INLAND EMPIRE HEALTH PLAN

Clinical Practice Guideline for the Diagnosis and Management of Hyperlipidemia

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ICSI

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:
Lipid Management in Adults

Twelfth Edition
October 2011

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;
- health care teaching institutions;
- health care information technology departments;
- 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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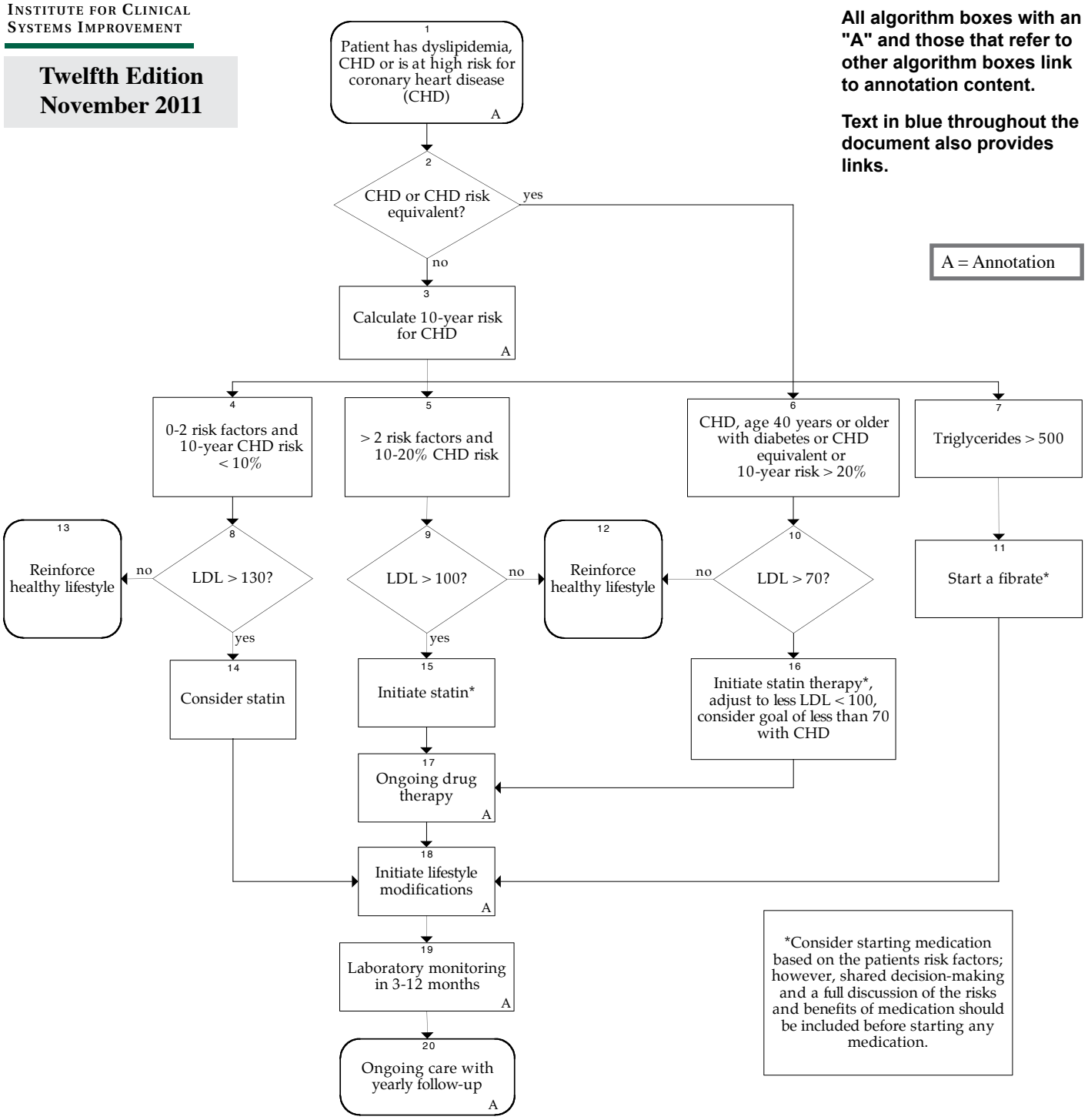
All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content.

Text in blue throughout the document also provides links.



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Disclosure of Potential Conflict of Interest

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. It is not assumed that these financial interests will have an adverse impact on content. They are simply noted here to fully inform users of the guideline.

Steven Kopecky, MD receives consulting fees from Applied Clinical Intelligence for chairing the data and safety monitoring committee for a multinational research study of a percutaneous device used to close patent foramen ovale. Receives personal compensation for consulting with Prime Therapeutics.

Patrick O'Connor, MD received consulting fees from ECRI to review their position on nutrition. Received personal and professional compensation for Chronic Disease Decision Support tool that is licensed to Phillips Inc. for patent pending on simulated learning technology for chronic disease care. Received personal payment from Park Nicollet Foundation for educational presentation on personalized care. Received institutional payment for research grants from NIH (National Institute of Health), AHRQ (Agency for Healthcare Research and Quality), NIMH (National Institute of Mental Health), NHLBI (National Heart, Lung and Blood Institute) and to develop standards of diabetes care for American Diabetes Association. Received personal and institutional payment for industry grants to fund salary related to grant review committees for International Diabetes Federation and NIH.

No other work group members have potential conflicts of interest to disclose.

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Evidence Grading

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. Literature search terms for the current revision of this document and include lipids, hypercholeserolemia, LDL and HDL literature from June 2009 through March 2011.

Following a review of several evidence rating and recommendation writing systems, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

GRADE has advantages over other systems including the current system used by ICSI. Advantages include:

- Developed by a widely representative group of international guideline developers
- Explicit and comprehensive criteria for downgrading and upgrading quality of evidence ratings
- Clear separation between quality of evidence and strength of recommendations that includes a transparent process of moving from evidence evaluation to recommendations
- Clear, pragmatic interpretations of strong versus weak recommendations for clinicians, patients and policy-makers
- Explicit acknowledgement of values and preferences and
- Explicit evaluation of the importance of outcomes of alternative management strategies.

At ICSI we have established a GRADE Implementation Team to provide overall direction for this transition. We intend to complete the transition in phases. In 2011 the following work to transition to GRADE will be done:

- Select documents that will undergo complete implementation of GRADE

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- For all other documents, including Lipid Management in Adults, beginning March 2011:
  - All original ICSI Class A (RCTs) and ICSI Class B (Cohort) studies were reviewed by work group members and the quality of evidence assessed using GRADE. Other literature was labeled by ICSI staff according to Crosswalk between ICSI Evidence Grading System and GRADE.
  - New literature was reviewed and graded by work group members using the new ICSI GRADE system.
  - Key Points in all documents become Recommendations.

Crosswalk between ICSI Evidence Grading System and GRADE

Design of Study Current ICSI System		ICSI GRADE System
Class A:	Randomized, controlled trial	**High**, if no limitation **Moderate**, if some limitations **Low**, if serious limitations
Class B:	[observational] Cohort study	 **High,** if well done with large effect **Moderate,** if well done with effect **Low,** most studies
Class C:	[observational] Non-randomized trial with concurrent or historical controls Case-control study Population-based descriptive study Study of sensitivity and specificity of a diagnostic test	 **Low** **Low** ***Low**
* Following individual study review, may be elevated to Moderate or High depending upon study design		
Class D:	[observational] Cross-sectional study Case series Case report	 **Low**
Class M:	Meta-analysis Systematic review Decision analysis Cost-effectiveness analysis	**Meta-analysis** **Systematic Review** **Decision Analysis** **Cost-Effectiveness Analysis**
Class R:	Consensus statement Consensus report Narrative review Guideline	**Low** **Low** **Low** **Guideline**
Class X:	Medical opinion	**Low**
Class Not Assignable		**Reference**

Evidence Definitions:

High Quality Evidence = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate Quality Evidence = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low Quality Evidence = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate or any estimate of effect is very uncertain.

Supporting Literature:
In addition to evidence that is Graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a **Reference** throughout the document.

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Foreword

Scope and Target Population

This guideline describes the treatment of adults age 20 and older who are dyslipidemic.

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Aims

1. Increase the percentage of patients with (a) CHD, (b) with a CHD risk equivalent or (c) whose 10-year risk is greater than 20% who are on a statin **OR** have LDL < 70 ml/dL.
2. Improve the percentage of patients with (a) diabetes and are age 40 and over, or (b) who have a 10-year Framingham CVD risk of 10-20% who are appropriately treated for lipids.
3. Improve the percentage of patients on lipid-lowering medication who receive regular follow-up care for lipid disorder.
4. Increase the percent of patients on lipid-lowering therapy who remain on therapy.

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Clinical Highlights

- Initiate a statin with patients who have a history of CHD or CHD risk equivalent. *(Annotation #17)*
- Establish lipid goals based on risk level. *(Annotation #3)*
- Instruct patients on healthy lifestyle and adjunctive measures. *(Annotation #18)*
- Patient adherence with recommended therapy should be reinforced during scheduled follow-up. *(Annotation #20)*
- An LDL goal of less than 70 mg/dL can be considered for patients with established CAD, non-cardiac atherosclerosis or coronary artery disease equivalent.

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Implementation Recommendation Highlights

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Develop a system for assessment of target population.
2. Develop a system for results of this assessment to be used for identification of treatment options/ recommendations.
3. Develop systems that allow for consistent documentation and monitoring based on type of dyslipidemia.
4. Develop a system for follow-up assessment that identifies success in management of dyslipidemia in the primary care setting.
5. Develop a process that will remove barriers to referral to a specialist if indicated.
6. Develop a system for consistent documentation and monitoring of medication administration.
7. Develop systems for providing patient education on dyslipidemia management.
8. Consider the use of motivational interviewing as a method for addressing behavior change. Motivational interviewing is defined as a client-centered, directive counseling style for eliciting behavior change by helping patients to explore and resolve ambivalence. Rather than telling a client what changes to make, the interviewer elicits "change talk" from them, taking into account an individual's priorities and values.

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Related ICSI Scientific Documents

Guidelines

- Diagnosis and Treatment Management of Type 2 Diabetes Mellitus
- Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)
- Healthy Lifestyles
- Heart Failure in Adults
- Hypertension
- Preventive Services for Adults
- Stable Coronary Artery Disease

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Algorithm Annotations

1. Patient Has Dyslipidemia, CHD or is at High Risk for Coronary Heart Disease (CHD)

- Secondary causes of abnormal lipid levels should be considered and treated when appropriate.
- Patients with a history of non-coronary atherosclerosis (including carotid occlusive vascular disease, abdominal aortic aneurysm, or peripheral vascular disease) or who have diabetes are at high risk for CHD and are considered CHD risk equivalent.

See Appendix A, "Identified Secondary Causes and Conditions Associated with Hyperlipidemia."

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3. Calculate 10-Year Risk for CHD

Recommendation:

- Coronary heart disease risk factors should be considered in evaluating the 10-year risk in screening patients for hypercholesterolemia.

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) defines high risk as a net of two or more (CHD) risk factors, which leads to more vigorous intervention *(National Cholesterol Education Program, 2001 [Guideline])*. Identified risk factors are:

- Age 45 years or older for men; age 55 years or older for women. CHD rates are higher in the elderly than in the young, and in men more than in women of the same age.
- A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative.
- Currently smoking.
- Hypertension, defined as blood pressure greater than 140/90 mmHg (confirmed by measurement on several occasions) or current use of any antihypertensive medication.
- Low HDL-cholesterol level (less than 40 mg/dL).

Emerging non-traditional risk factors such as C-reactive protein (CRP) and total homocysteine have been shown to have some predictive values in screening vascular disease. The value of screening for these risk factors is not yet known.

A **cardiac risk calculator** based on the Framingham study can be accessed through the following Web site: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof

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 HDL-cholesterol and diabetes mellitus).

If HDL-cholesterol is 60 mg/dL or higher, one risk factor may be subtracted because high HDL-cholesterol levels decrease CHD risk. (For example, if a patient has three risk factors but his or her HDL-cholesterol level is 60 mg/dL or higher, one risk factor is subtracted, leaving a total of two risk factors.)

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Family history

The National Cholesterol Education Program (NCEP) identified family history of coronary artery disease as a risk factor 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 fourfold between the ages of 20 and 74. (Myocardial infarction leading to sudden death often occurs in these men in their 30s or 40s, and by age 50, 80 percent 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 equaled that in women at age 40 in contrast to the typical 10-year lag between men and women.

(Bild, 1993 [Low Quality Evidence]; Goldstein, 1989 [Low Quality Evidence]; Thompson, 1989 [Low Quality Evidence]; Yamamoto, 1989 [Low Quality Evidence]; Williams, 1986 [Low Quality Evidence])

High-sensitivity C-reactive protein (CRP) may have an independent value as a predictor of cardiovascular disease risk and independent value in identifying patients with normal lipids who could benefit from treatment *(Albert, 2002 [Low Quality Evidence])*.

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17. Ongoing Drug Therapy

Recommendations:

- The use of statin therapy is recommended in patients with established CHD or CHD risk equivalent (which includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes).
- Combination therapy can be considered on an individual basis.

The decision to begin drug therapy must be based on a clinical discussion with the patient in which the evidence-based outcome data, possible side effects, and cost are weighed.

No primary prevention studies have addressed pharmacologic lipid treatment in persons at low risk for CHD, and there is no evidence to support drug treatment in this population. In particular, the incidence of CHD in men under 40 and premenopausal women is very low, and drug treatment in these groups is discouraged.

Primary prevention studies of pharmacologic lipid lowering have not shown a decrease in mortality, although most studies have shown about a 30% reduction in CHD events. Study populations have consisted predominately of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated.

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Table 7: Absolute Risk Reduction and Number Needed to Treat (NNT) with Pharmacologic Lipid Lowering

10-year* risk for CHD	Events prevented/1,000 patients treated	NNT to prevent one event over five 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 four- to six-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 8: 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
* The literature supports a dose of aspirin between 81 mg and 162 mg.			

(Ridker, 2008 [High Quality Evidence]; Downs, 1998 [High Quality Evidence]; West of Scotland Coronary Prevention Group, 1998 [High Quality Evidence]; Shepherd, 1995 [High Quality Evidence]; Levy, 1993 [Low Quality Evidence]; Physicians' Health Study, 1989 [High Quality Evidence]; Frick, 1987 [High Quality Evidence]; Lipid Research Clinics Program, 1984 [High Quality Evidence])

Statin Therapy Management

Patients with risk factors for coronary heart disease but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of coronary heart disease. *[Conclusion Grade I: See Conclusion Grading Worksheet A – Annotation #17 (Risk Factors and Lipid-Lowering Therapy)] (Sever, 2003[High Quality Evidence]; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The, 2002 [Low Quality Evidence]; Heart Protection Study Collaborative Group, 2002 [High Quality Evidence]; Shepherd, 2002 [High Quality Evidence]; Pignone, 2000 [Meta-analysis]; Downs, 1998 [High Quality Evidence]; Shepherd, 1995 [High Quality Evidence]; Frick, 1987 [High Quality Evidence]; Lipid Research Clinics Program, 1984 [High Quality Evidence]).*

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Patients with a history of coronary disease (including unstable angina and acute myocardial infarction) often benefit from treatment with a statin. Studies have consistently shown a decrease in risk of death from coronary heart disease *[Conclusion Grade I: See Conclusion Grading Worksheet B – Annotation #17 (History of CHD)] (Cannon, 2004 [High Quality Evidence]; Nissen, 2004 [High Quality Evidence]; Goldberg, 1998 [Moderate Quality Evidence]; Heart Protection Collaborative Study, 2002 [A]; Shepherd, 2002 [High Quality Evidence]; LaRosa, 1999 [Meta-analysis]; LIPID Study Group, 1998 [High Quality Evidence]; Scandinavian Simvastatin Survival Study Group, 1994 [High Quality Evidence])*.

Thus, for care of patients with established CHD or CHD risk equivalent (which includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, or diabetes), the use of statin therapy is recommended.

- Bedtime or evening dose of statin is more effective (higher cholesterol synthesis).
- To maximize absorption, lovastatin needs to be taken with food, but lovastatin SR should be taken on an empty stomach.
- Use of fibrates in conjunction with thiazolidinediones may cause an major decrease in HDL levels in some patients. It may be advisable to check an HDL value one to two months after initiating this combination of medications *(Mymin, 2009 [Low Quality Evidence]; Normén, 2004 [Low Quality Evidence])*.
- Dosage adjustments should not be made more often than every four weeks after a fasting lipid panel.
- Please consult manufacturer's product label insert, PDR, etc., for full prescribing information.

Monotherapy

Reducing LDL-cholesterol (LDL-C) levels is the primary approach to lowering risk of CHD in both primary and secondary prevention. In some patients, triglycerides may be elevated along with LDL-C, so reducing triglycerides and increasing HDL-cholesterol (HDL-C) may also be desirable. Selection of drug therapy is dependent on several factors including lipoprotein levels and percent reduction needed to attain goal; concurrent drug therapies that could increase the risk of side effects occurring with specific lipid-lowering drugs; and presence of other medical disorders that may affect drug metabolism, increase risk of side effects or be adversely affected by a specific lipid-lowering drug.

Statins are the drugs of choice for lowering LDL-cholesterol, and aggressive treatment with statins should be pursued. Seven statins are available: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, pitavastatin.

Statins also have a modest effect on reducing triglycerides and increasing HDL-cholesterol. Several studies with clinical endpoints support use of statins in primary and secondary prevention.

If a patient is intolerant to a statin, clinicians are encouraged to have the patient try the other statins before ruling them all out. This is especially important in secondary prevention. In the Heart Protection Study, there was no significant difference between the simvastatin 40 mg and placebo groups, in the number of patients with elevations of serum transaminases or unexplained muscle aches or weakness.

The secondary-prevention VA-HIT trial – utilizing gemfibrozil 600 mg twice daily in patients with normal LDL-cholesterol, low HDL-cholesterol and triglycerides less than or equal to 300 mg/dL – showed a 22% reduction in the combined incidence of CHD death and non-fatal MI. Almost 50% of this study population had evidence of metabolic syndrome or diabetes, and they showed the greatest benefit. Fibric acids have a variable effect on LDL-cholesterol. Fenofibrate may be more effective at lowering LDL-cholesterol than gemfibrozil. They are usually reserved for hypertriglyceridemia or for an isolated low HDL-cholesterol.

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In the Coronary Drug Project, a large-scale secondary prevention trial, niacin 3 grams/day reduced mortality 11% over placebo. Niacin has a favorable effect on LDL-cholesterol, triglycerides and HDL-cholesterol and is good for mixed hyperlipidemia. Niacin has a greater effect on HDL-cholesterol than other currently available lipid medications. To improve tolerability and compliance, doses of niacin need to be titrated.

Ezetimibe mainly reduces LDL-cholesterol, with minimal effect on triglycerides or HDL-cholesterol. No clinical outcome studies are currently available, but ezetimibe appears useful for reducing LDL-cholesterol in patients who cannot take a statin and in combination with other LDL-reducing medications.

In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), participants were to take cholestyramine 12 gm twice daily, but compliance varied. A linear relationship was seen with reduction in CHD risk corresponding to cholestyramine dose and reduction in LDL-cholesterol. A 19% reduction in risk of fatal and non-fatal MI was seen in patients taking cholestyramine 24 gm/day. The bile-acid sequestrants reduce LDL-cholesterol, but they can increase triglycerides, so should only be used as monotherapy in patients with baseline triglycerides less than or equal to 200 mg/dL.

Safety Considerations in Prescribing Statins in Primary Care Settings

DO

- ☐ Check baseline renal function prior to initiating statin therapy.
- ☐ Check ALT or AST levels prior to prescribing a statin and after any planned increase in statin dose.
- ☐ Consider the potential for drug-drug interactions when prescribing statins. Vitamin E intake may reduce the benefit of statins.
- ☐ Be alert for patient characteristics that may increase the risk for myopathy during statin therapy, such as advanced age (particularly elderly women), renal or liver impairment, diabetes with evidence of hepatic fatty changes, hypothyroidism, drugs of abuse (amphetamines, phencyclidine, heroin, cocaine), surgery, trauma, ischemia-reperfusion, debilitated status, excessive alcohol intake, heavy exercise.
- ☐ Provide patient education regarding recognition and reporting of symptoms of myopathy during statin therapy.
- ☐ Counsel patients to discontinue statin therapy during a short course of a macrolide or ketolide antibiotic (e.g., azithromycin, clarithromycin, erythromycin or telithromycin).
- ☐ Suspect myopathy when a statin-treated patient complains of unexplained, generalized muscle pain, tenderness or weakness. Joint pain, nocturnal leg cramps or localized pain are not symptoms of myopathy.
- ☐ Check CK levels when a patient reports symptoms of myopathy.
- ☐ If CK levels are abnormal and less than five times upper limit of normal, repeat measurement in one week.
- ☐ If CK levels are elevated to five times upper limit of normal or greater, discontinue statin therapy and monitor serum CK levels.
- ☐ Assess for signs of dehydration or renal compromise in patients with myopathy.
- ☐ When adding a statin to the regimen of a patient already receiving a fibrate, initiate at the lowest starting dose of statin.
- ☐ Consider the differences in pharmacokinetic profiles among statins, particularly in patients requiring long-term therapy with drugs that are CYP3A4 substrates, inhibitors or both.

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DON'T

- ☐ Prescribe statin-fibrate combination therapy in patients with the following conditions: impaired liver or renal function (creatinine level greater than 2.0 mg/dL), cyclosporine or tacrolimus therapy, long-term macrolide antibiotic therapy or azole antifungal therapy, advanced age (greater than 70 years), skeletal muscle conditions.
- ☐ Prescribe high-dose statin therapy for patients with renal insufficiency, or in combination with fibrates or cyclosporine.
- ☐ Vitamin E may reduce the benefit of statins or of statin-niacin combination therapy. Vitamin E does not appear to reduce the risk of major cardiovascular events.
- ☐ Use of fibrates in conjunction with thiazolidinediones may cause an major decrease in HDL levels in some patients. It may be advisable to check an HDL value 1-2 months after initiating this combination of medications.

(Ballantyne, 2003 [Low Quality Evidence]; Heart Protection Study Collaborative Group, 2002 [High Quality Evidence])

Statin Safety and the Muscle

Myalgia

Myalgia is defined as pain or soreness and/or weakness in skeletal muscles in the absence of serum creatinine elevation. Symptoms of myalgia are quite variable and include cramping, pain, aches, tenderness, soreness, stiffness, heaviness, and weakness either at rest or only during physical exertion. Muscle cramping at night only is not likely statin related.

Myopathy

Myopathy is defined as complaints of myalgia, plus elevation in serum CK (creatinine kinase) greater than 10 times the upper limit of normal (ULN).

Rhabdomyolysis

Rhabdomyolysis is defined as CK elevation > 10,000 U/L, in accord with the definition currently used by the FDA, regardless of whether the patient has experienced a change in renal function, because such a CK level places the patient at high risk for acute renal failure. A second component is CK > 10X the ULN with worsening renal function and/or a requirement for medical intervention with intravenous hydration therapy, along with myalgia.

Incidence

Incidence of muscle symptoms or signs (CK = creatinine kinase elevations) is the most prevalent and important adverse effect of statin therapy. The occurrence of serious muscle toxicity with currently marketed statins is rare.

Myopathy occurs in five patients per 100,000 person-years (in clinical trials, the rate is 1.5-3.0%, most often without CK elevation and at an equivalent rate in patients given placebo). In the practice setting, the range is 0.3-33%. The higher rate may occur partly because statin-intolerant patients and high-risk patients are likely to be excluded from clinical trials. In most patients this occurs in the first six months; however, it could be years before myopathy appears.

Rhabdomyolysis occurs in 1.6 patients per 100,000 person-years.

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Recommendations regarding statin safety and muscle symptoms

1. Muscle symptoms or increased CK due to statin therapy is rare. Rule out other causes including increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dematomyositis, polymyalgia rheumatica alcohol abuse and drug abuse (cocaine, amphetamines, heroin or PCP).

2. Baseline pretreatment CK levels are not necessary; however, they can be considered in high-risk patients. Risk factors for muscle toxicity include advanced age and frailty, small body frame, deteriorating renal function, infection, untreated hypothyroidism, interacting drugs, perioperative patients and alcohol abuse.

3. It is not necessary to measure CK levels in asymptomatic patients during treatment. Marked increases are rare and usually related to physical exertion or other causes.

4. Patient education regarding the muscle symptoms to watch for and report is essential for all patients taking statins.

5. Measure CK levels in symptomatic patients to help decide whether to continue therapy or alter dose.

6. Discontinue statin in patients with intolerable muscle symptoms with or without CK elevation when other etiologies are ruled out.

   Once asymptomatic, resume the same or different statin at the same or lower dose. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.

   Patient counseling regarding intensification of therapeutic lifestyle changes (reduced intake of trans fat, saturated fats and cholesterol, increased physical activity, and weight control) should be an integral part of management in all patients with statin-associated intolerable muscle symptoms.

7. If patient is asymptomatic or has tolerable muscle complaints but CK less than 10x the ULN, continue statin at same or lower dose while monitoring symptoms.

8. If patient develops rhabdomyolysis (CK greater than 10,000 IU/L or CK greater than 10x the ULN with elevation in serum creatinine, OR requiring IV hydration therapy), stop statin. Hospitalization may be required. Once recovered, the risk vs. benefit of therapy should be carefully reconsidered.

(Jacobson, 2008 [Low Quality Evidence]; McKenney, 2006 [Low Quality Evidence])

Patients Unable to Use Statin Therapy

Myalgias are common in patients with statins; however, the cause and effect relationship is unclear. We recommend trying other statins or lowering the dose. Consider a 10- to 14-day vacation from statins and see if the myaligia symptoms abate as a diagnostic maneuver. The evidence is inconclusive at this time for treating myalgia with vitamin D and coenzyme Q.

If patients are intolerant to a statin, clinicians are encouraged to have the patient try the other statins in reduced doses before ruling out all statins.

If patients are unable to take a statin, then bile-acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), cholestyramine 24 grams/day showed a 10% reduction in risk of fatal and non-fatal MI. Adherence in this study varied, but a linear relationship was seen with reduction in CHD risk corresponding to cholestyramine dose and reduction in LDL-cholesterol *(Lipid Research Clinics Program, 1984 [High Quality Evidence])*.

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In the Coronary Drug Project, niacin 3 grams/day reduced mortality 11% over placebo. There are also studies with angiographic endpoints that showed benefits of bile-acid sequestrants alone and in combination with niacin *(Coronary Drug Project Research Group, The, 1975 [Moderate Quality Evidence])*.

The VA-HIT trial, utilizing gemfibrozil 600 mg twice daily, showed a 22% reduction in the combined incidence of CHD death and non-fatal MI.

The ENHANCE study evaluated simvastatin with and without ezetimibe on carotid intima-media thickness in patients with familial hypercholesterolemia and did not find a significant difference after 24 months in this surrogate endpoint, though the LDL was significantly lower with combination therapy *(Kastelein, 2008 [Moderate Quality Evidence])*.

The SEAS study, while not showing a difference in aortic stenosis progression with combination therapy, did show a significant reduction in the secondary endpoint of non-fatal ischemic events in the simvastatin/ezetimibe-treated group compared to placebo after 52 months *(Rossebø, 2008 [Moderate Quality Evidence])*.

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 is a major contraindication. 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 *(Antiplatelet Trialists' Collaboration, 1994 [Meta-analysis])*.

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 *(Eidelman, 2003 [Meta-analysis]; Hayden, 2002 [Meta-analysis]; Nowak, 2003 [Low Quality Evidence])*.

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 *(Manson, 1991 [Low Quality Evidence]; Peto, 1988 [Moderate Quality Evidence])*.

Other Medications

Niacin

Many crystalline (immediate-release) and SR (sustained release) preparations are available over the counter. The ER (extended-release) preparation niacin is a prescription drug.

Efficacy

- In the Coronary Drug Project, a large-scale secondary prevention trial, niacin 3 grams/day reduced mortality 11% over placebo *(Canner, 1986 [High Quality Evidence])*.
- Exerts favorable effects on all lipids and lipoproteins, good for mixed hyperlipidemia.
- Crystalline niacin reduces triglycerides 20-40%, increases HDL-cholesterol 15-35%, and decreases LDL-cholesterol 6-25%.

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- Extended-release niacin reduces triglycerides 11-35%, increases HDL-cholesterol 15-26%, and decreases LDL-cholesterol 9-17%.
- Sustained-release niacin reduces triglycerides 10-40%, increases HDL-cholesterol 5-15% and decreases LDL-cholesterol 6-50% (but this latter effect may be due to hepatic toxicity).

Safety

- Long-term use of niacin is usually limited for many patients due to side effects. For this reason, Adult Treatment Panel III (ATP III) guideline recommends its use be reserved for those at highest short-term risk, i.e., those with CHD, CHD risk equivalents or 2+ risk factors with 10-year risk of CHD of 10-20% or higher. Use of niacin for long-term prevention of CHD in patients with a 10-year risk less than 10% is not well established and should be used more cautiously. For example, it is not known whether long-term use of niacin for lower-risk patients with isolated low HDL-cholesterol is beneficial.
- Flushing and pruritis 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, and appears dose related (most occurring with doses of 2 grams/day or higher). Hepatoxicity has occurred when patients switched from crystalline niacin to a 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 three 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 two weeks and lab abnormalities should resolve within one to four months. In a long-term (59 weeks) study of niacin in an extended-release, median dose of 2 grams/day, less than 1 percent of participants with normal serum transaminases at baseline had elevations greater than three times the upper limit of normal.
- GI complaints (nausea and abdominal pain) are more common with SR niacin; this can be minimized by taking with meals. Activation of peptic ulcer has occurred, so history of peptic ulcer is a relative contraindication.
- Uric acid may be slightly increased. Rarely, this may lead to acute gouty arthritis.
- Serum glucose concentrations may be increased with higher doses (greater than 3 grams/day), especially in patients with NIDDM or glucose intolerance. Glucose monitoring is critical for use of niacin in these patients. Some adjustment in their hypoglycemic therapy may be needed. However, data from the Arterial Disease Multiple Intervention Trial (ADMIT) indicate that niacin can usually be safely used in patients with diabetes. Niacin use in patients with diabetes resulted in a small but significant change in HbA1c levels of 0.3% versus placebo.
- 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

Please consult drug reference for full prescribing information.

- Slow dosage titration allows patient to develop tolerance to flushing and pruritis.
- Crystalline niacin can be taken twice a day. Avoiding hot beverages and alcohol at time of dosing is recommended. A single brand should be used to prevent the inadvertent switch to an SR form.

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- SR niacin should also be titrated. Further increase should be based on response and tolerance. A single brand should be used because of significant variability in bioavailability.
- Extended-release niacin should be taken at bedtime with a low-fat snack. Further titration should be based on patient response and tolerance. Women may respond at lower doses.

Lovastatin and Niacin

Efficacy

Substantial effects on all lipid parameters (dose dependent) with decreases in LDL-cholesterol of 30-42%, increases in HDL-cholesterol 20-30%, and decreases in triglycerides 32-44%.

Dosing

- Niacin plus lovastatin should be taken at bedtime with a low-fat snack.
- Patients already receiving a stable dose of extended-release niacin may be switched to an equivalent dose of niacin plus lovastatin. Patients receiving a form of niacin other than ER niacin should be started on ER niacin with the recommended dosage titration.
- Patients already receiving a stable dose of lovastatin may be titrated with ER niacin and then switched to niacin plus lovastatin once a stable dose of ER niacin has been reached.
- To reduce flushing, patients may pretreat with an aspirin approximately 30 minutes prior to taking the niacin plus lovastatin.
- If niacin plus lovastatin therapy is interrupted for an extended period (greater than seven days), therapy should be retitrated, starting with the lowest dose.

(McKenney, 2001 [Reference]; National Cholesterol Education Program, 2001 [Guideline]; Elam, 2000 [Moderate Quality Evidence]; Canner, 1986 [High Quality Evidence])

Gemfibrozil, Fenofibrate and Fenofibrate Micronized

Efficacy

- Prior to initiating a fibric acid, lifestyle therapies should be intensified for moderately elevated triglycerides. These include reduction of liquid sugar, all refined starches and saturated fat; increase moderate intensity exercise; and weight reduction.
- With fibric acids, triglycerides are reduced 30-50%, HDL-cholesterol increases 10-20%. Total cholesterol is only modestly reduced 5-20% 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 statins (dependent on baseline triglyceride level).
- Good for severe hypertrigylceridemia (triglycerides > 500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate) when patient has an abnormal lipid triad of depressed HDL-cholesterol, elevated LDL-cholesterol and elevated triglycerides. May be particularly useful in diabetics with mixed hyperlipidemia and for patients with dysbetalipoproteinemia. The combination of simvastatin and fenofibrates did not reduce fatal or non-fatal cardiovascular events as compared to simvastatin alone in patients with type 2 diabetes in the ACCORD lipid trial.
- The VA-HIT trial utilizing gemfibrozil showed a 22% reduction in CHD death and non-fatal MI in patients with documented CHD and low HDL-cholesterol as their primary lipid abnormality.

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Safety

- Myositis has occurred rarely in patients on monotherapy with fibric acids. Risk of myopathy and possibly rhabdomyolysis appears increased when taken with statins, particularly with gemfibrozil in combination with statins.

  There may be a potential difference in risk of myopathy between gemfibrozil and fenofibrate when combined with statins. Gemfibrozil is contraindicated in coordination with simvastatin. Combination therapy with lovastatin and rosuvastatin should be avoided. Fenofibrate had no effect on plasma levels of rosuvastatin. Generally, fenofibrate may be used in combination with statins if the benefits outweigh the risk.

- Cholelithiasis and cholecystitis can occur (0.3-1% incidence) due to increased cholesterol excreted in the bile. Fibric acids are contraindicated in patients with pre-existing gallbladder disease.
- Use with caution in patients with a history of liver disease. Fibric acids are contraindicated in patients with hepatic impairment, including primary biliary cirrhosis, or in severe renal impairment.
- Hematologic adverse reactions are rare.
- Warfarin's anticoagulant effect may be potentiated; INR should be monitored closely and the initiation of a fibric acid, with dose changes, and with discontinuing a fibric acid.

Dosing

Please consult manufacturer's product labeling insert for specific dosing.

Gemfibrozil

- 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.

Fenofibrate

- In the elderly and in patients with impaired renal function, therapy should be initiated with 48 mg per day, increasing only after reviewing effect on lipids and renal function.

Fenofibrate micronized

- In the elderly and in patients with impaired renal function, therapy should be initiated with 67 mg per day, increasing only after reviewing effect on lipids and renal function.

Fenofibric acid

- In the elderly and in patients with impaired renal function, therapy should be initiated with 45 mg per day, increasing only after reviewing effect on lipids and renal function.

Ezetimibe

Efficacy

- Long-term effects on cardiovascular morbidity and mortality are unknown.
- LDL-cholesterol lowered about 18%.
- Additive LDL-cholesterol reduction when used in combination with statins.
- FDA approved Ezetimibe with fenofibrate.

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Safety

- Short-term tolerability is similar to placebo. Long-term safety is unknown.
- Not recommended for use in patients with moderate to severe hepatic impairment based on Child-Pugh score. The AUC of ezetimibe increased fourfold in patients with moderate hepatic impairment (Child-Pugh score 7 to 9).
- Co-administration with cyclosporine increased ezetimibe blood level 12-fold in one renal transplant patient. Patients on cyclosporine and ezetimibe should be monitored carefully.
- Cholestyramine co-administration decreased the mean AUC of total ezetimibe by 55%. Ezetimibe should be given two hours before or four hours after bile-acid sequestrants.

Dosing

Please consult manufacturer's product labeling insert.

(Dujovne, 2002 [Low Quality Evidence]; Gagne, 2002 [Low Quality Evidence]; McKenney, 2002 [Low Quality Evidence])

Bile-Acid Sequestrants

Efficacy

- In the Lipid Research Clinics Coronary Primary Prevention Trial (LRD-CPPT), a 19% reduction in risk of fatal and non-fatal MI was seen in patients taking cholestyramine 24 g/day. In those patients who didn't take 24 g/day, a linear relationship was seen with reduction in CH risk corresponding to cholestyramine dose and reduction in LDL-cholesterol *(Lipid Research Clinics Program, 1984 [High Quality Evidence])*.
- LDL-cholesterol lowered 15-30% (dose dependent).
- Triglycerides may increase 15% – should not be used as sole therapy if triglycerides are greater than 200 mg/dL and should not be used at all if triglycerides are greater than 400 mg/dL.
- Effects apparent within one week and maximum at two to three weeks.
- Useful for patients with moderately elevated LDL-cholesterol.
- Good for combination therapy.
- LDL-cholesterol reductions enhanced with low doses.
- Most potent with statin.

Safety

- Not systemically absorbed – side effects limited to GI tract.
- Patients who have phenylketonuria (PKU) 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 one hour before the sequestrant or four 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 reduced; thus, the net effect on coagulation is hard to predict. Colestipol

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and colesevelam have been reported not to interact with warfarin, and thus may be safer agents. Separating these agents by at least four hours from warfarin and close monitoring of INR is 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.

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

(McKenney, 2001 [Reference]); National Cholesterol Education Program, 2001 [Guideline]; Lipid Research Clinics Program, 1984 [High Quality Evidence])

Combination Therapy

As national lipid guidelines have focused on specific LDL goals, it has become common practice to adjust medication therapy, including using combinations of medications, to achieve these goals. Common combinations include statin-fibrate, statin-niacin and statin-ezetimibe.

A systematic review of combination therapy for dyslipidemia concluded that the limited evidence available suggests that combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy.

Combination therapy can be considered on an individual basis, but the additional cost, complexity and risk for side effects argue against routine use until further studies indicate what groups of patients might benefit *(Sharma, 2009 [Systematic Review])*.

Statin-Fibrate

A fibrate (gemfibrozil or fenofibrate) is commonly added to a statin, which results in enhanced LDL lowering as well as a higher incidence of myopathy. Only one randomized controlled trial to date has evaluated the clinical benefit of this combination on vascular events.

In the lipid arm of the ACCORD study, people with type 2 diabetics were randomized to simvastatin plus fenofibrate versus simvastatin alone. No benefit in the combined vascular outcome or individual clinical outcome was seen.

Statin-Niacin

No published clinical trial to date has evaluated the clinical benefit of this combination on vascular events. Preliminary results from AIM-HIGH, a large NHLBI-funded clinical trial of simvastatin-extended release niacin versus simvastatin alone, showed no benefit and a small increased risk for stroke. This study is scheduled to be published in 2012.

Statin-Ezetimibe

The addition of ezetimibe to a statin significantly improves LDL-cholesterol over either agent alone. To date no large clinical trials have been completed evaluating the effect of this combination versus statin alone on clinical vascular endpoints.

Two recent trials cast doubt on the cardiovascular benefit of ezetimibe. In ENHANCE, the combination of ezetimibe-simvastatin versus simvastatin alone failed to show any benefit in carotid intimal thickness (CIMT) despite greater LDL lowering. In ARBITER-6 ezetimibe was inferior to niacin in reducing CIMT, causing the trial to be halted after 14 months. Neither study reported data on vascular events *(Taylor, 2009 [High Quality Evidence])*.

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Cholesterylester transfer protein (CETP) inhibitors

There are negative trials of CETP inhibitors and statins in combination on both CIMT and clinical endpoints. This drug class is not currently clinically available *(Cannon, 2010 [High Quality Evidence]; Barter, 2007 [High Quality Evidence])*.

Bile acid or fish oils

No randomized control trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile acid sequestrants used in combination therapy.

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18. Initiate Lifestyle Modifications

Recommendations:

- Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss.
- Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-cholesterol level is lowered to the target range.
- A diet low in saturated and trans fats, and high in soluble fiber, with consideration given to adding 2 grams of plant sterol/stanol is recommended.
- Vitamin E supplements should not be used.
- Light to moderate consumption of alcohol (no more than one drink per day for women or two drinks per day for men) may lower coronary heart disease rates.
- Omega-3 fatty acids should be recommended in patients with dyslipidemia (1 gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).

Diet and exercise are the cornerstones of treatment for asymptomatic patients with dyslipidemia *(Stefanick, 1998 [High Quality Evidence])*. Patients with an elevated LDL-cholesterol level should begin the Therapeutic Lifestyle Changes program and an individualized program of regular exercise. A diet low in saturated and trans fats, and high in soluble fiber, with consideration given to adding 2 grams of plant sterol/stanol is recommended.

- Patients who are overweight should be advised to reduce their calorie intake to achieve weight loss.
- Patients should follow the diet and exercise program for a reasonable amount of time to determine whether their LDL-cholesterol level is lowered to the target range. For many asymptomatic patients, a diet and exercise program is sufficient.

Lifestyle modifications include diet; aerobic exercise; weight management; smoking cessation; evaluation of alcohol consumption; and a nutritional supplement containing sitostanol ester, a saturated derivative of a plant seed oil (EPA-DHA). The addition of 2 grams of plant sterol/stanol can effectively lower LDL. To avoid unintended toxic effects from vitamins, patients should be cautioned not to exceed recommended doses.

Vitamin E supplements should not be used. Studies have shown no benefit in preventing clinical outcomes, and smaller studies suggest a blunting of the benefit from antidyslipidemic medications on HDL-C and angiographic progression of vascular disease *(Brown, 2001 [High Quality Evidence]; Cheung, 2001 [Low Quality Evidence])*.

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Other management strategies – therapeutic lifestyle change (TLC) may include the following.

Diet

The evidence in the literature and the NCEP Adult Treatment Panel Consensus Position suggest that adults with elevated lipids, CHD or CHD risk equivalent should be following the ATP III Therapeutic Lifestyle Changes (TLC) diet or something more aggressive.

The TLC diet lowers saturated fat to less than 7% of calories – avoiding trans fat, limiting dietary cholesterol to less than 200 mg/day – and adds dietary options such as 2 grams/day of plant stanols/sterols and at least 5-10 grams/day of viscous water-soluble fiber to enhance LDL lowering, and has an increased emphasis on weight management and physical activity.

It is desirable to have the assessment and education for these individuals carried out by a registered dietitian when possible *(National Cholesterol Education Program, 2002 [Guideline]; Stefanick, 1998 [High Quality Evidence]; Schuler, 1992 [High Quality Evidence]; Blankenhorn, 1990 [Low Quality Evidence]; LaRosa, 1999 [Low Quality Evidence]; Ornish, 1990 [High Quality Evidence]; Arntzenius, 1985 [Low Quality Evidence])*.

Aerobic 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 *(Stefanick, 1998 [High Quality Evidence]; Berg, 1994 [Low Quality Evidence]; Pronk, 1993 [Low Quality Evidence])*.

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 *(Williams, 1997 [Low Quality Evidence])*.

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 also the timing of the studies relative to the menstrual cycle affects 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 *(Taylor, 1993 [Low Quality Evidence])*.

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%.

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Weight management should be considered an important component of interventions intended to maximize lipid management and reduce risk of cardiovascular disease *(Denke, 1999 [Low Quality Evidence])*.

Smoking cessation

As well as being an independent risk factor for the development of CHD, 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 CHD risk *(McBride, 1992 [Low Quality Evidence]; Billimoria, 1975 [Low Quality Evidence])*.

Evaluation of alcohol consumption

Light to moderate consumption of alcohol 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 12 ounces of regular beer, 5 ounces of wine or 1.5 ounce of distilled spirits (80 proof).

Alcohol may help protect against heart disease by raising levels of HDL-cholesterol. Risks for CHD, hypertriglyceridemia, pancreatitis, hypertension and cardiomyopathy may increase in women who consume more than one drink per day and for men who consume more than two drinks per day.

Alcohol consumption should be avoided by women who are pregnant or trying to conceive, individuals operating a motor vehicle or other equipment, individuals taking prescription or non-prescription medication, recovering alcoholics, and those with a history of chemical dependency. Most authorities do not recommend initiation of alcohol consumption for non-drinkers with lipid disorders *(Rimm, 1996 [Low Quality Evidence]; Jackson, 1993 [Low Quality Evidence]; Criqui, 1990 [Low Quality Evidence]; Klatsky, 1981 [Low Quality Evidence])*.

Sterol and stanol ester nutritional supplement

Clinical studies in men and women with Type 2 diabetes mellitus, hyperlipidemia, and known CHD have shown that sitostanol ester, a saturated derivative of a plant sterol, can lower total cholesterol 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 simvastatin. Caution should be exercised in patients on medications because of limited information about drug interactions *(Grundy, 2005 [Low Quality Evidence]; Gylling, 1997 [Moderate Quality Evidence]; Miettinen, 1995 [Low Quality Evidence]; Gylling, 1994 [Low Quality Evidence]; Vanhanen, 1993 [Moderate Quality Evidence])*.

Fish oil (EPA-DHA)

Omega-3 fats are found in some fatty fish and in some plant sources, such as walnuts, canola and soybean oils, and flaxseed. They do not affect LDL levels but may help protect the heart in other ways. In some studies, people who ate fish had a reduced death rate from heart disease. It is possible that this is related to the effects of omega-3 fats, which may help prevent blood clots from forming and inflammation from affecting artery walls. Omega-3 fats also may reduce the risk for heart rhythm problems and, at high doses, reduce triglyceride levels. Studies have suggested that omega-3 fats reduce the risk for heart attack and

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death from heart disease for those who already have heart disease *(National Cholesterol Education Program, 2001 [Guideline])*.

The recommended daily amount of omega-3 fatty acids in patients with dyslipidemia is 1 gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish. Studies show that 1.5 grams of ALA or more per day from plant sources is associated with a 40-65% reduced risk of death from cardiac events. The amounts of omega-3 fatty acids in various foods are found in the following table, "Omega-3 Fatty Acids." Plant-based sources of omega-3 fatty acids would be ground flaxseed, flaxseed oil, walnut oil, canola oil and soybean oil. Fish meals can be difficult for patients to maintain, and there are issues of potential environmental contaminants including mercury, PCBs, dioxin and others. Because of this, capsule supplements may be preferred, although there is no uniformity of EPA/DHA content or purity. Patients should consult their health providers or nutritionists regarding this issue *(Kris-Etherton, 2002 [Low Quality Evidence])*.

Dietary and non-dietary intake of n-3 polyunsaturated fatty acids may reduce overall mortality and sudden death in patients with stable CAD *(Bucher, 2002 [Meta-analysis])*.

Omega-3 fatty acids

Omega-3 fatty acids are found in fish oil and in some vegetable oils, nuts, seeds and soy. You can get omega-3 fatty acids from some foods or from over-the-counter and prescription supplements. Fish oil contains two important omega-3 fatty acids: EPA (eicosapentanoic acid) and DHA (docosahexanoic acid). Plant sources provide ALA (alpha-linolenic acid). Studies of EPA and DHA, suggest that:

- doses of up to 1 gram per day reduce risk of heart attacks in high-risk patients, and
- doses of up to 3 grams per day lower serum triglyceride levels.

Tips for getting more omega-3 fatty acids

- Use vegetable oils that are high in omega-3 fatty acids. Examples are canola oil, soybean oil, flaxseed oil and walnut oil.
- Select fish from the following table and eat at least 7 ounces per week. Prepare fish by grilling, baking, broiling or poaching.
- Add walnuts or ground flaxseed to cereals, yogurt and salads. Whole flaxseeds will not work as well – they simply pass through the body undigested.
- Substitute ground flaxseed for fat (butter or oil) in baked products. Try using 3 tablespoons of ground flaxseed instead of 1 tablespoon of oil.
- Snack on edamame (steamed soybeans, sold fresh or frozen).
- Omega-3 fatty acid supplements should be refrigerated and eaten with food. This will reduce the possibility of a mild fishy aftertaste.

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Fish Sources of Omega-3 Fatty Acids
Serving Size: 3.5 ounces, cooked

Safety Note: Pregnant and nursing women and young children should avoid shark, swordfish, king mackerel and tilefish. These contain high levels of mercury. Albacore tuna has more mercury than canned light tuna. Albacore tuna should be limited to no more than 6 ounces per week.

Fish	EPA + DHA content (g/Serving)	Calories/Serving
Farmed salmon	2.15	206
Atlantic herring	2.01	203
Wild salmon	1.84	182
Sardines, canned in tomato sauce	1.35	186
Atlantic mackerel	1.20	262
Farmed rainbow trout	1.15	169
Wild rainbow trout	0.980	150
White tuna, canned in water	0.860	128
Halibut	0.470	140
Shrimp	0.320	99
Fresh yellowfin tuna	0.280	139
Light tuna, canned in water	0.270	116
Atlantic cod	0.160	105

Plant Sources of Omega-3 Fatty Acids

Food	Amount	Omega-3 fatty acids (g/serving)	Fiber (g/serving)	Calories/Serving
Flaxseed oil	1 tablespoon	7.249	n/a	120
Ground flaxseed	1 tablespoon	1.597	1.9	37
English walnuts	1 tablespoon (7 halves)	1.290	0.9	93
Soy oil	1 tablespoon	0.940	n/a	120
Canola oil	1 tablespoon	0.862	n/a	120
Tofu, raw, firm	1/2 cup	0.733	2.9	183
Green soybeans, cooked	1/2 cup	0.319	3.8	127
Navy beans, cooked	1 cup	0.213	19.1	255
Wheat germ	1/4 cup	0.208	3.8	104
Avocado, raw	1 cup sliced	0.182	9.8	234
Black walnuts	1 tablespoon (7 halves)	0.155	0.5	48
Kidney beans, canned	1 cup	0.125	19.1	210
Baked beans, canned	1 cup	0.104	10.4	239

2006 American Dietetic Association Disorders of Lipid Metabolism Tool Kit.
Sources: www.nal.usda.gov/fnic/foodcomp/search, www.nutritiondata.com, U.S. Food and Drug Administration. *What you need to know about mercury in fish and shellfish*. FDA/CFSAN Consumer Advisory EPA-823-R-04-005. March 2004.
http://www.fda.gov/downloads/Food/ResourcesForYou/Consumers/UCM182158.pdf

See the ICSI Stable Coronary Artery Disease guideline for more information.

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19. Laboratory Monitoring in 3-12 Months

Obtain a fasting lipid panel or lipid panel with direct LDL and transaminase as indicated (or see drug insert or drug companion) *(Mckenney, 2001 [Reference])*.

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20. Ongoing Care with Yearly Follow-Up

Adherence and Lifestyle Modifications

Poor adherence can limit the effectiveness of therapies. In asymptomatic conditions such as hyperlipidemia, this can be especially problematic. Long-term adherence to drug therapy for chronic conditions is estimated to be only about 50%. Adherence 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 adherence are number of drugs, complexity and frequency of drug administration, adverse side effects, asymptomatic conditions, cost and psychosocial problems.

The first step is to identify potential non-adherence. Some signs of non-adherence include missed visits, inability to reach by phone, medication refill history, 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 adherence 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 lifelong 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.

Assess the patient's knowledge of his/her medication and medical condition:

"Can you explain why you are taking this medication?"

"How do you take your medication (with food or on an empty stomach; in the morning or the evening)?"

Assess the patient's medication administration process:

"Many patients have difficulty remembering to take their medication. From what you recall, have you ever had trouble remembering to take your medications?"

"How do you remember to take your medication each day? Do you use a reminder device such as a pillbox or alarm?"

Assess the patient's barriers to adherence:

"What is the most difficult task for you in reaching your cholesterol goal?"

"Are you comfortable with your ability to follow the treatment plan that we have designed for you?"

"Are you experiencing any unusual symptoms that you fear may be due to your medication?"

"Is the cost of your medications interfering with your treatment?"

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For more information on adherence please refer to Appendix B, "NCEP Recommendations on Strategies to Improve Adherence."

(Riesen, 2004 [Low Quality Evidence]; Nichols-English, 2000 [Low Quality Evidence]; Insull, 1997 [Low Quality Evidence])

Management of Elevated Triglycerides and/or Low HDL

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 and 499 mg/dL and occasionally between 500 and 1,000 mg/dL. If triglycerides are greater than 500, triglyceride-lowering drugs become first-line therapy. The clinician may wish to consider the use of statin therapy. This is especially true 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. Treatment can also be supported in diabetics with or without low HDL-cholesterol.

Patients with very high triglycerides (greater than 1,000 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 less than 1,000 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 and/or oral contraceptives), the National Institutes of Health recommend dietary measures for initial management of borderline and high triglycerides (please see Appendix A, "Identified Secondary Causes and Conditions Associated with Hyperlipidemia," for additional secondary causes). 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.

Uncontrolled glucose levels in patients with diabetes mellitus contribute to hypertriglyceridemia. Glucose levels in patients with diabetes should be under control to bring triglyceride levels under control.

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 minus HDL-cholesterol minus (triglyceride divided by 5).

Non-HDL-cholesterol becomes a secondary target when triglycerides are 200-499. The non-HDL target is 30 mg/dL higher than the LDL target.

Non-HDL-cholesterol = total-cholesterol minus HDL-cholesterol.

(McKenney, 2001 [Reference]; National Cholesterol Education Program, 2001 [Guideline]; Grundy, 1998 [Low Quality Evidence])

Laboratory Monitoring

Coronary risk status and a lipid profile should be obtained at least annually *(McKenney, 2001 [Reference]; National Cholesterol Education Program, 2001 [Guideline])*.

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This section provides resources, strategies and measurement for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Aims and Measures
  - Measurement Specifications
- Implementation Recommendations
- Resources
- Resources Table

Aims and Measures

1. Increase the percentage of patients with (a) CHD, (b) with a CHD risk equivalent or (c) whose 10-year risk is greater than 20% who are on a statin **OR** have LDL < 70 ml/dL.

   Measure for accomplishing this aim:

   a. Percentage of patients with (a) CHD, (b) with a CHD risk equivalent or (c) whose 10-year risk is greater than 20% who are on a statin **OR** have LDL < 70 mg/dL.

2. Improve the percentage of patients with (a) diabetes and are age 40 and over, or (b) who have a 10-year Framingham CVD risk of 10-20% who are appropriately treated for lipids.

   Measure for accomplishing this aim:

   a. Percentage of patients with (a) diabetes and age >= 40 years, or (b) who have 10-year Framingham CVD whose 10-year risk is greater than 20% who are on a statin **OR** who have an LDL < 100 mg/dL.

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

   Measures of accomplishing this aim:

   a. Percentage of patients on lipid-lowering medication who have a fasting lipid panel within 24 months.

   b. Of visits in the last month for patients with CHD or CHD risk equivalent who are on lipid-lowering medication, but with most recent LDL > 100 mg/dL, the percentage who are on a maximal recommended dose of a potent statin (such as simvastatin, pitavistatin, rosuvastatin or atorvastatin).

4. Increase the percent of patients on lipid-lowering therapy who remain on therapy.

   Measure for accomplishing this aim:

   a. Percentage of patients who initiate lipid-lowering pharmacotherapy who remain on any lipid-lowering pharmacotherapy 12 months later.

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Measurement Specifications

Measurement #1a

Percentage of patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20%, who are on a statin **OR** have LDL < 70 mg/dL.

Population Definition

Patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20%.

Data of Interest

$$\frac{\text{\# of patients on a statin therapy OR have LDL < 70 mg/dL}}{\text{\# of patients as specified in the population definition}}$$

Numerator/Denominator Definitions

Numerator: Patients who are on a statin therapy **OR** have LDL < 70 mg/dL.

Denominator: Patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20%.

Following ICD-9 diagnoses could be included: 410-414.9, V45.81 (coronary bypass), or V45.82 (angioplasty).

For patients who have not been diagnosed with coronary heart disease but have the 10-year risk of having CHD greater than 20%, this is defined as the following:

- Men: age 45 years or older.
- Women: age 55 years or older.
- A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative.
- Currently smoking.
- Hypertension, defined as blood pressure greater than 140/90 mmHg (confirmed by measurement on several occasions) or current use of any antihypertensive medication.
- Low HDL-cholesterol level (less than 40 mg/dL).

Method/Source of Data Collection

Query EMR for patients seen in the clinic in the last 12 months and who fit denominator criteria. Then of those patients who fit denominator criteria, find the number of patients who are on a statin therapy **OR** have LDL < 70 mg/dL.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is both a process and outcome measure, and improvement is associated with a higher score.

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Measurement #2a

Percentage of patients with (a) diabetes and age > = 40 years, or (b) who have 10-year Framingham CVD whose 10-year risk is greater than 20% who are on a statin **OR** who have LDL < 100 mg/dL.

Population Definition

Patients, (a) 40 years and older with diabetes or (b) who have 10-year Framingham CVD whose 10-year risk is greater than 20%.

Data of Interest

$$\frac{\text{\# of patients on a statin therapy } \textbf{OR} \text{ have LDL < 100 mg/dL}}{\text{\# of patients as specified in the population definition}}$$

Numerator/Denominator Definitions

Numerator: Patients who are on a statin therapy OR have LDL < 100 mg/dL.

Denominator: Patients (a) 40 years and older and diabetes or (b) who have 10-year Framingham CVD whose 10-year risk is greater than 20%.

For patients who have not been diagnosed with coronary heart disease but have the 10-year risk of having CHD greater than 20%, this is defined as following:

- Men: age 45 years or older.
- Women: age 55 years or older.
- A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative.
- Currently smoking.
- Hypertension, defined as blood pressure greater than 140/90 mmHg (confirmed by measurement on several occasions) or current use of any antihypertensive medication.
- Low HDL-cholesterol level (less than 40 mg/dL).

Method/Source of Data Collection

Query EMR for patients seen in the clinic in the last 12 months and who fit denominator criteria. Then of those patients who fit denominator criteria, find the number of patients who are on a statin therapy **OR** have LDL < 100 mg/dL.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is both a process and outcome measure, and improvement is associated with a higher score.

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Measurement #3a

Percentage of patients on lipid-lowering medication who have a fasting lipid panel within 24 months.

Population Definition

Patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20% and are prescribed a lipid-lowering medication.

Data of Interest

$$\frac{\text{\# of patients on who have a fasting lipid panel}}{\text{\# of patients as specified in the population definition}}$$

Numerator/Denominator Definitions

Numerator: Patients who have a fasting lipid panel within 24 months of prescription for lipid-lowering medication.

Denominator: Patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20%.

Following ICD-9 diagnoses could be included: 410-414.9, V45.81 (coronary bypass), or V45.82 (angioplasty).

For patients who have not been diagnosed with coronary heart disease but have the 10-year risk of having CHD greater than 20%, this is defined as following:

- Men: age 45 years or older.
- Women: age 55 years or older.
- A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative.
- Currently smoking.
- Hypertension, defined as blood pressure greater than 140/90 mmHg (confirmed by measurement on several occasions) or current use of any antihypertensive medication.
- Low HDL-cholesterol level (less than 40 mg/dL).

Method/Source of Data Collection

Query EMR for patients seen in the clinic in the last 24 months and who fit denominator criteria. Then of those patients who fit denominator criteria, find the number of patients who had fasting lipid panel within 24 months of prescription for lipid lowering medication.

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is associated with a higher score.

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Measurement #3b

Percentage of patients with LDL > 100 who are on a maximal dose of a potent statin (such as simvastatin, pitavistatin, rosuvastatin, or atorvastatin).

Population Definition

Patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20% and LDL > 100.

Data of Interest

$$\frac{\text{\# of patients on a maximal dose of a potent statin}}{\text{\# of patients as specified in the Population Definition}}$$

Numerator/Denominator Definitions

Numerator: Patients with LDL > 100 who are prescribed a maximal dose of a potent statin.

Denominator: Patients with (a) CHD, (b) CHD risk equivalent or (c) whose 10-year risk is greater than 20% and have LDL > 100.

Following ICD-9 diagnoses could be included: 410-414.9, V45.81 (coronary bypass), or V45.82 (angioplasty).

For patients who have not been diagnosed with coronary heart disease but have the 10-year risk of having CHD greater than 20%, this is defined as following:

- Men: age 45 years or older.
- Women: age 55 years or older.
- A family history of premature CHD, defined as definite myocardial infarction (MI) or sudden death before age 55 in the father or a male primary relative, or before age 65 in the mother or a female primary relative.
- Currently smoking.
- Hypertension, defined as blood pressure greater than 140/90 mmHg (confirmed by measurement on several occasions) or current use of any antihypertensive medication.
- Low HDL-cholesterol level (less than 40 mg/dL).

Method/Source of Data Collection

Query EMR for patients seen in the clinic in the last 12 months and who fit denominator criteria. Then of those patients who fit denominator criteria, find the number of patients who were prescribed a maximal dose of a potent statin (such as simvastatin, pitavistatin, rosuvastatin, or atorvastatin).

Time Frame Pertaining to Data Collection

Monthly.

Notes

This is a process measure, and improvement is associated with a higher score.

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Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design
- Training and education
- Culture and the need to shift values, beliefs and behaviors of the organization

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Develop a system for assessment of target population.
2. Develop a system for results of this assessment to be used for identification of treatment options/ recommendations.
3. Develop systems that allow for consistent documentation and monitoring based on type of dyslipidemia.
4. Develop a system for follow-up assessment that identifies success in management of dyslipidemia in the primary care setting.
5. Develop a process that will remove barriers to referral to a specialist if indicated.
6. Develop a system for consistent documentation and monitoring of medication administration.
7. Develop systems for providing patient education on dyslipidemia management.
8. Consider the use of motivational interviewing as a method for addressing behavior change. Motivational interviewing is defined as a client-centered, directive counseling style for eliciting behavior change by helping patients to explore and resolve ambivalence. Rather than telling a client what changes to make, the interviewer elicits "change talk" from them, taking into account an individual's priorities and values.

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Resources

Criteria for Selecting Resources

The following resources were selected by the guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are ***only*** available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

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Resources Table

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	American Dietetic Association (ADA)	Sponsored by the ADA, this site provides useful and reliable information on food and nutrition. This site is prepared by registered dietitians.	Patients and Families; Health Care Providers	http://www.eatright.org
	American Dietetic Association	Low Fat Living; foldout brochure	Patients and Families	(800) 877-1600 x 5000 #0853
	Cyber Diet	This interactive site is packed full of self-assessment tools that make it interesting and fun. Recipes, food facts and fitness information is provided.	Patients and Families	http://www.cyberdiet.com
	Mayo Clinic	This top-of-the-line health information site offers information on current hot topics in nutrition and recipes, and provides the opportunity to ask a Mayo dietitian your nutrition questions.	Patients and Families	http://www.mayoclinic.com
	NHLBI/NCEP	Sponsored by the National Heart, Lung and Blood Institute's National Cholesterol Education Project, this site provides comprehensive information on the connection between lipid disorders and heart disease. It provides personalized quizzes and guides for diet and lifestyle changes, as well as a resource library.	Patients and Families; Health Care Providers	http://www.nhlbi.nih.gov/about/ncep
	Statcoder.com™	Provides a calculator of risk for CAD based on LDL-cholesterol, HDL-cholesterol and Framingham Heart Study Prediction Scores (1998 update). This application is available free of charge.	Health Care Providers	http://www.statcoder.com/cardiac.htm

* Available to ICSI members only.

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The subdivisions of this section are:

- Conclusion Grading Worksheet Summary
  - Conclusion Grading Worksheets
- References
- Appendices

Conclusion Grading Worksheet Summary

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in the Foreword and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols **+**, **–**, **ø**, and **N/A** found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

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Conclusion Grading Worksheet A – Annotation #17 (Risk Factors and Lipid-Lowering Therapy)

Work Group's Conclusion: Patients with risk factors for coronary heart disease but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of coronary heart disease.

Conclusion Grade: I

Author/Year	Design Type	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Lipid Research Clinics Program, 1984 (LRC-CPPT)	RCT	0	-Men, ages 35-69 yrs (mean 47.8 yrs); plasma cholesterol >265 mg/dL; LDL≥175 mg/dL at 3rd and 4th screening visit; free of CHD (but high risk); free of conditions associated with secondary hyperlipoproteinemia -Excluded: triglyceride level >300mg/dL; type III hyperlipoproteinemia; clinical manifestations of CHD; hypertension (or antihypertensive treatment); life-limiting or comorbid conditions -Randomized to cholestyramine resin (24 g/d) or placebo -Both groups followed moderate cholesterol-lowering diet (introduced prior to randomization) -Clinic visits every 2 months; minimum 7 yrs follow-up	-3,806 randomized; groups similar at baseline except for height, weight, 2-hr post-challenge glucose, SGOT, and albumin levels (5 of 83 baseline variables) -Average follow-up 7.4 years; mean compliance in first year 4.2 (of 6 packets/day) (active tx) and 4.9 (placebo); at seventh year 3.8 (active tx) and 4.6 (placebo); no difference in adherence to diet; no difference in weight gain (mean of 2 kg in each group over 7 years) -Pre-entry cholesterol changes: similar for the two groups; by year 7 total cholesterol decreased 23.3 mg/dL in active tx group and 1.9 mg/dL in placebo group, LDL decreased 20.4 mg/dL in active tx group and 6.9 mg/dL in placebo group (total and LDL average % changes greater for active tx group, $p<0.001$) -Definite CHD death and/or non-fatal MI: 8.1% of active tx group, 9.8% of placebo group (19% reduction in risk; $p<0.05$); reduction in both CHD death and non-fatal MI; no difference in all-cause mortality -Changes in other risk factors for CHD: blood pressure, Quetelet index, weight, % current smokers, cigarettes/day, % regular exercisers, alcohol consumption did not differ between groups -GI side-effects: 43% of placebo and 68% of active tx group in 1st year; 26% & 29%, respectively, in 7th year; no differences in non-GI side effects	-The findings show that reducing total cholesterol by lowering LDL-cholesterol levels can diminish the incidence of CHD morbidity and mortality in men at high risk for CHD because of raised LDL levels. This clinical trial provides strong evidence for a causal role for these lipids in the pathogenesis of CHD. NOTES: study conducted at 12 clinics; 4 screening visits (monthly) with randomization at 5th visit; double-blind design; monitored adherence to medication; primary endpoint – combination of definite CHD death and/or definite non-fatal MI

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Author/Year	Design Type	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Frick et al., 1987 (Helsinki Heart Study)	RCT	0	-Men; ages 40-55 yrs; "healthy"; non-HDL cholesterol ≥200 mg/dL -Excluded: any clinical manifestation of CAD or ECG abnormalities, CHF, any other disease that could influence study outcome -Randomized to either gemfibrozil (600 mg twice daily) or placebo -Clinic visit every 3 months	-4,081 randomized; groups comparable at baseline in age, BMI, blood pressure, cholesterol, triglycerides, hypertension, diabetes, rate of smoking, Frederickson lipoprotein type, behavioral scale, alcohol consumption, family history of MI and angina -70.1% continued in trial to completion; none lost to follow-up -Lipid levels: minimal and random changes in placebo group; increased HDL, decreased LDL, total cholesterol, and triglycerides in gemfibrozil group -Cardiac endpoints: 27.3 per 1,000 in gemfibrozil group, 44.1 per 1,000 in placebo group ($p<0.02$) -Mortality: no differences between groups -Other events: no differences in total numbers of cancers or major operations; more GI operations in gemfibrozil group ($p<0.02$); no differences in hospitalizations -Adverse events: more events in gemfibrozil group in first year (11.3% vs. 7%; $p<0.001$); more similar in subsequent years	-Modification of lipoprotein levels with gemfibrozil reduces the incidence of coronary heart disease in men with dyslipidemia. NOTES: non-HDL-cholesterol is the sum of LDL- + VLDL-cholesterol; 3-step screening procedure over 3-5 months; randomized at 3rd visit; compliance of 82-86% (capsule count); study done at 37 clinics; intention-to-treat analysis with no loss to follow-up; principle endpoints were fatal and non-fatal myocardial infarction and cardiac death
Shepherd et al. for the West of Scotland Coronary Prevention Study Group, 1995 (WOSCOPS)	RCT	0	-Men; ages 45-64 yrs; fasting LDL ≥155 mg/dL at 2nd and 3rd screening visit (at least one value ≥174 mg/dL and one value <232 mg/dL); no serious ECG abnormalities; no history of MI or other serious illness -Randomized to pravastatin (40 mg each evening) or placebo -Clinic visits every 3 months	-6,595 randomized; no differences at baseline; mean follow-up of 4.9 years -Lipid levels: no differences between groups in changes in cholesterol levels with intention-to-treat analysis; analysis by treatment received showed 20% reduction in plasma cholesterol, 26% reduction in LDL, 12% reduction in triglycerides, and 5% increase in HDL in pravastatin group -Definite death from CHD or non-fatal MI: 31% reduction in risk ($p<0.001$) in pravastatin group -Other endpoints: reduced angiography (31% risk reduction, $p=0.007$) and PTCA or CABG (37% risk reduction, $p=0.009$) in pravastatin group; 32% risk reduction in death from all cardiovascular causes ($p=0.03$) and 22% reduction in all-cause mortality ($p=0.05$) in pravastatin group; no difference in death from noncardiovascular causes -Adverse events: no differences between groups	-Treatment with pravastatin significantly reduced the incidence of myocardial infarction and death from cardiovascular causes without adversely affecting the risk of death from noncardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction. NOTES: 4 screening visits with randomization at 4th visit; primary end point was non-fatal MI or death from coronary heart disease; no loss to follow-up

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Author/Year	Design Type	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Downs et al. for the AFCAPS/ TexCAPS Research Group, 1998	RCT	+	-Men (45-73 yrs), women (postmenopausal, 55-73 yrs); total cholesterol 180-264 mg/dL, LDL 130-190 mg/dL, HDL ≤ 45 mg/dL for men or ≤ 47 mg/dL for women, triglycerides ≤ 400 mg/dL; no prior history, signs, or symptoms of definite MI, angina, claudication, cerebrovascular accident, or transient ischemic attack -Excluded: uncontrolled hypertension, secondary hyperlipidemia, diabetes managed with insulin or associated with glycohemoglobin level ≥ 10%, body wt > 50% greater than desirable wt for ht -12 wk dietary run-in (including 2-wk placebo run-in) -Randomized to lovastatin (20 mg/d) or placebo; lovastatin titrated to 40 mg/d if LDL > 110 mg/dL at 3-month visit -Clinic visits every 6 wks in 1st year; if continued treatment had clinic visit every 6 mos, otherwise annual contact	-6,605 enrolled (3,304 lovastatin; 3,301 placebo); groups similar at baseline -Study terminated early for efficacy (267 had experienced endpoint event) -Mean follow-up 5.2 years; 71% of active tx and 63% of placebo continued to take medications until trial termination -Lipid levels: from baseline to 1 year LDL reduced 25%, total cholesterol reduced 18%, triglyceride reduced 15%, HDL increased 6%, total/HDL decreased 28% in active tx group; little change in placebo group; significant differences between groups for all parameters ($p<0.001$); at 1 year 42% of active tx and 3% of placebo groups reached target of LDL ≤110 mg/dL -First acute coronary event: at 5 years 37% lower incidence in lovastatin group (RR=0.63, 95%CI 0.50-0.79, $p<0.001$) -Other endpoints: at 5 years decreased incidence of revascularization (33%), unstable angina (32%), fatal and non-fatal MI (40%), fatal and non-fatal cardiovascular events (25%), fatal and non-fatal coronary events (25%) (all $p\leq0.02$) in lovastatin group -Adverse events: no differences in overall mortality, cancer incidence, serious adverse events	-Lovastatin reduces the risk for the first acute major coronary event in men and women with average TC and LDL levels and below-average HDL levels. These findings support the inclusion of HDL in risk-factor assessment, confirm the benefit of LDL reduction to a target goal, and suggest the need for reassessment of the National Cholesterol Education Program guidelines regarding pharmacological intervention. NOTES: lipid inclusion criteria had to be met at both 4 and 2 wks before randomization; included LDL 125-129 mg/dL if total/HDL ratio was > 6.0; did sample size estimation for 90-97% power to detect a 30%-35% reduction in number of participants with primary endpoint events (first acute coronary event defined as fatal or non-fatal MI, unstable angina, sudden cardiac death); planned to continue until 320 had primary endpoint or at least 5 years follow-up after last patient randomized; each group included approximately 2,800 men and 500 women; compliance monitored; 50% of lovastatin group titrated to 40 mg/dL (none back-titrated)

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Author/Year	Design Type	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Pignone, Phillips, & Mulrow, 2000	Syst. Review	–	-Randomized trials; at least 1 year duration; clinical endpoints -Excluded: non-randomized trials; studies of <1 year; serum cholesterol changes or angiographic outcomes only; non-English; abstracts; secondary prevention	-Analysis based on Lipid Research Clinic study, Helsinki heart study, WOSCOPS, and AFCAPS/TexCAPS -Overall odds ratios: **Outcome*** **OR** **95%CI** CHD events 0.70 0.62-0.79 CHD mortality 0.71 0.56-0.92 All-cause mortality 0.94 0.81-1.09 *all tests for heterogeneity non-significant -Statin studies (WOSCOPS & AFCAPS/TexCAPS plus ACAPS) **Outcome*** **OR** **95%CI** CHD events 0.65 0.55-0.77 CHD mortality 0.65 0.48-0.89 All-cause mortality 0.89 0.75-1.06 *tests for heterogeneity non-significant except all-cause mortality (p=0.04)	-Treatment with lipid-lowering drugs lasting 5 to 7 years reduces coronary heart disease events but not all-cause mortality in people with no known cardiovascular disease. NOTES: ACAPS (Asymptomatic Carotid Artery Progression Study) considered "possibly suitable for inclusion" (difficulty categorizing as primary or mixed primary/secondary prevention); in ACAPS, groups receiving lovastatin (with or without warfarin) had lower incidence of fatal/non-fatal cardiovascular disease (p=0.04) and lower all-cause mortality (p=0.02) at 3 years than groups receiving placebo lovastatin; enrolled 919 asymptomatic men and women, 40-79 yrs old, early carotid atherosclerosis (ultrasound) and LDL between 60th-90th percentiles

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Author/Year	Design Type	Quality +,–, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Heart Protection Study Collaborative Group, 2002	RCT	+	-Men and women; ages approx. 40-80 yrs; non-fasting total cholesterol of ≥135mg/dL; considered to be at substantial 5-yr risk of death from CHD based on past history of coronary disease, occlusive disease, diabetes mellitus, treated hypertension -Excluded: chronic liver disease or evidence of abnormal liver function; severe renal disease or evidence of impaired renal function; inflammatory muscle disease or evidence of muscle problems; child-bearing potential; severe heart failure; life-threatening condition other than vascular disease or diabetes; conditions that might limit long-term compliance -4-wk placebo run-in followed by 4-6 wks of 40 mg simvastatin/day; if compliant randomized to simvastatin (40 mg/d) or placebo -3 clinic visits in 1st year then 2 per year for minimum of 48 month follow-up	-20,536 randomized (10,269 simvastatin, 10,267 placebo; 15,454 men, 5,082 women); 35% reported no history of coronary disease -For all subjects: average statin use in treatment group was 85% (over 5 years) including 82% on allocated simvastatin, 3% on non-study statin only, 2% on both; average non-study statin use in placebo group was 17% -First major vascular event (subjects with no prior CHD only): 16.1% of simvastatin group, 20.8% of placebo group (event rate ratio 0.75, 95%CI 0.67-0.84, p<0.0001) -Mortality (all subjects): 12.9% of simvastatin group, 14.7% of placebo group (death rate ratio 0.87, 95%CI 0.81-0.94, p=0.0003) due largely to reduction in vascular deaths (death rate ratio 0.83, 95%CI 0.75-0.91, p<0.0001); non-significant difference in non-vascular death rates -Events (all subjects): reduction in major coronary events, strokes, revascularizations, any major vascular event (all p<0.0001 vs. placebo) -Adverse events (all subjects): no differences in incidence of cancer or in levels of liver and muscle enzymes	-Adding simvastatin to existing treatments safely produces substantial additional benefits for a wide range of high-risk patients including those with no history of coronary disease at entry. The size of the 5-year benefit depends chiefly on the overall risk for major vascular events rather than on blood lipid concentrations alone. NOTES: not randomized if statin therapy was clearly indicated by the patient's own physician; 69 hospitals in United Kingdom; study was factorial design with antioxidant vitamins as the other factor; if unwilling or unable to make clinic visits treatment was stopped; use of non-study statins was permitted (initially in place of simvastatin and then concomitantly); primary outcome was death (all causes, CHD, non-CHD); did sample size estimation

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Shepherd et al. on behalf of the PROSPER study group, 2002	RCT	0	-Men and women; 70-82 yrs; pre-existing vascular disease (coronary, cerebral, or peripheral), or raised risk of disease (smoking, hypertension, or diabetes); total cholesterol of 154-347 mg/dL; triglyceride <531 mg/dL -4-wk placebo run-in; excluded if compliance <75% or >120% -Excluded: poor cognitive function -Randomized to pravastatin (40 mg/d) or placebo -Reviewed every 3 months	-5,804 randomized (2,891 pravastatin, 2,913 placebo); groups similar at baseline; 1,654 in pravastatin group and 1,585 in placebo group were considered primary prevention cases -Mean follow-up 3.2 years for subjects who did not die or withdraw consent **MAIN STUDY OUTCOMES:** **-Primary prevention subgroup**: no reduction in risk for CHD death, non-fatal MI, and fatal or non-fatal stroke; CHD death or non-fatal MI; fatal and non-fatal stroke; TIA **-CHD death, non-fatal MI, and fatal or non-fatal stroke (all subjects):** 14.1% of pravastatin group, 16.2% of placebo group (hazard ratio 0.85, 95%CI 0.74-0.97, p=0.01) **-Other outcomes (all subjects)**: reduced risk of CHD or non-fatal MI, all cardiovascular events (primary endpoint, CABG, PTCA, peripheral artery surgery, or angioplasty), CHD death (all p<0.05 vs. placebo) **-Adverse events (all subjects):** no difference between groups in serious adverse events; new cancer diagnoses more frequent in pravastatin group (hazard ratio 1.25, 95%CI 1.04-1.51, p=0.02)	-Pravastatin given for 3 years reduced the risk of composite measure of coronary disease in elderly individuals. Coronary risk reduction seemed more pronounced in those with previous vascular disease. *NOTES: primary outcome was combined endpoint of definite or suspect death from coronary heart disease, non-fatal MI, and fatal or non-fatal stroke; did sample size estimation; not considered adequately powered to detect an effect on all-cause mortality* *This is one of the earlier studies that show the benefit of LDL lowering in elderly men and women.*

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ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002 (ALLHAT-LLT)	RCT	0	-Participants in ALLHAT antihypertensive trial; men and women >55 yrs old, stage 1 or 2 hypertension with ≥1 additional CHD risk factor; fasting LDL 120-189 mg/dL if no known CHD (100-129 mg/dL if known CHD); fasting triglyceride <350 mg/dL -Excluded: currently receiving lipid-lowering therapy; taking large doses of niacin; taken probucol in past year; known intolerance of statins or significant liver or kidney disease; known secondary cause of hyperlipidemia -Randomized to open-label pravastatin (40 mg/d) or usual care (vigorous cholesterol lowering therapy discouraged); all patients advised to follow NCEP Step I diet -Follow-up visits at 3, 6, 9, & 12 months then every 4 months	-10,355 randomized (5,170 pravastatin, 5,185 usual care); groups similar at baseline except history of CHD (13.4% of pravastatin group, 15% of usual care group, p=0.02) -Mean follow-up of 4.8 years; 2.4% had unknown vital status at end of trial; adherence to pravastatin regimen decreased from 87% at year 2 to 80% at year 4 -Lipid levels: after 4 years total cholesterol decreased by 17.2% in pravastatin group and 7.6% in usual care group; changes for LDL were 27.7% and 11.0%, respectively (p values not reported) -All-cause mortality (pravastatin vs. usual care) at 6 years: RR=0.99 (95%CI 0.89-1.11) -Other outcomes at 6 years: no significant reduction in risk of deaths due to cardiovascular disease, deaths from other causes, fatal CHD and non-fatal MI, stroke, heart failure, or cancer -Subgroup analyses: pravastatin was associated with reduced risk for CHD events or strokes in blacks (both p=0.03 vs. non-blacks); no differences due to age, gender, or presence or absence of diabetes	-Pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL-cholesterol. The results may be due to the modest differential in total cholesterol (9.6%) and LDL-cholesterol (16.7%) between pravastatin and usual care compared with prior statin trials supporting cardiovascular disease prevention. NOTES: study conducted at 514 sites; population described as "not purely primary or secondary prevention"; non-blinded; did sample size estimation (goal of 20,000 enrolled was unrealistic and reduced to 10,000 providing 84% power to detect a 20% reduction in mortality); primary outcome was all-cause mortality; by year 4, 17% of usual care group received statins (vs. 8% at year 2)

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Sever et al. for the ASCOT Investigators, 2003 (Lipid Lowering Arm - ASCOT-LLA)	RCT	+	-Men and women; ages 40-79 yrs at randomization; untreated hypertension (systolic ≥ 160 mmHg, diastolic ≥ 90 mmHg, or both) or treated hypertension with systolic ≥ 140 mmHg, diastolic ≥ 90 mmHg, or both; total cholesterol ≤ 6.5 mmol/L; not taking statin or fibrate; eligible for blood-pressure-lowering arm; at least 3 of identified risk factors for cardiovascular disease -Excluded: prior MI; current treated angina; cerebrovascular event in past 3 mos; fasting triglycerides ≥4.5 mmol/L; heart failure; uncontrolled arrhythmias; any clinically important hematological or biochemical abnormality -4-wk run-in before randomization to atorvastatin (10 mg/day) or placebo	-Lipid-lowering arm terminated early - atorvastatin had significantly reduced primary endpoint of CHD events and stroke relative to placebo -10,305 patients (of 19,342 in hypertension study) further randomized to atorvastatin (n=5,168) or placebo (n=5,137); no differences at baseline; mean age of 63 yrs -Study terminated after 33,041 person-years follow-up (median 3.3 yrs); complete information for 10,186 patients (98.8%); at 3 yrs, 87% of atorvastatin group still taking a statin and 9% of placebo were prescribed a statin -Primary endpoint – non-fatal MI: hazard ratio=0.64 (95%CI 0.50-0.83) or 36% reduction for atorvastatin group -Secondary endpoints: significant reductions in revascularization procedures, total cardiovascular events, non-fatal MI (excluding silent MI), and fatal and non-fatal stroke (all p≤0.02) -Lipid levels: at end of follow-up atorvastatin group was 1.0 mmol/L lower than placebo on total and LDL cholesterol ; triglyceride 0.2 mmol/L lower than placebo; HDL cholesterol levels similar -Blood pressure: similar control for both groups -Subgroups: benefit of atorvastatin on primary endpoint consistent with overall result except no benefit for women -Adverse events: serious adverse events and rates of liver-enzyme abnormalities similar in both groups	-In hypertensive patients, who on average were at moderate risk of developing cardiovascular events, cholesterol lowering with atorvastatin (10 mg/day) conferred a 36% reduction in fatal CHD and non-fatal MI compared with placebo. NOTES: patients were allowed to continue to use lipid-lowering treatment (other than statin or fibrate) in use before randomization; after randomization open-label treatment could be added if additional lipid-lowering therapy was needed; blood-pressure arm included 19,342 patients assigned to 1 of 2 antihypertensive regimens; did sample size estimation for hypertension arm; 2X2 factorial design; 95% of patients were white and 81% were male; non-fatal MI included silent MI and fatal CHD

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Conclusion Grading Worksheet B – Annotation #17 (History of CHD)

Work Group's Conclusion: Patients with a history of coronary disease (including unstable angina and acute myocardial infarction) often benefit from treatment with a statin. Studies have consistently shown a decrease in risk of death from coronary heart disease.

Conclusion Grade: I

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Scandinavian Simvastatin Survival Study Group, 1994 (4S trial)	RCT	+	-3,617 males and 827 females; ages 35-70 years; history of angina pectoris or acute MI; serum total cholesterol 5.5-8 mmol/L (approx. 213-309 mg/dL) and triglyceride ≤2.5 mmol/L (approx. 223 mg/dL) -Excluded: MI in preceding 6 mos, CHF requiring treatment, persistent a-fib, history of stroke, and other conditions -Randomized to either simvastatin (20 mg) or placebo -Clinic visits every 6 wks for 18 mos then every 6 mos -Simvastatin dose adjusted, if needed, at 12 wks and 6 mos	-Study was terminated after 3rd (last) interim analysis by the data safety and monitoring committee; median follow-up was 5.4 years -Groups were comparable at baseline in gender, age, qualifying diagnosis, time since first diagnosis of angina or MI, secondary diagnosis, other therapy, BMI, blood pressure, heart rate, cholesterol -13% of placebo group and 10% of simvastatin group stopped taking medication -37% of simvastatin group had dose raised to 40 mg, 2 patients had dose reduced to 10 mg -Lipid levels: little change in placebo group; decreased total cholesterol (28%), LDL-cholesterol (38%), and triglycerides (15%) and increased HDL-cholesterol (8%) by 6 wks in simvastatin group (maintained over course of study); 35 in placebo group were switched to lipid-lowering drugs -Mortality: 13% (placebo) vs. 8% (simvastatin) (RR=0.70, 95%CI 0.58-0.85, p=0.0003); for coronary deaths RR=0.58 (95%CI 0.46-0.73) -Major coronary events (coronary death, non-fatal definite or probable MI, silent MI, resuscitated cardiac arrest): 28% (placebo) vs. 19% (simvastatin) had ≥1 event (RR=0.66, 95%CI 0.59-0.76); for any coronary event RR=0.73 (95%CI 0.66-0.80); for death or any atherosclerotic event RR=0.74 (95%CI 0.67-0.81); for bypass surgery or angioplasty RR=0.63 (95%CI 0.54-0.74) (all p<0.00001); no difference in non-MI acute CHD events -Subgroups: probability that a woman would escape major coronary event RR=0.65 (95%CI 0.47-0.90, p=0.01); RR values were lower for patients ≥60 yrs but significant for mortality and major events -Adverse events: 6% in each group discontinued treatment because of adverse events; no differences in overall frequency of adverse events	-Simvastatin resulted in an improvement in survival without any suggestion of an increase in non-CHD mortality. The addition of simvastatin (20-40 mg/day) to treatment regimens of 100 CHD patients similar to those in the study could be expected to preserve the lives of 4 of the 9 patients who would otherwise die from CHD, prevent non-fatal MI in 7 of an expected 21 patients, and avoid myocardial revascularization procedures in 6 of the 19 anticipated patients. NOTES: study was done at 94 clinics; sample size estimation called for 4,400 patients to be followed until 440 deaths for power of 95% to detect 30% reduction in mortality at α=0.05; goal of treatment was serum total cholesterol of 3.0-5.2 mmol/L; simvastatin was increased to 40 mg/day or decreased to 10 mg/day, if needed; intention-to-treat analysis with no loss to follow-up (given that patients stopped treatment, this may have resulted in slight attenuation of treatment effect over time); exclusion criteria resulted in patients in placebo group having lower risk of death than in typical post-infarction population

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LIPID Study Group, 1998 (LIPID trial)	RCT	+	-7,498 males and 1,516 females; ages 31-70 years; acute MI or hospital-discharge diagnosis of unstable angina between 3 and 36 months before study entry; plasma total cholesterol of 155-271 mg/dL (4.0-7.0 mmol/L) and triglyceride <445 mg/dL (5.0 mmol/L) -Excluded: significant medical event within 3 mos before entry; cardiac failure; renal or hepatic disease, current use of cholesterol-lowering agents -Randomly assigned to pravastatin (40 mg/day) or placebo -Clinic visits every 6 months	-Study was terminated by data and safety monitoring committee after median follow-up of 6.1 years -Groups were comparable at baseline in age, gender, qualifying event, time from event to entry, risk factors, other vascular disease, previous revascularization, medication use, and lipid levels -At end of study, 19% of pravastatin group had discontinued drug and 24% of placebo group had started open-label therapy with cholesterol-lowering drug -Lipid levels: pravastatin group had decreased total cholesterol, LDL-cholesterol, and plasma triglyceride, and increased HDL-cholesterol (all p<0.001 vs. placebo at 5 years) -Cardiovascular outcomes: Death from CHD was 6.4% in pravastatin group vs. 8.3% in placebo group (relative risk reduction 24%, p<0.001); overall mortality was 22% lower in pravastatin group (p<0.001); mortality from cardiovascular causes was 25% lower in pravastatin group (p<0.001); mortality from CHD and overall mortality were also lower in subgroups based on qualifying event (MI or unstable angina); incidence of MI or stroke, and rate of bypass surgery were all lower in pravastatin group (all p<0.001); rates of angioplasty (p=0.02) and hospitalization for unstable angina (p=0.005) were also lower; pravastatin group spent less time in hospital (p<0.001), had fewer admissions, and spent less time per admission (p=0.002) -Adverse Events: no significant increase in incidence of adverse events attributed to the study medication or of serious adverse events	-Lowering cholesterol levels with pravastatin in patients with a broad range of initial cholesterol levels and a history of myocardial infarction or unstable angina reduces the risk of death from CHD, cardiovascular disease, and all causes combined. The risk of MI or stroke is significantly reduced. Over 6.1 years, it is estimated that 30 deaths, 28 nonfatal MIs, and 9 non-fatal strokes were avoided in 48 patients for every 1000 randomly assigned to treatment with pravastatin. Also, 23 bypass surgeries, 20 angioplasties, and 82 hospital admissions for unstable angina were avoided. NOTE: study was done in 87 centers; sample size estimation called for 700 deaths from CHD to have 80% power to detect reduction of 18.3% in risk of death due to CHD at 5 years (p<0.05); intention-to-treat analysis (including 91 patients [1%] who were found to be not eligible after randomization) with one patient lost to follow-up; patients who stopped taking pravastatin or who received cholesterol-lowering therapy outside the study likely reduced the difference in incidence of events between groups; patients were at lower risk than the general population of patients with MI or unstable angina

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Goldberg et al., 1998 (CARE trial)	RCT	ø	-Males & post menopausal females; ages 21-75 years; MI 3-20 mos before randomized; plasma total cholesterol <240 mg/dL; LDL-C 115-174 mg/dL, triglycerides <350 mg/dL -Excluded: fasting glucose >220mg/dL; LVEF <25%; symptomatic CHF -All patients entered dietary program (NCEP) -Randomized to 40 mg/d pravastatin (n=2,081) or placebo (n=2,078) -Patients previously told they had diabetes or given medication for diabetes were identified -Non-diabetes group subdivided into normal fasting glucose (<110 mg/dL) or impaired (110-135 mg/dL) -Average follow-up of 5 years	-586 in diabetes group (14.1%); 3,573 in no diabetes group; diabetes group differed from no diabetes group (demographic, physical, and laboratory data) -Lipid Results (**pravastatin relative to placebo**): Diabetes No Diabetes Total Chol ↓19% ↓20% LDL-C ↓27% ↓28% Decrease in triglycerides (approx 13%) and increase in HDL levels (approx 4%) similar for both groups -Relative risk reduction (**pravastatin vs. placebo**): Diabetes No Diabetes CHD death or non-fatal MI 13% 26%* Above plus CABG or PTCA 25%* 23%* Stroke 14% 37%* *p<0.05 for pravastatin vs. placebo; no interaction between diabetes status and response to pravastatin -For non-diabetics: significantly greater risk of CHD death or non-fatal MI in patients with fasting glucose levels >110 mg/dL (RR=1.41, p=0.01); pravastatin decreased the risk (relative to placebo) of recurrent events in non-diabetics with fasting glucose of 110-125 mg/dL (NS due to small sample size); no difference in effects of pravastatin on plasma lipids or lipoprotein cholesterol fractions in patients with fasting glucose of 110-125 mg/dL vs. <110 mg/dL	-Pravastatin treatment significantly reduced the frequency of recurrent coronary events in diabetic patients with established CHD and average cholesterol levels. In non-diabetic patients, a fasting glucose of 110-125 mg/dL was associated with an increased risk of recurrent coronary events that was ameliorated by pravastatin treatment. NOTES: study was done at 80 centers in the US and Canada; intention-to-treat analysis *Work Group's Comments: compliance was not reported; no information on loss to follow-up*
LaRosa, He, & Vupputuri, 1999	Meta-Analysis	N/A	-Clinical trials published in English-language journals; human subjects; randomization to statin or placebo groups; no intervention difference other than statin use; ≥ 4 yrs duration of intervention; clinical disease or death as endpoint	-3 secondary prevention studies (4S, LIPID and CARE) included (total of 17,617 participants) -Active treatment associated with 30% risk reduction (95%CI 24%-35%, p<0.001) in major coronary events, a lower risk of coronary disease mortality (OR=0.71, 95%CI 0.63-0.80, p<0.001), and a lower risk of all-cause mortality (OR=0.77, 95%CI 0.70-0.85, p<0.001) -No reduction in noncardiovascular mortality	-Reduction in LDL-cholesterol associated with statin drug treatment decreases the risk of coronary heart disease and all-cause mortality.

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Nissen et al. for the REVERSAL Investigators, 2004	RCT	0	-Men and women; 30-75 yrs, required coronary angiography for clinical indication; demonstrated ≥1 obstruction with luminal diameter narrowing of ≥20%; LDL-C 125-210 mg/dL after 4-10 wk wash-out period; intravascular ultrasound image met prespecified image quality -Wash-out period ≥4 wks; 2-wk placebo run-in; randomized to 80 mg (2 X 40 mg) atorvastatin plus pravastatin placebo or 40 mg (1 X 40 mg) pravastatin plus 2 atorvastatin placebos -Intravascular ultrasound exam before treatment and after 18 mos treatment; scheduled clinic visits every 3 mos	-657 randomized; 654 received study drug; 502 had evaluable ultrasound at baseline and 18 months -Primary analysis: n=249 in pravastatin group, n=253 in atorvastatin group; safety analysis had 327 in pravastatin group, 327 in atorvastatin group -Atheroma volume: increase for pravastatin group only (p=0.01); difference between groups at follow-up (p=0.05); change from baseline (+5.1 mm^3 for pravastatin group, -0.4 mm^3 for atorvastatin group; p=0.02) -Percent atheroma volume: increase for pravastatin group only (p<0.001); difference between groups at follow-up (p=0.004); change from baseline (+1.9% for pravastatin group, +0.6% for atorvastatin group; p<0.001) -Atheroma volume in 10 mm subsegment with greatest disease burden: both groups had decrease from baseline (both p<0.05) with greater change in atorvastatin group (-4.2 mm^3 vs. -1.7 mm^3, p=0.01) -Subgroup analysis (subgroups created based on all variables): absence of progression in all subgroups receiving atorvastatin; absence of progression in pravastatin subgroups based on age below median, non-white, current smoker, BMI<30, no history of hypertension, presence of metabolic syndrome, no history of statin use -Laboratory results: atorvastatin group had greater decreases in total cholesterol, LDL-C, triglycerides, apolipoprotein B 100, and C-reactive protein (all p<0.001 vs. pravastatin group) -Adverse events: death, MI, or stroke for 9 in pravastatin group and 6 in atorvastatin group; drug discontinued in 6.7% of pravastatin group and 6.4% of atorvastatin group	-For patients with coronary heart disease, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. Patients treated with atorvastatin had no change in atheroma burden while patients treated with pravastatin showed progression of coronary atherosclerosis. The differences may be related to the greater reduction in atherogenic lipoproteins and C-reactive protein in patients treated with atorvastatin. NOTES: "target vessel" for intravascular ultrasound must have not undergone angioplasty or have luminal narrowing of ≤50% throughout a "target segment" of ≥30 mm; study was double-blind; did sample size estimation (200 per group for 90% power to detect 7.4% difference in TAV with 5% Type I error rate); anticipated dropout of 35%; study conducted at 34 sites; at start of study, 40 mg was highest FDA approved dose of pravastatin (80 mg dose was approved midway through the trial); findings must be confirmed in large outcome studies comparing morbidity and mortality using alternative lipid-lowering regimens

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Author/Year	Design Type	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Cannon et al. for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT–TIMI 22), 2004	RCT	+	-Men and women; age ≥18 yrs; hospitalized for an acute coronary syndrome in past 10 days; stable condition; enrolled after percutaneous revascularization (if planned); total cholesterol ≤240 mg/dL (≤200 mg/dL if receiving long-term lipid-lowering therapy) -Excluded: expected survival <2 yrs; statin therapy (80 mg/day) at time of index event; lipid-lowering therapy with fibric acid derivative or niacin that could not be discontinued before randomization; received drugs that are strong inhibitors of cytochrome P-450 3A4 in past month (or likely to need during study period); percutaneous coronary intervention in past 6 months (other than current event) or coronary-artery bypass in past 2 months (or scheduled); factors that might prolong QT interval, obstructive hepatobiliary disease (or other serious hepatic disease): unexplained elevation in creatine kinase level (>3X upper limit of normal); creatinine>2 mg/dL -Randomized to 40 mg pravastatin or 80 mg atorvastatin -Follow-up visits and dietary counseling: 30 days, 4 mos, and every 4 mos until final visit	-Groups: pravastatin (n=2,063), atorvastatin (n=2,099); similar except more history of peripheral arterial disease in pravastatin group (p=0.03) -Average follow-up: 24 mos (range 18-36 mos) -Lipids: median LDL-C dropped by 22% at 30 days in pravastatin group and 51% in atorvastatin group (p<0.001) (patients with no prior statin use); median HDL-C increased 8.1% in pravastatin group and 6.5% in atorvastatin group (p<0.001); median C-reactive protein decreased to 2.1 mg/L in pravastatin group and 1.3 mg/L in atorvastatin group (p<0.001) -Primary endpoint (event rate at 2 years): 26.3% in pravastatin group, 22.4% in atorvastatin group (16% reduction in hazard ratio, p=0.005) -Components of primary endpoint: favor atorvastatin (14% decrease in need for revascularization [p=0.04], 29% decrease in risk of recurrent unstable angina [p=0.02] -Secondary endpoint (death due to coronary heart disease, MI, or revascularization): decreased by 14% in atorvastatin group (p<0.03); 2-yr event rate of 19.7% vs. 22.3% with placebo -Subgroups: benefit of atorvastatin maintained; significant for patients with baseline LDL-C ≥125 mg/dL (34% reduction in hazard ratio vs. 7% reduction if LDL-C<125 mg/dL, p=0.02) -Safety/tolerability: 33% of pravastatin group and 30% of atorvastatin group discontinued treatment at 2 years (adverse event or patient's preference); treatment discontinued by investigators due to reported myalgias or muscle aches or elevations in creatine kinase in 2.7% of pravastatin group and 3.3% of atorvastatin group (non-significant)	-Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering stating regimen proves greater protection against death or major cardiovascular events than does a standard regimen. Such patients benefit from early and continued lowering of LDL-cholesterol to levels substantially below current target levels. NOTES: patients received standard medical and interventional treatment for acute coronary syndromes (including daily aspirin with or without clopidogrel or warfarin); the study drug was the only permitted lipid-modifying therapy; patients were also randomly assigned to a 10-day course of gatifloxacin or placebo each month of the trial (results not reported here); trial continued until 925 events reported (all patients requested to return for final visit at that time); 8 (0.2%) lost to follow-up; did sample size estimation (2,000 per group for 87% power); primary endpoint was: death from any cause, MI, documented unstable angina requiring hospitalization, revascularization (percutaneous coronary intervention or bypass) at least 30 days after randomization, stroke

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Links are provided for those new references added to this edition (author name is highlighted in blue).

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Appendix A – Identified Secondary Causes and Conditions Associated with Hyperlipidemia

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

(Mckenney, 2001 [Reference]; Stone, 1994 [Low Quality Evidence])

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Appendix B – NCEP Recommendations on Strategies to Improve Adherence

The ATPIII guideline "Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," includes recommendations on strategies to improve adherence by patients and providers. Adult Treatment Panel III (ATPIII) guideline recommends the use of state-of-the-art multidisciplinary methods that target the patients, providers and health delivery systems to achieve maximum adherence to primary and secondary prevention efforts. The following table summarizes the ATPIII recommendations regarding adherence.

Interventions to Improve Adherence

Focus on the Patient

- Simplify medication regimens
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
- Encourage the use of prompts to help patients remember treatment regimens
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase visits for patients unable to achieve treatment goal
- Increase the convenience and access to care
- Involve patients in their care through self-monitoring

Focus on the Physician and Medical Office

- Teach physicians to implement lipid treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Remind patients of appointments and follow up missed appointments

Focus on the Health Delivery System

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

Source: *(National Cholesterol Education Program, 2001 [Guideline])*

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ICSI Document Development and Revision Process

Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

Document Development and Revision Process

The development process is based on a number of long-proven approaches. ICSI staff first conducts a literature search to identify pertinent clinical trials, meta-analysis, systematic reviews, regulatory statements and other professional guidelines. The literature is reviewed and graded based on the ICSI Evidence Grading System.

ICSI facilitators identify gaps between current and optimal practices. The work group uses this information to develop or revise the clinical flow and algorithm, drafting of annotations and identification of the literature citations. ICSI staff reviews existing regulatory and standard measures and drafts outcome and process measures for work group consideration. The work group gives consideration to the importance of changing systems and physician behavior so that outcomes such as health status, patient and provider satisfaction, and cost/utilization are maximized.

Medical groups that are members of ICSI, review each guideline as part of the revision process. The medical groups provide feedback on new literature, identify areas needing clarification, offer recommended changes, outline successful implementation strategies and list barriers to implementation. A summary of the feedback from all medical groups is provided to the guideline work group for use in the revision of the guideline.

Implementation Recommendations and Measures

Each guideline includes implementation strategies related to key clinical recommendations. In addition, ICSI offers guideline-derived measures. Assisted by measurement consultants on the guideline development work group, ICSI's measures flow from each guideline's clinical recommendations and implementation strategies. Most regulatory and publicly reported measures are included but, more importantly, measures are recommended to assist medical groups with implementation; thus, both process and outcomes measures are offered.

Document Revision Cycle

Scientific documents are revised every 12-24 months as indicated by changes in clinical practice and literature. Each ICSI staff monitors major peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group mid-cycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

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Shared Decision-Making Resources

Shared Decision-Making Resources

Shared Decision-Making Resources from the ENCOUNTER RESEARCH – THE WISER CHOICES PROGRAM AT MAYO CLINIC

http://mayoresearch.mayo.edu/mayo/research/ker_unit/decision-aids.cfm

Shared Decision-Making Aids

Average Risk

http://mayoresearch.mayo.edu/mayo/research/ker_unit/upload/StatinDecAid_AVG_Mayo.pdf

Elevated Risk

http://mayoresearch.mayo.edu/mayo/research/ker_unit/upload/StatinDecAid_ELEV_Mayo.pdf

High Risk

http://mayoresearch.mayo.edu/mayo/research/ker_unit/upload/StatinDecAid_HIGH_Mayo.pdf

ICSI Shared Decision-Making Model

The technical aspects of Shared Decision-Making are widely discussed and understood. **Decisional conflict** occurs when a patient is presented with options where no single option satisfies all the patient's objectives, where there is an inherent difficulty in making a decision, or where external influencers act to make the choice more difficult. **Decision support** clarifies the decision that needs to be made, clarifies the patient's values and preferences, provides facts and probabilities, guides the deliberation and communication, and monitors the progress. **Decision aids** are evidence-based tools that outline the benefits, harms, probabilities and scientific uncertainties of specific health care options available to the patient.

However, before decision support and decision aids can be most advantageously utilized, a **Collaborative Conversation™** should be engaged in between the provider and the patient to provide the supportive framework for Shared Decision-Making.

Collaborative Conversation™

A collaborative approach towards decision making is a fundamental tenet of Shared Decision-Making (SDM). Collaborative Conversation is an inter-professional approach that nurtures relationships, enhances patients' knowledge, skills and confidence as vital participants in their health, and encourages them to manage their health care. Within a Collaborative Conversation, the perspective is that the patient, rather than the provider, knows which course of action is most consistent with the patient's values and preferences.

Use of Collaborative Conversation elements and tools is even more necessary to support patient, care provider and team relationships when patients and families are dealing with high stakes or highly charged issues. A diagnosis of a life-limiting illness presents such a circumstance.

The overall framework for the Collaborative Conversation approach is to create an environment in which the patient, family, and care team work collaboratively to reach and carry out a decision that is consistent with the patient's values and preferences. A rote script or a completed form or checklist does not constitute this approach. Rather, it is a set of skills employed appropriately for the specific situation. These skills need to be used artfully to address all aspects of the person involved in making a decision: cognitive, affective, social and spiritual.

Key communication skills help build the Collaborative Conversation approach. These skills include: (Adapted from O'Connor, Jacobsen Decisional Conflict: Supporting People Experiencing Uncertainty about

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Options Affecting their Health [2007], Neely,C., Interaction Model for Motivating Behavior Change, 2006, and Bunn H, O'Connor AM, Jacobsen MJ Analyzing decision support and related communication [1998,2003]).

1. **Listening skills:**

   Encourage patient to talk by providing prompts to continue such as ***go on, and then?, uh huh,*** or by repeating the last thing a person said: ***It's confusing****....*

   Paraphrase content of messages shared by patient to promote exploration, clarify content and to communicate that the person's unique perspective has been heard. The provider should use his/her own words rather than just parroting what he/she heard.

   Reflection of feelings usually can be done effectively once trust has been established. Until the provider feels that trust has been established, short reflections at the same level of intensity expressed by the patient without omitting any of the message's meaning is appropriate. Reflection in this manner communicates that the provider understands the patient's feelings and may work as a catalyst for further problem solving. For example, the provider identifies what the person is feeling and responds back in his/her own words like this: "***So, you're unsure which choice is the best for you.***"

   Summarizes the person's key comments and reflect them back to the patient. The provider should condense several key comments made by the patient and provide a summary of the situation. This assists the patient in gaining a broader understanding of the situations rather than getting mired down in the details. The most effective times to do this are midway through and at the end of the conversation. An example of this is "***You and your family have read the information together, discussed the pros and cons, but are having a hard time making a decision because of the risks.***"

   Perception checks ensure that the provider accurately understands a patient or family member, and may be used as a summary or reflection. They are used to verify that the provider is interpreting the message correctly. The provider can say, "***So you are saying that you're not ready to make a decision at this time. Am I understanding you correctly?***"

2. **Questioning skills:**

   Open and closed questions are both used with the emphasis on open questions. Open questions ask for clarification or elaboration and cannot have a yes or no answer. An example would be "***What else would influence you to choose this?***" Closed questions are appropriate if specific information is required such as "***Does your daughter support your decision?***"

   Other skills such as summarizing, paraphrasing, and reflection of feeling can be used in the questioning process so that the patient doesn't feel pressured by questions.

   Verbal tracking, referring back to a topic the patient mentioned earlier, is an important foundational skill (Ivey & Bradford-Ivey). An example of this is the provider saying, "***You mentioned earlier…***"

3. **Information-giving skills:**

   Providing information and **providing feedback** are two methods of information giving. The distinction between providing information and giving advice is important. Information giving allows a provider to supplement his/her knowledge and helps to keep the conversation patient centered. Giving advice, on the other hand, takes the attention away from the patient's unique goals and values and places it on those of the provider.

   Providing information can be sharing facts or responding to questions. An example is "***If we look at the evidence, the risk is…***" **Providing feedback** gives the patient the provider's view of the patient's reaction. For instance, the provider can say, "***You seem to understand the facts and value your daughter's advice.***"

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Additional communication components

Other elements that can impact the effectiveness of a Collaborative Conversation include:

- Eye contact
- Body language consistent with message
- Respect
- Empathy
- Partnerships

Self-examination by the provider involved in the Collaborative Conversation can be instructive. Some questions to ask oneself include:

- Do I have a clear understanding of the likely outcomes?
- Do I fully understand the patient's values?
- Have I framed the options in comprehensible ways?
- Have I helped the decision makers recognize that preferences may change over time?
- Am I willing and able to assist the patient in reaching a decision based on her values, even when her values and ultimate decision may differ from my values and decisions in similar circumstances?

When to Initiate Collaborative Conversations

Certain seminal events occur along the care continuum creating especially opportune times for a Collaborative Conversation. These opportunities occur both at the time of and several times after the diagnosis of a life limiting illness. Use each opportunity along the care continuum to support patient preferences and values when dealing with life-limiting diagnoses.

Cues for the Care Team to Initiate a Collaborative Conversation:

- **Life goal changes:** Patient's priorities change related to things the patient values such as activities, relationships, possessions, goals and hopes, or things that contribute to the patient's emotional and spiritual well-being.
- **Diagnosis/prognosis changes:** Additional diagnoses, improved or worsening prognosis.
- **Change or decline in health status:** Improving or worsening symptoms, change in performance status or psychological distress.
- **Change or lack of support:** Increase or decrease in caregiver support, change in caregiver, change in caregiver status, change in financial standing, difference between patient and family wishes.
- **Disease progression:** Change in physical or psychological status as a result of the disease progression.
- **Provider/caregiver contact:** Each contact between the provider/caregiver presents an opportunity to reaffirm with the patient that their care plan and the care they are receiving is consistent with their values.

Patient and Family Needs within a Collaborative Conversation

- **Request for support and information:** Decisional conflict is indicated by, among other things, the patient verbalizing uncertainty or concern about undesired outcomes, expressing concern about

choice consistency with personal values, exhibiting behavior such as wavering, delay, preoccupation, distress or tension. Support resources may include health care professionals, family, friends, support groups, clergy, social workers. When patient expresses need for information regarding options and their potential outcomes, the patient should understand the key facts about options, risks and benefits, and have realistic expectations. The method and pace with which this information is provided to the patient should be appropriate for the patient's capacity at that moment.

- **Advance care planning:** With the diagnosis of a life-limiting illness, conversations around advance care planning open up. This is an opportune time to expand the scope of the conversation to other types of decisions that will need to be made as a consequence of the diagnosis of a life-limiting illness.
- **Consideration of values:** The personal importance a patient assigns potential outcomes must be respected. If the patient is unclear how to prioritize his/her preferences, value clarification can be achieved through the use of decision aids.

  Detailing the benefits and harms of potential outcomes in terms of how they will directly affect the patient, and through a Collaborative Conversation with the provider.
- **Trust:** Patient must feel confident that his/her preferences will be communicated and respected by all caregivers.
- **Care coordination:** Should the patient require care coordination, this is an opportune time to discuss the other types of care-related decisions that need to be made. These decisions will most likely need to be revisited often. Further, the care delivery system must be capable of delivering coordinated care throughout the continuum of care.
- **Responsive care system:** The care system needs to support the components of patient and family centered care so the patient's values and preferences are incorporated into the care he/she receives throughout the care continuum.

Evaluating the Decision Quality

Adapted from O'Connor, Jacobsen Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting their Health (2007).

When the patient and family understand the key facts about the condition and their options, a good decision can be made. Additionally, the patient should have realistic expectations about the probable benefits and harms. A good indicator of the decision quality is whether or not the patient follows through with his/her chosen option. There may be implications of the decision on patient's emotional state such as regret or blame, and there may be utilization consequences.

Decision quality can be determined by the extent to which the patient's chosen option best matches his/her values and preferences as revealed through the Collaborative Conversation process.

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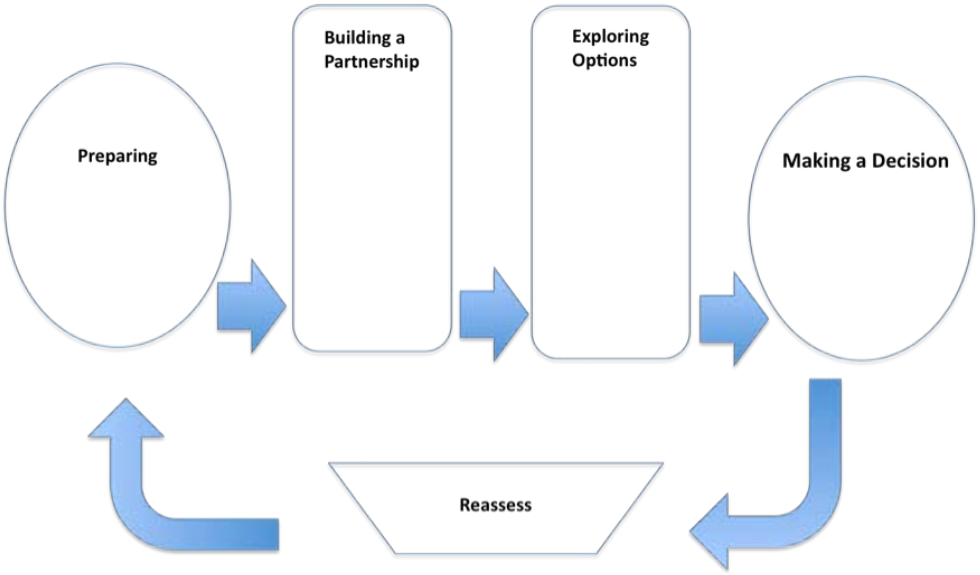
Map of Shared Decision-Making Process

SDM Collaborative Conversation™ Map



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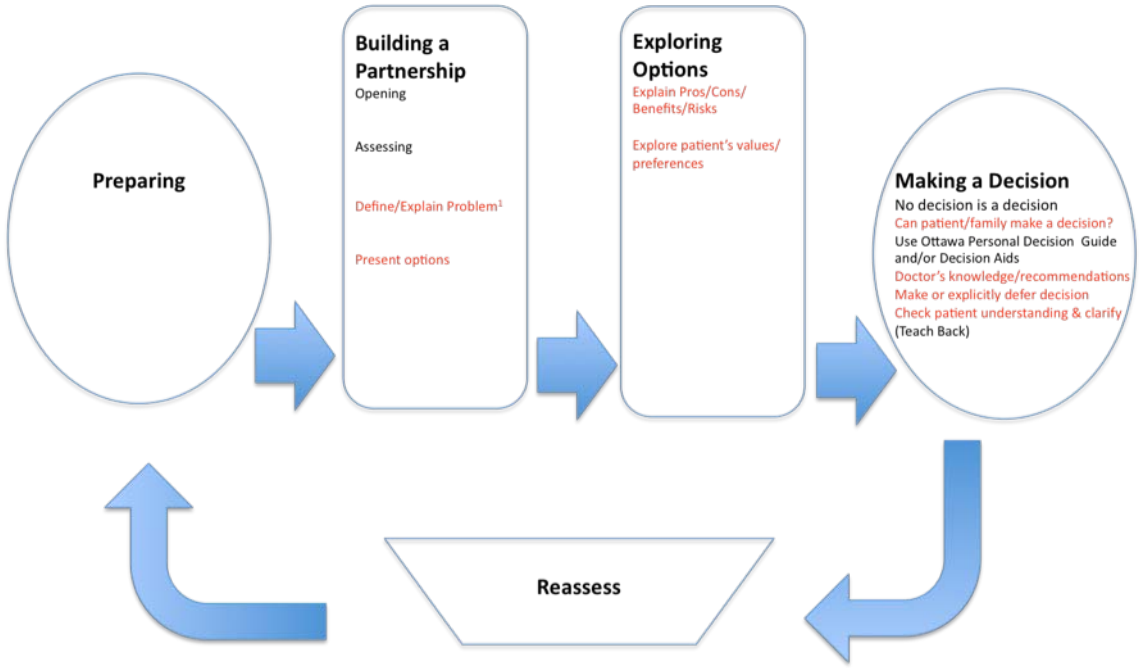
SDM Collaborative Conversation™ Map



[1]Makoul G, Clayman M, An integrative model of shared decision making in medical encounters, *Patient Education and Counseling, 60 (2006) 301-312*

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