, but would not be eligible by the PCE. Patient C illustrates the small contribution of total cholesterol towards the estimated 10 year risk by PCE, with only an absolute difference in risk of 1.2% compared to Patient B despite significantly different cholesterol levels.

Since age has the most robust association with ASCVD risk, some may argue that statin therapy be delayed in younger individuals. A counter-argument would be that opportunities to prevent a significant amount of ASCVD events would be missed. Even though the incidence of ASCVD events progressively increase with age, the numbers at risk decreases in higher age groups, so that one-half of all ASCVD events in men and 1/3 of all ASCVD events in women occur before the age of 65 years.<sup>26</sup>

#### *Variations of the ACC/AHA PCE*

In an effort to better assess the 10 year absolute risk of ASCVD, several groups have attempted to develop alternative risk calculators using variations of the PCE. One approach incorporating inclusion criteria for the statin clinical trials in those with ASCVD risk  $\geq 7.5\%$  would decrease the number of statin eligible patients by more than 1/3 compared to those who would be eligible based on risk alone.<sup>27</sup> However, this method of risk stratification proved to be inferior to the PCE when evaluated in a European cohort.<sup>28</sup> Another model integrates predicted absolute risk and relative risk reduction from clinical trials to individualize the benefit of statin therapy, using a 10 year absolute risk reduction of 2.3% to determine eligibility.<sup>29</sup> Estimates from the primary prevention population of NHANES estimated that this approach would increase the number of Americans using moderate dose statins, while increasing the number of ASCVD events prevented from 728,572 to 995,080 compared to a 10 year absolute risk  $> 7.5\%$ - based approach over a 10 year period. This would partially be due to better capture of younger individuals with higher LDL-C levels. Another potential strategy explored sex- and age-specific thresholds of 10 year absolute risks, lowering the thresholds  $< 7.5\%$  in younger individuals, which improved sensitivity of the risk calculator to a greater extent than it decrease specificity.<sup>30</sup> In older individuals, the 10 year absolute thresholds would be increased  $> 7.5\%$ , which led to an improvement in specificity without significantly affecting the sensitivity.

Comparison of ACC/AHA PCE with different prediction models demonstrates that overestimation of risks is seen with most models. For example, in the Rotterdam Study cohort, predicted risks by ACC/AHA PCE, ATP-III criteria, and the European Society of Cardiology's SCORE calculator all overestimated actual risks.<sup>31</sup> Statin therapy was recommended in 96% of

men and 66% of women in the ACC/AHA PCE, 66% of men and 39% of women by SCORE, and 52% of men and 36% of women by the ATP-III criteria.

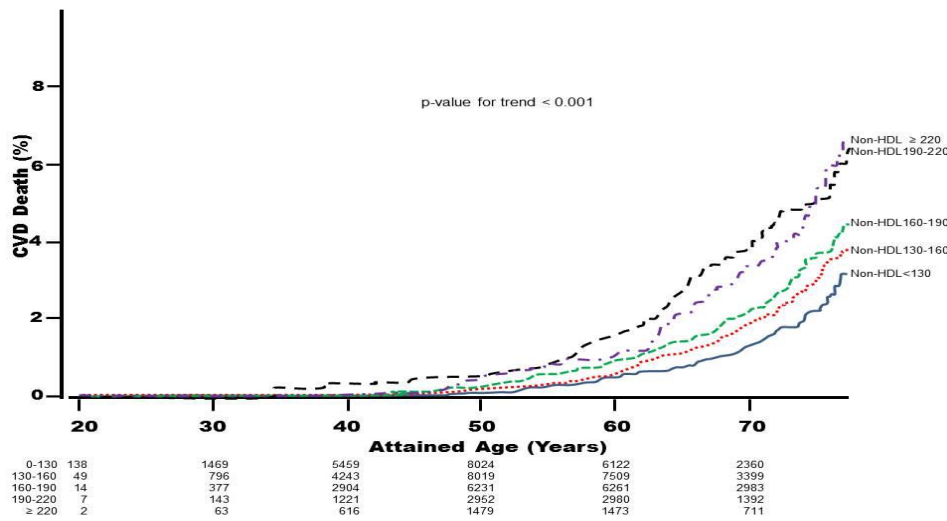
### **Cost-Effectiveness in Primary Prevention**

The release of generic statins has significantly lowered the cost of statin treatment and most data suggest that the use of statins for primary prevention is cost-effective. In the WOSCOPS study, the use of pravastatin 40mg daily compared with placebo was estimated to save over \$900,000 and led to 136 quality adjusted life years (QALY) gained for every 1000 patients treated over a 15 year period, including 163 fewer admissions and saving 1,836 days in the hospital.<sup>32</sup> Treatment of the US population > 35 years old using LDL-C goals more lenient than ATP-III criteria with generic statins was estimated to lead to \$430 million in additional reduced annual health care costs.<sup>33</sup> In fact, aiming for very low LDL-C thresholds of > 130 mg/dL in those with no other ASCVD risk factors, LDL-C > 100 mg/dL in those with 1 risk factor and all moderate risk individuals would cost \$9900 per QALY gained. Using a microsimulation model, another study estimated that treating all patients with an absolute risk threshold of 7.5% by the Framingham Risk Score was acceptable, costing \$37,000 per QALY gained, and a threshold of > 5% costs \$100,000 per QALY gained.<sup>34</sup> At least 1 microsimulation model demonstrated that compared to risk prediction strategies, including the ACC/AHA recommendations, ATP-III recommendations, and approaches that use coronary artery calcium (CAC) and high sensitive C-reactive protein (hsCRP), treating all men > 45 years old and all women > 55 years old was the most cost effective.<sup>35</sup> Such a strategy over 30 years would lead to 15.7 million QALY gained, prevent 7.3 million myocardial infarctions, and save over \$238 billion compared to what the prevalence of statin use is currently. Caution must be taken when interpreting these results, since in addition to the costs of statin therapy, these models are very sensitive to changes in expected reduction in ASCVD events, compliance rates, and adverse event rates. Nevertheless, it appears that with the availability of generic statins, cost of therapy is acceptable for most primary prevention situations.

### **Lifetime Risk Assessment**

Recognizing the limits of using 10 year risk calculators, such as the PCE, estimating an individual's life time risk may assist in the decision of whether to initiate statin therapy. As mentioned, since age is the dominant factor determining risk in the 10 year calculators, a substantial number of younger individuals with low 10 year risk may have elevated life time risk. For example, in patient B from the previous section, while the 10 year ASCVD risk is only 3.2% by the PCE, her lifetime risk as measured by the score provided by the ACC/AHA guidelines is 39%. In contrast, patient C with ideal cholesterol levels and a 10 year risk of 2.0%, still continues to have a low lifetime risk of 8%. In an analysis of the Framingham Heart Study cohort, elevated levels of cholesterol in younger individuals, especially women, was associated with a low predicted short term risk, but a substantially higher lifetime risk.<sup>36</sup> In the Cooper

Clinic Longitudinal Study analysis, increases in CVD mortality with increasing levels of cholesterol are more clearly seen in the later years of life.



The life time estimate associated with the ACC/AHA guidelines is determined by defining optimal, elevated, and significantly elevated levels of 5 traditional risk factors, total cholesterol, systolic blood pressure, diastolic blood pressure, smoking status, and diabetes mellitus.<sup>37</sup>

Table: Lifetime Risk of CVD

Risk Factors	Men	Women
All Optimal	5%	8%
≥ 1 Not Optimal	36%	27%
≥ Elevated	46%	39%
1 Major	50%	39%
≥ 2 Major	69%	50%

Having all optimal levels of risk factors, estimated life time risk is 5% in men and 8% in women, incrementally increasing so that in those with 2 major risk factors, the life time risk is 69% in men and 50% in women. One limitation of this method is that there are only 5 strata of risk each for men and women. In addition, only a very small percentage of the population has all optimal risk and no clear cut-offs have been defined as to when to consider an individual for statins. Improvement is needed in terms of precision, however developing and validating life time risk estimates of ASCVD will be more difficult than 10 year estimates. Despite these limitations, life time risk estimates provide a good additional measure to further assess overall risk burden, especially in the young and in women.

### Non-Traditional Risk Factors for Risk Assessment

Several novel risk factors have been evaluated over the last several years to better risk stratify individuals to better direct therapy. Two, C-reactive protein and coronary artery calcium, will be further discussed.

### *C-reactive protein*

C-reactive protein (CRP) is an acute phase reactant and marker of systemic inflammation that is associated with ASCVD risk factors and outcomes. Post-hoc analysis of the AFCAPS/TexCAPS trial suggested that the efficacy of lovastatin to prevent ASCVD events was influenced by CRP in addition to LDL-C levels.<sup>38</sup> These observations led to the Justification for the Use of Statins for Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, where 17802 men and women without diabetes or ASCVD, LDL-C < 130 mg/dL, and high sensitivity CRP level  $\geq 2$  mg/L, were randomized to either rosuvastatin 20mg daily or placebo.<sup>39</sup> The study showed a 44% relative risk reduction in the combined end-point of myocardial infarction, stroke, revascularization, unstable angina, and CVD death with rosuvastatin.

Despite these results, it is still not clear whether the decrease in ASCVD events was driven by a decrease in CRP levels or a decrease in LDL-C levels. Several studies assessing the effects of targeting inflammation directly in secondary prevention populations are currently underway, including the Cardiovascular Inflammation Reduction Trial (CIRT), assessing low dose methotrexate versus placebo in patients with a previous of coronary artery disease, and Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), assessing the effects of interleukin 1 $\beta$  in patients with a history of myocardial infarction. In addition, while JUPITER and HOPE-3 demonstrate the efficacy of statins to decrease ASCVD events in mostly intermediate risk patients, the question remains whether statins may be beneficial in an even lower risk population. The Eliminate Coronary Artery Study (ECAD) is currently enrolling men 35-50 years old and women 45 to 59 years old without ASCVD with 1 risk factor and randomizing to either atorvastatin 20mg daily or placebo. The primary outcome will be a composite of non-cancer and non-trauma related death, myocardial infarction, revascularization, and stroke after an expected follow-up of 10 years.<sup>40</sup>

Currently, with the availability of generic statins, widespread risk assessment using hs-CRP does not appear cost-effective in low risk, primary prevention population.<sup>41</sup> Although it may be used to better define risk at the individual level, until more data is available, including from the mentioned ongoing clinical trials, routine screening does not appear justified.

### *Coronary Artery Calcium*

The presence of coronary artery calcium (CAC) detected by low radiation, non-contrast CT correlates with the burden of coronary artery disease. The addition of CAC to risk scores improves the score's ability to discriminate those in low predicted risk group who are more likely to have events (improved sensitivity), and those in the high risk group that will not have events (improved specificity).<sup>42</sup> When added to the MESA score, CAC improved the score's discrimination and calibration properties in externally validated cohorts, including the Dallas Heart Study.<sup>43</sup> Similar to hsCRP, due to the low costs of generic statins, it does not appear cost-effective as a screening tool for the entire population.<sup>44</sup> In addition, in younger patients, especially women, CAC may underestimate risk due to non-calcified coronary artery plaque. However, due to its ability to improve discrimination and calibration over traditional risk factors, it may be used in middle-aged individuals who are considered low or borderline

risk by a risk score using traditional risk factors, but may still have further concerns about having subclinical coronary artery disease. Alternatively, CAC may also be more useful to ‘de-risk’ individuals, especially in elderly populations, where the predicted 10 year risk of ASCVD is high, but the absence of CAC portends a favorable CVD prognosis.<sup>42, 45</sup> In the ongoing Risk Or Benefit IN Screening for Cardiovascular Disease (ROBINSICA) trial, 33,000 adults are being randomized in a 1:1:1 to no intervention, risk score guided intervention, and CAC score guided intervention to see if one screening strategy is superior to the others.

### **Statin Adverse Effects**

Although reported adverse events attributed to statins in clinical trials is low, and in many cases not different than what was seen with placebo, observational studies have associated statins with a greater numbers of adverse events. Along with the increased incidence of myopathy, diabetes, and increased liver transaminases seen in clinical trials, observational studies have raised concerns about cognitive and psychological effects, eye disorders, and renal disorders. Many of these potential adverse events are of particular concern in using statins for primary prevention, where younger patients may be taking this therapy for decades. While all confounders can not be accounted for as well in observational studies as they can in randomized, blinded clinical trials, observational studies do have the advantage of longer follow-up, evaluating a less selected population, and the ability to detect very rare adverse events. However, for many of these suspected adverse events, observational studies have not consistently shown an association with statin use. A meta-analysis of 90 studies reporting 48 potential adverse events found that statin use was consistently associated with only myopathy, elevated liver enzymes, and diabetes.<sup>46</sup>

#### *Myopathy*

Statin associated myalgias have been reported to occur in < 5% of patients in clinical trials, but in 10-20% of patients reported in observational studies. Cases of more serious rhabdomyolysis are estimated to occur in less than 1 in 20,000 patients treated with atorvastatin, simvastatin, or pravastatin monotherapy.<sup>47</sup> Although statins do not appear to affect objective measures of muscle strength or exercise capacity in the short term,<sup>48</sup> myalgias may be lifestyle limiting and long term effects of statin associated myopathy are unclear.

#### Diabetes Mellitus

Statins use in clinical trials appears to increase the risk of incident diabetes mellitus compared to placebo, with estimated risk of 1-2 new cases a year attributed to statins for every 1,000 patients treated. The vast majority of patients who develop diabetes mellitus attributed to statins have risk factors for diabetes mellitus, including the metabolic syndrome, impaired fasting glucose, body mass index > 30 kg/m<sup>2</sup>, or HgbA1C > 6. Among the 486 participants who developed diabetes mellitus in the JUPITER study, the relative risk reduction for ASCVD events was similar with rosuvastatin as compared to the risk reduction seen in the trial as a whole, suggesting that even in those who develop diabetes, statins reduce ASCVD risk.<sup>49</sup>

### *Adverse Cognitive and Psychological Effects*

There have been conflicting reports about whether statin use is associated with an increased risk of neurocognitive and psychological adverse events. Lilly et al. reported that non-persistent statin use was associated with an increased incidence of schizophrenia, psychosis, and cognitive disorders.<sup>50</sup> Due to ongoing concerns about the longterm effects of statins on neurological function, the FDA has placed a warning in the package insert for statins.

Additional data is needed to better establish the risks of many of these potential adverse events. Current data suggests that for the majority of primary prevention patients at increased risk of ASCVD, the benefits of therapy outweigh the risks of known adverse events. Statin therapy appears to be as effective as other primary preventive measures, including aspirin and blood pressure medication, with possibly less risks.<sup>51</sup>

### **Lifestyle Interventions**

Although lifestyle interventions have more modest effects on LDL-C than statin therapy, non-medical intervention should be pursued in all patients prior to initiating statin therapy. The use of combinations of different non-medical interventions are more likely lower LDL-C to a greater extent than attempting individual interventions. Interventions that may not significantly lower LDL-C but still decrease the risk of CVD, such as tobacco cessation and increased exercise, should also be prescribed.

Dietary recommendations that have been shown to decrease LDL-C include decreasing saturated fatty acids to < 5-10% of total energy expenditure, increasing fiber intake, and increasing uptake of plant sterols.<sup>52</sup> Every 5% of energy shifted from saturated fatty acids to polyunsaturated fatty acids is estimated to be associated with a decrease in LDL-C of 9 mg/dL. Compared to a diet rich in carbohydrates, a high protein diet appears to decrease LDL-C to a greater extent.<sup>53</sup> More aggressive diets with multiple interventions appear to decrease LDL-C to a greater extent than less aggressive diets. For example, a trial randomizing individuals to 2 different ‘diet portfolios’ with high intake of plant sterols (0.94 g/1000kcal), viscous fibers (9.8 g/1000kcal), soy protein and nuts decreased LDL-C significantly more than a low saturated fatty acid diet.<sup>54</sup> Weight loss also appears to modestly lower LDL-C levels. A meta-analysis of 70 weight loss studies estimated that for each 1 kg of weight loss, LDL-C decreases slightly less than 1 mg/dL.<sup>55</sup>

A recent report found increased caloric intake and higher weight gain among statin users compared to non-users.<sup>56</sup> Once it has been decided to initiate a statin, optimizing dietary and exercise habits should continue to be encouraged to the patient, emphasizing the importance of these lifestyle interventions.

### **The Clinician Patient Discussion Regarding Statin Therapy**



The 2013 ACC/AHA guidelines stress that meeting eligibility criteria for statins should not lead to immediate initiation of statin therapy without a clinician-patient discussion regarding the benefits, risks, and patient personal preferences. In this process of shared decision making, discussion with the patient should include modification of other ASCVD risk factors, the absolute 10 year and lifetime risk for ASCVD events, the relative risk reduction expected to be derived from statin and other interventions, lifestyle interventions, risk of adverse events, compliance issues, need for any additional testing, and patient preferences.

### **Considering both LDL-C levels and ASCVD risk in Determining Statin Eligibility**

Most national and international cholesterol guidelines do not recommend indiscriminant use of statins without risk assessment. In very low risk individuals, the risk of adverse events, including those that are not currently linked to statin use but may become more established in the future, over a long period of treatment may not be justifiable. In addition, if the risk is low, an individual may not wish to take a medication over a 3 to 4 decade period to decrease their risk of one event by 30%. Although risk prediction calculators, including the ACC/AHA PCE are imperfect, considering statin therapy for an individual should start with estimation of their intermediate term absolute risk of ASCVD because of the importance of this risk in defining the magnitude of the benefits that will be seen with statin therapy. This approach also is important because it allows an individual to quantify their risk of an ASCVD event when participating in the shared decision making process with the physician as to whether to start a statin.

While there are no randomized clinical trial data, based on epidemiological and genetic data that demonstrate the increased risks of long term exposure to elevated cholesterol levels, LDL-C or non-HDL-C levels should be considered along with the intermediate term absolute risks in deciding statin eligibility. A variety of pleiotropic effects have been proposed that may also explain some of the reduction of ASCVD events with statins, however emerging evidence that other classes of lipid lowering medications also lower ASCVD rates suggest that reduction in atherogenic lipoprotein levels, such LDL-C, is likely a major mechanism. Therefore, as data supporting the lipid hypothesis continues to accumulate, complete risk assessment includes accounting for serum LDL-C or non-HDL-C levels.

Once intermediate term ASCVD risk and LDL-C levels have been determined, additional data may be considered in those whose 10 year risk is < 7.5%, LDL-C <160 mg/dL and non-HDL-C <160-190 mg/dL, including family history of premature coronary artery disease, CAC score, hsCRP, 10 year ASCVD risk < 5%, and lifetime estimate of ASCVD. In those with ASCVD risk  $\geq$  7.5%, CAC testing may be performed in select individuals, including the elderly, as the absence of CAC significantly decreases the risk of ASCVD.

### **Conclusions**

Statin therapy has been shown to significantly decrease the risk of ASCVD in the primary prevention setting, but little data are present defining subgroups with the greatest benefit. The

absolute reduction in events appears to be proportional to the baseline risk, as determined both by elevated cholesterol levels and other ASCVD risk factors. Intermediate-term risk prediction models are an essential tool in the determination in statin eligibility, however are heavily influenced by age, and most calculators likely overestimate true risks. Refinements are needed to both the intermediate- and long-term ASCVD risk prediction models, but in the meantime several non-traditional risk markers may improve risk stratification. Additional studies are also needed to establish the role novel markers play in risk stratification in low ASCVD risk populations.

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