MANAGEMENT AND TREATMENT OF LIPID DISORDER IN ADULTS

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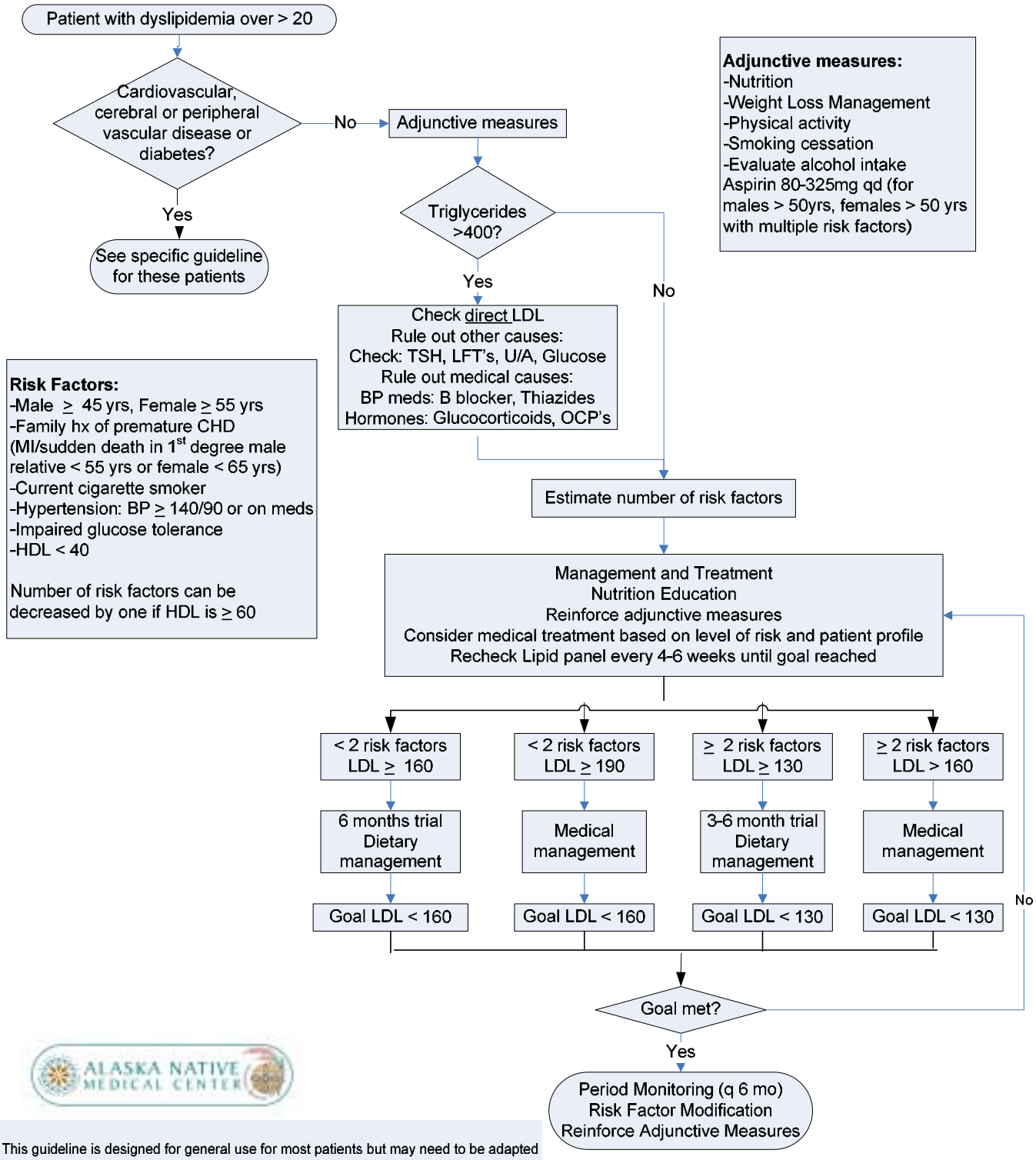
Treatment of Lipid Disorder in Adults <u>without</u> Cardiovascular, Cerebral or Peripheral vascular disease or Diabetes mellitus



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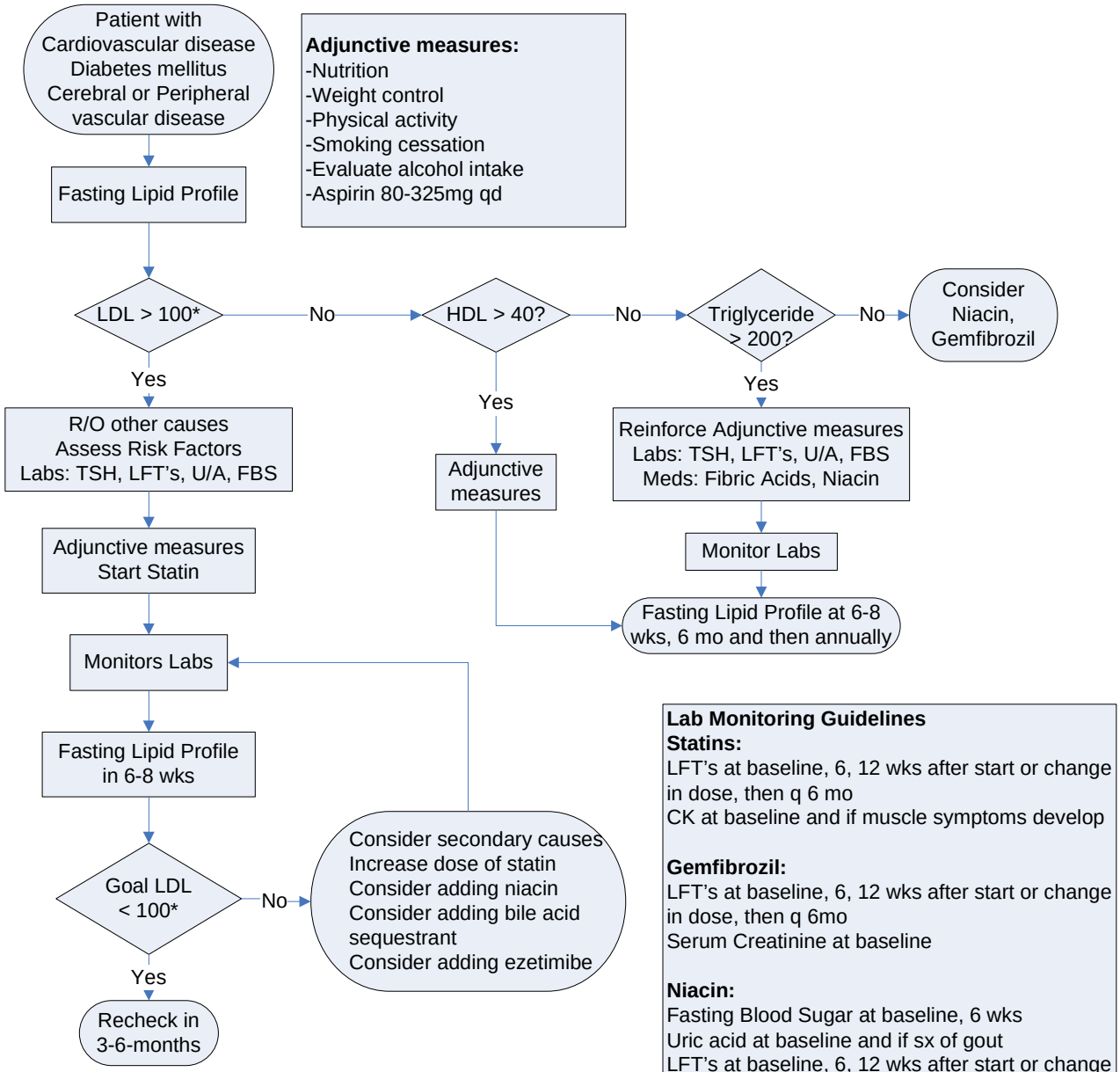
This guideline is designed for general use for most patients but may need to be adapted to meet the special needs of a specific patient as determined by the patient's provider.

Treatment of Lipid Disorder in Adults
<u>with</u> known Cardiovascular, Cerebral or Peripheral vascular disease or Diabetes mellitus



Lab Monitoring Guidelines

Statins:
LFT's at baseline, 6, 12 wks after start or change in dose, then q 6 mo
CK at baseline and if muscle symptoms develop

Gemfibrozil:
LFT's at baseline, 6, 12 wks after start or change in dose, then q 6mo
Serum Creatinine at baseline

Niacin:
Fasting Blood Sugar at baseline, 6 wks
Uric acid at baseline and if sx of gout
LFT's at baseline, 6, 12 wks after start or change in dose, then q 6mo

Bile acid sequestrants: None

Ezetimibe: None

*There is a therapeutic option to set the goal at an LDL less than 70 mg/dL for very high-risk patients–those who have had a recent heart attack, or those who have cardiovascular disease combined with either diabetes, or severe or poorly controlled risk factors (such as continued smoking), or metabolic syndrome (a cluster of risk factors associated with obesity that includes high triglycerides and low HDL cholesterol).

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MANAGEMENT AND TREATMENT OF LIPID DISORDER IN ADULTS

Management and Treatment should include the following:
- Adjunctive Measures
- Ruling out Secondary causes
- Consideration of pharmacological treatment based on level of risk and patient preference

I) ADJUNCTIVE MEASURES

a. Proven Effectiveness

Low fat diet
- 32-66% reduction in cardiac mortality with low fat diet in patient with CHD
- 2-3% reduction in CHD risk for every 1% lowering of LDL cholesterol (10)

Dietary therapy should occur in two steps. Step I and Step II diets are designed to progressively reduce intake of saturated fats, cholesterol and total calories to decrease lipoprotein values and promote weight loss in overweight persons.
In the average American diet, fat comprises about 35% of total calories, with total saturated fat accounting for 14 percent. Cholesterol intake averages about 360 mg per day in American men; less in American women. Clinical trials show that lipid-lowering effects of dietary measures are greatest in persons with higher initial values of total cholesterol, LDL, and triglycerides.
Dietary therapy should occur in two steps. The Step I and Step II diets are designed to progressively reduce intake of fatty acids and to promote weight loss in patients who are overweight. If the patient has not been adhering to any diet, the Step I diet outlined below should be initiated. For many patients the Step I diet recommendations can be achieved without a radical change in diet but patients are more likely to comply with diet changes that are tailored to the individual. Initial dietary counseling should be done through the provider and case manager although referral to the dietician or dietary classes is acceptable at any point, call 729-2669. Refer patients also to various web sites that have recommendations on healthy nutrition; the American Heart Association www.americanheart.org, Shapeup America at www.shapeup.com, and the American Diatetic Association, www.eatright.org.

The Step I American Heart Association Diet (9)

- Total fat intake should be no more than 30 percent of total calories
- Saturated fatty acids intake should be no more than 8-10 percent of total calories. Wild game meat is much leaner than farm fed beef.
- Polyunsaturated fatty acid intake should be no more than 10 percent of total calories. Omega-3 fatty acids, which are polyunsaturated fatty acids found in many fish, have been shown to reduce serum triglyceride concentrations but minimal effect on LDL in those with normal triglycerides. Polyunsaturated fats are also found in seal and whale blubber.
- Monounsaturated fatty acids should be no more than 15 percent of total calories. Monounsaturated fats, such as those found in peanuts, almonds and canola oil have less adverse effect on HDL cholesterol than polyunsaturated fats
- Cholesterol intake should be less than 300 milligrams per day
- Carbohydrate intake should make up 55-60 percent or more of calories, with emphasis on increasing sources of complex carbohydrates
- Total calories should be adjusted to achieve and maintain a healthy body weight

Patients should be seen by the provider and/or case manager at 4-6 weeks and at 12 weeks to obtain a total cholesterol level and to assess compliance with dietary changes. If the patient does not achieve the set goals after 12 weeks they should be referred to a dietician and started on a Step II diet. Patients who have already been on a Step I diet for over 6 months or who have established coronary artery disease, other atherosclerotic disease or diabetes should begin immediately on the Step II diet. The Step II diet further restricts calories from saturated fats to less than 7 percent of total calories and restricts cholesterol intake to less than 200 mg per day. This diet requires careful attention to the whole diet to reduce intake of saturated fat and cholesterol to a minimal level while maintaining an acceptable and nutritious diet. Involvement of a dietician is important.

Dietary Fiber
Soluble fiber has been shown to modestly reduce total cholesterol and LDL cholesterol levels. Current dietary guidelines recommend a total daily fiber intake of at least 20 to 30 g for adults, with 25 percent of the fiber being soluble fiber. These levels can be attained with six or more daily servings of grain products and five or more daily servings of fruits and vegetables. Adding 3 g per day of soluble fiber from oat bran can reduce total cholesterol by 5-6 mg per dl. Higher daily intake of soluble fiber promotes a further modest reduction. (1)

Approximate LDL cholesterol reduction achieved by dietary modification (9)

Dietary Component	Dietary Change	Approximate LDL Reduction
Saturated fat	<7% of calories	8-10%
Dietary Cholesterol	<200mg/day	3-5%
Weight reduction	Lose 10 lbs	5-8%
Viscous fiber	5-10 grams/day	3-5%
Plant sterols\stanol esters	2g/day	6-15%
Cumulative estimate		20-30%

Dietary Questions for Assessment of Intake Saturated Fat and Cholesterol (9)

- **C-Cheese** (and other sources of dairy fats-whole milk, 2% milk, ice cream, cream, whole fat, yogurt
- **A-Animal fats** (hamburger, ground meat, frankfurters, bologna, salami, sausage, fried foods, fatty cuts of meat
- **G-Got it away from home** (high-fat meals either purchased and brought home or eaten in restaurants
- **E-Eat** (extra) high fat commercial products: candy, pastries, pies, doughnuts, cookies

-every 1% reduction in saturated fatty acids will reduce serum cholesterol by about 2%

Aspirin (secondary prevention only)

- 10-15% reduction in mortality; 20-30% reduction in recurrent MI: 20-30% reduction in stroke
- 33% decrease in second MI (men only) (10)

Aspirin irreversibly inhibits platelet cyclooxygenase and impairs platelet aggregation in doses as low as 60mg every other day. A clinical history of bleeding diathesis, active ulcer disease or aspirin allergy are major contraindications. Dosage appears unimportant, ranging from 60mg every other day to 325 mg daily. (icsi) Aspirin is probably effective for primary prevention in patients with elevated cholesterol. Aspirin should be recommended only for primary prevention in males > 50 yrs or females > 50 yrs with multiple risk factors. Low risk populations have minimal benefit.

Diabetes management

- Hyperglycemia may increase CHD by 3-4 fold.

Hyperlipidemia, particularly hypertriglyceridemia, will often improve with better diabetes control through diet, weight loss, and medication.

Hypertension

- 35-40% reduction in stroke; 14% reduction in MI; 16% reduction in CHD with 5-6 mmHg reduction in BP with diuretics and beta blockers.
- 2-3 % reduction in MI risk for each 1% reduction in diastolic BP (10)

Hypertension is defied as blood pressure > 130/80mmHg in patients with diabetes, target organ damage, or cardiovascular disease, > 140/90 mm Hg in others, or taking any antihypertensive medications. If uncontrolled, hypertension can lead to endothelial damage, atherogenesis and stroke. Refer to the hypertension treatment guidelines based on JNC VI for management of these patients.

Smoking Cessation

- 50-75% reduction in MI risk in former vs. current smokers, within 5 years of cessation (hphc)
- Risk of MI decreased to levels similar to non-smokers within 2-3 years after cessation (regardless of quantity smoked or duration of habit)
- Significant rise in HDL cholesterol after cessation

In addition to being an independent risk factor for coronary artery disease, cigarette smoking is associated with changes in the lipoprotein distribution and other metabolic factors that promote atherogenesis. Nicotine stimulation of sympathetic nervous system activity results in elevation of plasma free fatty acids and VLDLs. Smoking clearly reduces HDL cholesterol. Smoking cessation trials have documented a significant rise in HDL after smoking cessation. Cigarette smoking in women is associated with earlier menopause and lower estrogen levels which contribute to an increased CAD risk. (11)
If patient demonstrates any interest in quitting tobacco, then start them in the smoking cessation program. Send referral to Health Education. This program involves comprehensive behavioral counseling by health educators with clinical pharmacists providing medication management of bupropion SR and NRT.

Beta-blocker therapy (secondary prevention only)

- 13% reduction in incidence of sudden death inpatients with no prior cardiac failure, 47% in those with evidence of failure during the acute phase of MI. (10)

b) Probable Effectiveness

Weight Loss

- 35-55% reduction in risk of MI for patients at their ideal weight compared with obese patients (> 20% above ideal body weight) (10)

Obesity frequently elevates cholesterol levels in both very-low-density lipoprotein (VLDL) and LDL fractions, raises triglyceride levels, lowers HDL cholesterol levels, raises blood pressure and promotes glucose intolerance. Weight loss lowers total cholesterol and its LDL and VLDL fractions, lowers triglycerides and raises HDL cholesterol. Weight loss also lowers blood pressure and improves glycemic control. Obese patients should try to lose at least 5-10 percent of their weight. The weight loss goal should be about 1-2 pounds per week. See Obesity treatment guidelines.

Physical activity

- 20-30% reduction in CHD deaths with regular aerobic exercise (10)

Cross-sectional studies in men suggest that aerobic exercise may increase HDL by 5-10% and decrease TG, LDL and TC (6) Patients are more likely to comply with physical activity programs that are tailored to meet individual goals, interests and needs. Most patients benefit from aerobic physical activity that targets large muscle groups (walking, jogging, cycling), performed for 30-60 minutes (duration depends on intensity of exertion), four or more times a week. Overweight patients should engage in low-intensity activity frequently and for longer durations. (10) Patients should also be encouraged to incorporate physical activity into their daily lifestyle activities (e.g. walking or cycling to work, walking breaks at work, using stairs, gardening, household work) Patients should be shown how to measure their pulse. An aerobic target heart rate in patients not on beta-blockers will be calculated {(220-age) x 0.65 = beats per minute}. Compliance with physical activity should be evaluated at each visit.

The American College of Cardiology/American Heart Association Guidelines for Exercise Testing (July 1997) does not endorse or criticize an Exercise Treadmill Test (ETT) in asymptomatic individuals without CAD before beginning an exercise program. Asymptomatic individuals who may obtain useful prognostic information from exercise testing include (11):

1. Persons with 2 or more risk factors (as listed above)
2. Asymptomatic men older than 40 years and women older than 50 years:
3. Who plan to start vigorous exercise (especially if sedentary?)
4. Who are involved in occupations in which impairment might impact public safety?
5. Who are at high risk for CAD due to other diseases (e.g. chronic renal failure?)

Alcohol
Alcohol exerts several effects on lipid levels, which include raising triglyceride and HDL levels. It has minimal effect on LDL. Although case control studies have shown a reduction in coronary event risk it is not advocated for use in prevention of coronary artery disease.

c) <u>Limited Supporting Evidence</u>

Folic Acid
- 60% reduction in risk of MI in men, 80% in women
- Elevated homocysteine level associated with 3.4 fold increase in 5-year risk of MI (10)

Homocysteine is a highly reactive amino acid that is toxic to the endothelium, potentiates auto-oxidation of LDL, and promotes thrombosis. Recent investigations indicate that mildly elevated serum homocysteine levels are associated with an increased risk for CVA, peripheral vascular disease and CAD. Low B6, B12 and folate plasma levels are associated with higher homocysteine levels. Daily intake of B6 (2mg), B12 (6ug) and folate (0.4mg), is associated with lowest homocysteine concentrations. These doses are found in inexpensive multivitamins. Homocysteine levels are very expensive (about $127). As hyperhomocysteinemia is common and treatment is cheap, it is not cost-effective to get levels. Make sure patients do not take excess amounts of vitamins. (11)

Fish oil
- Epidemiologic and randomized controlled trials indicate a reduction in cardiovascular events with intake of omega-3 fatty acid

Fish oil preparations containing omega-3 fatty acids can be used to decrease triglycerides and are an option for patients with hypertriglyceridemia whose levels remain elevated while taking niacin or gemfibrozil. A recent meta-analysis showed a decrease of 30% in TG and slight increase in LDL of 7mg/dl with no change in A1C(5). The American heart Association recommends consuming fish at least twice/week for patients without CAD, taking omega-3 fatty acids 1g/day for patients with CAD and taking 2-4 g/day for patients who need to lower triglyceride levels. (5, 12)

II) SECONDARY CAUSES

Common causes of secondary dyslipidemia include diabetes mellitus, the nephrotic syndrome, chronic renal failure, liver failure and hypothyroidism. Other pathophysiologic and medications are listed below.

An initial work-up for secondary causes should include:

- TSH, BUN, Creatinine
- U/A – r/o significant proteinuria
- LFTs, (T. Bili, SGOT, SGPT, +/- Alk Phos)
- Fasting Glucose level or HbA1C if diabetic

a) Pathophysiological conditions (11)

DISORDER/PATIENT CHARACTERISTIC	**Cholesterol**	**Triglyceride**	**HDL-cholesterol**
METABOLIC/ENDOCRINE			
Diabetes	↑	↑	↓
Hypothyroidism	↑	↑	-
Anorexia nervosa	↑	-	-
Pregnancy	↑	↑	-
Obesity	↑	↑	↓
Acromegaly	↑	↑	-
Hyperuricemia/gout	↑	↓	-
LIVER DISORDERS			
Hepatocellular	↑	↓	-
Cholestasis	↑	-	↓
RENAL DISEASE			
Nephrotic syndrome	↑	↑	↓
Chronic Renal Failure	↕	↕	↓
OTHERS			
SLE	↑	↑	-
Rheumatoid Arthritis	↓	↕	↑
Pancreatitis	-	↑	-
LIFESTYLE FACTORS			
Inactivity	-	↑	-
Smoking	-	-	↓
Alcohol abuse	-	↑	↑

b) Medication causing secondary dyslipidemia(2,11)

DRUG	TC	TG	HDL	COMMENT
ANTIHYPERTENSIVES				
Alpha-blockers	3%	4%	No change	Favorable effect on lipids
β-BLOCKERS Non-selective selective alpha blocking	 No change No change No change	 20-50% 15-30% No change	 10-15% 5-10% No change	 Transient effects; cardio-selective agents affect lipids less Alpha blocking and intrinsic sympathomimetic agents are lipid neutral
DIURETICS Thiazides	 5-7% initially 0-3% later	 30-50-%	 13mg/dL	 Effects may be transient
HORMONES				
Hormone Replacement Therapy (HRT) Oral Contraceptive Pills Monophasics Triphasics	Unknown 5-20% 10-15%	10-15% 10-45% 10-15%	Up to 9% ± 15% 5-10%	HRT may ↑LDL by 10-15%. OCP can CHOL and TRIG primarily due to progestin component
Glucocorticoids	5-10%	15-20%	Unknown	
Cyclosporine	15-20%	No change	No change	LDL by 30%
Isotretinoin	5-10%	50-60%	10-15%	Reversible changes see 8 weeks after stopping the drug
Ethanol	No change	up to 50%	Modest ethanol (20z. /day) may?	Marked elevations may occur in hypertriglyceridemic patients

TC=total cholesterol; TG=triglycerides; HDL=density lipoprotein cholesterol

III) THERAPY

a. Treatment decisions based on LDL cholesterol (4,6)

Risk Category	LDL Goal	Dietary therapy	Initiate drug therapy
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optimal goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL‡‡
Moderately high risk:2+ risk factors‡ (10-year risk 10% to 20%)§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL consider drug options) ##
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk:0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

* CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
† CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.
‡ Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).
§ Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.
‖ Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.
¶ Optimal LDL-C goal <100 mg/dL.
# Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.
‡‡ If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.
For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

b. Choice of medications

- When the commitment is made to initiate drug therapy in moderate or high risk persons, the intensity of therapy should be sufficient to lower LDL levels by ≥30% to 40%
- Statins are the most effective of all agents in lowering LDL, with simvastatin being the preferred initial agent
- Statins are the preferred initial therapy in secondary prevention
- Niacin or bile acid sequestrants should also be considered for primary prevention
- If the therapeutic goal is not achieved after at least 30 days consider: doubling dose of statin (6-7% LDL lowering), adding ezetimibe (addn. 15-20% LDL lowering), adding BAS or niacin and/or re-evaluating compliance with drugs, diet, or secondary causes.
- Choice of drug may change in the following situations:
    - HDL < 35mg/dL
    - Elevated triglyceride levels
    - Patients with familial combined dyslipidemia, diabetic dyslipidemia, or other secondary causes
- There is no consistent evidence that drug treatment of isolated low HDL decreases CHD events if TC and LDL are normal (5)

c. Triglycerides

The link between triglycerides and CHD is complex, and may be explained by the association between high triglycerides, low HDL levels and unusually atherogenic forms of LDL. Elevated triglycerides also often reflect an increase in triglyceride-rich, remnant lipoproteins that have atherogenic potential. Triglyceride levels are classified as:

Normal < 150 mg/dl
Borderline high 150-199 mg/dl
High 200-499 mg/dl
Very High > 500 mg/dl

Patients with borderline-high and high triglyceride levels may have accompanying dyslipidemias that increase risk for CHD (e.g. familial combined hyperlipidemia and diabetic dyslipidemia). Those with very high levels >500 mg/dl are at increased risk for pancreatitis and are candidates for immediate nonpharmacologic therapy (low fat diet <15% of calorie intake, weight reduction, alcohol restriction, and increased activity) and triglyceride lowering medication (gemfibrozil and niacin). Once TG have been lowered to <500 mg/dl should LDL lowering be the focus. After ruling out and addressing secondary causes initial nonpharmacologic therapy is recommended for all patients. If triglycerides are elevated in association with "atherogenic" dyslipidemias (e.g. familial combined hyperlipidemia), or the patient fails dietary and lifestyle modification, drug therapy is indicated. The drugs of choice include nicotinic acid and gemfibrizol. (9)

d. Treatment of Secondary Causes

Noninsulin-dependent diabetes mellitus (NIDDM) is frequently accompanied by elevated triglycerides and low HDL; in addition, LDL levels are commonly in the borderline high-risk range. Because of the high risk for CHD in NIDDM, aggressive lowering of LDL similar to that recommended for established CHD should be applied to these patients. This includes female patients also, as the protection against CHD in women appears to be abolished in diabetes. Although nicotinic acid produces a favorable modification of the lipoprotein profile in NIDDM patients, it tends to worsen glucose tolerance, limiting the drug's utility. When high cholesterol levels predominate in diabetics, bile acid sequestrants or statin drugs are preferable, whereas fibric acids may be preferred when elevated triglycerides predominate. The dyslipidemia of the nephrotic syndrome should first be addressed with the treatment of the underlying renal disease. Hypercholesterolemia is the major lipid abnormality in the chronic nephrotic syndrome, and is responsive to statins. Nicotinic acid or fibric acids can be used when the predominant abnormality is hypertriglyceridemia. The major lipid abnormality of chronic renal failure is hypertriglyceridemia, but because of potential side effects of lipid lowering drugs the preferred therapy is nonpharmocologic, i.e. weight control and minimizing use of drugs that raise triglyceride level.

Summary of treatment options (11)

Type of dyslipidemia	Lipid subfractions	Primary Therapy	Secondary Therapy
High LDL and TG	↑ LDL HDL ≥ 40 TG>200	• Weight loss • Exercise • D/C Tobacco • D/C alcohol • Improve DM control • Step I or Step II diet	Statin Niacin
	↑ LDL HDL<40 TG > 200		Statin Gemfibrozil Niacin Fish oil (EPA-DHA) Ezetimibe
High LDL	↑ LDL HDL ≥ 35	• Weight loss • Exercise • Step I or Step II diet	Statin Fibric acid Niacin Bile acid sequestrant Ezetimibe
	↑LDL HDL < 35		Statin Fibric acid Niacin Bile acid sequestrant Ezetimibe
Isolated Low HDL (treatment controversial except in CAD/diabetes)	HDL <40 LDL is normal	• Exercise • D/C Tobacco • D/C alcohol	Gemfibrozil * Statin Niacin
High Triglycerides	↑ TG	• Weight Loss • D/C Tobacco • D/C alcohol • Improve DM control • Step I or Step II diet	Gemfibrozil Niacin Fish oil (EPA-DHA)

*** Not FDA approved supported use by VA-HIT study**

Comparative efficacy of available statins (8)

Statin dose (mg)					% Reduction		LFT >3 X ULN
Atorvastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	TC	LDL	
-	10	20	20	40	22	27	0.25%
10	20	40	40	80	27	34	0.50%
20	40	80		160	32	41	1%
40	80				37	48	2%
80					42	55	2%

-Generally doubling statin dose lowers LDL cholesterol 6-7% and total cholesterol 5%

Drug Interactions (2,6)

PRECIPITANT AGENT	INTERACTIVE AGENT	CLINICAL MANIFESTATIONS OF DRUG INTERACTIONS	COMMENT
Gemfibrozil	Warfarin	Risk of ? anticoagulant activity	
Resins	Digoxin Gemfibrozil Levothyroxine Phenobarbital Propranolol Statins Thiazides Warfarin Carbamazepine Glipizide Valproic Acid	Can decrease the absorption of interactive agents	Take other drugs 1 hour before or 4 hours after resins
Statins	Cyclosporine	Risk of rhabdomylosis or myopathy with concomitant use	-Recommend a dose reduction of lovastatin to 20mg/d or less -Recommend a dose reduction of simvastatin to 10mg/d or less -Limited trials have shown fluvastatin to be safe -Pravastatin has extensive data to recommend it use in this population
Statins	Erythromycin	Risk of rhabdomylosis or myopathy	-Reported with lovastatin, but cannot be ruled out with other HMG CoA-RI's
Statins	Gemfibrozil	Risk of myositis, acute renal failure, rhabdomyolysis	-Myopathy including rhabdomylolysis reported in up to 5% of lovastatin patients -Interaction also reported with pravastatin
Statins	Digoxin	May increase steady state plasma levels of digoxin by as much as 20%	-Reported with atorvastatin
Statins	Oral Contraceptives	Atorvastatin increased AUC values for norethindrone (30%) and ethynyl estradiol (20%)	-Combination contraceptives, particularly those containing norethindrone or ethinyl estradiol, should be carefully considered in women taking atorvastatin
Statins	Niacin	Risk of myositis, acute renal failure, rhabdomyolysis	-Myopathy reported in 2% of lovastatin patients with or without rhabdomyolysis -Recommend a dose reduction of fluvastatin, simvastatin, and pravastatin
Statins	Itraconazole Ketoconazole Fluconazole Verapamil other CYP3A4 inhibitors	Toxicity including rhabdomyolysis my occur (may lead to kidney and cardiac damage)	-Increased risk in doses of azoles >200mg if necessary temporarily discontinue, reduce dose or consider change to pravastatin
Statins	Nefazodone	Myositis and rhabdomyolysis	Reported with simvastatin
Statin/Niacin	Vitamin E	May blunt rise in HDL seen with simvastatin/niacin combination	Should not be used. (3)
Statins	Warfarin	May effect INR	Reported with both lovastatin and simvastatin
Statins	Grape fruit juice	Inhibition of gut wall cyp 3A4 and increase in blood levels	>1 qt/day resulted in 12-15 fold increase in AUC of lovastatin >8 oz/day resulted 2 fold increase in AUC of lovastatin

Drug Monographs (2,11,13,14)

STATINS

Statins Should Be Avoided In The Following Situations

1. Patients with active liver disease or persistent elevations in liver function tests.
2. Patients who abuse alcohol.
3. Pregnancy, lactation, and women of child bearing age.

Dosing Recommendations

Simvastatin is available as 10 mg, 20 mg, 40 mg and 80 mg tablets.
Atorvastatin is available as 10mg, 20mg, 40mg

1. Doses should generally be initiated to reduce LDL levels by 30-40%. First line statin therapy consists of standard doses of simvastatin 20 to 40mg which reduces LDL by 35 to 41% respectively; as compared to second line atorvastatin 10mg which reduces LDL by 39%. Lower doses may be warranted in patients at high risk for myopathy [age>80yrs, small body frame, chronic renal insufficiency and medications listed above]

2. Simvastatin is recommended at bedtime once daily although alternate day dosing has shown effectivness. (4) Atorvastatin is taken once daily and may be taken at any time of day.

Monitoring Guidelines

1. Hepatic enzymes should be evaluated at baseline, within 6-12 weeks of initiation or any dose increase, and every 6 months while on chronic therapy. If elevated perform a second test to confirm the finding followed thereafter by frequent liver function tests until abnormalities return to normal. Dose reduction, continued administration, discontinuation and/or rechallenge frequently result in reversal of transaminase elevations. For persistent increases > 3 X ULN discontinuation is recommended. Elevated hepatic transaminases occur in 0.5-2.0% of patients and are dose dependant. Since clinically important elevations (>3X ULN) in large trials is the same for statins as placebo and progression to liver failure is rare, whether elevated transaminases constitutes true hepatotoxicity or is related to cholesterol-lowering per se has not yet been determined. There is no evidence that statins are harmful in patients with transaminase elevations due to nonalchoholic fatty liver disease (NAFLD).

Consider referral to hepatitis clinic or to http://home.alaska.ihs.gov/viralhepatitis/providerinformation.htm

2. Myopathy (muscle weakness, myalgias, muscle tenderness in conjunction with increases of CK exceeding 10 times the ULN) is rare (0.09%) with only isolated case reports. This risk is increased in combination statin and fibrate (1% with CK >3X ULN) with statin and niacin combination carrying a lower risk.

3. CK levels should be checked if muscle symptoms develop during therapy but may be checked also at baseline since pre-treatment knowledge can aid later decision making. If symptoms present rule out exercise, strenuous work, hypothyroidism and obtain CK.

ACC/AHA/NHLBI clinical advisory on statins	CK levels	Clinical recommendation
Symptomatic patient	> 10 X ULN	Discontinue statin therapy
	No elevation or moderate elevation (3-10 X ULN)	Follow patient symptoms and CK levels weekly
	Progressive CK elevations on serial measurements	Decrease statin dose or temporary discontinuation
Asymptomatic patient	> 10 X ULN	Strong consideration of stopping statin therapy
	Moderate elevation (3-10 X ULN)	Usually can continue statin treatment without harm, frequent and careful monitoring of symptoms and CK are indicated

Statins should also be withheld in any patient experiencing an acute or serious condition predisposing the patient to the development of renal failure secondary to rhabdomyolysis (e.g. severe acute infection, major surgery and uncontrolled seizures)

4. Insomnia, headache, fatigue, and GI complaints are uncommon and would rarely result in discontinuation of simvastatin.

5. Drug interactions:
   a. Colestipol - decreases bioavailability, this potential interaction is usually avoided if simvastatin given at bedtime
   b. Warfarin - enhanced prothrombin time
   c. Gemfibrozil – increased risk of myopathy, don't exceed 10mg simvastatin
   d. Cyclosporine- concurrent administration predisposes user to myopathy, don't exceed 10mg simvastatin
   e. Niacin - increased risk of myopathy and hepatotoxicity
   f. Amiodarone,Verapamil - concurrent administration predisposes user to myopathy, don't exceed 20mg simvastatin
   g. Itraconazole - coadministration increases statin levels (up to 20 fold). Avoid other azoles as well, if necessary temporarily discontinue or reduce dose.
   h. Nefazodone – concurrent administration predisposes user to myopathy
   i. Digoxin - may increase steady state plasma levels of digoxin by as much as 20%
   j. Grape fruit juice- may increase levels through gut cyp 3A4 inbibition, don't exceed 8 oz or ½ of fruit per day
   k. Oral Contraceptives -atorvastatin increases AUC for norethindrone (30%) and ethynyl estradiol (20%)

Ezetimibe

Long term effects on cardiovascular morbitidy and mortality are unknown

Dosing Recommendations
Ezetimibe is available 10mg tablet and also available in combination with simvastatin 10/80 and 10/40mg tablets

a. FDA approved dose is 10mg although initial Phase II study showed fairly flat dose response curve with 5mg reducing LDL by 16 % as compared to 19% reduction with 10mg so using ½ tablets remains an cost effective option.

b. Combining ezetimibe to simvastatin will result in additional 15-20% LDL and 10% TG lowering with increase of 2-3% in HDL.

c. Maximal response (LDL reduction) occurs cases at 2 weeks after initiation.

d. Renal Function Impairment – No dose adjustment recommended in mild or moderate impairment. Caution in severe renal impairment as AUC increased approximately 1.5-fold (CrClr up to 30 mL/min), dose of ezetimibe/simvastatin should not exceed 10/10 mg daily.

e. Hepatic Impairment – No dose adjustment needed in mild hepatic impairment (AUC increased approximately 1.7-fold). Not recommended in moderate and severe hepatic impairment (3- to 4-fold in moderate and 5- to 6-fold in severe impairment).

f. Elderly – No dose adjustment recommended although plasma concentrations are approximately 2-fold higher

Monitoring Guidelines

1. When used alone no special monitoring requirements. If used with statin same monitoring requirements as statin.

2. Generally well tolerated with adverse effects similar to placebo. Long term safety unknown. No reports of myopathy or CK elevations

3. Drug Interactions
    a. Antacids: Aluminum- and magnesium-containing antacids decrease the peak concentration of ezetimibe but not the AUC
    b. Cholestyramine: Dose ezetimibe 2 hrs before or 4 hr after a bile acid sequestrant as the AUC of ezetimibe may be decreased by 55%.
    c. Cyclosporine: Dose of ezetimibe/simvastatin should not exceed 10/10 mg daily. Concentrations of ezetimibe/simvastatin may be increased, especially in patients with severe renal insufficiency.
    d. Amiodarone or Verapamil: Dose of ezetimibe/simvastatin should not exceed 10/20 mg daily

GEMFIBROZIL

Gemfibrozil Should Be Avoided In the Following Situations

1. Patients with preexisting gallbladder disease.
2. Patients with severe hepatic or renal dysfunction (may reduce clearance and increase side effects).
3. Patients with primary biliary cirrhosis.
4. Pregnancy, lactation, and women of child bearing age.

Gemfibrozil Dosing Recommendations -- Gemfibrozil is available as 600 mg tablets.

1. Therapeutic note: indications for gemfibrozil should be limited to the following:
   a. Patients with marked elevations of triglycerides at risk for pancreatitis.
   b. Patients with dyslipidemia (increased TGs, decreased HDL) who are refractory to niacin or in whom niacin should be avoided.
2. The standard dose is 600 mg twice daily 30 minutes before breakfast and dinner.
3. The dose should be reduced to 300 mg BID in the presence of moderate renal failure (10 -50 ml/min); decrease dose to 150 mg BID for patients with GFR < 10 ml/min.

Gemfibrozil Monitoring Guidelines

1. The most frequent adverse effects are GI including abdominal pain, diarrhea, and nausea (2-5% incidence). This infrequently results in discontinuation of gemfibrozil.

2. Because gemfibrozil may increase cholesterol secreted in the bile and may result in cholelithiasis and cholecystitis (0.3-1%) - if cholelithiasis is suspected, gallbladder studies are indicated and gemfibrozil should be discontinued if gallstones are found.

3. Severe hematologic changes such as anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have rarely been reported. Consider checking CBC at baseline, and with each clinic visit for one year. Gemfibrozil should be discontinued if abnormalities are apparent.

4. Liver function tests should be evaluated at baseline, within 6-12 weeks of initiation and every 6 months while on chronic therapy. Though uncommon, persistent elevations of serum transaminase levels (2 or more occasions) exceeding 3 times the upper limit of normal indicates that gemfibrozil should be discontinued.

5. Baseline serum creatinine should be evaluated. Use with caution if above 2.0 mg/dl.

6. Drug interactions:
   a. Statins - increase risk for myositis, rhabdomyolysis reported
   b. Warfarin - caution is advised, may need to decrease dose of warfarin to avoid prolongation of PT.
   c. Colestipol - decreases bioavailability of gemfibrozil, give 2 hours before colestipol or 4-6 hours after colestipol.

NIACIN

Niacin Should Be Avoided In The Following Situations

1. Patients with active liver disease or preexisting liver disease (elevated SGOT, ALK PHOS, SGPT).
2. Uncontrolled type 2 DM with high dose niacin >3mg/d
3. Patients who abuse alcohol (> 3 drinks/day).
4. Patients with uncontrolled gout or a history of gout (uric acid > 10 mg/dl).
5. Patients with active peptic ulcer disease.

Niacin Dosing Recommendations
Niacin (crystalline niacin) available at ANMC: 50mg, 100mg & 500mg scored tablets.
Niaspan (extended release niacin) available at ANMC: 500mg XR, 750 mg XR, 1000mg XR

1. Side effects associated with niacin can be minimized by starting at a low dose and gradually increasing to the target dose over several weeks. If during the first few weeks of the dose titration, a particular dose is not tolerated, return to the previously tolerated dose and attempt to increase dose again after one week. If still not tolerated, continue on previously tolerated dose until next scheduled follow-up clinic visit. Niaspan provides a once daily dosing that is better tolerated that crystalline niacin and has reduced hepatic toxicity compared to other sustained release niacin products.

Dosing:	Crystalline Niacin	Niaspan
Week 1:	Niacin 50mg BID after meals	Niaspan 500mg qhs with snack
Week 2:	Niacin 100mg BID after meals	Increase Niaspan by 500mg every 4 weeks
Week 3:	Niacin 250mg BID after meals	“”
Week 4:	Niacin 500mg BID after meals	“”
Week 5:	Niacin 1000mg BID after meals	Niaspan 1000mg qhs with snack for 3 weeks
Week 6:	Niacin 1500mg BID after meals	“”
	Usual range 1.5-3 g daily (max 4.5g/day)	Usual range 1-2 g daily (max 2g/day)

2. Gastrointestinal phenomena (N/V/D and anorexia) can be decreased by taking each dose of niacin immediately after a large meal...
3. Cutaneous effects (flushing, pruritis and rash) may occur within 15 to 30 minutes after taking niacin. These effects usually last for 5 to 10 minutes and can be minimized by taking aspirin 325mg orally 30 minutes before each dose of niacin. Aspirin can be discontinued after 6 months without symptoms of flushing. Avoid administration of niacin with ethanol or hot drinks
4. Titration of niacin to a minimum target dose of 1-1.5 grams daily.
5. Doses higher than 3.0 g/day crystalline niacin may be required in some patients, and are more likely to cause hepatotoxicity necessitating more frequent monitoring.
6. Retitrate dose if patient restarting after extended period.

Niacin Monitoring Guidelines

1. Fasting blood glucose, liver function tests and uric acid should be evaluated at baseline, within 6-12 weeks of initiation or any dose increase, and every 4 to 6 months while on chronic therapy. Fasting glucose should be repeated at 6 weeks, and uric acid if symptoms of gout.
2. Suspect possible hepatotoxicity when total cholesterol is markedly reduced (low 100s), serum albumin is decreased, elevations of transaminase levels > 3 times or alkaline phosphatase > 2 times the upper limit of normal, edema is present, or new onset "flu-like" complaints or vague abdominal complaints. Hepatotoxicity is rare and appears to be dose related occurring with daily doses of three grams or more administered for a minimum of three months. It has been reported as early as three weeks and as late as four years after initiation of niacin.
3. If elevations of liver enzymes occur but no other signs of hepatotoxicity are present, niacin does not have to be discontinued, a dose reduction will result in a reduction of liver enzyme levels. Liver enzyme elevations up to 3 times upper limit of normal in the absence of any other adverse effect (e.g., hypoalbuminemia) are common. Niacin should be discontinued if liver enzymes exceed 3 times upper limit of normal.

COLESTIPOL/CHOLESTYRAMINE

These drugs should be avoided in the following situations:

1. Moderate to severe pre-existing constipation
2. As monotherapy in the presence of elevated triglycerides (> 250 mg/dL). Can be used in combination with drugs that lower triglycerides. Is contraindicated in patients with triglycerides > 500 mg/dL.
3. Use cautiously in patients with hemorrhoids.
4. Uncontrolled PUD

Dosing Recommendations
Colestipol is available in 1gm tablets.
Cholestyramine is available in 4gm packets, or 210 gm cans

1. Therapeutic Note: The percent LDL reduction is greatest in those patients with moderate LDL elevation at baseline (160-200 mg/dl) compared to those with marked LDL elevations at baseline (+220 mg/dl) {Am J Cardiol, 1992; 70:135-1401}.

2. Dosing:
Colestipol: 2 tabs (2g) once or twice daily with breakfast and dinner for 1-2 months, then increase by 2g once or twice daily at 1-2 month intervals. Usual maintenance is 2-16 g/day in 1 or more divided doses
Cholestyramine: 4g one or two times/day. Increase at 4-week intervals. Usual maintenance is 2-4 pkts or scoops divided into 2 doses. Max: 6 pkts or scoops (24g)/day

3. Constipation can be reduced by mixing one heaping teaspoonful of psyllium (Konsyl or Metamucil) with each mealtime dose. Precede initial dose with 3 days of psyllium in patients who have a tendency for constipation. Encourage use of fruits, vegetables and fiber rich food items, especially dry fruit.

4. To avoid accidental inhalation or esophageal distress, these drugs must not be taken as powder. Add to at least 3 ounces of water or beverage (tastes best in orange drink, apple juice, pulpy fruits or applesauce). It should not be mixed with carbonated or hot beverages. It should be mixed thoroughly, and the glass should be rinsed with a little more liquid to make sure the full dose is taken.. A gritty sandy texture leads to poor patient compliance. To improve texture and taste, it should be mixed in a beverage and stored overnight in the refrigerator to be used the next day.

Monitoring Guidelines

1. Constipation is the major complaint. If it becomes a problem despite concurrent use of psyllium, the patient should be counseled to:
    a. Drink more fluids and consider a stool softener (docusate) twice daily.
    b. If it continues to be a problem, reduce the dose of the drugs.

2. Counsel the patient to contact the provider and to discontinue drug in the event of severe stomach pain associated with nausea and vomiting or if rectal bleeding occurs.

3. These drugs may bind with and prevent absorption of many drugs, including lipid-lowering agents. The following interacting drugs must be given 2 hours before or 4-6 hours after taking the drug:

Digoxin	Iron	Anticonvulsants (phenobarbitol, carbamazepine,
Levothyroxine	Warfarin	valproic acid, phenytoin)
Statins	Gemfibrozil	Antibiotics (Penicillin, cephalosporin, tetracycline,
NSAIDS/ASA	Ursodiol	clindamycin)
Propranolol	Thiazides	Furosemide
Vitamins A, D, E, K	Imipramine	glipizide/tolbutamide

Watch for patients with diverticulitis, rectal bleeding, signs of significant interactions with digoxin, warfarin, amiodarone, propranolol.

FOLLOW-UP (2)

An evaluation of the patient at follow-up visits should include:

A. History

1. Diet compliance
2. Medication compliance (if indicated) and presence of adverse events
3. Current medications or pertinent changes in other drug therapy
4. Compliance with exercise program if prescribed
5. Reevaluation of the modifiable cardiovascular risk factors
6. Evaluation of symptoms of myositis or liver disease

B. Physical Examination

1. Weight
2. Blood pressure
3. Pulse

C. Laboratory Tests

1. Periodic fasting lipid profiles
2. Creatinine kinase (CK) for symptoms of myositis
3. LFT's for patients on gemfibrozil, statins, or niacin
4. Fasting blood sugar and uric acid for patients on niacin
5. Baseline serum creatinine for new starts on gemfibrozil

D. Adverse event monitoring requiring PCP consultation: (including but not limited to):

1. Significant elevations of glucose or uric acid and/or clinical manifestations of DM or gout while on niacin
2. Significant elevations of liver enzymes (> 3 times the ULN) while on niacin, statins, or gemfibrozil therapy
3. Symptoms of myositis and CK (>10 ULN) while on gemfibrozil or statin therapy alone or in combination with other drugs

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