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Health Care Guideline

The information contained in this *ICSI Health Care Guideline* is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

This *ICSI Health Care Guideline* should not be construed as medical advice or medical opinion related to any specific facts or circumstances. If you are not one of the expert audiences listed above you are urged to consult a health care professional regarding your own situation and any specific medical questions you may have. In addition, you should seek assistance from a health care professional in interpreting this *ICSI Health Care Guideline* and applying it in your individual case.

This *ICSI Health Care Guideline* is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An *ICSI Health Care Guideline* rarely will establish the only approach to a problem.

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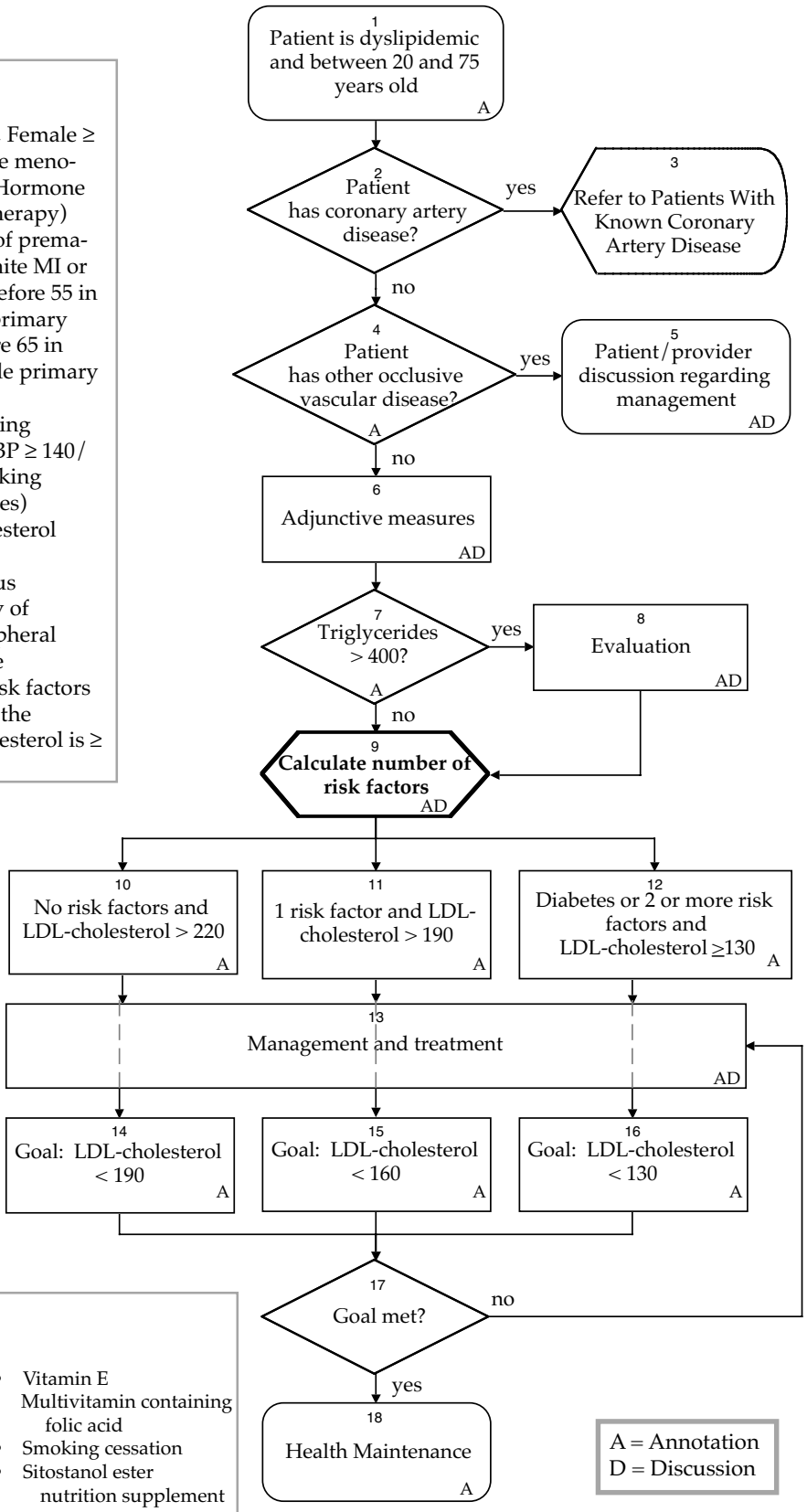
Health Care Guideline:

Treatment of Lipid Disorder in Adults

Patients Without Known Coronary Artery Disease



9
Risk Factors

- Age: Male ≥ 45, Female ≥ 55 (or premature menopause without Hormone Replacement Therapy)
- Family history of premature CAD (definite MI or sudden death before 55 in father or male primary relative or before 65 in mother or female primary relative)
- Currently smoking
- Hypertension (BP ≥ 140/90 mm Hg or taking antihypertensives)
- Low HDL-cholesterol (<35)
- Diabetes Mellitus
- Personal history of cerebral or peripheral vascular disease

One of the above risk factors may be removed if the patient's HDL-cholesterol is ≥ 60.

6
Adjunctive Measures

- Diet
- Aerobic exercise
- Weight Management
- Hormone replacement therapy
- Consider aspirin
- Evaluate alcohol consumption
- Vitamin E
- Multivitamin containing folic acid
- Smoking cessation
- Sitostanol ester nutrition supplement

A = Annotation
D = Discussion

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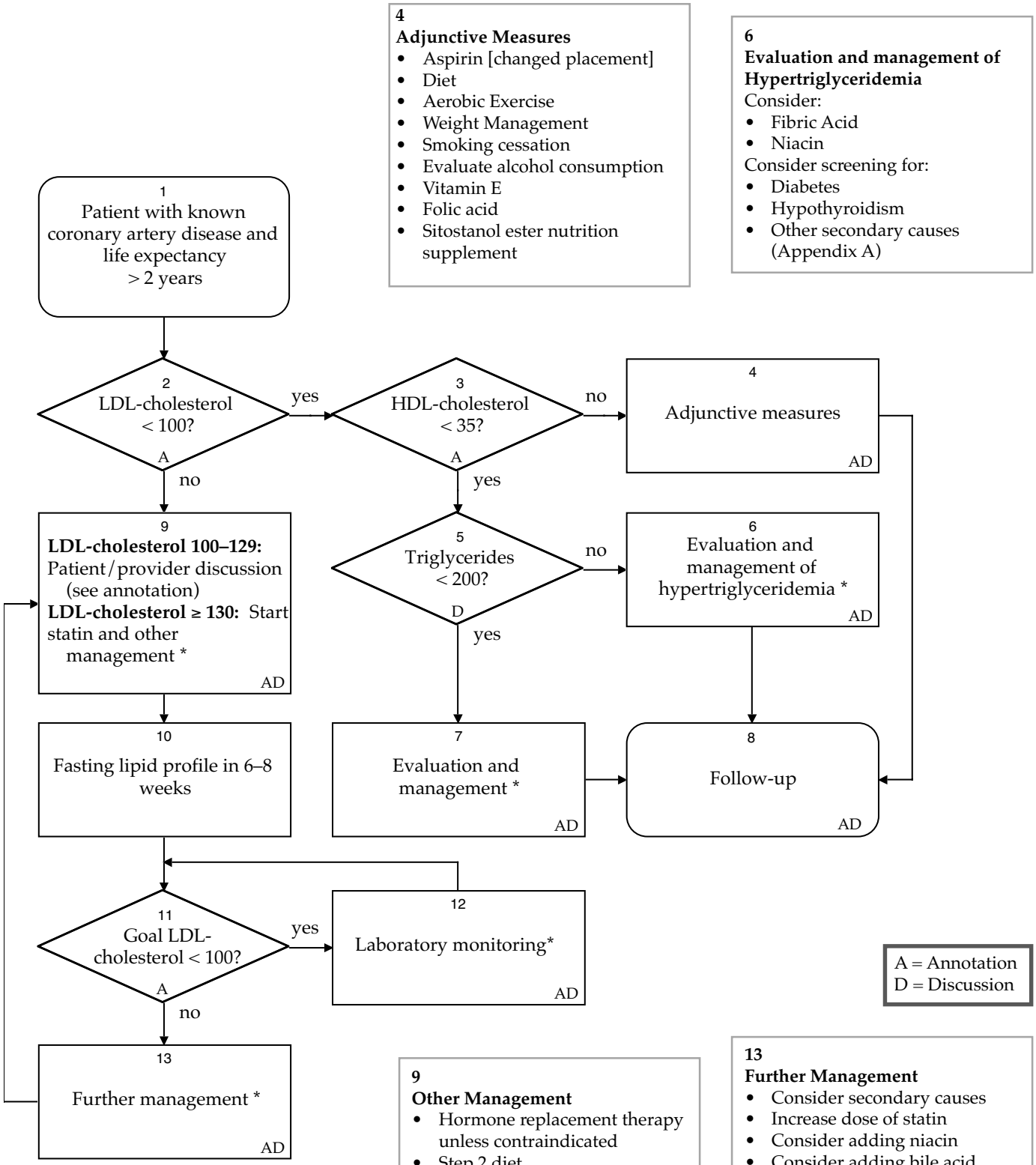
These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

Patients With Known Coronary Artery Disease Algorithm



* Refer to Annotations Appendix C, "Drug Companion Document."

TARGETED POPULATION

Adults between the ages of 20 and 75 who are dyslipidemic.

PRIORITY AIMS FOR MEDICAL GROUPS WHEN USING THIS GUIDELINE

1. Improve the percentage of patients with known coronary artery disease with lipid disorders who meet their treatment goal.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with diagnosed coronary artery disease who have LDL-cholesterol less than 100 mg/dl.

   b. Percentage of patients with diagnosed coronary artery disease who have LDL-cholesterol less than 130 mg/dl.

2. Improve the percentage of patients without known coronary artery disease with lipid disorders who meet their treatment goal.

   Possible measures of accomplishing this aim:

   a. Percentage of patients without known coronary artery disease who are on lipid lowering medications, within each of three starting LDL-cholesterol and risk factor levels, who achieve the goal range for LDL-cholesterol for the group.

3. Increase compliance with non-pharmacological treatment of patients with coronary artery disease through education.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with coronary artery disease for whom a diet evaluation has been completed.

   b. Percentage of patients with coronary artery disease with referral for individual diet instruction or class.

   c. Percentage of patients with coronary artery disease with documentation of receiving advice about an exercise program.

4. Improve the proportion of patients on lipid lowering medication who receive regular follow-up care for lipid disorder.

   Possible measures of accomplishing this aim:

   a. Percentage of patients on lipid lowering medication who have a fasting lipid panel every six to twelve months.

EVIDENCE GRADING SYSTEM

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X. A full explanation of these designators is found in the Discussion and References section of this guideline.

In future versions of this guideline, selected conclusions will include a statement of the grade assigned to the conclusion.

ALGORITHM ANNOTATIONS

1. Patient is dyslipidemic and between 20 and 75 years old

To maintain consistency with the ICSI Lipid Screening guideline, the population targeted in this algorithm will be patients between the ages of 20 and 75 years old who are dyslipidemic.

Secondary causes for the abnormal lipid level should be considered and treated when appropriate. For a list of possible causes and conditions, see Annotations Appendix A, "Secondary Causes and Conditions Associated with Hyperlipidemia."

The cornerstone of treatment for asymptomatic patients with dyslipidemia should be diet and exercise. Asymptomatic patients with an elevated LDL-cholesterol should be started on the NCEP Step 1 diet and at the same time be advised to begin a program of regular aerobic exercise that is tailored to their situation. The recommended diet should be a low fat, especially low saturated fat, diet that is also high in soluble fiber. Also, individuals who are overweight should be advised to reduce their calorie intake such that a modest weight loss is achieved. This program of diet and exercise should be given a reasonable time to see if it is sufficient to bring the LDL-cholesterol into the target range. Many asymptomatic patients will not require more than diet and exercise.

Evidence supporting this recommendation is of class: A

4. Patient has other occlusive vascular disease?

Occlusive vascular disease is defined as a diagnosis of carotid occlusive vascular disease and/or peripheral vascular disease.

5. Patient/Provider Discussion Regarding Management

Patients and providers need to discuss the patient's risk for developing coronary artery disease. Patients with occlusive vascular disease (OVD) are at increased risk for coronary artery disease (CAD), even without clinical symptoms of CAD. Health care providers should help the patient decide whether aggressive lipid lowering is indicated. Patients needing aggressive lipid lowering could be managed through the Known Coronary Artery Disease algorithm in this guideline.

It may be advisable to treat patients with a history of stroke or cerebrovascular atherosclerosis aggressively with a statin based regimen.

Evidence supporting these recommendations is of classes: A, B, C, D, R, M

6. Adjunctive Measures

Adjunctive Measures include diet, exercise, weight management, hormone replacement therapy, smoking cessation, evaluation of alcohol consumption, vitamin E*, multiplevitamin with folic acid*, aspirin, and sitostanol ester nutrition supplement.

The clinician should evaluate the patient's diet using a tool such as the American Heart Association's Heart Smart Nutrition Quiz, which may not be appropriate for all individuals. It is desirable to have the nutritional assessment and evaluation for these individuals carried out by a registered dietitian whenever possible.

* In terms of vitamins, many patients seem to believe that if a little is good, more is better. In order to avoid unintended toxicity, it is appropriate to caution the patient not to exceed recommended vitamin doses.

Evidence supporting these recommendations is of classes:

Diet: A, B, R.

Exercise: A, D, R

Weight Management: R.

Hormone replacement therapy: A, B, R.

Smoking cessation: C, R.

Evaluate alcohol consumption: B, R.

Vitamin E: A, B, R.

Multivitamin with folic acid: B.

Aspirin: Primary Prevention: A, B.

Sitostanol ester nutrition supplement: A, C

7. Triglycerides > 400?

If triglycerides are > 400, LDL-cholesterol measurement cannot be calculated according to the Friedenwald equation.

8. Evaluation

Evaluation of elevated triglycerides includes:

1. Screening for:

   diabetes

   hypothyroidism

2. Consideration of Secondary Causes**

3. Consider medications:

   fibric acid*

   niacin*

Considerable controversy exists regarding the benefits of medication therapy. Please refer to the Discussion and References section under this annotation.

Evidence supporting these recommendations is of classes: A, R

*Refer to Annotations Appendix B, "Therapy" and Annotations Appendix C, "Drug Companion Document."

**Refer to Annotations Appendix A, "Secondary Causes Associated with Hyperlipidemia."

9. Calculate number of Risk Factors

NCEP II defines high risk as a net of two or more coronary artery disease (CAD) risk factors which leads to more vigorous intervention by the patient and clinician.

The following are identified as **risk factors**:

Age: Male ≥ 45 or Female ≥ 55 or premature menopause without hormone replacement therapy. Defined differently for men and women, age is a risk factor because rates of CAD are higher in the elderly than in the young, and in men than in women of the same age.

Family history: Family history of premature CAD is defined as definite MI or sudden death before 55 in father or male primary relative or before 65 in mother or female primary relative.

Currently smoking

Hypertension: Hypertension is defined as blood pressure ≥ 140/90 mm Hg (confirmed by measurement on several occasions) or taking any antihypertensive medications.

Low HDL-cholesterol (< 35)

Diabetes Mellitus: According to NCEP II, "Non-insulin-dependent diabetes mellitus is frequently accompanied by elevated triglycerides and low HDL-cholesterol; in addition, LDL-cholesterol levels commonly are in the borderline-high-risk range. Because of the high risk for CHD resulting from non-insulin-dependent diabetes mellitus, aggressive lowering of LDL-cholesterol levels, similar to that recommended for established CHD, can be applied to diabetic patients. This is true for women diabetic patients as well as men, because the protection against CHD normally afforded to women appears to be abolished in the presence of diabetes."

Personal History of Cerebral or Peripheral Vascular Disease

Obesity and physical inactivity are not listed as risk factors, but should be considered as targets for intervention. Obesity operates through other risk factors (hypertension, hyperlipidemia, decreased high-density lipoprotein [HDL] cholesterol, and diabetes mellitus).

If the HDL-cholesterol is ≥ 60 mg/dl (1.6 mmol/L), one risk factor may be subtracted because high HDL-cholesterol levels decrease CHD risk. For instance, if the patient has 3 risk factors but his or her HDL-cholesterol is 60 or greater, the provider would subtract one risk factor for a total of 2 risk factors.

Evidence supporting these recommendations is of classes: B, D, R

10. LDL-cholesterol > 220

The patient has no risk factors and an LDL-cholesterol > 220.

11. LDL-cholesterol > 190

The patient has one risk factor and an LDL-cholesterol > 190.

12. LDL-cholesterol > 130

The patient has diabetes or two or more risk factors and an LDL-cholesterol > 130.

TABLE 1 – A POINT SCORE APPROACH FOR ESTIMATING 10 YEAR CORONARY HEART DISEASE RISK

I) Age - Men

Age	Points	Age	Points
30	-2	48-49	9
31	-1	50-51	10
32-33	0	52-54	11
34	1	55-56	12
35-36	2	57-59	13
37-38	3	60-61	14
39	4	62-64	15
40-41	5	65-67	16
42-43	6	68-70	17
44-45	7	71-73	18
46-47	8	74	19

I) Age - Women

Age	Points	Age	Points
30	-12	41	1
31	-11	42-43	2
32	-9	44	3
33	-8	45-46	4
34	-6	47-48	5
35	-5	49-50	6
36	-4	51-52	7
37	-3	53-55	8
38	-2	56-60	9
39	-1	61-67	10
40	0	68-74	11

II) Total Cholesterol

Total Chol.	Points
139-151	-3
152-166	-2
167-182	-1
183-199	0
200-219	1
220-239	2
240-262	3
263-288	4
289-315	5
316-330	6

III) HDL Cholesterol

HDL Chol.	Points
25-26	7
27-29	6
30-32	5
33-35	4
36-38	3
39-42	2
43-46	1
47-50	0
51-55	-1
56-60	-2
61-66	-3

IV) Systolic Blood Pressure

SBP	Points
95-104	-2
105-112	-1
113-120	0
121-129	1
130-139	2
140-149	3
150-160	4
161-172	5
173-185	6

V) Other Risk Factors

Other Risk Factors	Points if Present (0 points if absent)
Cigarettes	4
Diabetes - male	3
Diabetes - female	6
ECG LVH	9

TABLE 2 – A POINT SCORE APPROACH FOR ESTIMATING 10 YEAR CORONARY HEART DISEASE RISK (cont)

Step 2) Add up Point Scores for Risk Factors

Risk Factor	Points
Age	_____
Cholesterol	_____
HDL	_____
Systolic BP	_____
Smoking	_____
Diabetes	_____
ECG LVH	_____
Total	_____

Step 3) Look UP CHD Risk Corresponding to Total Score

Total Points	10 Year Risk	Total Points	10 Year Risk	Total Points	10 Year Risk
3	2%	13	8%	23	23%
4	2%	14	9%	24	25%
5	3%	15	10%	25	27%
6	3%	16	12%	26	29%
7	4%	17	13%	27	31%
8	4%	18	14%	28	33%
9	5%	19	16%	29	36%
10	6%	20	18%	30	38%
11	6%	21	19%	31	40%
12	7%	22	21%	32	42%

These tables reproduced from:

Levy D. "A Multifactorial Approach to Coronary Disease Risk Assessment." *Clin Exp Hypertens* 15(6):1077-1086, 1993. (Class R)

13. Management and Treatment

Management and Treatment may include the following:

- Dietary Instruction: Dietary instruction should be obtained through a class or by individual instruction from a registered dietitian or trained professional.
- Reinforcement of Adjunctive Measures (Refer to Annotation # 6).
- Consider secondary causes (Appendix A)
- Recheck lipid panel in 3 months.
- Consideration of pharmacological treatment based on level of risk and patient preference.
- Consider referral to a lipid clinic.

Consideration of pharmacological treatment based on patient preference

No primary prevention studies have addressed pharmacologic lipid treatment in low risk persons, and there is no evidence to support drug treatment in this population. In particular, the incidence of coronary artery disease (CAD) in men under 40 and premenopausal women is very low. Drug treatment of these groups of patients is discouraged.

Primary prevention studies with pharmacologic lipid lowering have not shown a decrease in mortality. Most studies have shown approximately a 30% reduction in CAD events. These studies have been in middle aged men, some with other risk factors. Similar benefit in higher risk women can be assumed, but has not been demonstrated.

The rationale for pharmacologic lipid lowering is strongest in patients who are at highest risk. Primary prevention studies with pharmacologic lipid lowering have shown a 25-44% reduction in coronary events and a trend toward lowered mortality. Most studies have involved middle aged men, but similar relative risk reduction also occurred in women in the AFCAPs trial.

The decision to begin and continue lipid lowering medication should be a mutual decision made by the patient and the provider. Information about absolute risk reduction and the number needed to treat (NNT) to prevent a CAD event should be provided to the patient to assist in this decision. (See Table 3 below.)

Table 3: Absolute Risk Reduction and NNT with Pharmacologic Lipid Lowering

10 year* risk for CAD	Events prevented/1000 patients treated	NNT to prevent one event over 5 years
35%	105	9.5
30%	90	11
25%	75	13
20%	60	17
15%	45	19
10%	30	33
5%	15	67
2.5%	7.5	133

The NNT can be presented to the patient as the number of people who would have to take medication for five years to prevent a non-fatal heart attack. (The major primary prevention studies have been 4–6 year studies.) For example, if the NNT is 13, then 1 of 13 patients would benefit from treatment and 12 of 13 would not.

* Assumes 30% Risk Reduction

Table 4: Primary Prevention for CHD

Therapy	Population	NNT over 5 years	Trial
Statin	Men >45	40	WOSCOPS
Statin	Men >45 and HTN	24	WOSCOPS
Statin	Men >45 and FHx	23	WOSCOPS
Statin	Men >45/Women >55 with HDL-cholesterol <50, LDL-cholesterol >130	50	AFCAPS
Aspirin	Men >50	63	NEJM 321:129, 1989
Estrogen	Pmenop Women >50	212	Lancet 349(S1):S13, 1997

Refer toAnnotations Appendix B, "Therapy," and Annotations Appendix C, "Drug Companion Document."

Evidence supporting these recommendations is of classes: A, R

14. Goal: LDL-cholesterol < 190

The treatment goal for a person with no risk factors is an LDL-cholesterol < 190.

15. Goal: LDL-cholesterol < 160

The treatment goal for a person with one risk factor is an LDL-cholesterol < 160.

16. Goal: LDL-cholesterol < 130

The treatment goal for a person with diabetes or two or more risk factors is an LDL-cholesterol < 130.

Note, however, that many clinicians advocate a goal LDL-cholesterol <100 for individuals with diabetes because: 1) 50% of individuals with type two diabetes mellitus have coronary heart disease at the time of diagnosis, 2) patients with both CHD and diabetes have poorer outcomes than those with CHD alone, and 3) patients with diabetes and no prior history of myocardial infarction are as likely to experience a myocardial infarction over a seven year interval (a 20% incidence) as patients without diabetes who have a history of myocardial infarction.

Evidence supporting this recommendation is of class: A

17. Goal Met?

Patient compliance with planned therapy contributes to the success of that treatment plan. The clinician should assess for compliance issues by asking patients about compliance with therapies using open-ended, non-threatening questions.

Evidence supporting this recommendation is of class: R

18. Health Maintenance

Health Maintenance includes:

Periodic monitoring (Refer to Annotations Appendix C, Drug Companion Document.)

Risk Factor Modification

Reinforcement of Adjunctive Measures. (Refer to Patients Without Known CAD, Annotation # 6.)

2. LDL-cholesterol < 100?

This will identify patients with known coronary artery disease who have elevated LDL-cholesterol levels.

3. HDL-cholesterol < 35?

This will identify patients with known coronary artery disease who have low HDL-cholesterol levels.

4. Adjunctive measures

Adjunctive Measures include: aspirin, diet, exercise, weight management, smoking cessation, evaluation of alcohol consumption, vitamin E*, multivitamin with folic acid*, and sitostanol ester nutrition supplement.

* In terms of vitamins, many patients seem to believe that if a little is good, more is better. In order to avoid unintended toxicity, it is appropriate to caution the patient not to exceed recommended vitamin doses.

Evidence supporting these recommendations is of classes:

Aspirin: Secondary Prevention: M

Diet: A, B, R

Exercise: A, D, R

Weight Management: R

Smoking cessation: C, R

Evaluate alcohol consumption: B, R

Vitamin E: A, B, R

Multivitamin with folic acid: C, D, M, R

Sitostanol ester nutrition supplement: A, C

6. Evaluation and Management of Hypertriglyceridemia

The clinician may wish to consider the following:

- Fibric Acid
- Niacin
- Screening for Diabetes
- Screening for hypothyroidism
- Screening for other secondary causes

Please refer to Annotations Appendix A, "Secondary Causes Associated with Hyperlipidemia," Appendix B, "Therapy," andAppendix C, "Drug Companion Document."

Evidence supporting these recommendations is of classes: A, B, R

7. Evaluation and Management

The clinician may wish to consider the following:

- Gemfibrozil
- Niacin
- Lovastatin

Please refer to Annotations Appendix A, "Secondary Causes Associated with Hyperlipidemia," Appendix B, "Therapy," andAppendix C, "Drug Companion Document."

Evidence supporting this recommendation is of class: A

8. Follow up

Follow a lipid profile yearly. If the patient is on fibric acid or niacin, then follow up per the recommended protocol.

Please refer to Annotations Appendix A, "Secondary Causes Associated with Hyperlipidemia," Appendix B, "Therapy," andAppendix C, "Drug Companion Document."

Evidence supporting this recommendation is of classes: A, R

9. LDL-cholesterol 100–129 or LDL-cholesterol ≥ 130

LDL-cholesterol 100–129:

If the LDL-cholesterol level is in the range of 100–129 mg/dl, clinical discussion which weighs evidence-based outcome data, possible side effects, and cost must be used in the decision for drug therapy.

See Other Management below.

LDL-cholesterol ≥ 130:

Start Statin:

Patients with known coronary artery disease who have an LDL-cholesterol > 130 should be started on a statin.

See "Other Management"

Other Management:

Management of a patient with an elevated LDL-cholesterol may include the following:

- Step II Diet
- Exercise
- Weight Management
- Vitamin E
- Folic Acid

- Aspirin
- Sitostanol ester nutrition supplement

Please refer to Annotations Appendix "Therapy," and Appendix C, "Drug Companion Document."

Evidence supporting this recommendation is of classes: A, B, C, D, M, R

11. Goal LDL-cholesterol<100?

This identifies patients who have not met the goal LDL-cholesterol of < 100.

12. Laboratory monitoring in 3-6 months

Refer to Appendix C, "Drug Companion Document."

Evidence supporting this recommendation if of class: R

13. Further Management

Further management may include the following:

- Consider secondary causes of hyperlipidemia
- Increase dose of statin
- Consider adding niacin
- Consider adding a bile acid sequestrant
- Consider referral to lipid specialist
- Reinforce Adjunctive Measures

Please refer to Annotations Appendix A, "Secondary Causes Associated with Hyperlipidemia," and Appendix B, "Therapy."

Evidence supporting this recommendation if of classes: A, B, C, D, M, R

Annotation Appendix A– Secondary Causes and Conditions Associated with Hyperlipidemia

	Cholesterol	Triglyceride	HDL-Cholesterol
Drugs			
Antihypertensives:			
Thiazides	↑	↑	
Loop diuretic			↓
Beta blockers		↑	↕
Hormones:			
Glucocorticoids	↑	↑	
Anabolic steroids	↑		↑
Oral contraceptives	↑/↔	↑	↑/↓
Estrogens	↓	↑	↑
Progestins	↑		↓
Growth hormone		↑	
Others:			
Amiodarone	↑		
Isotretinoin	↑	↑	↓
Cyclosporine	↑		
Diseases/Conditions			
Metabolic/Endocrine:			
Diabetes (esp NIDDM)	↑	↑	↓
Hypothyroidism	↑	↑	
Anorexia nervosa	↑		
Obesity	↑	↑	↓
Pregnancy	↑	↑	
Acromegaly		↑	
Hyperuricemia/gout	↑	↓	
Liver Disorders			
Hepatocellular	↑	↓	
Cholestasis	↑		↓
Renal Diseases:			
Nephrotic syndrome	↑	↑	↓
Chronic renal failure	↑/↓	↑/↓	↓
Others:			
SLE	↑	↑	
Rheumatoid arthritis	↓	↓	↑
Pancreatitis		↑	
Dietary Factors			
Alcohol abuse		↑	↑
High fat diet	↑	↑	
Low fat diet	↓	↓	↓
High cholesterol diet	↑		
Weight gain		↑	
Very high fiber diet	↓		

Sources: McKenney JM, and Hawkins DW. Handbook on the Management of Lipid Disorders. National Pharmacy Cholesterol Council, 1995. (Class R)
Stone NJ. "Secondary causes of hyperlipidemia." *Med Clin North Am* 78:117-41, 1994. (Class R)

Annotation Appendix B – Therapy

Type of dyslipidemia	Lipid subfractions	Primary therapy	Secondary therapy
High LDL-cholesterol and triglycerides	LDL HDL Trigl. ↑ ≥ 35 > 200	• Weight loss • Exercise • Discontinue smoking • No alcohol • Improved diabetes mellitus control • Step 1/Step 2 low concentrated carbohydrate diet	Niacin * Statin
	LDL HDL Trigl. ↑ < 35 > 200		Niacin * Gemfibrozil ** Statin
High LDL-cholesterol	LDL HDL ↑ ≥ 35	• Weight loss • Exercise • Step 1/Step 2 low concentrated carbohydrate diet	Niacin * Statin Bile Acid Resin Binder Gemfibrozil **
	LDL HDL ↑ < 35		<u>MEN</u>: Niacin * Statin Bile Acid Resin Binder Gemfibrozil <u>WOMEN</u>: Estrogen Niacin * Statin Bile Acid Resin Binder Gemfibrozil **
Isolated Low HDL-cholesterol		• Exercise • Discontinue smoking • Discontinue excessive alcohol	(drug recommendations for treatment remain controversial except in coronary artery disease) <u>MEN</u>: Niacin * Gemfibrozil ** <u>WOMEN</u>: Estrogen Niacin * Gemfibrozil **
High Triglycerides		• Weight loss • Discontinue smoking • No alcohol • Improved diabetes mellitus control • Step 1/Step 2 low concentrated carbohydrate diet	Niacin * Gemfibrozil **

* Niacin can elevate glucose in diabetics. Review the drug education sheet with the patient when initiating Niacin therapy.

** Gemfibrozil is not reommended for only HDL-cholesterol elevation attempt (per maufacturer).

If considering combination therapy or alternative agents, suggest lipid clinic consultation.

This document may provide assistance to the clinician initiating and providing ongoing pharmacologic management of the dyslipidemic patient.
It includes the following informational pieces:

- Treatment Options for Dyslipidemia
- Drug Discussions on the following medications:

  Bile Acid Sequestrants

  Estrogen

  Gemfibrozil

  Niacin

  Statins

- Table outlining medication, lipid effect, contraindication, drug interactions, potential side effects, dosing considerations, and required monitoring.

Please note: Information provided is not all-inclusive, and providers should consult manufacturer's product labeling insert, PDR, etc. for full prescribing information.

Treatment Options for Dyslidemia

Lipid Disorder	Monotherapy	% LDL	HDL	Trig	Combination Therapy	Ldl **	Hdl**	Trig
Hypercholesterolemia	Statin	-25 to 60			Statin + BAS***	-45 to 64		
↑ LDL, normal Trig,	BAS***	-15 to 30			Statin + Niacin	-36 to 42	+16 to 27	
normal HDL	Niacin	-6 to 25			Statin + Niacin + BAS ***	-66		
	Estrogen*	-15 to 20			Niacin + BAS ***	-25 to 55		
					Statin + Estrogen	-28		
Combined Hyperlipidemia	Statin	-25 to 45		-5 to 37	Niacin + Statin	-36 to -42	+16 to 27	-35
↑ LDL and ↑ Trig	Niacin	-6 to 25		-10 to 50	Statin + Fibric Acid	-20 to 35		-15 to 45
	Fibric Acids	+10 to -28		-30 to 50	Niacin + BAS***	-25 to 55		-20 to 37
					Niacin + Fibric Acid			
Hypertriglyceridemia	Niacin			-10 to 50	Niacin + Fibric Acid			
	Fibric Acids			-30 to 50				
Hypercholesterolemia	Niacin	-6 to 25	+5 to 35		Statin + Niacin	-36 to 42	+16 to 27	
with isolated low HDL	Statin	-25 to 60	+5 to 15					
	Estrogen*	-15 to 24	+5 to 22		Statin + Estrogen	-28		+21

* Postmenopausal women
**Approximate mean change from baseline. Note: the +/- sign applies to both numbers.
***BAS = Bile Acid Sequestrant

HMG reductase inhibitors, niacin and bile acid sequestrants are the major drugs for lowering LDL-cholesterol. The bile acid sequestrants are considered the safest because they are not systemically absorbed. The HMG reductase inhibitors are the drug of first choice because they are the most potent and have a record of safety with over a decade of use. Niacin can be the least expensive and has the greatest effect of these drugs on decreasing triglycerides and increasing HDL-cholesterol. Oral estrogen hormone replacement therapy may be considered for postmenopausal women.

Monotherapy of patients with hypertriglyceridemia depends on the triglyceride level. Patients with triglycerides > 500 mg/dl are at increased risk of developing acute pancreatitis. This risk increases very significantly as triglycerides increase to > 1000 mg/dl. Fibric Acids and niacin are the drugs of choice. Although triglycerides may not normalize with either drug, the risk of pancreatitis is reduced.

Combination Therapy
Some patients with moderate to severe hypercholesterolemia or mixed hyperlipidemia will require combination therapy to reach their lipoprotein goals. Most likely, these patients will have CHD. Using low doses of two complimentary agents can often reduce LDL-cholesterol to a greater extent than a higher dose of either agent alone with fewer side effects and possibly less cost.

If triglycerides are < 200 mg/dl, a bile acid sequestrant could be added to the HMG reductase inhibitor. Because of the synergistic effect, low doses are usually adequate. In one study, lovastatin 20 mg plus colestipol 5 grams reduced LDL-cholesterol 38% , which is comparable to the effect of lovastatin 80 mg/day and at approximately $35.00 per 1% LDL-cholesterol reduction per year is less than half the cost. In the same study, lovastatin 20 mg/day plus colestipol 10 grams/day reduced LDL-cholesterol 48%.

In very resistant cases, triple therapy may be needed. Niacin (if no contraindications) could be added to either above combination. A bile acid sequestrant could be added to the HMG reductase inhibitor/hormone replacement regimen but only if triglycerides are < 200 mg/dl.

In patients with mixed hyperlipidemia (increased LDL-cholesterol and triglycerides), the primary goal of decreasing LDL-cholesterol is the same as in patients with hypercholesterolemia alone. Decreasing triglycerides to < 200 mg/dl and increasing HDL-cholesterol to > 35 mg/dl if necessary is also desired.

A borderline hypertriglyceridemia (200 mg/dl to 500 mg/dl) with hypercholesterolemia signals a relatively high risk of CHD. These patients often have a low HDL-cholesterol. Combination of a cholesterol lowering drug with triglyceride lowering drug may be most warranted in patients with established coronary artery disease who are at very high risk of recurrent coronary events. Combining nicotinic acid with an HMG reductase inhibitor is favorable for improving LDL-cholesterol, HDL-cholesterol, and triglycerides. Use of fibric acids leads to effective decrease in triglycerides and increased HDL-cholesterol, but effect on LDL-cholesterol is varied.

An increased incidence of severe myopathy has been reported when an HMG reductase inhibitor was combined with nicotinic acid or fibric acids. Most of these cases involved a high dose of the HMG reductase inhibitor in patients with reduced renal function. When these combinations were evaluated in patients with normal renal function in controlled clinical trials myopathy rarely occurred.

These combinations should generally be avoided in patients with acute or serious chronic illness (especially chronic renal disease), patients undergoing surgery or in patients who are already receiving cyclosporine, macrolide antibiotics, nefazodone, or azole antifungal agents.

Patients must be asked to report promptly any unexplained muscle aches or weakness, especially if malaise or fever is present, flu-like symptoms (without upper respiratory infection) or brownish urine. In these patients the drug should be discontinued and a repeat CPK done. If detected early, the myopathy is reversible. Acute renal failure generally occurs only in patients that continue to take their medication even with symptoms.

In general, these combinations need not be avoided but careful patient selection, monitoring, and patient education are required.

Please consult manufacturer's product labeling insert, PDR, etc. for full prescribing information.

McKenney JM, Hawkins DW. "Treatment of Lipid Disorders." In Handbook on the Management of Lipid Disorders. National Pharmacy cholesterol Council, pp 74-88, 1995. (Class R)

Schrott HG, Stein EA, Dujovne CA, et al. "Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low-dose colestipol plus lovastatin combination therapy." *Am J Cardiol* 75:34-9, 1995. (ClassA)

Lobo RA. ""Clinical review 27: effects of hormonal replacement on lipids and lipoproteins in postmenopausal women." *J Clin Endocrinol Metab* 73:925-30, 1991. (Class R)

Schwartz J, Freeman R, Frishman W. "Clinical pharmacology of estrogens: cardiovascular actions and cardioprotective benefits of replacement therapy in postmenopausal women." *J Clin Pharmacol* 35:314-29, 1995. (Class R)

Grundy SM. "Consensus statement: role of therapy with "statins" in patients with hypertriglyceridemia." *Am J Cardiol* 81:1B-6B, 1998. (Class R)

Darling GM, Johns JA, McCloud PI, Davis SR. "Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women." *N Engl J Med* 337:595-601, 1997. (Class A)

Davidson MH, Testolin LM, Maki KC, et al. "A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women." *Arch Intern Med* 157:1186-92, 1997. (Class A)

Niacin product monograph

Cholestyramine (Questran, Questran Lite, Prevalite) and colestipol (Colestid) are currently available. All are available in powder form and colestipol is also available in 1 gram tablets.

Efficacy

* LDL-cholesterol lowered 15% to 30% (dose dependent)
* Triglycerides may increase 15% - should not be used as sole agent if triglycerides are > 200 mg/dl unless used in combination with a triglyceride lowering agent such as fibric acid or niacin
* Effects apparent within one week and maximum at 2 to 3 weeks
* Useful for patients with moderately elevated LDL-cholesterol
* Good for combination therapy - LDL-cholesterol reductions enhanced with low doses - most potent is with statin

Safety

* Not systemically absorbed - side effects limited to GI tract
* PKU patients should know that Questran Lite, Prevalite, and flavored colestipol powder contain aspartame. Regular Questran and unflavored colestipol powder and tablets do not.
* Drug interactions are minimized by taking other medications 1 hour before the sequestrant or 4 hours after.

  The net effect of combination warfarin is unpredictable. Cholestyramine decreases the absorption of warfarin and may reduce warfarin's half life by interfering with enterohepatic circulation. Vitamin K absorption may also be decreased, so the net effect on coagulation is hard to predict. Separating the warfarin by 4 hours before or after colestipol and close monitoring of INR is recommended.

  Cholestipol has been reported not to interact with warfarin so may be safer agent. Separating these agents by at least 4 hours and close monitoring of INR is still recommended.
* While not contraindicated in pregnancy and lactation, consideration must be given to potential adverse effects on the baby because of impaired maternal absorption of nutrients and vitamins.

Dosing

* Limited by patient tolerance of GI side effects
* Initiate with very low dose and titrate slowly (i.e., 1/2 scoop or 1 to 2 tabs with largest meal; if tolerated, may increase weekly [or monthly if preferred] by 1/2 scoop or 1 to 2 tabs until at 1 scoop or 4-5 tablets BID with meals - titration can then continue until the response required is obtained or side effects are encountered). (Average wholesale price of Colestid tablets is about twice the cost of Colestid powder.)
* Maximum daily dose: cholestyramine 24 grams/day, colestipol 30 grams/day of powder, 16 grams/day of tablets (based on impracticality of patients taking more than 16 tablets/day.)
* Powders must be mixed in liquid or food with high moisture content (i.e. gelatin, apple sauce, soup, nonfat yogurt, etc.) prior to ingestion (may be mixed day ahead and stored in refrigerator to improve palatability, but if adding to soup can only add after soup has been heated).
* Cholestyramine 4 g/scoop is equivalent in activity to Cholestipol 5 g/scoop.

Please consult manufacturer's product labeling insert, PDR, etc. for full prescribing information.

McKenney JM, Hawkins DW. Lipid Modifying Drugs. In Handbook on the Management of Lipid Disorders. National Pharmacy cholesterol Council, pp 89-94, 1995. (Class R)

Efficacy

* Triglycerides are reduced 30% to 50%, HDL-cholesterol increases 10% to 20%. Total cholesterol is only modestly reduced 5% to 20% in patients without elevated triglycerides. Effect on LDL-cholesterol is variable: fenofibrate may lower LDL-cholesterol more than gemfibrozil but it is less effective than HMG reductase inhibitors.
* Good for severe hypertrigylceridemia in patients at risk for pancreatitis, for prevention of CHD (not proven for fenofibrate) when patient has abnormal lipid triad of depressed HDL-cholesterol, elevated LDL-cholesterol and elevated triglycerides. May be particularly useful in diabetics with mixed hyperlipidemia.
* The HITS trial utilizing gemfibrozil, showed a 22% reduction in CHD death/nonfatal MI in patients with documented CHD and low HDL-cholesterol as their primary lipid abnormality.

Safety

* Myositis has occurred rarely in patients. Risk of myopathy and possibly rhabdomyolysis appears increased when taken with statins, but controlled clinical trials have failed to document a substantial risk in patients with normal renal function.
* Cholelithiasis and cholecystitis can occur (0.3-1% incidence) due to increase cholesterol excreted in the bile, contraindicated in patients with preexisting gallbladder disease.
* Use with caution in patients with history of liver disease, contraindicated in patients with hepatic or severe renal impairment, including primary biliary cirrhosis.
* Hematologic adverse reactions are rare.
* Warfarin's anticoagulant effect may be potentiated; INR should be monitored closely.

Dosing

Gemfibrozil -

* Usual dose is 600 mg BID. The manufacturer recommends taking this 30 minutes before morning and evening meals, but all clinical trials were conducted without regard to meals and efficacy has never been linked to specific blood levels. If patients have stomach upset taking it with the meal may diminish this. If significant improvement in lipid levels has not occurred after 3 months of treatment it should be d/c.

Fenofibrate micronized -

* Starting dose usually 67 mg qd with a meal depending on physician's assessment of risk of pancreatitis. Dose may be increased after 4-8 weeks based on triglyceride determination to maximum dose of 3 capsules (201 mg)/day. Dosage reduction may be necessary in patients with impaired renal function and should be initiated at 67 mg/day and increased only after evaluation of effects on renal function and triglyceride levels. In the elderly initial dose should be limited to 67 mg/day.

Please consult manufacturer's product labeling insert, PDR, etc. for full prescribing information.

McKenney JM, Hawkins DW. Lipid Modifying Drugs. In Handbook on the Management of Lipid Disorders. National Pharmacy Cholesterol Council, pp 114-122, 1995. (Class R)

HIT Trial. (Class A)

Two formulations are available: crystalline (immediate release) and modified (sustained-release).

Efficacy

* Exerts favorable effects on all lipids and lipoproteins - good for mixed hyperlipidemia.
* Crystalline niacin reduces triglycerides 20 % to 40%, increases HDL 15% to 35%, and decreases LDL-cholesterol 6% to 25%.
* Sustained-release niacin reduces triglycerides 10% to 40%, increases HDL 5% to 28% and decreases LDL-cholesterol 6% to 50% (but this latter effect may be due to hepatic toxicity).

Safety

* Flushing and puritis of face and upper trunk are common. Tolerance usually develops and patients are more accepting if they know what to expect. With crystalline niacin, flush and pruritis usually occur within 30 minutes and are gone in about that time. Flushing is reduced with SR niacin, but it still occurs.
* Liver toxicity may be associated with niacin. Risk appears greater with SR niacin excluding Niaspan and appears dose related (most occurring with 2 grams/day or more SR niacin. Many cases occurred when a patient switched from crystalline to SR form without a decrease in dose. Patients who are asymptomatic with only elevations in transaminases (to three times the upper limit of normal) may respond to dose reduction. If transaminases exceed 3 times the upper limit of normal or patients are symptomatic (e.g., nausea, vomiting, diarrhea, anorexia, fatigue and/or jaundice) niacin should be discontinued. With discontinuation, symptoms decline within 2 weeks and lab abnormalities should resolve within 1 to 4 months. In a long-term (59 weeks) study of Niaspan (niacin extended-release), median dose 2 gms/day, < 1% of participants with normal serum transaminases at baseline had elevations > 3 X ULN.
* GI complaints (nausea, abdominal pain) more common with SR niacin; minimized by taking with meals. Activation of peptic ulcer has occurred so history of peptic ulcer is relative contraindication.
* Uric acid may be slightly increased. Rarely, this may lead to acute gouty arthritis.
* Serum glucose concentrations may be increased especially in patients with NIDDM or glucose intolerance. Glucose monitoring is critical for use of niacin in these patients. Diabetics with poor glucose control should not receive niacin. The presence of insulin resistance syndrome may mitigate the use of niacin but additional information is needed regarding the benefits versus risks of niacin use in this syndrome.
* Worsening of angina is rare, probably due to coronary steal, in patients with unstable angina.
* Combination with a statin may increase risk of myopathy based on early experience with lovastatin. Subsequent controlled trials of statins with niacin have reported few or no cases.

Dosing

* Slow dosage titration allows patient to develop tolerance to flushing and pruritis.
* **Crystalline niacin** can be dosed BID. One method is 100 mg BID with meals (taken in the middle of the meal seems to work best) for 1 week, increasing 100 mg BID each week until at 500 mg BID; dosage can be titrated further based on response and tolerance to 3 grams per day (maximum dose is 6 grams per day but risk of adverse effects increase). Aspirin (if no contraindication) 160 mg to 320 mg can be taken 1/2 hour before niacin dose to reduce the prostaglandin mediated flush (usually only necessary with dosage titration). Avoiding hot beverages and alcohol at time of dosing is recommended.
* **SR niacin** should also be titrated and may be started with 125 mg to 250 mg BID with meals. Further increase should be based on response and tolerance. The maximum dose should be 1.5 grams per day. A single brand should be used; especially for SR niacin because of significant variability in bioavailability.
* Niaspan should be taken at bedtime with a low fat snack. A starter titration pack is available containing 7 days each of 375 mg, 500 mg, and 750 mg tablets. After this is completed, 1000 mg/day should be taken for 4 weeks. Further titration should be based on patient response and tolerance. Daily doses should not be increased more than 500 mg in 4 weeks not to exceed 2000 mg/day. Women may respond at lower doses.

Please consult drug reference for full prescribing information.

McKenney JM, Hawkins DW. Lipid Modifying Drugs. In Handbook on the Management of Lipid Disorders. National Pharmacy cholesterol Council, pp 94–101, 1995. (Class R)

Niaspan Package Insert

Currently there are 6 statins available: atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), and cerivastatin (Baycol).

Efficacy

* Substantial reductions in LDL-cholesterol.
* Reductions in triglycerides are dose dependent and are possible with all statin agents.
* The 4S trial reported reductions of 30 to 45% in deaths due to CHD, cardiovascular disease and all causes after 4.5 years treatment with simvastatin in patients with CHD. This was shown in men, women and elderly.
* The West of Scotland trial reported a 31% reduction in risk of non-fatal MI or death from CHD in men with hypercholesterolemia and no history of MI who were treated with pravastatin 40 mg daily.
* The CARE study, using 40 mg of pravastatin daily, showed a 24% reduction in major coronary events in men and women with a mean LDL-cholesterol of 139 mg/dl who had survived a myocardial infarction.
* In AFCAPS/TexCAPS treatment with lovastatin 20-40 mg daily resulted in a 37% reduction in the risk of first major coronary events. This reduction occurred in men and women without clinically evident atherosclerotic cardiovascular disease and average LDL-cholesterol (mean 150 mg/dl) and below average HDL-cholesterol (mean 36 mg/dl and 40 mg/dl respectively).

Mean LDL-cholesterol reductions of the statins based on direct comparative studies:*

Drug	LDL-cholesterol Reduction	AWP cost	Cost per year per 1% LDL-cholesterol Reduction
Fluvastatin 20 mg	18%	$1.26/day	$25.55/year to lower a patient's chlesterol by 1%
Pravastatin 10 mg	19%	$2.11/day	$40.53/year
Simvastatin 5 mg	23%	$1.78/day	$28.25/year
Cerivastatin 0.2 mg	25%	$1.42/day	$20.73/year
Pravastatin 20 mg	25%	$2.27/day	$33.14/year
Fluvastatin 40 mg	27%	$1.26/day	$17.03/year
Lovastatin 20 mg	27%	$2.33/day	$31.50/year
Pravastatin 40 mg	27%	$3.74/day	$50.56/year
Cerivastatin 0.3 mg	28%	$1.42/day	$18.51/year
Simvastatin 10 mg	28%	$2.18/day	$28.42/year
Lovastatin 40 mg	33%	$4.19/day	$46.34/year
Cerivastatin 0.4 mg	34%	$1.42/day	$15.24/year
Fluvastatin 80 mg	35%	$2.25/day	$26.28/year
Simvastatin 20 mg	35%	$3.81/day	$39.73/year
Simvastatin 40 mg	38%	$3.81/day	$36.60/year
Lovastatin 80 mg	38%	$8.38/day	$80.49/year
Atorvastatin 10 mg	39%	$1.88/day	$17.59/year
Atorvastatin 20 mg	43%	$2.90/day	$24.62/year
Simvastatin 80 mg	47%	$3.81/day	$29.59/year
Atorvastatin 40 mg	50%	$3.50/day	$25.55/year
Atorvastatin 80 mg	60%	$7.00/day	$42.58/year

*Activity of Atorvastatin is based on dose response studies, reported in the package circular. Cervistatin and Simvastatin 80 mg is based in a controlled clinical trial reported in the package circular.

Safety

* Asymptomatic increases in serum transaminases to > 3 times the upper limit of normal on 2 consecutive lab tests estimated to occur 0.1% to 2.3%. Dosage reduction or discontinuation of statin reverses these abnormalities.
  Use with caution at reduced dosages in patients with primary biliary cirrhosis.

* Myopathy appears dose dependent and is rare with monotherapy (0.1%). Cases have been reported as early as one week and as long as 2 years after initiation of therapy. Risk appears increased if patients are also receiving immunosupressants (cyclosporine), fibric acids, lipid lowering doses of niacin, macrolide antibiotics, azole antifungals and nefazodone. The highest risk seems to occur when patients are taking other drugs that are metabolized by or inhibit the CYP450 enzyme, particularly CYP450 3A4. Fluvastatin and Pravastatin are not significantly metabolized by CYP450 3A4. Pravastatin has been allowed to change its labeling to reflect this. Stating "a lack of significant interaction potential has been shown with known CYP450 3A4 inhibitors such as diltiazem and itraconazole." When a patient is on cyclosporine only low doses (such as the recommended initial dose) of the HMG reducatase inhibitor should be used. Controlled clinical trials with fibric acids have failed to document a substantial risk of myopathy in patients with normal renal function. When combined with fibrates, the dose of HMG reductase inhibitor should be kept relatively low such as 10-20 mg simvastatin, 10 mg atorvastatin, or 20-40 mg lovastatin. A review of current renal status is recommended before initiating.

  In the reported cases of myopathy with macrolide antibiotics, the myopathy occurred after completion of the antibiotic and most of the patients either had renal insufficiency or were on other drugs that inhibit cytochrome CYP450 3A4. It is important to note that azithromycin (unlikethe macrolides) does not inhibit the CYP450 3A4 isoenzyme, but it still was implicated in a case of lovastatin-induced rhabdomyolysis. If at all possible, macrolides should be avoided with HMG reductase inhibitors especially if the patient has renal insufficiency or is already on other drugs known to increase the risk of myopathy. If macrolides can't be avoided, consideration should be given to temporarily discontinuing the HMG reductase inhibitor.

  If treatment with systemic azole antifungals is necessary, then the HMG reductase inhibitor (unless pravastatin or fluvastatin) should be temporarily discontinued during treatment.

  Grapefruit juice is a known inhibitor of the CYP450 3A4 isoenzyme in the gut wall. Studies of grapefruit juice with lovastatin and simvastatin have shown dramatic increases in the area under the curve, but the amount of grapefruit juice consumed in these studies was the equivalent of 45 oz (5-6 glasses) of grapefruit juice a day, which does not reflect real life for the vast majority. However, the potential for a significant interaction exists. Until more definitive data is available, patients taking lovastatin or simvastatin should be advised to limit ingestion (e.g. 1 glass of regular-strength grapefruit juice or 1/2 grapefruit) in the morning or with the statin at bedtime. Since atorvastatin and cerivastatin are also metabolized by the CYP450 3A4 isoenzyme, this interaction could occur with them also.

Patients must be told to report promptly any unexplained muscle aches or weakness especially if malaise or fever is present or flu-like symptoms (without upper respiratory infection). If these symptoms occur and myopathy is suspected, the lipid-lowering medications should be temporarily discontinued and a medical evaluation including CPK is recommended.

* Major surgery is a known risk factor for rhabdomyolysis. Consider temporarily stopping statin until the patient is home and ambulatory.

Dosing

* Initial dose 20 mg qd fluvastatin, lovastatin, pravastatin, and simvastatin; 10 mg qd atorvastatin, 0.4 mg qd cerivastatin (0.2 mg or 0.3 mg if creatinine clearance ≤ 60 ml).
* Patients with total cholesterol > 300 mg/dl may start with double initial dose. (Maximum cerivastatin dose is 0.4 mg)
* Elderly patients can take 1/2 of the starting dose for lovastatin, pravastatin and simvastatin. Information regarding need for this is conflicting.
* Bedtime or evening dose is more effective (higher cholesterol synthesis).
* Lovastatin needs to be taken with food to maximize absorption.
* Dosage adjustments should not be made more often than every 4 weeks after a fasting lipid panel.

Please consult manufacturer's product label insert, PDR, etc., for full prescribing information.

McKenney JM, Hawkins DW. Lipid Modifying Drugs. In Handbook on the Management of Lipid Disorders. National Pharmacy cholesterol Council, pp 101-114, 1995. (Class R)

Shepherd J, Cobbe SM, Ford I, et al. "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia." *N Engl J Med* 333:1301-7, 1995. (Class A)

Blum CB. "Comparison of properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase." *Am J Cardiol* 73:3D-11D, 1994. (Class R)

Illingworth DR, Tobert JA. "A review of clinical trials comparing HMG-CoA reductase unhibitors." *Clin Ther* 16:366-84, 1994. (Class R)

Baycol product circular.

Grundy SM. "Consensus statement: role of therapy with "statins" in patients with hypertriglyceridemia." *Am J Cardiol* 81:1B-6B, 1998. (Class R)

Evaluation of Drug Interactions. Fredric Zucchero, editor. December 1997. The Hearst Corporation 18/12.04-18/12.04a.

Grunden JW, Fisher KA. "Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 31:859-63, 1997. (Class R)

Efficacy

* LDL-cholesterol is generally reduced 15-24%
  HDL-cholesterol is generally increased 5-22%
* While observational evidence suggested that estrogen reduced the risk of CHD by 35-50%, a recent randomized controlled trial (HERS) in women with known coronary artery disease found no reduction in cardiovascular events over 4.1 years of treatment..

Risks

* Please see the ICSI Hormone Replacement Therapy guideline for information regarding non-lipid associated risk.
* Concurrent use of progesterone eliminates the risk of uterine cancer in women with intact uteri.
* Risk of developing breast cancer may increase 10-30% after 5-10 years or more of HRT.
* The risk of venous thromboembolism may be slightly increased in current, or new users of HRT. The absolute risk is generally low (10 per 100,000 years), but increased 3 fold by the use of HRT.
* The risk of gallbladder disease returns to premenopausal levels in women taking HRT.
* Triglyceride levels may be increased by 5-30% in some women taking oral estrogen. This is usually only significant in a woman with pre-existing hypertriglyceridemia. Follow-up triglyceride levels should be determined in women on HRT.

Dosing

* Oral conjugated equine estrogen (CEE) was used in the observational studies and the HERS study. The HERS study included women with intact uteri on daily medroxyprogesterone plys CEE. The usual dose was 0.625 mg of CEE. This is the equivalent to one mg of micronized estrogen (Estrace).
  - All women with intact uteri require additional therapy with a progestin, either cyclic or continuous.
  - Transdermal estrogen does not significantly affect lipid profiles and cannot be recommended for treatment of hyperlipidemia.

Please consult drug reference for full prescribing information.

1998 ICSI Hormone Replacement Therapy guideline

McKenney JM, Hawkins DW. Treatment of Lipid Disorders. In Handbook on the Management of Lipid Disorders. National Pharmacy cholesterol Council, pp 74-88, 1995. (Class R)

Lobo RA. "Clinical review 27: effects of hormonal replacement on lipids and lipoproteins in postmenopausal women." *J Clin Endocrinol Metab* 73:925-30, 1991. (Class R)

Schwartz J, Freeman R, Frishman W. "Clinical pharmacology of estrogens: cardiovascular actions and cardioprotective benefits of replacement therapy in postmenopausal women." *J Clin Pharmacol* 35:314-29, 1995. (Class R)

DarlingGM, Johns JA, McCloud PI, Davis SR. "Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women." *N Engl J Med* 337:595-601, 1997. (Class A)

Davidson MH, Testolin LM, Maki KC, et al. "A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women." *Arch Intern Med* 157:1186-92, 1997. (Class A)

Hully S, Grady D, Bush T, et al. "Randomized trial of estrogen plus progestin for secondary prevention of coronary disease in postmenopausal women." *JAMA* 280:605-13, 1998. (Class A)

Drugs	Lipid Effect	Contraindications	Drug/Food Interactions	Potential Side Effects	Dosing Considerations	Monitoring
Statins: Atorvastatin (Lipitor) Cerivastatin (Baycol) Fluvastatin (Lescol) Lovastatin (Mevacor) Pravastatin (Pravachol) Simvastatin (Zocor)	Most potent agents for ↓ LDL-chol.; ↓ Trig, and ↑ HDL-chol. this is a mild effect.	Active Liver disease Pregnancy Lactation Relative contraindications - alcohol abuse, primary biliary cirrhosis.	Cyclosporine Fibric acid, macrolide antibiotics, niacin, azole antifungals, nefazodone, grapefruit juice ↑ risk of myopathy* rhabdomyolysis may occur.** Warfarin - anticoagulant effect may be increased monitor INR closely.****	Mild GI complaints, headache, insomnia, Myopathy*-rare with monotherapy (0.1%) appears dose dependent, risk is increased with combination therapy (see drug interactions). Hepatotoxicity-appears dose dependent with occurrence estimated at 0.1% to 2.3%	Starting / Range Ator 10mg / 10-80mg qd Cer 0.4 mg / 0.4 mg Flu 20mg / 20-80mg qd Prav 20mg / 10-40mg qd Lov 20mg / 10-80mg qd Sim 20mg / 5-80mg qd Evening doses-more effective due to higher chol synthesis then. Fluvastatin 80mg/dy must be 40mg bid. Lovastatin with food to maximize absorption. When patient is on cyclosporine dose of the Statin should be reduced.	Fasting lipid panel, serum transaminases, CPK at base line Fasting lipid panel, at 6–12 weeks after start or elevation in dose, then periodically approx. every 6 months. **FDA recommended transaminase monitoring varies by statin (see below),***** If the transaminases are increased they should be followed until the abnormality resolves. If transaminases ↑ > 3 X ULN and persist D/C med. CPK if muscle symptoms develop.
Nicotinic Acid Niacin Niacin extended release (Niaspan) (Nicobid) (Enduracin)	↓ LDL-chol, ↓Trig, ↑ HDL-chol.	Active liver disease Active Peptic Ulcer Pregnancy/Lactation Arterial hemorrhage Alcohol abuse Relative contraindications: history of gout, diabetes mellitus or glucose intolerance glaucoma, renal dysfunction	Statins-risk of myopathy appears increased but true incidence is probably low.	Flushing, transient pruritis, acanthosis nigracans GI upset (more common with SR forms) ↑ uric acid ↑serum glucose Hepatotoxicity-rare with usual doses of crystalline niacin risk ↑ with SR forms (excluding Niaspan)appears dose related most occurring at 2 or more gms/day	Crystalline niacin 1-3 gm/day Sustained release niacin 1-1.5 gm/day Niaspan 1-2 gm/day at hs with a low-fat snack. titrate dose slowly; take with food; avoid hot beverages and alcohol at time of dosing; may take 160 mg to 325 mg aspirin 30 minutes before niacin dose.	Fasting lipid panel, fasting glucose, transaminases and uric acid at baseline. Fasting lipid, glucose and tranaminases every 6-12 weeks the first year and with dosage increases, then periodically aprox. q 6months. If transaminase ↑ to 3 X ULN and persist D/C the med. Uric acid if symptoms of gout.
Bile Acid Sequestrants Cholesty-ramine Powder (Questran) Colestipol Powder/Tabs (Colestid)	↓ LDL-chol., may ↑ Trig good for combination therapy	Complete biliary obstruction. Do not use as sole therapy in patients with trig > 200mg/dl. Relative contraindication: Pt. on Warfarin - close monitoring of INR with initiation, change in dose or d/c of med	Documented ↓ in absorption of digoxin, warfarin, levothyroxine, thiazide diuretics. Any drug should be separated from the sequestrant by taking it either 1 hour before or 4 hours after the sequestrant.	Not absorbed so limited to GI tract. Constipation most common-minimize by ↑ fluid, fiber and exercise or adding fiber laxative or stool softener to regimen Bloating Belching-sip slowly thru straw to minimize air swallowed.	Tolerance may be improved by titrating dose slowly 1/2sc or 1-2 tbs with a meal ↑ slowly to 1 sc or 2-4 tbs bid Powder must be mixed with liquid or foods with high water content (e.g. gelatin, soup, non fat yogurt, apple sauce, etc.) prior to ingestion. To improve palatability mix and leave in fridge over night (unless mixed in something served hot)	Fasting lipid panel at 6-12 weeks, on initiation or with dose increases, then periodically approximately every 6 months. Other monitoring may be warranted if on concommittant medications.
Fibric Acids Gemfibrozil (Lopid) Fenofibrate (Tricor)	↓ Trig & ↑ HDL-chol. variable effect on LDL-chol.	History of gallstones or cholelithiasis Hepatic impairment Severe renal impairment. Relative contraindication: Pt. on Warfarin - monitor INR with initiation, change in dose or d/c of med.	Warfarin ↑ anticoagulant effect-monitor INR HMG reductase inhibitors ↑ risk of myopathy Nephrotoxic drugs ie., cyclosporine ↑ risk of severe myopathy	GI most common, dypepsia, abdominal pain, diarrhea, skin reactions Rarely anemia, leukopenia, gallstones, atrial fibrillation, myopathy (incidence appears increased when used with statins).	Gemfibrozil 600mg bid Fenofibrate 67 mg/day with food. maximum dose 201 mg/day Dosage reduction may be necessary in patients with impaired renal function.	Fasting lipid panel and transaminases at baseline then at 6-12 weeks after start or elevation in dose, then periodically approximately every 6 months. (Occurrence of liver abnormalities is not common with gemfibrozil but has been reported more with fenofibrate.)

↑ Increase ↓Decrease

*Myopathy defined as muscle pain &/or weakness plus elevation of CK to 10 X ULN. Patients should be asked to report promptly any unexplained muscle aches or weakness, especially if malaise or fever is present; also flu-like symptoms (without upper respiratory infection).

** Highest risk of myopathy seems to occur when patients are taking other drugs that are metabolized by or inhibit the CYP 450 enzymes particularly 3A4. Neither fluvastatin or pravastatin is significantly metabolized by CYP 3A4. Pravastatin has been allowed to change its product labeling to reflect this. Stating a lack of significant interaction potential has been shown with known CYP450 3A4 inhibitors such as diltiazem and itraconazole..

*** Pravastatin - transaminases are recommended at 12 weeks after start or elevation in dose. Simvastatin - transaminases are recommended periodically (semiannual) for the first year of treatment or until one year after elevation in dose. Atorvastatin, fluvastatin, lovastatin, cerivastatin - transaminases are recommended at 6 and 12 weeks after start or elevation in dose, and periodically (semiannually) thereafter.

****Pravastatin labeling has been revised to state that it has been shown to have no clinically significant effect on pro-thrombin time when given to normal elderly subjects stabilized on warfarin.

McKenney JM, Hawkins DW. "Lipid-Modifying Drugs." In Handbook on the Management of Lipid Disorders. National Pharmacy Cholesterol Council, 1995:89-134.

Product circular for all drugs

Discussion and References:

Treatment of Lipid Disorder in Adults

Document Drafted
Feb – May 1996

Critical Review
Jul – Aug 1996

Revision/Approval
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Pilot Implementation
Dec 1996 – Jun 1997

Revision/Approval
Jul – Sep 1997

Firrst Cycle General Implementation
Oct 1997 – May 1998

Revision/Approval
Jun – Sep 1998

Second Cycle General Implementation
Oct 1998 – May 1999

Revision/Approval
June – Oct 1999

Third Cycle General Implementation Begins Nov 1999

Released in October 1999 for General Implementation.
The next scheduled revision will occur within one year.

I. CLASSES OF RESEARCH REPORTS

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial

Class B: Cohort study

Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study

Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M: Meta-analysis
Decision analysis
Cost-benefit analysis
Cost-effectiveness study

Class R: Review article
Consensus statement
Consensus report

Class X: Medical opinion

PATIENTS WITHOUT KNOWN CORONARY ARTERY DISEASE ALGORITHM

1. Patient is Dyslipidemic and between 20 and 75 years old.

Stefanick ML, et al. "Effects of diet and exercise in men and postmenopausal women with low levels of HDL-cholesterol and high levels of LDL-cholesterol." *N Engl J Med* 339:12-20, 1998. (Class A)

5. Patient/Provider Discussion Regarding Management

Relationship of Occlusive Vascular Disease (OVD) to Coronary Artery Disease (CAD)

Studies as early as 1960 recognized an association between coronary artery disease (CAD) and peripheral or occlusive vascular disease (OVD). Data from Framingham, based on clinical diagnoses of CAD and intermittent claudication (IC), documented an increased risk of symptomatic CAD in women and men with IC (relative risks of 5.4 and 2.3 respectively). Studies show an increased risk of symptomatic CAD in patients with OVD involving the carotid and femoral arteries as well as the aorta.

A study of preoperative coronary angiography in 1000 patients under consideration of surgery for OVD classified patients into two groups based on whether or not there was clinical suspicion of CAD. Despite a lack of clinical indication of CAD in 446 patients, 36% of patients had advanced to severe CAD at angiography. Additionally, 49% of asymptomatic patients (for CAD) had mild to moderate CAD at angiography. Approximately 50% of late mortality in patients who undergo arterial reconstruction has been attributed to CAD.

A review article by Hertzer, summarizes the data for over 10,000 patients with OVD. Clinical evidence for CAD was found in 41-56% of patients with OVD. Cardiac stress testing found CAD in 21-38% of OVD patients, and angiography documented "serious" CAD in 57-65% of patients with OVD. Chimowitz reported a 40% frequency of angiographic CAD in asymptomatic patients with carotid OVD.

The reported data consistently show an increased risk of CAD in patients with OVD regardless of whether the patient is clinically symptomatic for heart disease, suggesting that the presence of OVD is a risk factor for CAD.

Lipid lowering studies document regression in femoral and carotid OVD. No studies to date have documented a statistically significant decrease in coronary endpoints when patients with OVD are treated to lower lipids. Two studies, KAPS and PLAC II, showed a trend towards decreased events that did not achieve statistical significance.

Conversely, studies in patients with documented CAD clearly show a benefit with a decrease in coronary endpoints. Post hoc analysis of two of these studies, the 4S and CARE studies, documented a decrease in the risk of cerebrovascular events (transient ischemic attack, fatal and non-fatal strokes), RR=0.7 (p=0.024) and RRR=31% (p=0.03) respectively. However, analysis of pooled data for 1891 patients in 4 studies using pravastatin did not find a significant difference in the number of cerebrovascular events in the treated versus placebo groups (p=0.054). Similarly, no significant difference was found in the West of Scotland study, a primary intervention study.

Other studies, currently underway, will hopefully provide additional evidence regarding whether treatment of hyperlipidemia in patients with documented OVD will decrease coronary and/or peripheral vascular events and help the clinician determine the appropriate goal(s) for lipid levels in patients with OVD.

Kannel WB, Skinner JJ, Schwartz MJ, Shurtleff D. "Intermittent claudication: incidence in the Framingham Study." *Circulation* XLI:875-83, 1970. (Class B)

Hertzer NR, Beven, EG, Young JR, et al. "Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management." *Ann Surg* 199:223-33, 1984. (Class B)

Hertzer NR. "Basic data concerning associated coronary disease in peripheral vascular patients." *Ann Vasc Surg* 1:616-20, 1987. (Class R)

Chimowitz MI, Mancini GBJ. "Asymptomatic coronary artery disease in patients with stroke: prevalence, prognosis, diagnosis, and treatment." *Stroke* 23:433-36, 1992. (Class R)

Urbinati S, Di Pasquale G, Andreoli A, et al. "Frequency and prognostic significance of silent coronary artery disease in patients with cerebral ischemia undergoing carotid endarterectomy." *Am J Cardiol* 69:1166-70, 1992. (Class B)

Gotto AM Jr. "Lipid lowering , regression and coronary events: a review of the interdisciplinary council on lipids and cardiovascular risk intervention, seventh council meeting." *Circulation* 92:646-56, 1995. (Class R)

Crouse JR, Byington RP, Bond MG, et al. "Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC II)." *Am J Cardiol* 75:455-59, 1995. (Class A)*

Salonen R, Nyyssonen K, Porkkala E, et al. "Kuopio artherosclerosis prevention study (KAPS): a population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries." *Circulation* 92:1758-64, 1995. (Class A)*

Blankenhorn DH, Azen SP, Crawford DW, et al. "Effects of colestipol-niacin therapy on human femoral atherosclerosis." *Circulation* 83:438-47, 1991. (Class A)*

Blankenhorn DH, Selzer RH, Crawford DW, et al. "Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound." *Circulation* 88:20-8, 1993. (Class C)*

Byington RP, Jukema JW, Salonen JT, et al. "Reduction in cardiovascular events during pravastatin therapy: pooled analysis of clinical events of the pravastatin atherosclerosis intervention program." *Circulation* 92:2419-25, 1995. (Class M)

Sacks FM, Pfeffer MA, Moye LA, et al. "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels." *N Engl J Med* 335:1001-9, 1996. (Class A)

With regard to stroke prevention, pooled data from statin clinical trials demonstrate a 29% reduction in stroke with statin treatment with a confidence interval of 14–41%. The trials included in this analysis did not include patients over 75 years of age.

Hebert PR, Gaziano JM, Chan KS, Hennekens CH. "cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials." *JAMA* 278:313-21, 1997. (Class M)

*For lipid end points, not CAD end points.

6. Adjunctive Measures.

Diet: Step II Diet:

This algorithm assumes that the patient has not achieved his or her lipid goal on a Step I Diet.

The evidence in the literature and the NCEP Adult Treatment Panel Consensus Position suggest that adults with elevated lipids should be following the American Heart Association (AHA) Step II diet or something more aggressive. The AHA eating plan includes less than 30% calories from total fat, less than 7% calories from saturated fat, less than 200 mg dietary cholesterol and calorie adjustment to achieve and maintain a reasonable body weight. It is desirable to have the assessment and education for these individuals carried out by a registered dietitian when possible.

LaRosa JC, Hunninghake D, Bush D, et al. "The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol, and coronary artery disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute." *Circulation* 81:1721-33, 1990. (Class R)

Blankenhorn DH, Johnson RL, Mack WJ, et al. "The influence of diet on the appearance of new lesions in human coronary arteries." *JAMA* 263:1646-52, 1990. (Class B)

Ornish D, Brown SE, Scherwitz LW, et al. "Can lifestyle changes reverse coronary heart disease?" *Lancet* 336:129-33, 1990. (Class A)

Schuler G, Hambrecht R, Schlierf G, et al. "Regular physical exercise and low-fat diet: effects on progression of coronary artery disease." *Circulation* 86:1-11, 1992. (Class A)

Arntzenius AC, Kromhout D, Barth JD, et al. "Diet, lipoproteins, and the progression of coronary atherosclerosis: the Leiden intervention trial." *N Engl J Med* 312:805-11, 1985. (Class B)

"Summary of the second report of the National cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II)." *JAMA* 269:3015-23, 1993. (Class R)

Stefanick ML, et al. "Effects of diet and exercise in men and postmenopausal women with low levels of HDL-cholesterol and high levels of LDL-cholesterol. *New Engl J Med* 339:12-20, 1998. (Class A)

Exercise:

Many cross-sectional studies demonstrate a more favorable lipoprotein profile in men and women who are more active and physically fit when compared to those who are sedentary. The strongest evidence comes from the National Runner's Health Study (NRHS), which included men and women who responded to a questionnaire assessing health habits. Lipid data was obtained from physicians and compared to running distance. Increasing distance correlated with increased beneficial lipid effects, including decreases in LDL-cholesterol and triglycerides along with an increase in HDL-cholesterol. These effects were also correlated with the "leanness" of the individual.

The evidence from cross-sectional studies in men suggest that aerobic exercise may induce an increase of 5 - 10% in HDL-cholesterol, primarily the HDL2 subfraction and decrease the triglycerides. Additionally, some studies found a decrease in LDL-cholesterol and total cholesterol. These changes are dependent on the intensity and frequency of physical activity. Short term studies show that baseline fitness affects the lipid response to exercise. Changes in lipids induced by a single exercise session persist about 48 hours, which has implications for the timing of lipid testing.

Interpretation of the data from some studies of exercise in women is complicated by the lack of control of the hormonal status. In the NRHS study of women runners, HDL-cholesterol increased irrespective of menstrual status. Interestingly, women using oral contraceptives in this study had a blunted increase in HDL-cholesterol induced by exercise. Not only whether an individual is menopausal, but the timing of the studies relative to the menstrual cycle affect the outcome. Cross-sectional studies continue to show a beneficial effect in HDL-cholesterol; however, interventional studies in pre- and postmenopausal women fail to consistently show a significant change in HDL-cholesterol.

Berg A, Frey I, Baumstark MW, et al. "Physical activity and lipoprotein lipid disorders." *Sports Med* 17:6-21, 1994. (Class R)

Pronk NP. "Short term effects of exercise on plasma lipids and lipoproteins in humans." *Sports Med* 16:431-48, 1993. (Class R)

Taylor PA, Ward A. "Women, high-density lipoprotein cholesterol, and exercise." *Arch Intern Med* 153:1178-84, 1993. (Class R)

Williams PT. "Relationship of distance run per week to coronary heart disease risk factors in 8283 male runners." *Arch Intern Med* 157:191-98, 1997. (Class D)

Williams PT. "High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners." *N Engl J Med* 334:1298-1303, 1996. (Class D)

Stefanick ML, et al. "Effects of diet and exercise in men and postmenopausal women with low levels of HDL-cholesterol and high levels of LDL-cholesterol. *New Engl J Med* 339:12-20, 1998. (Class A)

Weight Management:

Overweight and obesity increase the risk for cardiovascular disease and adversely affect plasma lipids. Each 1 kg increase in body weight has been observed to increase plasma triglycerides by 1.04% and decrease HDL-cholesterol by 0.83%. Conversely, decreases in body weight and body fat are associated with favorable changes in cardiovascular risk factors including increased HDL-cholesterol concentrations and decreased total cholesterol, LDL-cholesterol, and triglyceride concentrations. Every 1 kg decrease in body weight has been observed to decrease triglycerides by 0.77-0.87% and increase HDL-cholesterol by about 1%. Weight management should be considered an important component of interventions intended to maximize lipid management and reduce risk of cardiovascular disease.

Denk MA. "Revisiting the effectiveness of the National Cholesterol Education Program's Step I and Step II Diets: cholesterol-lowering diets in a pharmaceutically driven world." (Class R)

Hormone Replacement Therapy:

Numerous studies show that treatment with unopposed hormone replacement in postmenopausal women improves the lipid profile through increasing the amount of HDL-cholesterol, primarily the HDL2 subfraction, and decreasing the amount of LDL-cholesterol. The most studied estrogen replacement is conjugated equine estrogen (CEE), which increases HDL-cholesterol by up to 15% and decreases LDL-cholesterol by an average of 16%. Unfortunately, the use of CEE is associated with increases in triglycerides (TG), which may be dose dependent. The effects on lipoproteins are observed by three months and persist for the duration of therapy. Beneficial changes in HDL-cholesterol and LDL-cholesterol levels are also reported in studies with oral estradiol. Studies of transdermal estradiol report no decrease in LDL-cholesterol, indicating that a non-oral route of therapy may not be beneficial for treatment of lipid abnormalities. There are conflicting reports of the effect of transdermal estradiol on HDL-cholesterol levels.

Unopposed estrogen is recognized to increase the risk of endometrial hyperplasia and cancer; therefore, it is acceptable only in women who have had hysterectomies. The largest prospective study to date, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial studied CEE plus three different regimens of progestins, cyclic medroxprogesterone (MPA), continuous MPA, and cyclic micronized progesterone (MP). All regimens were successful in reducing the risk of endometrial hyperplasia and LDL-cholesterol (average 15.9 mg/dL) while increasing HDL-cholesterol. While MPA attenuated the beneficial effects of CEE on HDL-cholesterol, MP appeared to have little effect with increases in HDL-cholesterol comparable to unopposed CEE. This study confirmed results reported previously in smaller studies.

A third alternative for estrogen replacement therapy is the use of combined esterified estrogens with methyltestosterone (MT). Two small prospective studies reported the addition of MT to decrease the levels of HDL-cholesterol, with no change in the levels of LDL-cholesterol. This resulted in a less favorable total cholesterol/HDL-cholesterol ratio.

A randomized trial conducted in postmenopausal women with hypercholesterolemia compared treatment with CEE, and HMG reductase inhibitor and the combination. The combination was additive in lowering LDL-cholesterol with a neutral effect on triglycerides and may be considered when monotherapy does not attain lipid goals.

As in men, the rationale for the treatment of hyperlipidemia in women is the reduction of cardiovascular risk. Prior observational studies suggested that HRT reduced the risk of cardiovascular events by 35-50%. The reduction was in part due to the lipid lowering effects of HRT. A recent randomized controlled trial in women with known CAD, the HERS trial, found no reduction in CHD events despite a favorable effect on the lipid profile over 4 years of HRT treatment. There was an increase in CHD events in the first year of treatment leading the authors to caution against the initiation of HRT in women with CAD for "cardioprotective" effects. There was also an increase in venous thrombolembolic (VTE) events during the first year and an overall 3-fold increase in risk compared to placebo. A pooled analysis of HRT randomized trials lasting at least 3 months found no increase in risk of VTE, cancer or CHD events.

Summary: The decision to use HRT to lower lipids in postmenopausal women is less clear than prior to the publication of the HERS trial. There are many reasons to use HRT, but the best evidence suggests that in women with CAD, HRT may transiently increase the risk of CHD events and VTE during the first year of treatment. We cannot definitively recommend for or against the use of HRT for lipid lowering in this population. If HRT is used for lipid lowering, unopposed estrogen is preferred in patients who do not have a uterus nor hyperglyceridemia.

In women with an intact uterus a progestin must be added to prevent uterine hyperplasia. Cyclic MP may be the preferred agent.

Hemminki E and McPherson K. "Impact of postmenopausal therapy on cardiovascular events and cancer: pooled data from clinical trials." *BMJ* 315:149-53, 1997. (Class R)

HERS Study (Class A)

Writing Group for the PEPI Trial, The. "Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women." *JAMA* 273:199-208, 1995. (Class R)

Walsh BW, Schiff I, Rosner B, et al. "Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins." *N Engl J Med* 325:1196-204, 1991. (Class R)

Tufekci M, Colak Z, Ozan H, et al. "Effect of progestogens on estrogen-induced lipoprotein changes." *Eur J Obstet Gynecol Reprod Biol* 49:169-74, 1993. (Class A)

Luciano AA, De Souza MJ, Roy MP, et al. "Evaluation of low-dose estrogen and progestin therapy in postmenopausal women: a double-blind, prospective study of sequential versus continuous therapy." *J Reprod Med* 38:207-14, 1993. (Class A)

Darling GM, Johns JA, McCloud PI, Davis SR. "Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women." *N Engl J Med* 337:595-601, 1997. (Class A)

Davidson MH, Testolin LM, Maki KC, et al. "A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women." *Arch Intern Med* 157:1186-92, 1997. (Class A)

Hickok LR, Toomey C, Speroff L. "A comparison of esterified estrogens with and without methyltestosterone: effects on endometrial histology and serum lipoproteins in postmenopausal women." *Obstet Gynecol* 82:919-24, 1993. (Class A)

Watts NB, Notelovitz M, Timmons MC, et al. "Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause." *Obstet Gynecol* 85:529-37, 1995. (Class B)

Lobo RA. Clinical review 27: effects of hormonal replacement on lipids and lipoproteins in postmenopausal women." *J Clin Endocrinol Metab* 73:925-30, 1991. (Class R)

Schwartz J, Freeman R, Frishman W. "Clinical pharmacology of estrogens: cardiovascular actions and cardioprotective benefits of replacement therapy in postmenopausal women." *J Clin Pharmacol* 35:314-29, 1995. (Class R)

Miller VT. "Lipids, lipoproteins, women and cardiovascular disease." *Atherosclerosis* 108(suppl):S73-S82, 1994. (Class R)

Smoking Cessation:

As well as being an independent risk factor for the development of Coronary Artery Disease (CAD), 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 very low density lipoproteins. Smoking also clearly reduces HDL-cholesterol and may reduce HDL-cholesterol antiatherogenic effects by altering its composition. Smoking cessation trials have documented a significant rise in HDL-cholesterol after smoking cessation. Cigarette smoking in women is associated with earlier menopause and lower estrogen levels which contribute to an increased CAD risk.

Billimoria JD, Pozner H, Metselaar B, et al. "Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood." Artherosclerosis 21:61-76, 1975. (Class C)

Scheffler E, Wiest E, Woehrle J, et al. "Smoking influences the atherogenic potential of low-density lipoprotein." *Clin Investig* 70:263-68, 1992. (Class C)

McBride PE. "The health consequences of smoking: cardiovascular diseases." *Med Clin N Am* 76:333-53, 1992. (Class R)

Evaluate Alcohol Consumption:

Light to moderate alcohol intake has been associated with lower coronary heart disease rates. This is defined as no more than one drink per day for women or two drinks per day for men. One drink is defined as twelve ounces of regular beer, five ounces of wine or one and one half ounces of distilled spirits (80 proof).

The alcohol may help protect against heart disease by raising levels of HDL-cholesterol. If more than one drink for women or two drinks per day for men is consumed, then it may increase the risk for coronary heart disease and increase the risk for hypertriglyceridemia, pancreatitis, hypertension, and cardiomyopathy.

Some people should not drink alcoholic beverages: Women who are pregnant or trying to conceive; individuals who plan to drive or engage in other activities that require attention or skill; individuals using medicines, even over the counter kinds; individuals who cannot keep their drinking moderate, especially recovering alcoholics and other chemically dependent people, and people whose family members have alcohol problems. Most authorities do not recommend initiation of alcohol intake for teetotalers with lipid disorders.

Jackson R, Beaglehole R. "The relationship between alcohol and coronary heart disease: is there a protective effect?" *Curr Opin Lipidol* 4:21-6, 1993. (Class R)

Klatsky AL, Friedman GD, Siegelaub AB. "Alcohol and mortality: a 10 year Kaiser-Permanente experience." *Ann Intern Med* 95:139-45, 1981. (Class B)

Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. "Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits?" *BMJ* 312:731-36, 1996. (Class R)

Criqui MH. "The reduction of coronary heart disease with light to moderate alcohol consumption: effect or artifact?" *Br J Addict* 85:854-57, 1990. (Class R)

Vitamin E and the Prevention and Treatment of Coronary Atherosclerosis

Hypercholesterolemia and elevated low-density lipoprotein cholesterol (LDL-cholesterol) concentrations are known to be associated with accelerated atherogenesis and the development of coronary heart disease. Experimental evidence suggests that oxidized LDL-cholesterol rather than native LDL-cholesterol is atherogenic. Antioxidants such as vitamin E are believed to prevent atherosclerosis by inhibiting the oxidation of low-density lipoprotein. A variety of studies indicate that vitamin E has a role in the primary and secondary prevention of adverse coronary events and as an adjunct to diet and cholesterol lowering medication to promote the regression of coronary artery stenoses.

- Vitamin E intakes greater than 100 IU/day appear to result in a 40% reduction in adverse cardiac outcomes in both men and women (primary prevention).
- Supplemental vitamin E at doses of 400 IU or 800 IU daily has been shown to reduce the risk of nonfatal myocardial infarction and death plus nonfatal myocardial infarction by 77% and 47% respectively in patients with angiographically proven coronary atherosclerosis (secondary prevention).
- Vitamin E intakes > 100 IU/day have been shown to promote the regression of coronary artery stenoses in men with a history of coronary artery bypass grafting (secondary prevention).

Vitamin E exhibits very low toxicity, but may exacerbate blood coagulation defects associated with vitamin K deficiency. As warfarin therapy induces relative vitamin K deficiency, careful INR monitoring should be performed when these individuals are started on vitamin E.

Vitamin E is very inexpensive (400 IU/day = $10.00/year) and is very effective. The HMG-CoA reductase inhibitors are costly ($500.00+/year) and have been shown to reduce the combined endpoint of nonfatal myocardial infarction and death from coronary heart disease by a modest 31%.

Rimm EB, Stampfer MJ, Ascherio A, et al. "Vitamin E consumption and the risk of coronary heart disease in men." *N Engl J Med* 328:1450-56, 1993. (Class B)

Stampfer MJ, Hennekens CH, Manson JE, et al. "Vitamin E consumption and the risk of coronary disease in women." *N Engl J Med* 328:1444-49, 1993. (Class B)

Stephens NG, Parsons A, Schofield PM, et al. "Randomised controlled trial of Vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS)." *Lancet* 347:781-86, 1996. (Class A)

Riemersma RA. "Coronary heart disease and vitamin E." *Lancet* 347:776-77, 1996. (Class R)

Hodis HN, Mack WJ, LaBree L, et al. "Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis." *JAMA* 273:1849-54, 1995. (Class A)

Diplock AT. "Safety of antioxidant vitamins and beta-carotene." *Am J Clin Nutr* 62(suppl):1510S-6S, 1995. (Class R)

Folic Acid:

Homocysteinemia, Vascular Disease, and Vitamins B_{12}, B_6, and Folate

Homocysteine is a highly reactive amino acid that is toxic to the vascular endothelium, potentiates auto-oxidation of LDL-cholesterol, and promotes thrombosis. Recent investigations indicate that mildly elevated serum homocysteine levels* are associated with an increased risk of premature cerebrovascular (carotid stenosis and stroke), peripheral vascular, and coronary artery disease. Each 5 umol/L increment in the homocysteine level is associated with an increased odds ratio for cardiovascular disease of 1.6 for men and 1.8 for women. It has been estimated that a 5 umol/L reduction in homocysteine levels in men aged 45 years of age and older might prevent 35,000 deaths from cardiovascular disease annually. A similar reduction in women might prevent 19,000 deaths annually. Low B_6, B_{12} and folate plasma concentrations are associated with higher homocysteine levels. Daily B_6, B_{12}, and folate intakes approximating 2 mg, 6 ug, and 0.4 mg respectively are associated with the lowest homocysteine concentrations. These vitamin amounts correspond to those in inexpensive multivitamins costing about $0.05/day or $18.25/year. At least 40% of the population has a suboptimal intake of these vitamins and is at increased risk for occlusive vascular disease.** Therefore, it is reasonable to recommend that patients with occlusive vascular disease take a multivitamin daily for its B_{12}, B_6, and folate content.***

* Homocysteine levels are available commercially, but are very costly – about $127 per test. As hyperhomocysteinemia is common and the treatment (vitamins) for this condition is inexpensive, it is usually not cost effective to obtain homocysteine levels as part of the evaluation of patients with or at risk for occlusive vascular disease.

** In 1997, the FDA proposes to add 140 µg of folate per 100 g of cereals, grains, rice, and bean products.

*** In terms of vitamins, many patients seem to believe that if a little is good, more is better. In order to avoid unintended toxicity, it is appropriate to caution patients not to exceed recommended vitamin dosages. For example, high dose (>100mg/d) B_6 can cause a peripheral neuropathy and high dose (1–2g/d) folate supplementation can mask vitamin B_{12} deficiency. High dose vitamin A can be hepatotoxic.

Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. "A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes." *JAMA* 274:1049-57, 1995. (Class M)

Nygard O, Vollset SE, Refsum H, et al. "Total plasma homocysteine and cardiovascular risk profile: the hordaland homocysteine study." *JAMA* 274:1526-33, 1995. (Class C)

Mandel H, Brenner B, Berant M, et al. "Coexistence of hereditary homocystinuria and factor V leiden — effect on thrombosis." *N Engl J Med* 334:763-8, 1996. (Class D)

Den Heijer M, Koster T, Blom HJ, et al. "Hyperhomocysteinemia as a risk factor for deep-vein thrombosis." *N Engl J Med* 334:759-62, 1996. (Class C)

Stampfer MJ, Malinow MR, Willett WC, et al. "A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US physicians." *JAMA* 268:877-81, 1992. (Class C)

Selhub J, Jacques PF, Bostom AG, et al. "Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis." *N Engl J Med* 332:286-91, 1995. (Class D)

Selhub J, Jacques PF, Wilson PWF, et al. "Vitamin status and intake as primary determinants of homocysteinemia in an elderly population." *JAMA* 270:2693-98, 1993. (Class D)

Stampfer MJ, Willett WC. "Homocysteine and marginal vitamin deficiency: the importance of adequate vitamin intake." *JAMA* 270:2726-27, 1993. (Class R)

Clarke R, Daly L, Robinson K, et al. "Hyperhomocysteinemia: an independent risk factor for vascular disease." *N Engl J Med* 324:1149-55, 1991. (Class C)

Perry IJ, Refsum H, Morris RW, et al. "Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men." *BMJ* 346:1395-98, 1995. (Class C)

Stampfer MJ, Malinow MR. "Can lowering homocysteine levels reduce cardiovascular risk?" *N Engl J Med* 332:328-29, 1995. (Class R)

Aspirin:

Aspirin irreversibly inhibits platelet cyclooxygenase and impairs platelet aggregation in doses as low as 60 mg every other day. A clinical history of bleeding diathesis, active ulcer disease or aspirin allergy are major contraindications. Dosage appears unimportant, usually ranging from 60 mg every other day up to 325 mg daily.

Secondary prevention

Secondary prevention trials with aspirin have demonstrated reduced cardiovascular and cerebrovascular endpoints. A meta-analysis of over 70,000 patients with arterial disease or risk factors for arterial disease reported a 25% decrease in vascular events and an 18% decrease in vascular deaths with aspirin based antiplatelet therapy (reference 1).

Primary prevention

Primary prevention studies in patients not selected for cardiovascular risk factors have shown minimal benefit. Some studies have shown reduced non-fatal myocardial infarction, but this was not supported by meta-analysis (reference 1).

Patients with hyperlipidemia are at intermediate risk, and may derive greater benefit from aspirin than the lower risk populations studied in primary prevention trials. The recommendation for aspirin in hyperlipidemic patients is supported by this reasoning, and by the low cost and risk of this therapy.

Antiplatelet Trialists' Collaboration. "Collaborative overview of randomised trials of antiplatelet therapys – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients." *BMJ* 308:81-106, 1994. (Class M)

Manson JE, Stampfer MJ, Colditz GA, et al. "A prospective study of aspirin use and primary prevention of cardiovascular disease in women." *JAMA* 226:521-27, 1991. (Class B)

Peto R, Gray R, Collins R, et al. "Randomised trial of prophylactic daily aspirin in British male doctors." *BMJ* 296:313-16, 1988. (Class A)

Sitostanol ester nutritional supplement**:**

Clinical studies in men and women with type 2 diabetes mellitus, hyperlipidemia, and known coronary artery disease have shown that sitostanol ester, a saturated derivative of a plant sterol, can lower total and LDL-cholesterol approximately 10%. It has no significant effect on HDL-cholesterol and triglyceride levels. The primary mechanism is blockage of cholesterol absorption. One small randomized study of women demonstrated an additive effect of sitostanol in combination with simvistatin. Currently available preparations include the esterfied sterol in rapeseed oil, mayonnaise or margarine. Caution should be exercised in patients on medications because of limited information about drug interactions.

Miettinen TA, Puska H, et al. "Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population." *New Engl J Med* 333:1308-12, 1995. (Class A)

Gylling H and Miettinen TA. "Serum cholesterol and cholesterol and lipoprotein metabolism in hyper cholesterolaemic NIDDM patients before and during sitostanol ester-margarine treatment." *Diabetologia* 37:773-80, 1994. (Class C).

Vanhanen HT, Blomquist S, Enholm C, et al. "Serum cholesterol, cholesterol precursors, and plant sterols in hypercholesterolemic subjects with different apoE phenotypes during dietary sitostanol ester treatment. *J Lipid Res* 34:1535-44, 1993. (Class A)

Gylling H, Radhakrishan R, and Miettinnen TA. "Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine. *Circulation* 96:4226-31, 1997. (Class A)

8. Evaluation

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

Patients with primarily triglyceride elevation and normal or moderately elevated cholesterol are candidates for treatment if there is evidence of cholesterol rich VLDL and IDL particles, typically found in patients with triglyceride levels between 200 to 500 mg/dl and occasionally between 500 to 1000 mg/dl. Especially if there is a strong family history of CHD and dyslipidemia such as familial combined hyperlipidemia or if the patient has evidence of atherosclerotic disease. It can also be supported in diabetics with or without low HDL-cholesterol.

Patients with very high triglycerides, > 1000 mg/dl, are at increased risk of hepatomegaly, splenomegaly, hepatic steatosis and pancreatitis and are candidates for dietary and drug therapy. Patients with fasting triglycerides < 1000 mg/dl are at less immediate risk of pancreatitis. After ruling out or controlling for secondary causes (e.g. diabetes mellitus, hypothyroidism, chronic renal failure, alcohol abuse, hormone replacement therapy, oral contraceptives, beta-blockers [nonselective are worse offenders than selective], thiazide diuretics [effect modest with chronic therapy], please see appendix for additional secondary causes) the National Institutes of Health recommend dietary measures for initial management of borderline and high triglycerides. If dietary and lifestyle modification (weight reduction if needed, decrease in alcohol, increase physical activity, smoking cessation) does not lower triglycerides to desired level then drug therapy is indicated. (See Annotations Appendix C, "Drug Companion Document.")

When triglycerides are over 400 mg/dl, the LDL-cholesterol cannot be calculated and a direct measure of LDL, where available, is preferred. Although the LDL-cholesterol can be calculated when the triglycerides are moderately elevated (200-400 mg/dl), keep in mind that the LDL-cholesterol may be underestimated due to the Friedenwald equation.

LDL-cholesterol = Total cholesterol - HDL-cholesterol - (Triglycerides ÷ 5)

McKenney JM, Hawkins DW. "Treatment of Lipid Disorders." in Handbook on the Management of Lipid Disorders. pp 85–87. National Pharmacy cholesterol Council, 1995. (Class R)

"Summary of the second report of the National cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II)." *JAMA* 269:3015-23, 1993. (Class R)

Grundy SM. "Consensus statement: role of therapy with 'statins' in patients with hypertriglyceridemia." *Am J Cardiol* 81:1B-6B, 1998. (Class R)

9. Calculate number of Risk Factors.

Family History.

Family history of coronary artery disease was identified as a risk factor by the National cholesterol Education Program, in an attempt to screen for heterozygous familial hypercholesterolemia, as well as other genetically predisposed populations to coronary disease. Heterozygous familial hypercholesterolemia affects 1 in 500 persons in the United States with the risk of death from coronary artery disease increased almost four fold between the ages of 20 and 74. (Myocardial infarction leading to sudden death often occurs in these men in their 30's or 40's, and by age 50, 80% of males have ischemic heart disease.) Without intervention, approximately 50-75% of men with heterozygous familial hypercholesterolemia will have a myocardial infarction by age 60. Thompson showed the prevalence of coronary disease in men at age 35 equalled that in women at age 40 in contrast to the typical 10 year lag between men and women.

Goldstein JL, Brown MS. "Familial hypercholesterolemia." In The Metabolic Basis of Inherited Disease. pp 1215–1251 Scriver CS, Blaudet AL, Sly WS, et al eds. New York: McGraw-Hill, 1989. (Class R)

Yamamoto A, Kamiya T, Yamamura T, et al. "Clinical features of familial hypercholesterolemia." *Arteriosclerosis* 9(suppl I):I-66–I-74, 1989. (Class D)

Williams RR, Hasstedt SJ, Wilson DE, et al. "Evidence that men with familial hypercholesterolemia can avoid early coronary death." *JAMA* 255:219-24, 1986. (Class D)

Thompson GR, Seed M, Niththyananthan S, et al. "Genotypic and phenotypic variation in familial hypercholesterolemia." *Arteriosclerosis* 9(suppl I):I-75-I-80, 1989. (Class R)

Scientific Steering Committee on behalf of the Simon Broome Register Group. "Risk of fatal coronary heart disease in familial hypercholesterolemia." *BMJ* 303:893-96, 1991. (Class B)

Bild DE, Williams RR, Brewer HB, et al. "Identification and management of heterozygous familial hypercholesterolemia: summary and recommendations from an NHLBI workshop." *Am J Cardiol* 72:1D-5D, 1993. (Class R)

"Summary of the second report of the National cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II)." *JAMA* 269:3015-23, 1993. (Class R)

13. Management and Treatment.

Frick MH, Elo O, Haapa K, et al. "Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia." *N Engl J Med* 317:1237-45, 1987. (Class A)

Shepherd J, Cobbe SM, Ford I, et al. "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia." *N Engl J Med* 333:1301-7, 1995. (Class A)

Lipid Research Clinics Program. "The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease." *JAMA* 251:351-64, 1984. (Class A)

Levy D. "A multifactorial approach to coronary disease risk assessment." *Clin Exp Hypertens* 15:1077-86, 1993. (Class R)

Downs JR, Clearfield M, Weis S, et al. "Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS." JAMA 279:1615-22, 1998. (Class A)

West of Scotland Coronary Prevention Group. "Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS)." *Circulation* 97:1440-45, 1998. (Class A)

16. Goal: LDL-cholesterol <130

Haffner S, Letho S, et al. "Mortality for coronary heart disease subjects with type 2 diabetes mellitis and in nondiabetic subjects with and without prior myocardial infarction." *New Engl J Med* 338:229-34, 1998. (Class A)

17. Goal Met?

Poor compliance can limit the effectiveness of therapies. In asymptotic conditions such as hyperlipidemia, this can be especially problematic. Long-term compliance with drug therapy for chronic conditions is estimated to be only about 50%. Compliance in clinical trials is often much higher due to multiple factors including patient selection, close monitoring, and educational efforts of medical staff.

Some factors associated with poor compliance are number of drugs, complexity and frequency of drug administration, adverse side effects, asymptotic conditions, cost and psychosocial problems.

The first step is to identify potential noncompliance. Some signs of noncompliance include missed visits, inability to reach by phone, rescheduling of appointments, complaints about office visits, impatience during visits, failure to achieve therapeutic goals, and change in health care provider(s).

Suggested ways to improve compliance include asking about compliance in a non-threatening way at each visit; simplification of the drug regimen (frequency and complexity); reminder systems; drug-count devices; pill minders; involvement of family or friends; a health care team approach including nurses, dietitians, pharmacists and educators in addition to physicians; written instructions; and educating the patient about the medications including potential adverse effects, importance of therapy, realistic goals, necessity of life-long treatment, and importance of continued attention to non-pharmacologic therapy (i.e., diet, exercise).

Additionally, the doctor-patient relationship can play a key role in improving compliance, in part through the physician's efforts to understand the patient's perspective on compliance.

Morris L, Schulz RM. "Medication compliance: the patient's perspective." *Clin Ther* 15:593-606, 1993. (Class R)

PATIENT WITH KNOWN CORONARY ARTERY DISEASE ALGORITHM

4. Adjunctive Measures

Aspirin:

Please refer to the Discussion on Aspirin, Patients without CAD Discussion, Annotation #6, Adjunctive Measures.

Diet: Step II Diet:

This algorithm assumes that the patient has not achieved his or her lipid goal on a Step I Diet as addressed in the ICSI Lipid Screening in Adults guideline.

Nutrition Intervention in a Patient With Known CAD

The evidence in the literature and the NCEP Adult Treatment Panel Consensus Position suggest that adults with known coronary artery disease should be following the American Heart Association (AHA) Step II diet or something more aggressive. The AHA eating plan includes less than 30% calories from total fat, less than 7% calories from saturated fat, less than 200 mg dietary cholesterol and calorie adjustment to achieve and maintain a reasonable body weight. It is desirable to have the assessment and education for these individuals carried out by a registered dietitian when possible.

LaRosa JC, Hunninghake D, Bush D, et al. "The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol, and coronary artery disease. A joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute." *Circulation* 81:1721-33, 1990. (Class R)

Blankenhorn DH, Johnson RL, Mack WJ, et al. "The influence of diet on the appearance of new lesions in human coronary arteries." *JAMA* 263:1646-52, 1990. (Class B)

Ornish D, Brown SE, Scherwitz LW, et al. "Can lifestyle changes reverse coronary heart disease?" *Lancet* 336:129-33, 1990. (Class A)

Schuler G, Hambrecht R, Schlierf G, et al. "Regular physical exercise and low-fat diet: effects on progression of coronary artery disease." *Circulation* 86:1-11, 1992. (Class A)

Arntzenius AC, Kromhout D, Barth JD, et al. "Diet, lipoproteins, and the progression of coronary atherosclerosis: the Leiden intervention trial." *N Engl J Med* 312:805-11, 1985. (Class B)

"Summary of the second report of the National cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II)." *JAMA* 269:3015-23, 1993. (Class R)

Diet:

Please refer to the Patients Without Known CAD Discussion, #6, Adjunctive Measures, Diet.

Aerobic Exercise:

Please refer to the Patients Without Known CAD Discussion, #6, Adjunctive Measures, Exercise.

Weight Management:

Please refer to the Patients Without Known CAD Discussion, #6, Adjunctive Measures, Aspirin.

Smoking Cessation:

Please refer to the Patients Without Known CAD Discussion, #6, Adjunctive Measures, Smoking Cessation.

Evaluate Alcohol Consumption:

Please refer to the Patients Without Known CAD Discussion, #6, Adjunctive Measures, Moderate Alcohol Consumption.

Vitamin E:

Please refer to the Patients Without Known CAD Discussion, #6, Adjunctive Measures, Vitamin E.

Folic Acid:

Please refer to Patients Without Known CAD Discussion, #6, Adjunctive Measures, Folic Acid.

Sitostanol ester nutritional supplement:

Please refer to Patients Without Known CAD Discussion, #6, Adjunctive Measures, Sitostanol Ester Nutritional Supplement.

5. Triglycerides < 200?

The role of triglycerides in the development of atherosclerosis remains unclear. Due to the inverse correlation between HDL-cholesterol and triglycerides, it has been felt that hypertriglyceridemia may be atherogenic only through low HDL-cholesterol. However, in certain subgroups, i.e., diabetics, women, etc., studies strongly suggest that hypertriglyceridemia is an independent risk factor for atherogenesis. Current theory holds that triglycerides contribute to the formation of a subclass of LDL-cholesterol that is highly atherogenic. Even in a nondiabetic, non-female patient group, i.e. the PROCAM study, individuals with a ratio of LDL-cholesterol/HDL-cholesterol > 5.0, showed a significantly higher atherosclerotic event rate if triglycerides were over 200. Additionally, the risk of pancreatitis increased with triglycerides totaling over 500, and significantly increases when triglycerides are over 1000.

Drexel H, Amann FW, Beran J, et al. "Plasma triglycerides and three lipoprotein cholesterol fractions are independent predictors of the extent of coronary atherosclerosis." *Circulation* 90:2230-35, 1994. (Class C)

Assmann G, Schulte H. "Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience)." *Am J Cardiol* 70:733-37, 1992. (Class B)

Laakso M, Ronnemaa T, Pyorala K, et al. "Atherosclerotic vascular disease and its risk factors in non-insulin-dependent diabetic and nondiabetic subjects in Finland." *Diabetes Care* 11:449-63, 1988. (Class D)

6. Evaluation and Management of Hypertriglyceridemia.

Fibric Acid

No secondary prevention clinical trials have been reported with gemfibrozil. In the Helsinki Heart Study, a primary prevention trial in middle aged men, gemfibrozil resulted in a decrease in the combined endpoint of myocardial infarction and cardiovascular mortality at 5 years. An increase in HDL-C was the strongest predictor of risk reduction. No clinical trials with a primary intervention of pharmacologic manipulation of HDL-C have been reported.

Frick MH, Elo O, Haapa K, et al. "Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia." *N Engl J Med* 317:1237-45, 1987.. (Class A)

Hormone Replacement Therapy

Please refer to the Discussion on Hormone Replacement Therapy, Algorithm 1, #6 Adjunctive Measures.

Niacin

No primary or secondary prevention clinical trials have demonstrated a significant reduction of total mortality with niacin. In the Coronary Drug Project, niacin was associated with a 15% reduction in the combined endpoint of myocardial infarction and cardiovascular mortality at 5 years; no statistically significant effect on cardiovascular mortality was observed. In the Stockholm Ischemic Heart Disease Secondary Prevention Study, niacin added to clofibrate improved CHD death rate at 5 years.

Coronary Drug Project Research Group, The. "Clofibrate and niacin in coronary heart disease." *JAMA* 231:360-81, 1975. (Class A)

Canner PL, Berge KG, Wenger NK, et al. "Fifteen year mortality in coronary drug project patients: long-term benefit with niacin." *JACC* 8:1245-55, 1986. (Class A)

Rosenhamer G. "Reduction in mortality in the Stockholm ischemic heart disease secondary prevention study by combined treatment with clofibrate and nicotinic acid." *Acta Med Scand* 223:405-18, 1988. (Class A**)**

7. Evaluation and Management

Niacin

Please refer to Patients With Known CAD Discussion, #6, Evaluation and Management of Hypertriglyceridemia, Niacin.

Gemfibrozil and Lovastatin

The LIPID Study Group. "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels." *New Engl J Med* 339(19):1349-57, 1998. (Class A)

Frick MH, Elo O, Haapa K, et al. "Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia." *N Engl J Med* 317:1237-45, 1987. (Class A)

8. Follow up.

McKenney JM, Hawkins DW. "Lipid - Modifying Drugs." In Handbook on the Management of Lipid Disorders. pp 89-134. National Pharmacy cholesterol Council, 1995. (Class R)

9. LDL-cholesterol 100–129 or LDL-cholesterol ≥ 130

McKenney JM, Hawkins DW. "Lipids Modifying Drugs." In Handbook on the Management of Lipid Disorders. pp 89-134. National Pharmacy cholesterol Council, 1995. (Class R)

Scandinavian Simvastatin Survival Study Group. "Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)." *Lancet* 344:1383-89, 1994. (Class A)

The LIPID Study Group. "Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels." *New Engl J Med* 339(19):1349-57, 1998. (Class A)

Frick MH, Elo O, Haapa K, et al. "Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia." *N Engl J Med* 317:1237-45, 1987. (Class A)

12. Laboratory monitoring in 3-6 months.

McKenney JM, Hawkins DW. "Lipids Modifying Drugs." In Handbook on the Management of Lipid Disorders. pp 89-134. National Pharmacy cholesterol Council, 1995. (Class R)

13. Further Management.

See the Patients With Known CAD Discussion, #4, Adjunctive Measures.

McKenney JM, Hawkins DW. "Lipids Modifying Drugs." In Handbook on the Management of Lipid Disorders. pp 89-134. National Pharmacy cholesterol Council, 1995. (Class R)

When measuring for improvement, it is critical that the measurements used are responsive to individual medical groups, and support medical groups' own clinical improvements. The following section of Specifications for Selected Measures is included in the guideline document to serve as an aid to the medical groups' own implementation efforts. It is likely that medical groups may need to adapt these measures to specific clinical practice or administrative systems.

Overview of Ideas for Measurement

The following aims were identified by the guideline work group as key areas in which medical groups may receive benefits in implementing this guideline.

The measures associated with these aims are presented as possible measures. Measures of aim help medical groups determine progress in achieving that aim. The possible measures listed are suggestions from the work group. However, other approaches may be customized by individual medical groups to ferret out improvement information important to the medical group's individual practice.

Priority Aims for Medical Groups When Using This Guideline

1. Improve the percentage of patients with known coronary artery disease with lipid disorders who meet their treatment goal.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with diagnosed coronary artery disease who have LDL-cholesterol less than 100 mg/dl.

   b. Percentage of patients with diagnosed coronary artery disease who have LDL-cholesterol less than 130 mg/dl.

2. Improve the percentage of patients without known coronary artery disease with lipid disorders who meet their treatment goal.

   Possible measures of accomplishing this aim:

   a. Percentage of patients without known coronary artery disease who are on lipid lowering medications, within each of three starting LDL-cholesterol and risk factor levels, who achieve the goal range for LDL-cholesterol for the group.

3. Increase compliance with non-pharmacological treatment of patients with coronary artery disease through education.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with coronary artery disease for whom a diet evaluation has been completed.

   b. Percentage of patients with coronary artery disease with referral for individual diet instruction or class.

   c. Percentage of patients with coronary artery disease with documentation of receiving advice about an exercise program.

4. Improve the proportion of patients on lipid lowering medication who receive regular follow-up care for lipid disorder.

   Possible measures of accomplishing this aim:

   a. Percentage of patients on lipid lowering medication who have a fasting lipid panel every six to twelve months.

Possible Success Measure #1a

Percentage of patients with diagnosed coronary artery disease who have LDL-cholesterol less than 100 mg/dl.

Population Definition

All patients age 20 to 75 with diagnosed heart disease, as defined below.

Data of Interest

$$\frac{\text{Number of patients with heart disease with LDL-cholesterol} < 100 \text{ mg/dl}}{\text{Number of patients with diagnosed heart disease}}$$

Numerator/Denominator Definitions

Numerator: The patient is classified as having met the treatment goal of LDL-cholesterol < 100 mg/dl if the patient had at least one LDL-cholesterol test of < 100 mg/dl in the previous 12 months.

If no LDL-cholesterol test was done in the past 12 months, the patient is classified as NOT having met the lipid treatment goal of < 100 mg/dl.

If no LDL-cholesterol value in the previous 12 months is < 100 mg/dl, the patient is classified as NOT having met the lipid treatment goal of < 100 mg/dl.

If any LDL-cholesterol value in the previous 12 months is < 100 mg/dl, the patient is classified as HAVING MET the lipid treatment goal of < 100 mg/dl.

Denominator: Patients 20 to 75 years old with heart disease include all those who received one or more of the following ICD-9 codes in the previous 12 months: 410 to 414.9, V45.81 (coronary bypass), or V45.82 (angioplasty). Even if a patient has never been diagnosed with a lipid disorder, and/or is not on lipid lowering treatment, they may be included if they are 20 to 75 years old and have diagnosed heart disease.

Method/Source of Data Collection

The preferred way to collect these data:

1. All patients 20 to 75 years old with diagnosed heart disease could be identified. Each medical group would select at random 20 patients off this list for measurement each month.
2. Medical records or computerized laboratory records of these 20 patients may be reviewed to ascertain the lowest LDL-cholesterol value in the previous 12 months.

An alternative way to collect the data if automated databases are not available for all patients to be measured:

1. All patients 20 to 75 years old with diagnosed heart disease in the previous 12 months would be identified at the medical group using ICD-9 diagnostic codes from the previous 12 months. Each medical group would select at random 20 patients off this list for measurement each month.

2. Medical records or computerized laboratory records of these 20 patients would be reviewed to ascertain the lowest LDL-cholesterol value in the previous 12 months.

Sample Size: The recommended sample size of 20 patients a month was chosen in order to be both practical and meaningful. Trends over time may be measured accurately using this sample size.

Time Frame Pertaining to Data Collection

Data on 20 patients are collected monthly and reported quarterly.

Notes

While NCEP guidelines recommend a goal LDL-cholesterol of 100 mg/dl for patients with CHD, the level for treatment initiation is 130 mg/dl. Thus, some various medical groups may wish to use either 100 mg/dl or else 130 mg/dl as a measure of lipid control in CHD patients.

The optimal approach may be to use both levels. The ultimate goal is to increase the proportion of CHD patients who have LDL-cholesterol < 100 mg/dl, but if the proportion of CHD patients who have LDL-cholesterol < 130 mg/dl is also increasing, this is a clear measure of improvement in lipid control.

Here we define both measures. Please note that once the denominator of patients has been identified, there is virtually no incremental cost to do both measures, compared to doing just one.

Possible Success Measure # 3a

Percentage of patients with diagnosed coronary artery disease who have a diet evaluation.

Population Definition

All patients age 20 to 75 with diagnosed heart disease, as defined below.

Data of Interest

$$\frac{\text{Number of patients with heart disease who have had a diet evaluation}}{\text{Number of patients with diagnosed heart disease whose records are reviewed}}$$

Numerator/Denominator Definitions

Numerator: Patients with diagnosed heart disease who have a diet evaluation.

Denominator: Patients age 20 to 75 years old with heart disease include all those who received one or more of the following ICD-9 codes in the previous 12 months: 410 to 414.9, V45.81 (coronary bypass), or V45.82 (angioplasty). Even if a patient has never been diagnosed with a lipid disorder, and/or is not on lipid lowering treatment, they may be included if they are 20 to 75 years old and have diagnosed heart disease.

Method/Source of Data Collection

The preferred way to collect these data:

- All patients 20 to 75 years old with diagnosed heart disease could be identified. Each medical group would select at random 20 patients off this list for measurement each month.
- Medical records of these 20 patients would be reviewed to determine if a diet evaluation has been done.

An alternative way to collect the data if automated databases are not available for all patients to be measured.

- All patients 20 to 75 years old with diagnosed heart disease in the previous 12 months would be identified at the medical group using ICD-9 diagnostic codes from the previous 12 months. Each medical group would select at random 20 patients off this list for measurement each month.
- Medical records of these 20 patients would be reviewed to determine if a diet evaluation has been done.

Time Frame Pertaining to Data Collection

Data on 20 patients are collected monthly and reported quarterly.

Possible Success Measure # 4a

Percentage of patients on a lipid lowering medication who have a fasting lipid panel every six to twelve months.

Population Definition

All patients age 20 to 75 who are dyslipidemic and on a lipid lowering medication.

Data of Interest

Number of patients on lipid lowering medication who have a fasting lipid panel

---

Total number of patients who are on lipid lowering medication whose records are reviewed

Numerator/Denominator Definitions

Numerator: Of the patients in the denominator, those who have had a fasting lipid panel in the past 6-12 months (measurement of total cholesterol, HDL-cholesterol, triglycerides and calculated LDL-cholesterol after a 12-hour fasting period.

CPT-4 codes:

83718 Lipoprotein, direct measurement: HDL cholesterol

83719 & VLDL

83721 & LDL

80061 Lipid Profile

Denominator: Patients age 20 to 75 years old who are dyslipidemic on a lipid lowering medication,* including:

Bile Acid Sequestrant (BAS)

Fibric Acids

Niacin

Statin.

* Refer to *Appendix C: Drug Companion Document - Treatment Options for Dyslipidemia* for a complete listing of lipid lowering medications.

Method/Source of Data Collection

The preferred way to collect these data:

- Patients 20 to 75 years old who are dyslipidemic and on a lipid lowering medication could be identified. This would include patients with Hypercholesteriolemia (high LDL, normal Trig and HDL), combined Hyperlipidemia (high LDL and Trig), Hypertriglyceridenia and Hypercholesteriolemia (with isolated low HDL) who are on alipid lowering medication.
- Each medical group would select at random 20 patients for measurement each month to determine if a fasting lipid panel has been done.

Time Frame Pertaining to Data Collection

Data on 20 patients are collected monthly and reported quarterly.

PROBING MEASURES

1. Proportion of patients with diagnosed heart disease and LDL-cholesterol of 100 mg/dl or more who are being treated with a statin (lovastatin, simvastatin, pravastatin, or fluvastatin).

   Reasoning: It is difficult for most patients with a goal LDL-cholesterol of under 100 mg/dl to achieve this goal without aggressive pharmacologic management in addition to lifestyle changes and diet. The statins are the drug of choice for many patients with diagnosed coronary heart disease because they lower LDL-cholesterol up to 40% at maximum doses.

2. Proportion of patients with diagnosed heart disease and an LDL-cholesterol of 100 mg/dl or more who have chart documentation of structured education on the American Heart Association Step 2 Diet.

   Reasoning: Patients with coronary heart disease and LDL-cholesterol of 100 mg/dl or more will be unable to sustain low LDL-cholesterol levels over time unless they make sustained lifestyle changes, particularly in their diet. These patients are good candidates for the AHA Step 2 diet, which allows only 10% of calories from fat.

3. Proportion of patients with diagnosed heart disease and LDL-cholesterol of 100 mg/dl or more who receive a prompt to attend clinic if they have had no fasting lipid panel in the previous six months.

   Reasoning: Patients with coronary heart disease and uncontrolled dyslipidemias are a group at very high risk of adverse clinical outcomes. In the interests of the patient, they should have surveillance of their lipid status at least every 6 months as recommended in this guideline. Patients who are not getting this level of care should be contacted by the clinic or medical group and advised of the need for such care. This mechanism can be operationalized by front desk personnel and need not take any physician time in most cases.

4. Proportion of patients with diagnosed heart disease and an LDL-cholesterol of 100 mg/dl or more who, when they missed a clinic appointment, received a telephone or mailed reminder to reschedule the visit.

   Reasoning: These high risk patients need ongoing regular care, and it makes common sense to recall them when a clinic visit is missed because of a patient "no show." A telephone or mailed reminder system can be operationalized by front desk personnel and need not take any physician time in most cases. Note that responsibility for receiving regular medical care for chronic diseases resides with the patient. The suggestion that patients be encouraged to attend clinic for regular visits or to reschedule missed appointments is not meant to abrogate this fundamental patient responsibility.