

## PREVENTION GUIDELINES CLINICAL VIGNETTES

(Based on the 2013 Blood Cholesterol, Lifestyle Management, Obesity, and Risk Assessment Guidelines)

### **CASE 1.**

A 63-year-old man is seen in the office 2 weeks after a ST-elevation myocardial infarction (MI). A former smoker with hypertension, he was discharged on atorvastatin 80mg daily, dual anti-platelet therapy, long-acting metoprolol, and an ACE inhibitor. One year before the acute MI, he was prescribed simvastatin 40 mg which was then increased to simvastatin 80 mg. He stopped the simvastatin 80 mg 2 weeks later after developing muscle cramps in his legs. At that time he was also on a calcium channel blocker for his hypertension. Although he has no muscle symptoms since he started the atorvastatin 80 mg, he is concerned about having had muscle cramps in the past on a statin and would like to decrease the atorvastatin to 20 mg daily.

- I. Which of the following statements is the best answer?
  - a. Randomized trials of high intensity statin therapy versus moderate intensity statin therapy have not shown a significant difference in outcomes. He should decrease the atorvastatin to 20 mg to minimize adverse effects.
  - b. Systematic meta-analyses of randomized clinical trials support using an intensive statin dose such as atorvastatin 80 mg/day over a moderate intensity statin. He should stay on atorvastatin 80 mg.
  - c. He should be followed with creatine kinase (CK) values when his lipids are checked at each visit for the first year.
  - d. Although his liver panel was normal in the hospital, he should have an alanine aminotransferase (ALT) done at each subsequent visit.

### **II. The best answer is b.**

Individuals with clinical atherosclerotic cardiovascular disease (ASCVD) are in a statin benefit group, and if  $\leq 75$  years of age, they should be treated with a high intensity statin unless conditions are present that may increase the risk of adverse effects. An additional-reduction in ASCVD events from a high intensity statin was shown specifically in individuals with acute coronary syndromes in the PROVE-IT trial where those assigned to atorvastatin 80 mg/day a greater reduction in ASCVD events than those assigned to pravastatin 40 mg daily after 2 years of treatment. An additional ASCVD risk reduction benefit was also observed in 2 randomized controlled trials (RCTs) of atorvastatin 80 mg compared to either atorvastatin 10 mg or simvastatin 20-40 mg in individuals with chronic coronary heart disease (TNT and IDEAL). In these trials, there was no lower limit to LDL-C for eligibility; therefore, individuals with clinical ASCVD should be treated with a statin regardless of the LDL-C level. Although he did have muscle symptoms on simvastatin 80 mg, he was able to tolerate simvastatin 40 mg without difficulty. It is therefore reasonable to initiate atorvastatin 80 mg with patient instructions to monitor for muscle symptoms.

Although CK may be useful at baseline in certain high-risk individuals or in those with a history of statin myopathy, the CK should not be routinely measured. In the

statin RCTs, CK elevations occurred with similar frequencies in the statin and placebo/control groups. A CK should be performed if the patient complains of severe muscle pain or weakness. This patient may have an SLC01B1 deficiency to explain the interaction between simvastatin 80 mg/day and the calcium channel blocker that may have caused his muscle symptoms. He was never rechallenged to determine whether the muscle aches were indeed caused by the simvastatin 80 mg. On 12/15/11, the FDA indicated that simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury. They emphasized that simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug.

On 2/28/12, the FDA determined, based on all available data, including the RCT data reviewed by the Expert Panel, that “all currently marketed statins appear to be associated with a very low risk of serious liver injury and that routine periodic monitoring of serum alanine aminotransferase (ALT) does not appear to detect or prevent serious liver injury in association with statins.”

Thus, neither routine CK nor liver panel tests are required. Nonetheless, some patients may experience myalgias with statins. If these recur in this patient now on atorvastatin, after a wash-out period a dose reduction could be contemplated at that time, or an attempt with another statin, such as rosuvastatin. If symptoms persist after a reasonable statin-free interval (2 weeks or more) other causes of myalgia should be considered.

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### **CASE 2.**

After 2 years of treatment with atorvastatin 80 mg daily free of muscle symptoms, the patient developed progressive muscle pains in both lower legs. He stopped the statin 2

weeks prior to his clinic visit but the muscle pain and weakness did not noticeably improve. He now wants to know if he can be switched to red yeast Chinese rice. On examination, he has mild difficulty getting out of a chair and also has weakness after doing 3 squats. He remembers he felt fine doing squats at the gym about 6 months ago.

- I. Which of the following is the best answer?
  - a. He should be switched from the atorvastatin 80 mg daily to red yeast Chinese rice based on evidence in U.S. studies.
  - b. He should stay off the statin until he is evaluated for possible causes of his muscle problems. A useful approach is to look for exogenous causes (e.g., medications, alcohol), systemic causes (examples include hypothyroidism, rheumatologic disorders such as polymyalgia rheumatica), and primary muscle disorders. He should be questioned about a family history of primary muscle disorders or others in the family with muscle problems taking a statin.
  - c. He should be switched to rosuvastatin 40 mg daily and given CoQ10.
  - d. He should be rechallenged with atorvastatin 80 mg daily.
  - e. If he is African-American, CK levels are not useful in evaluating muscle symptoms.

**II. The best answer is b.**

The history is consistent with statin-associated muscle symptoms, but muscle symptoms on a statin can be mimicked by a variety of other conditions, including polymyalgia rheumatica in older adults. Because his muscle symptoms had not shown any improvement within 2 weeks and the muscle weakness persisted after discontinuing the atorvastatin 80 mg, he was evaluated for systemic causes of myopathy. His CK was normal but his sedimentation rate was over 100 mm/hr and he was treated for his polymyalgia rheumatica. In general, statin-related muscle symptoms begin resolving within 1-2 weeks after statin discontinuation and muscle symptoms have completely resolved within 2 months. Failure of muscle symptoms to resolve within this time frame suggests another cause for the muscle symptoms.

Switching to another statin without determining the underlying etiology for the muscle symptoms denies the patient the opportunity to have a correct diagnosis. If his symptoms had instead resolved within two weeks, the cholesterol guidelines suggest he should be re-challenged with a lower dose of the same statin or switched to a comparable lower dose of another statin. The statin dose should then be increased as tolerated.

CoQ10 would not be useful in this case of polymyalgia rheumatica. The data supporting the use of CoQ10 for statin-associated muscle symptoms is inconsistent.

African Americans have higher CK levels on average than nonAfrican Americans. However, CK elevation above baseline can still be useful for monitoring statin-associated muscle symptoms.

Finally, a Chinese formulation containing red yeast rice was shown to reduce

ASCVD events more than placebo in a randomized trial performed in China. There are no ASCVD outcomes data from U.S. RCTs trials available for red yeast Chinese rice.

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### **CASE 3.**

A 44-year-old woman has a 10-year history of type 2 diabetes. She is a nonsmoker with well-controlled hypertension and microalbuminuria. She is on dietary management, metformin, and takes one omega-3 fatty acid capsule with 840 mg of EPA and DHA. She also takes lisinopril/hydrochlorothiazide for her blood pressure. She has a family history of diabetes, but not premature ASCVD. She has a BP 134/78 and a BMI of 36.0. Her fasting lipid panel reveals an LDL-C 95 mg/dL, triglycerides 350 mg/dL, and HDL-C 38 mg/dL. Her hemoglobin A1c is 7.5%.

- I. Which of the following statements is the best answer?
  - a. Her LDL-C is under 100 mg/dL so she is at “goal” and does not require a statin.
  - b. She should start simvastatin 20 mg and fenofibrate 160 mg daily.
  - c. To reduce her risk of an ASCVD event, the dose of omega-3 fatty acid should be increased to 4 capsules daily to lower her triglycerides.
  - d. If she does not want to start a statin, a bile acid sequestrant is the next best choice for her.
  - e. Her 10-year ASCVD risk should be calculated to determine if she needs a high- or moderate-intensity statin.

### II. The best answer is e.

This patient has diabetes, is between the ages of 40 and 75 years, and has an LDL-C between 70 and 189 mg/dL, placing her in a statin benefit group. The primary prevention CARDS trial showed that men and women with diabetes, but without clinical ASCVD, experienced a reduction in ASCVD events from a moderate intensity statin, atorvastatin 10 mg/day. Although no RCTs have evaluated a high intensity statin in a primary prevention population of individuals with diabetes, such a trial has been performed in a lower risk primary prevention population without diabetes. In the JUPITER trial, rosuvastatin 20 mg/day reduced ASCVD events compared to placebo. In addition, the Cholesterol Treatment Trialists (CTT) 2008 and 2010 meta-analyses have found that statins reduce ASCVD events in proportion to the magnitude of LDL-C lowering in individuals with and without diabetes, and in individuals with diabetes with and

without clinical ASCVD. Therefore, a high-intensity statin is also an option for individuals with diabetes and 10-year ASCVD risk  $\geq 7.5\%$ , as it is in those without diabetes. (Note: the Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in Black and nonHispanic White women and men with or without diabetes). In addition, the 2010 CTT meta-analysis also found the reduction in the relative risk of ASCVD was similar across the range of LDL-C levels  $\geq 70$  mg/dL.

While some might order an apolipoprotein B or LDL particle number, neither is needed to make a decision to start a statin because she is already in a statin benefit group due to having diabetes.

The ACCORD trial did not show benefit of fenofibrate added to a statin in women with elevated triglycerides and low HDL-C levels. Moreover, the 2008 and 2010 CTT meta-analyses found that statins reduce ASCVD events regardless of HDL-C or triglyceride levels, and are therefore the drugs of choice for ASCVD risk reduction in individuals with abnormal triglyceride or HDL-C levels.

Although the JELIS trial evaluated 1800 mg of EPA added to a low dose statin in Japanese women, no benefit was seen in primary prevention individuals in that trial.

Although bile acid sequestrants can lower hemoglobin A1c, they can also markedly elevate triglyceride levels. Bile acid sequestrants are best started with the triglycerides are  $< 250$ - $300$  mg/dL. Tighter diabetes control and lifestyle modification with more physical activity and a heart healthy diet with vegetables, fruits, and less sugar sweetened foods and drinks (often a Mediterranean style diet) would help control the diabetes as well as lower the triglycerides. To date, there are no HDL-C raising drugs that have been shown to reduce ASCVD events in statin-treated individuals.

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**CASE 4.**

A 26-year-old woman has an LDL-C of 260 mg/dL, HDL-C of 51 mg/dL, and triglycerides of 102 mg/dL. She reports having elevated LDL-C levels of over 200 mg/dL since her teens and has tried various diets without success but has never taken a drug to lower her cholesterol. She is worried because her father died suddenly at age 38 and her father's brother had a myocardial infarction at age 32. Both were smokers. She is currently on a 2<sup>nd</sup> generation oral contraceptive and wonders if she should get off the contraceptive pill since she is engaged to be married in 6 months. She has an occasional cigarette and says that it is "social smoking." On exam, BP is 110/60 mm Hg and BMI is 24. She has bilateral inferior pole corneal arcus, no xanthelasma, and thickened Achilles tendons. Her cardiovascular examination is normal.

- I. Which of the following is the best answer?
  - a. She likely has heterozygous familial hypercholesterolemia and should start a high-intensity statin.
  - b. If her fiancée has normal cholesterol values, the likelihood of her child having her genetic condition is 1 in 4.
  - c. Cigarette smoking should be stopped because she is thinking about becoming pregnant.
  - d. She should have her oral contraceptive stopped and started on a high-intensity statin.
  - e. She should have an estimation of her 10-year risk of an ASCVD event before deciding if she needs statin therapy

**II. The best answer is a.**

She has heterozygous familial hypercholesterolemia (FH), which places her in a statin benefit group. Adults with LDL-C  $\geq 190$  mg/dL are likely to have a genetic cholesterol disorder since childhood, placing them at high risk of ASCVD. Therefore, statin therapy should be started by age 21 years, if not started before then. Although no RCTs were performed exclusively in FH populations, many randomized trials enrolled individuals with LDL-C levels  $\geq 190$  mg/dL. The 2010 CTT meta-analysis found that statins reduce ASCVD events across the range of LDL-C levels  $>70$  mg/dL and also showed that the magnitude of ASCVD risk reduction is proportional to the degree of LDL-C lowering. Therefore, individuals with FH should receive a high-intensity statin. Addition of non-statin therapy to further lower LDL-C may be considered in some FH patients.

This patient should continue effective contraception during statin therapy. She

should avoid getting pregnant or nursing on the statin due to classification of statins (and most nonstatin drugs) as pregnancy category X. Once she definitely plans to become pregnant, she should stop the statin 2-3 months before discontinuing her oral contraceptive. Once child-bearing and nursing is complete, the effective contraception and the statin should be resumed.

Because she has a long-standing history of markedly elevated total cholesterol and LDL-C levels there is no need to rule out secondary causes of hypercholesterolemia prior to initiating therapy. If this was the initial evaluation of a patient with LDL-C  $\geq 190$  mg/dL, secondary causes of hypercholesterolemia should be ruled out (hypothyroidism, obstructive biliary disease, nephrotic syndrome are common causes).

The degree of LDL-C elevation at her age, normal weight, HDL-C of 51 mg/dL and the presence of stigmata of FH (arcus, Achilles tendon xanthomas) make heterozygous FH the most likely diagnosis and a familial form of combined hyperlipidemia unlikely. The early MIs in her father and his brother also make autosomal dominant FH highly likely. Therefore, the risk of her children having her condition is 1 in 2, not 1 in 4 as with each pregnancy there is a 50:50 chance of her passing on her mutant allele. Once an individual is identified with LDL-C  $\geq 190$  mg/dL, family members should also be screened with a fasting or nonfasting lipid panel to identify other affected individuals for early statin therapy

Individuals with FH should never smoke. In an older series of untreated FH patients, cigarette smoking strikingly increased rates of cardiac events in younger women as well as in younger men. Smoking also explains the early manifestation of myocardial infarction in her father and her paternal uncle. Control of other ASCVD risk factor is also important to further reduce ASCVD risk.

Adults with primary LDL-C  $\geq 190$  mg/dL are already identified in a statin benefit group, for whom statin therapy is indicated by age 21 years. Therefore there is never a need to estimate 10-year ASCVD risk in these individuals.

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### **CASE 5.**

A 60-year-old African-American woman has asked whether she should be taking a statin to reduce her risk of stroke, but is worried about the statin causing diabetes. Her mother had diabetes and had a stroke at age 62. She is a nonsmoker. Blood pressure is 142/88 mm Hg on 2 antihypertensive medications and BMI is 31. Her fasting lipid panel reveals a total cholesterol 200 mg/dL, HDL-C 55 mg/dL, triglyceride 100 mg/dL, and LDL-C 125 mg/dL. Her fasting blood sugar is 109 mm/dL and hemoglobin A1c is 5.9%. According to the Pooled Cohort Equation for African-American Women, her estimated 10-year ASCVD risk is 8.7 %.

- I. Which of the following statements is the best answer?
  - a. She should focus on lifestyle change to improve her risk factors because lifestyle has been shown to reduce ASCVD events more than statin therapy.
  - b. The risk of progression to diabetes with a statin outweighs any ASCVD risk reduction benefits from statin therapy. The decision about a statin to be deferred.
  - c. She should start a moderate or high intensity statin.
  - d. A high-sensitivity C-reactive protein (hs-CRP) >2 would be needed before the decision can be made whether to start a statin.

### **II. The best answer is c.**

She has no clinical ASCVD and no diabetes with an LDL-C between 70 and 189 mg/dL. Due to her elevated 10-year ASCVD risk  $\geq 7.5\%$ , she is in a statin benefit group. She should initiate moderate or high intensity statin therapy based on evidence from 3 RCTs performed in exclusively primary prevention populations (AFCAPS/TexCAPS, MEGA, and JUPITER). These trials showed that moderate- and high-intensity statin therapy reduce ASCVD events compared to placebo/control. JUPITER enrolled individuals with LDL-C <130 mg/dL, with additional evidence from the 2010 CTT meta-analysis that statins reduce ASCVD events across the range of LDL-C levels >70 mg/dL.

African-American women have higher risk of ASCVD at a given age than similarly aged nonHispanic White women. In addition, women are more likely to have stroke as the first manifestation of ASCVD and a significant reduction in the risk of stroke has been demonstrated in RCTs of women receiving statin therapy. The Pooled Cohort Equations more accurately estimate the heart attack and stroke risk in African-Americans. The use of the Framingham "hard CHD" risk score underestimates her total ASCVD risk because it does not consider stroke and is derived from a nonHispanic white population.

This patient is already at high risk of developing diabetes even without taking a statin due to the presence of multiple diabetes risk factors: blood glucose 100-

125 mg/dL, BMI  $\geq$ 30, and a family history of diabetes. Moderate-intensity statin therapy in primary and secondary prevention studies results in about 1 excess case of new diabetes while preventing 5.4 ASCVD events per 1000 individuals treated for 1 year. A High intensity statin used in a primary prevention population results in about 3 excess cases of new diabetes while preventing 5.9 ASCVD events per 1000 individuals treated for 1 year. A post hoc analysis of JUPITER found that the diagnosis of new onset diabetes occurred 6 weeks earlier in the rosuvastatin 20 mg group than in the placebo group. This may suggest the modest risk of excess diabetes even with high intensity statins may be of little long-term consequence, and certainly not comparable to the excess risk of a nonfatal or fatal MI or stroke arising from no treatment. This patient needs intensive lifestyle change, including weight loss and regular physical activity, to prevent progression to diabetes, along with statin therapy to reduce her risk of stroke and MI.

In JUPITER women  $\geq$ 60 years with hs-CRP  $\geq$ 2.0 had a reduction in ASCVD events with rosuvastatin 20 mg/dL compared to placebo. This patient already qualifies for statin treatment on the basis of her 10-year ASCVD risk so there is no reason to measure an hs-CRP level. In a patient with estimated 10-year ASCVD risk  $<$ 7.5%, an hs-CRP  $>$ 2.0 mg/L may be one factor to consider in the decision to use statin therapy.

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### **CASE 6.**

A 35-year-old man has a strong family history of premature coronary disease, with both father and brother having an MI before age 55. He is a nonsmoker, nondiabetic and exercises for 150 minutes/week. He has gained 10 lbs since age 18. His BP is 140/90 mm Hg, weight is 170 pounds, height is 70 inches, and BMI is 24.4. On a fasting lipid panel, his LDL-C is 160 mg/dL, HDL-C 45 mg/dL and triglyceride 100 mg/dL. His fasting blood glucose is 92 mg/dL. He is on a heart-healthy diet and exercises 150 minutes a week. He and his wife would like to discuss statin therapy given his strong family history.

- I. Which of the following is likely to be helpful in making a decision regarding statin therapy in this patient?
  - a. Strong family history of premature ASCVD
  - b. Coronary calcium score of 300 units or more
  - c. hs-CRP  $\geq 2.0$  mg/L
  - d. Lifetime risk of ASCVD
  - e. LDL-C  $\geq 160$  mg/dL
  - f. All of these factors can be considered

### **II. The best answer is f.**

This patient is not in 1 of the 4 statin benefit groups. Yet there may be some individuals who still merit therapy. No individuals <40 years were included in the primary prevention statin RCTs. Nor were individuals <40 years included in the Pooled Cohort Equations for estimating 10-year ASCVD risk. Therefore, in selected cases, clinical judgment is needed for patients <40 years or for those individuals where quantitative ASCVD risk assessment alone is felt inadequate to guide the treatment decision.

After an extensive review of data from epidemiologic studies and meta-analyses of epidemiologic studies, the Risk Assessment Panel Work Group found that additional factors may be used to inform treatment decisions. These factors include family history of premature ASCVD, coronary calcium score of  $\geq 300$  units or more, hs-CRP  $\geq 2.0$  and lifetime risk of ASCVD. The Cholesterol Expert Panel also considers an LDL-C  $\geq 160$  mg/dL to identify individuals likely to benefit from statin therapy. This individual is likely to have a 10-year ASCVD risk <5%, and the risk of adverse events from high intensity statin therapy may outweigh the potential for an ASCVD risk reduction benefit. However, moderate intensity of statin therapy, such as simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, or rosuvastatin 10 mg/day may be reasonable but the benefits and risks should be carefully discussed with the patient and his wife.

A heart healthy dietary pattern and regular physical activity should be reinforced.

### **III. References**

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### **CASE 7.**

A 32-year-old man has gained 35 pounds since he graduated from college and started working as computer programmer. He has never smoked. He has treated hypertension. He has tried several popular diets to lose weight and lost about 20 pounds each time, but he always regains the weight lost within one year. He bowls once a week. He weighs 220 lbs and his BMI is 32.5, and the highest it has ever been. His BP is 138/92. His labs show total cholesterol 218 mg/dL, triglycerides 188 mg/dL, HDL-C 40 mg/dL, LDL-C 138 mg/dL, and non HDL-C 178 mg/dL. His fasting glucose is 101 mg/dL. His father died of an MI at age 73.

- I. Which of the following should be incorporated into your advice for ASCVD risk reduction for him?
- a. Refer to a program providing a series of group counseling comprehensive lifestyle change sessions.
  - b. Start a moderate intensity statin.
  - c. Try to encourage a diet that will get at least 10-15 pounds off in 6 weeks so he can keep his motivation for weight loss high.
  - d. Reassure him that by following a strict diet he does not need to increase his physical activity and will be able to maintain his weight over the long haul.
  - e. Refer for bariatric surgery.

**II. The best answer is a.**

This patient is not in 1 of the 4 statin benefit groups. While he currently has an increased ASCVD lifetime risk due to multiple risk factors, there is much he can do now since his 10-year ASCVD risk is low. He does not qualify for statin therapy but his lipids along with other risk factors need to be assessed at regular intervals. A major focus on his weight gain since college is appropriate and should help with risk factor control.

The Obesity Guidelines recommend delivery of high intensity comprehensive lifestyle intervention as the most effective approach to weight loss. This includes delivery of 14 or more group or individual sessions in the first 6 months by a trained interventionist. Therapy for at least a year is recommended. Of course, not all patients have access to the programmatic lifestyle counseling that produces successful weight loss skill building as demonstrated in the Diabetes Prevention Program study. Referral to other sources when this is not available is also endorsed. This may be telephonic counseling, electronic delivery or even referral for commercial programs where an evidence base supports efficacy. The

Obesity Guidelines indicate that the choice of diet should be determined by the patient's preferences and health consideration. In the case of this patient, a reduced calorie diet with sodium restriction would be the obvious choice.

The Guidelines also recommend that physicians refer to registered dietitians when diets are prescribed for a specific health target, such as hypertension or diabetes.

This patient has shown by his history that he needs help in building the skills to sustain long term weight loss. This patient needs more than encouragement, he needs counseling and this is a central feature of the Obesity Guidelines.

The essential component of a weight loss effort is creating a negative energy balance. Dieting is not enough if weight loss is to be sustained. The Guidelines endorse incorporating physical activity into the weight loss effort and emphasize the role of physical activity in weight loss maintenance. The patient must also find ways to increase physical activity to >200 minutes a week, as recommended in the Guidelines.

Finally, at his current weight he does not qualify for bariatric surgery.

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### **CASE 8.**

This 55-year-old man developed exertional chest pain. He had a positive stress exercise test and a coronary angiogram that revealed 2-vessel nonobstructive coronary disease. His risk profile indicates he is a nonsmoker with treated hypertension, and a low HDL–C. His father had an MI at age 67. His mother had type 2 diabetes diagnosed at age 60. He is on a low dose aspirin, long acting beta blocker, a high-intensity statin, and an ACE

inhibitor. His BP 135/86, pulse 58, weight 183 lbs and BMI 26.3. His LDL-C is 95 mg/dL, his HDL-C 39 mg/d and triglycerides are 145 mg/dL. His fasting glucose is 109 mg/dL. He wants to know what dietary change recommendations you would make. His cardiologist has given him physical activity recommendations.

I. The best answer is:

- a. His lifestyle is not important as long as he is on a statin and beta blocker.
- b. He should consume a dietary pattern that emphasizes vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red meats.
- c. Fatty meats should be restricted, but not processed meats.
- d. Not adding salt is crucial because the salt in food is negligible.
- e. A Mediterranean style diet that allows commercial baked goods and French fries.

II. The best answer is b.

Lifestyle modification, both diet and physical activity, are an important adjunct to pharmacotherapy in improving ASCVD risk factors and should be coupled with efforts to achieve and maintain a healthy body weight. This recommendation is based largely on studies of the Dietary Approaches to Stop Hypertension (DASH) dietary pattern (DASH and DASH-Sodium) and Mediterranean-type dietary patterns and is consistent with that described by the AHA Diet and Lifestyle Recommendations and 2010 Dietary Guidelines for Americans.

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### **CASE 9.**

A 48-year-old man with FH and history of 3-vessel coronary artery bypass surgery 7 years ago sees you now for statin intolerance. The maximum dose of statin that he can

tolerate is rosuvastatin 10 mg twice a week. On more frequent dosing he developed shoulder, low back, and thigh aching without weakness and a normal CK level. He had similar symptoms on low doses of simvastatin, atorvastatin and pravastatin. On rosuvastatin 10 mg twice a week, his most recent LDL-C was 168 mg/dL, triglycerides were 138 mg/dL, and HDL-C was 46 mg/dL.

- I. Which of the following statements is the most correct answer?
  - a. Ezetimibe has been shown to further reduce ASCVD events when added to statin therapy. He should continue the rosuvastatin and ezetimibe 10 mg should be added.
  - b. Gemfibrozil has been shown to reduce ASCVD events when used as monotherapy in men with coronary heart disease. He should continue the rosuvastatin and gemfibrozil 600 mg twice daily should be added.
  - c. Bile acid sequestrants have been shown to reduce ASCVD events when used as monotherapy in men with primary hypercholesterolemia. . He should continue the rosuvastatin and cholestyramine 4 g packet twice daily should be added.
  - d. He should discontinue the rosuvastatin and begin lovastatin 40 mg daily.

**II. The best answer is c.**

This patient has FH, placing him in a statin benefit group. In patients with untreated primary LDL-C  $\geq 190$  mg/dL, a high-intensity statin should be used if tolerated and he would be expected to achieve a  $>50\%$  LDL-C reduction. With an untreated baseline LDL-C of about 240 mg/dL, this patient has experienced about a 30% reduction in LDL-C. Although this percent reduction in LDL-C is suboptimal it still is providing substantial ASCVD risk reduction benefit. According to the CTT 2010 meta-analysis, each 39 mg/dL reduction in LDL-C is associated with a 22% reduction in ASCVD events. Therefore this patient's 72 mg/dL reduction is LDL-C from rosuvastatin 10 mg twice a week might be expected to reduce his relative risk ASCVD by about 40%.

LDL-C lowering nonstatin drugs that have been shown to reduce ASCVD events when used as monotherapy include niacin and the bile acid sequestrant cholestyramine. However, the incremental ASCVD event reduction benefit of these drugs added to statin therapy has yet to be established. No ASCVD outcomes trials of bile acid sequestrants added to statins have been performed or are planned. A trial of extended-release (ER) niacin coadministered with laropriprant, a drug to block flushing, did not find an ASCVD event reduction benefit from niacin/laropriprant compared to placebo in statin-treated patients. The AIM-HIGH trial found 2 strategies that lowered LDL-C to 40-80 mg/dL had similar ASCVD event rates (simvastatin/ER niacin  $\pm$  ezetimibe versus simvastatin  $\pm$  ezetimibe). The incremental benefit of ezetimibe added to simvastatin is undergoing evaluation in the IMPROVE-IT trial. However, a trial of ezetimibe coadministered with simvastatin in individuals with chronic kidney disease did reduce ASCVD events compared to placebo.

Thus, due to the lack of ASCVD outcomes data to determine the incremental benefit of a non-statin added to statin therapy at this time, there is no best LDL-C lowering therapy to recommend when the maximal tolerated statin dose is

suboptimal. Use of a nonstatin is therefore a matter of clinical judgment. Considerations include results in clinical trials as monotherapy and in combination with a statin, tolerability, potential for drug-drug interactions, cost, and patient preference.

Gemfibrozil has been shown to reduce ASCVD events in men with coronary heart disease, low HDL-C and low LDL-C when compared to placebo. However, gemfibrozil does not lower LDL-C and it should not be combined with statin due to an unacceptable potential for myopathy and rhabdomyolysis. Fenofibrate is safer to administer with a statin, but does not appear to provide additional ASCVD event reduction benefits when used with a statin.

Although he might tolerate lovastatin 40 mg daily, given his prior history of intolerance to 3 other statins at low doses, this seems less likely. Moreover, less than daily doses of lovastatin are unlikely to result in a reduction in LDL-C comparable to the 30% reduction in LDL-C he is experiencing with rosuvastatin 10 mg twice a week. Rosuvastatin results in the greatest percent reduction in LDL-C per milligram. An alternative is pitavastatin. At the maximum dose of 4 mg daily, pitavastatin has comparable LDL-C lowering efficacy to simvastatin 40 mg daily.

A rule of thumb for comparing statin doses that lower LDL-C approximately 30% to 35% is:

Fluvastatin	80 mg
Lovastatin	40 mg
Pravastatin	40 mg
Simvastatin	20 mg
Atorvastatin	10 mg
Rosuvastatin	5 mg
Pitavastatin	1 mg

Each doubling of the statin dose usually results in an additional 5% to 7% reduction in LDL-C (i.e. the 6% rule).

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### **CASE 10. (New case added 12/12/13)**

Two months ago, a 63-year old Hispanic male had a myocardial infarction (MI) followed by an angioplasty and coated stent. He was discharged on 80 mg atorvastatin, low-dose aspirin, clopidogrel, a long-acting beta blocker, and lisinopril 5 mg. One year ago his LDL-C was 140 mg/dL. He was prescribed a low dose of pravastatin 10 mg/day at that time but never returned for a follow-up lipid panel. He reported stopping the pravastatin about 6 months before his MI. He returns now for a follow-up visit. He reports adhering to a heart healthy diet and taking atorvastatin 80 mg/day for the first month after discharge. He had no musculoskeletal or other symptoms during this period but did not refill the prescription. He thought he was already taking too many pills and did not understand why he was taking a pill for cholesterol. His fasting lipid panel returns with an LDL-C of 125 mg/dL.

#### **I. Which of the following statements is the most correct answer?**

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- a. According to a large registry of patients with cardiovascular disease, more than 75% were adherent to guideline-recommended medications after 4 years of follow-up.
- b. He has many characteristics of a patient who would be adherent to medication.
- c. A pill count is one strategy that has been shown to improve adherence.
- d. Nonadherence to statin therapy is associated with an increased risk of stroke, MI and death.

**II. The best answer is d.**

A large prospective registry with complete adherence data showed 47% were adherent to guideline-recommended recommendations after 1 year, and 48% after 4 years. Nonadherence at 1 year was associated with a 19% increased risk of stroke, MI, cardiovascular death, and total mortality over the next 3 years.

In 2 registries of 31 U.S. hospitals, nearly all patients were discharged on appropriate evidence-based secondary prevention medications. This patient was discharged as recommended by the guidelines on atorvastatin 80 mg. Statin dose at discharge is an important predictor of subsequent dose. Uptitration to higher statin doses occurs infrequently. However, this patient had numerous other characteristics predicting statin nonadherence over the long term.

Characteristics of those who are adherent include being younger, white, less polyvascular disease, and having insurance. This patient is Hispanic, putting him in a category with East Asians, as being less adherent as compared to white patients. Adverse effects are not the main cause for medication nonadherence.

There are at least 6 nonadherence phenotypes, representing different behaviors and barriers that exist for patients: 1) the patient lacks an understanding of the relationship between medication adherence to continued health and well-being; 2) the patient has concluded that the costs of taking a medication outweigh the benefits; 3) the complexity of the medication regimen is beyond the capacity of the patient to understand; 4) the patient is not sufficiently vigilant; 5) the patient's belief regarding medications are inaccurate, irrational, or conflicting; and 6) the patient does not believe the medication will help them. Educational interventions with behavioral support through continued patient contact over several weeks or months has been shown to be effective. The guideline recommends follow-up every 4-12 weeks until the patient has achieved an acceptable level of lifestyle and medication adherence as evidenced by the LDL-C response.

Clinical strategies to improve adherence are discussed in the paper by Bosworth et al (2011). ICD-9 code (V15.81) can be used for medication nonadherence counselling billing purposes. In addition, significant variation in the use of evidence-based secondary medication has been observed across outpatient medical practices, suggesting that quality improvement efforts are needed.

The new cholesterol guidelines strongly emphasize adherence to evidence-based cholesterol-lowering therapies rather than targeting a fixed LDL-C cutoff. Thus, assessment of adherence to lifestyle and his statin therapy by checking a fasting lipid panel is needed at future visits. The guideline does note, however, that in participants in randomized trials who were taking a high-intensity statin, almost all had an LDL-C <100 mg/dL. This is not a target or performance measure but designed to give the clinician an idea of the anticipated LDL-C response to treatment. In this patient with an untreated LDL-C 125-140 mg/dL, atorvastatin 80 mg would be expected to decrease LDL-C by about 50% on average, to a level of 65-70 mg/dL.

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