VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF DYSLIPIDEMIA

Department of Veterans Affairs
Department of Defense

Updated Version 2.0 – 2006

Prepared by:

THE MANAGEMENT OF DYSLIPIDEMIA

Working Group

With support from:

The Office of Quality and Performance, VA, Washington, DC
&
Quality Management Directorate, United States Army MEDCOM

Version 1.0 – 1999

Updated Version 2.0 - 2006

Based on evidence reviewed until December 2004.

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INTRODUCTION

This clinical practice guideline (CPG) on the management of dyslipidemia is intended to promote reduction of cardiovascular risk via evidence-based management of dyslipidemia, thereby improving clinical outcomes. It can assist primary care providers or specialists in the detection of high blood cholesterol, assessment of the global risk for cardiovascular disease (CVD), determination of treatment goals and appropriate therapies, and delivery of individualized interventions. Although it was developed for a broad range of clinical settings, it should be applied with enough flexibility to accommodate local practice and individual situations.

The guideline was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs. VHA and DoD define clinical practice guidelines as:

> "Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes the following:
> 1. Determination of appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction; and
> 2. Literature review to determine the strength of the evidence in relation to these criteria."

Dyslipidemia is widely regarded as a major risk factor for coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) (NCEP ATP-III, 2002). It is thus a serious public health problem in the DoD, the VHA healthcare system, and in the nation at large. The Global Burden of Disease Study has estimated that cardiovascular disorders are currently the second leading worldwide cause of disability adjusted life years (the sum of lost life due to mortality and years of life adjusted for the severity of disability) in industrialized countries (Murray, 1997). Projections into the future suggest that cardiovascular disorders will rise to become the most important cause of disability adjusted life years. Based on the above statistics, there is little doubt that dyslipidemia is a major risk factor for morbidity and mortality within the DoD and VHA communities.

In the development of this guideline update, the Working Group heavily relied on the following evidence based guidelines:

> USPSTF 2001: U.S. Preventive Services Task Force. Screening for Lipid Disorders: Recommendations and Rationale. Am J Prev Med 2001;20(3S):73-76 (http://www.elsevier.com/locate/ajpmonline).
>
> NCEP ATP-III, 2002: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002, 106, (25), 3143-421.

Lipid-related risk factors for ASCVD include high levels of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) (NCEP III, 2002). Other risk factors include age, male sex, high blood pressure, tobacco use, diabetes mellitus, and family history of premature CHD (ACP, 1998). Because the range of CVD 10-year absolute risk is wide, targeted screening for patients at high absolute risk to develop CVD is recommended. All adults—regardless of age—with a history of CVD should undergo lipoprotein screening. For asymptomatic individuals (i.e., for primary prevention), available evidence supports cholesterol screening only if other characteristics place them at high-risk. The debate over screening recommendations thus centers on young people without risk factors and older people without a history of CVD.

The NCEP ATP-III Guidelines define LDL-C as the primary target of therapy. It also defines elevated serum triglycerides as a risk factor, along with low HDL-C. Obtaining a lipid profile in fasting state is necessary in order to make meaningful decisions. This new approach also emphasizes the focus on the LDL-C level, rather than the TC/HDL ratio as a predictor for outcomes or treatment initiation.

Why Does the VA/DoD Guideline Differ from NCEP in their LDL Goals?

Most NCEP recommendations are consensus statements designed to guide the broad clinical field of dyslipidemia. Many of the recommendations are based on observational studies with rational inferences based on biologic plausibility. Clinical practice guidelines have to guide practical decision-making in real world practice among patients for whom there are most often no applicable clinical trials, and in whom there is an intricate balance of patient preferences, co-morbidities, medication interactions, and other psychosocial factors. Therefore, the VA/DoD Dyslipidemia Guidelines Working Group was tasked to design a rigorous evidence-based guideline whereby recommendations were based on high quality clinical data (typically randomized controlled trials [RCT] using hard outcomes). The Guideline Working Group's knowledge of the DoD and VHA clinical practice settings allows for adaptation of these recommendations to our specific system of care. This is the basis upon which there are differences between NCEP and the VA/DoD CPG recommendations. The decisions on treatment will always be guided by clinical judgment of the providers who may strive to achieve lower LDL-C goals for their individual patient.

Most high-risk patients (those with CVD or CVD equivalent and LDL-C >100 mg/dL) may benefit from statin therapy, regardless of baseline LDL. However, patients with very high baseline LDLs may have difficulty in achieving an LDL of less than 100 despite moderate to high dose statin therapy (greater than 25 percent reduction in LDL-C). Most recent studies achieving very low treatment LDLs started with low baseline LDL (mean LDL-C in HPS was 131 mg/dL; median LDL-C in PROVE-IT was 106 mg/dL) as opposed to 188 mg/dL in the 4S study. Thus, in those patients with a high LDL at baseline, the full risk-benefit of high dose statin or combination drug therapy required to achieve very low LDL goals is unknown, especially among patients with significant disease comorbidities or concomitant drug therapy. The data from meta-analysis of the major statin RCTs indicate that an LDL-C reduction of 30-40 percent from baseline may be considered a therapeutic strategy for patients who can not meet the above target goals.

Changes From Previous Version (1999) Of The Guideline

This guideline recommends a global assessment of cardiovascular risk as part of the screening for dyslipidemia. In the past, stratification of lipid lowering therapy was based on risk categories determined by counting risk factors. Atherosclerosis is a disease of many facets and pathological features. In the context of overall management of cardiovascular (CV) risk reduction, management of LDL-C is only one factor of many. A multifactor risk management strategy is necessary to optimize risk. To emphasize treatment of only a single parameter, such as LDL-C, over simplifies the reduction of CVD risk. Counting the number of risk factors without considering their severity also oversimplifies a vastly complex problem. This guideline recommends the calculation of a 10-year CVD risk based on the Framingham model. The high-risk and very high-risk groups that are subject to secondary prevention now include patients with CHD risk equivalence (i.e., diabetes). The evidence gathered in recent years has demonstrated that patients with diabetes have a comparable risk for CVD as patients who already had a myocardial infarction or stroke. The evidence provided by several lipid-lowering RCTs has now provided enough data to base the recommendations for this guideline on absolute risk reductions (as opposed to relative risk reduction in the past). Finally, there is emerging data on the metabolic syndrome as a CVD risk indicator and a variety of treatments that may mitigate CVD risk. This emphasizes the value of recognizing the metabolic syndrome in assessing CVD risk.

Specific recommendations for the management of lipid disorders in those with metabolic syndrome have been described in recent national guidelines (NCEP ATP-III). The recommendations emphasize lifestyle management (weight loss, physical activity, dietary fat restriction). Medications can potentially favorably alter low levels of HDL and high levels of triglycerides (TG) and in theory reduce the risk of CVD in individuals with metabolic syndrome. However, specific treatment targets and recommendations have not been fully clarified, particularly with regards to drug therapy, largely on the basis of a lack of hard outcomes data from clinical trials. Further clinical trial data will be required before more specific recommendations can be made regarding the treatment of low level of HDL and high level of TG in

metabolic syndrome. These issues will be addressed in detail in future revisions of the guidelines as more definitive data become available.

Although this guideline represents the best evidence-based practice on the date of its publication, it is certain that medical practice is evolving and that this evolution will require continuous updating of published information. In addition, the reader is reminded that this document is intended as a guideline and can never supersede the clinical judgment of the healthcare provider.

Change In Format

Great effort was taken in this update to provide clear objectives and direct recommendations in a behavioral format. Establishing a set of desired treatment behaviors will hopefully make implementation much easier. Elaboration of the recommendations and a review of the evidence are included in the Discussion section of each annotation. A more detailed comprehensive summary of major recent research studies (the evidence) is also provided in the appendices – which served as the basis for recommendations in this guideline.

Guideline Development

A systematic approach was used to develop this guideline update. It is described in detail in Appendix A. The section below presents the key elements of the updated Guideline for the Management of Dyslipidemia.

Key Elements to the Management of Dyslipidemia

1. Base recommendations on high quality evidence with a focus on interventions that improve clinically significant patient-centered outcomes.
2. Address primary and secondary prevention of coronary disease.
3. Use specific screening criteria to identify the patient with dyslipidemia who is most likely to benefit from appropriate intervention.
4. Incorporate global cardiovascular risk assessment to guide treatment for dyslipidemia.
5. Use lipid lowering therapies to reduce cardiovascular risk and events that include:
    a. Evidence driven rationale for medication choices
    b. Lifestyle modification and diet with appropriate intensity
6. Manage modifiable cardiovascular risks, not just dyslipidemia.
7. Define treatment goals.
8. Clarify contribution of triglycerides (TG) and HDL-C to cardiovascular disease (CVD) risk.

Performance Measurement

Performance indicators are different from guidelines. Guidelines are meant to impact the delivery of care at the time of the clinical patient encounter using principles of shared decision-making in the context of individual risk assessment of harm and benefit for the individual patient. Performance indicators are designed to measure performance (usually of health plans) in order to motivate improvement in performance for populations. Therefore, PIs identify target metrics where maximal benefit will be expected to occur, and they incorporate adjustments for heterogeneous populations with co-morbidities and polypharmacy in whom "ideal" metrics would be impractical and potentially harmful. Recommendations from CPGs strive for "ideal" care which tend to set goals on the margins of efficacy. Ideally, performance measures should be based on the highest evidence (QE = I; R = A) that is most generalizable and should include specific inclusion/exclusion criteria in order to permit valid comparisons across populations.

Overview of the Dyslipidemia Guideline

The Management of Dyslipidemia guideline is a single module that addresses three aspects of lipid-related care:

Module A: Management of Dyslipidemia - Screening

Module B: Management of Dyslipidemia - Initiation of Therapy

Module C: Management of Dyslipidemia - Follow-up of Therapy

This guideline also contains appendices that provide more information on the spectrum of treatment options, and give details on pharmacologic and other interventions.

Appendix A: Guideline Development Process

Appendix B: 10-Year CV-Risk Assessment

Appendix C: Medical Nutrition Therapy

Appendix D: Exercise

Appendix E: Pharmacologic Therapy: Drug Information

Appendix F: Pharmacologic Therapy: Summary of Supporting Studies

Appendix G: Acronym List

Appendix H: Participant List

Appendix I: Bibliography

GUIDELINE UPDATE WORKING GROUP

VA	DoD
John R. Downs, MD (co-chairman)	**Vincent F. Carr, Col, MC, CFS (co-chairman)**
C. Bernie Good, MD	**Patrick G. O'Malley, LTC, MD, MPH**
Leonard Pogach, MD	**Carl A. Gibson, LTC, MC**
Robert L. Jesse, MD	**Zoë C. Hawes, Capt, NC**
Teresa M. Hoos, MS, RD	**Janetta R. Blackmore, Capt, MS, RD, LD**
Catherine L. Kelley, PharmD, BCPS	**Vincent P. Fonseca, LtCol, MD, MPH**
Connie Foster, MSN, APRN	**Angela V. Klar, MSN, RN, ANP-CS**
Acquanetta Lancaster, RN, NP	

GUIDELINE FACILITATOR
Oded Susskind, MPH

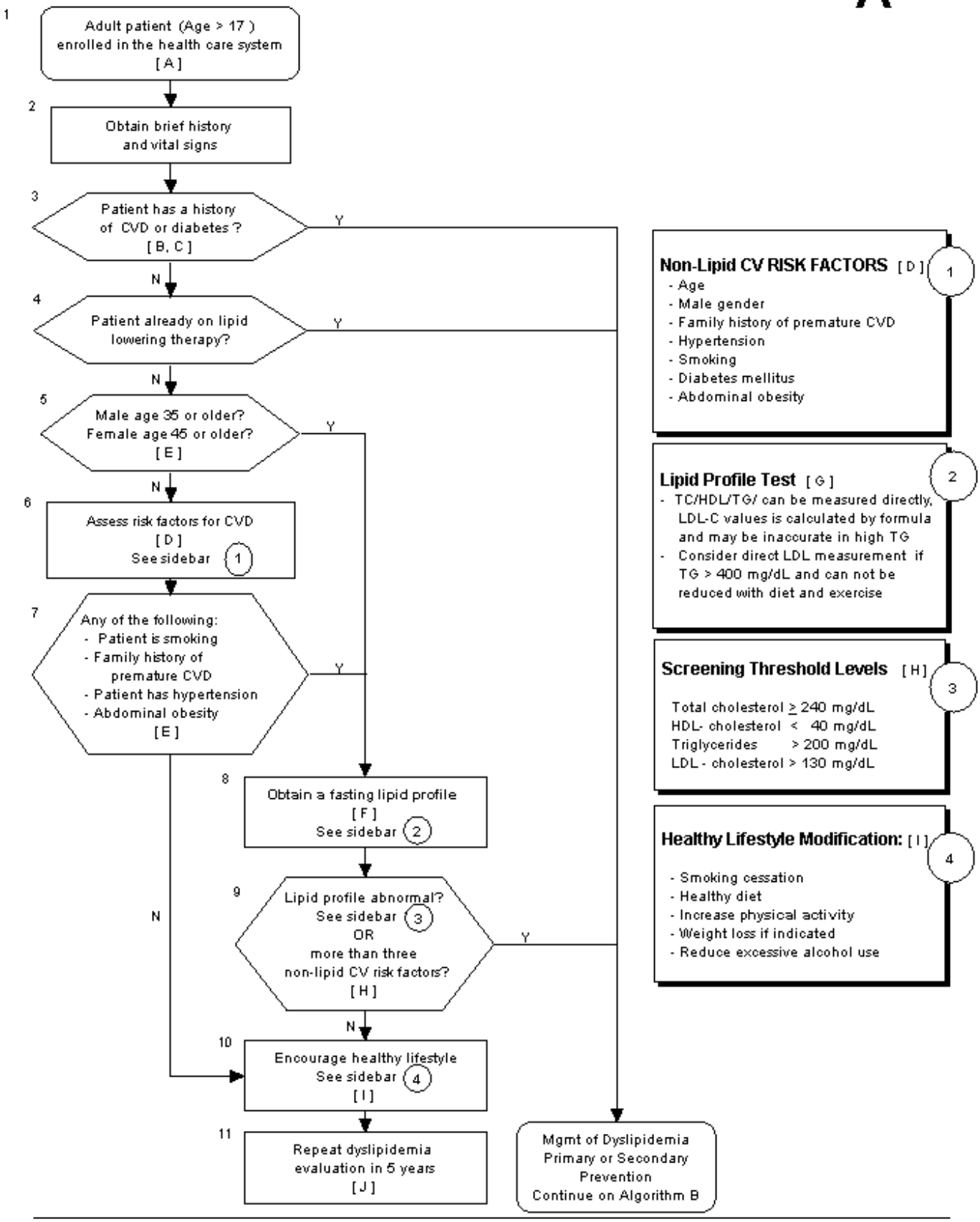
RESEARCH TEAM–EVIDENCE APPRAISAL	STAFF
Vivian H. Coates, MPH	**Rosalie Fishman, RN, MSN**
Charles Turkelson, PhD	**Martha D'erasmo, RN, MPH**
Eileen G. Erinoff	**Joanne Marko, MS, SLP**
Wendy Bruening, PhD	**Pam Zingeser**
Stephen Tregear, PhD	**Kristyn O'Reilly**

Management of Dyslipidemia

11/20/2005

Module A. Screening

A



CVD - Cardiovascular disease ; TC - Total Cholesterol; HDL-C - High density lipoprotein cholesterol; LDL-C - Low density lipoprotein cholesterol; TG - Triglycerides

ANNOTATIONS

A. Adult Patient (Age ≥17) Enrolled in the Health Care System

DEFINITION

This guideline addresses adults (age 17 years or older) eligible for care in the Veterans Health Administration/ Department of Defense (VHA/DoD) healthcare systems.

DISCUSSION

Patients of any age will benefit from recommendations for lifestyle modification regardless of lipid levels. Appropriate screening for primary prevention can lead to timely detection and intervention. However, targeted lipid screening is only recommended for men ≥ age 35 and women ≥ age 45 (USPSTF, 2001; NCEP ATP-III, 2002). There is evidence to support screening in younger patients when other risk factors are present (NCEP ATP-III, 2002; USPSTF, 2001; AACE Lipid Guidelines, 2000). There is clinical and epidemiological evidence to continue screening until age 75 for primary prevention (AACE, 2000). There is some disagreement, however, as to the efficacy of screening beyond the age of 75. The USPSTF has not established an age at which to stop screening for primary prevention, and therefore, screening beyond age 75 should be left to clinical considerations (USPSTF, 2001).

B. Does Patient Have a History of Cardiovascular Disease?

OBJECTIVE

Identify patients who may benefit from lipid lowering therapy.

BACKGROUND

Secondary prevention refers to patients with known atherosclerotic cardiovascular disease (CVD). It is an inclusive term for coronary peripheral and cerebrovascular diseases.

RECOMMENDATIONS

1. All patients with known CVD are considered high-risk and should be treated with aggressive lipid-lowering therapy to prevent acute vascular events. These include, but are not limited to, acute myocardial infarction (AMI) or cerebrovascular accident (CVA).

DISCUSSION

Trials with a variety of agents have demonstrated that treatment of dyslipidemias improves low density lipoprotein-cholesterol (LDL-C) and/or high density lipoprotein–cholesterol (HDL-C) profiles, and in addition, reduces coronary events (4S, 1994; CARE, 1996; LIPID, 1998; VA-HIT, 1999; LIPS, 2002; PROVE-IT, 2004; HPS, 2002), angiographic progression (CLAS, 1987; FATS, 1990; REVERSAL, 2004; LIPS, 2002), and CHD mortality along with total mortality (Oslo, 1986; Oslo, 1995; 4S, 1994; LIPID, 1998; FLARE, 1999). Meta-analysis and subgroup analysis from coronary heart disease (CHD) trials have shown that statins or niacin reduce the incidence of stroke. In the Heart Protection Study (HPS), the reduction in stroke was highly statistically significant for simvastatin (HPS, 2002). A Cochrane review found that cholesterol-lowering therapy reduces progression of peripheral vascular disease (Leng et al., 2000).

C. Does Patient Have Diabetes Mellitus?

OBJECTIVE

Identify patients known to be at high-risk due to diabetes mellitus (DM).

RECOMMENDATIONS

1. Patients with Type 2 DM are at significantly increased risk of CVD compared with non-diabetic patients of similar age and should, therefore, be treated more aggressively according to secondary prevention protocols. [A]

DISCUSSION

Type-2 DM was considered as an independent risk factor for CVD and associated with a two-fold to four-fold increase in coronary events (Neaton & Wentworth, 1992; CARDS, 2004; HPS, 2002). Haffner et al. (1998) found that DM patients had an incidence of first myocardial infarction (MI) (20.2 percent) similar to the incidence of recurrent MI among non-DM patients (18.8 percent) over a seven-year follow-up period. Further, the hazard ratio for death from CVD for diabetic subjects without prior MI as compared with non-diabetic subjects with prior MI was not significantly different (hazard ratio, 1.4, P=NS). Diabetes is now considered to be a CVD equivalent.

NCEP ATP-III (2002) indicated that most patients with diabetes are at high-risk even in the absence of established CVD. Most patients with hyperglycemia who have Type-2 DM are older and have multiple risk factors. Epidemiological studies and clinical trials demonstrate that in higher-risk populations these patients have a risk for CVD events approximately equal to that of non-diabetic patients with established CVD (Grundy et al., 2004).

Mortality from all causes was significantly reduced by 13 percent (P-0.0003) in patients treated with simvastin (HPS, 2002). Major vascular events were reduced by 24 percent, coronary death rate by 18 percent, MI death by 27 percent, nonfatal or fatal stroke by 25 percent, and cardiovascular revascularization by 24 percent. The relative risk reduction (RRR) rate was similar in each subcategory, including patients without diagnosed CVD who had cerebrovascular disease, or peripheral artery disease, or diabetes (HPS, 2002). These results support the inclusion of patients with diabetes in the high-risk category and confirm the benefits of more aggressive LDL-lowering therapy in these patients (HPS, 2002).

Similar results were obtained from the OASIS Study (2000), in which persons with Type-2 DM without CVD, and an average age of 65, had rates of CHD events equal to that of persons with established CVD. Moreover, in the HOPE trial (2000), persons with Type-2 DM without prior CVD, but with one or more cardiovascular risk factors, had an annual event rate for CVD of 2.5 percent. The results of these two trials further support the concept that persons with Type-2 DM, even without clinical CVD, belong in the category of CVD risk equivalent.

EVIDENCE

	Recommendation	**Source**	**QE**	**Overall Quality**	**R**
1	Persons with Type-2 DM, even in the absence of CVD, should be treated as CVD equivalent	Haffner et al., 1998 HOPE, 2000 HPS, 2002 OASIS, 2000	I	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix A)

D. Assess Risk Factors for Cardiovascular Disease (CVD)

OBJECTIVE

Identify clinical markers that predict an increased risk for developing CVD, thereby changing the interpretation of LDL levels.

BACKGROUND

An important objective in screening for lipid disorders is to identify accurately which patients are (or are not) at high-risk of experiencing CVD events. The amount of CVD risk attributable to abnormal lipids depends on the degree of lipid abnormality and the presence of other CVD risk factors.

Lipid lowering goals should be based upon patient-specific attributes and family history. There are several studies that have documented that a family history of premature CVD is an independent risk factor for CVD. Risk for CVD is higher, the younger the age of onset in the affected family member and the greater number of first degree relatives affected.

Cigarette smoking has proven to contribute to the risk for individuals in developing CVD by accelerating the development of coronary plaques and may lead to the rupture of plaques. Randomized clinical trials have shown that smoking cessation has decreased the risks for CVD events.

Elevated blood pressure or treated hypertension is a risk factor that should modify the goals of LDL-lowering therapy in primary prevention. Patients with hypertension (HTN) should be treated according to the VA/DoD Guideline for Hypertension.

Diabetes also increases the individual's risk for developing CVD. Patients with diabetes commonly have other CVD risk factors such as hypertension, low serum HDL levels, and hypertriglyceridemia.

Many epidemiological studies have shown that low level of HDL-C (<40 mg/dL) is also a risk factor for CVD. Low HDL-C, in combination with other lipid risk factors, can further increase an individual's risk for developing CVD. It has been established that the protective effect of a high level of HDL-C is present even when the individual has a high LDL-C.

Obesity, defined as a Body Mass Index (BMI) ≥30, is also associated with CVD. Abdominal obesity is associated with CVD, dyslipidemia, and metabolic syndrome. The presence of metabolic syndrome accentuates the risk accompanying elevated LDL-C. This increase in risk appears to be mediated through multiple major and emerging risk factors. Clinical trials show that modifying three major components of metabolic syndrome—atherogenic dyslipidemia, hypertension, and the prothrombotic state will reduce risk for CVD.

Box 1. Major Non-Lipid Risk Factors for CVD

Non-Modifiable	**Modifiable**
- Increasing age	- Cigarette smoking
- Male gender	- Dyslipidemia (low HDL-C)
- Family history of premature CVD	- Diabetes Mellitus
	- Hypertension
	- Abdominal Obesity

Risk factors are multiplicative in their effect. Therefore, in the assessment and management of coronary risk in any individual, it is essential to adopt a global approach consisting of an evaluation and treatment of all existing risk factors.

RECOMMENDATIONS

1. Patients screened for dyslipidemia should be assessed for risk factors for CVD. Assessment should include, but not be limited, to the following:

    a. Age (males ≥age 45 and females ≥age 55)
    b. Family history of premature coronary artery disease; definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative
    c. Current tobacco use/cigarette smoking (or within the last one month)
    d. Hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg confirmed on more than one occasion, or current therapy with anti-hypertensive medications)

e. Diabetes mellitus (DM) (elevated fasting blood sugar [≥126 mg/dL], or a random blood sugar [≥ 200 mg/dL] confirmed on more than one occasion, an abnormal glucose tolerance test or current therapy with anti-diabetic medications)
f. Level of HDL-C (Less than 40 mg/dL confirmed on more than one occasion).

2. In obese patients (BMI ≥30), waist circumference measurement should be obtained to assist in the diagnosis of metabolic syndrome.

DISCUSSION

Prevention of smoking and smoking cessation should receive prime emphasis in the clinical strategy to reduce CVD risk (see VA/DoD Guideline for the Management of Tobacco Use).

Hypertension, defined as blood pressure ≥140/90 mmHg or current use of anti-hypertensive medication, is a major, independent risk factor for CVD that increases as the blood pressure increases. Clinical trials have shown that reducing hypertension will decrease the patient's risk for developing CVD. However, hypertension remains a risk factor for CVD even when the individual's blood pressure is normalized with anti-hypertensive medication.

The presence of diabetes should result in modified treatment goals for LDL cholesterol. Because of growing evidence that many people with diabetes carry a risk for CVD similar to those with established CVD, diabetes should be treated as a separate high-risk category, equivalent to secondary prevention of people with a history of CVD (NCEP ATP-III, 2002).

Large epidemiologic trials have shown that a low HDL-C is associated with an increased risk for CHD, and thus, it is classified as a major risk factor for CHD (Gordon, 1989; Robins, 1999). Clinical trials suggest that raising HDL-C levels will reduce risk for CVD (Wilson et al., 1998). However, it remains uncertain whether raising HDL-C levels per se, independent of other changes in lipid and/or nonlipid risk factors will reduce risk for CVD. Low HDL-C should be defined as a level of <40 mg/dL, in both men and women (NCEP ATP-III, 2002).

Obesity should be considered a direct target for clinical intervention rather than as an indicator for lipid modifying drug treatment. Because of the association of obesity with other risk factors, obesity should not be included as a factor influencing treatment goals of LDL-C in primary prevention (See VA/DoD guideline for the Management of Overweight and Obesity –under development; NHLBI, 1998).

The presence of metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-C goals are set according to the major risk factors. Primary emphasis nonetheless, should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with metabolic syndrome (NCEP ATP-III, 2002).

E. Lipid Screening Criteria

OBJECTIVE

Appropriately target individuals for lipid profile screening.

BACKGROUND

The relationship between CVD and cholesterol levels is continuous and curvilinear with clinically relevant risk of CVD beginning at total cholesterol (TC) 150mg/dL (3.9mmol/L) and escalating sharply when the TC exceeds 200 mg/dL (5.2mmol/L). The fraction of cholesterol shown to be the most important is the low-density lipoprotein cholesterol (LDL-C), which increases as TC increases.

A fasting lipoprotein profile including major blood lipid fractions, e.g., TC, LDL-C, HDL-C, and triglycerides (TG) should be obtained at least once every 5 years in all adults. More frequent measurements are required for persons with multiple risk factors or, in those with 0–1 risk factor, if the LDL-C level is only slightly below the goal level.

Atherosclerosis is a continuous life long process beginning in childhood and progressing with advancing age. Mass screening of lipid levels in the general population regardless of age is not recommended. Blood lipid testing is recommended for all adults (men age 35 or older and women age 45 or older) and for younger adults who may be at higher risk because of other (non-lipid) risk factors (family history of premature CVD, smoking or HTN). A fasting lipid profile may be needed for obese individuals to complete the assessment for the presence or absence of metabolic syndrome as low HDL-C and TG levels are part of the syndrome definition.

Box 2. Lipid Screening Criteria

a. Male age 35 or older OR female age 45 or older OR
b. Young adults with more than one of the following:
- Family history of premature CVD
- Patient is smoking
- Patient has or is being treated for hypertension

c. Consider obtaining lipid profile for young adults with abdominal obesity

RECOMMENDATIONS

1. Fasting lipid profile testing should be obtained in all men age 35 and older and women age 45 years or older every 5 years. [A]
2. Fasting lipid profile testing should be obtained in individuals with a family history or clinical evidence of familial hyperlipidemia. [A]
3. Fasting lipid profile testing in young adults may be considered depending upon the association with other risk factors. Younger adults (men younger than age 35 and women age 45 or younger) should be screened for lipid disorders if they have one or more of the following risk factors: family history of premature CVD, hypertension (or under treatment for HTN), or smoking. [B]
4. A lipid profile should be obtained for individuals with abdominal obesity (waist circumference >40 inches in men and >35 inches in women) to aid in assessment of metabolic syndrome. [B]
5. All persons with average or below average risk for atherosclerotic events should be screened for dyslipidemia every five years. [I]
6. Elderly patients age 75 or older should be screened if they have multiple CVD risk factors, or a history of CVD and good quality of life with no other major life-limiting diseases. [I]

Box 3. The Recommended Screening Schedules for Dyslipidemia

For young adults (men <age 35; women <age 45)

- Every 5 years when no CVD risk factors are present
- More often, if family history of premature CVD exists (definite MI or sudden death before 55 years of age in father or other male first-degree relative or before age 65 in mother or other female first-degree relative)

For middle-aged adults (men ≥age 35; women ≥age 45)

- Every 5 years, when no CVD risk factors are present
- Annually, if CVD risk factors exist (HTN, smoking, family Hx of premature CVD)

For elderly patients up to age 75 years

- Every 5 years when no CVD risk factors are present
- More often if CVD risk factors exist

For elderly patients >age 75

- Evaluate if patient has multiple CVD risk factors, established CVD, *or* a history of revascularization procedures *and* good quality of life with no other major life-limiting diseases.

DISCUSSION

Lipids and CVD

NCEP–ATP II (1994) recommended screening all adults aged 20 years and older every 5 years with serum TC and with serum HDL-C, focusing on the TC/HDL ratio as the predictor for outcomes or treatment. The NCEP ATP-III Guideline identifies LDL-C as the primary focus of therapy. It also defines elevated serum TGs as a risk factor, along with a low HDL-C. This change in focus requires a fasting lipid profile to be obtained in order to make meaningful decisions. This new approach to dyslipidemia assessment moves away from the TC/HDL ratio as the predictor for outcomes or treatment initiation.

The USPSTF (2001) summary of the rationale for screening adults for dyslipidemia states:

> *In adults, mean TC increases with age for both men and women (NHANES III). In men, mean TC increases steadily from early adulthood to middle age and then reaches a plateau, falling only in men older than age 75. Mean TC is initially lower in premenopausal women than in men, but it rises at a similar rate. After menopause, however, women experience an additional 10- to 20-mg/dL rise, and their mean TC remains higher than for men throughout the remainder of life. HDL-C levels do not change greatly throughout adulthood and are consistently higher in women than in men (NHANES III). Mean TC is similar for those identifying themselves as Caucasian or African American (Sempos et al., 1993). HDL-C is higher for African Americans than for Caucasians.*
>
> *Large observational cohort studies have found a strong, graded relationship between increasing levels of LDL-C or decreasing levels of HDL-C and increasing risk of CVD events (Anderson et al., 1987; Neaton & Wentworth, 1992). The increased risk for CVD events is continuous, linear, and graded: No clear "cut-off" value separates normal from abnormal values. A 50-year-old man with a blood pressure of 120/80 mmHg, a TC of 180 mg/dL, and an HDL-C of 40 mg/dl has a 10-year risk for CHD events of 7 percent. If the same man had a TC of 240 mg/dL and an HDL-C of 30 mg/dL, his 10-year risk would be 14 percent, a relative risk of 2.0, and an absolute risk difference of 7 percent (Wilson et al., 1998).*

Screening Lipid Profile in Young Adults

There is insufficient evidence to recommend for or against screening of young adults, although it may be recommended on other grounds to young adults at high-risk, such as the greater absolute risk attributable to high cholesterol and potential long-term benefits of early lifestyle interventions. Risk factors include: family history of very high cholesterol, premature CVD in a first-degree relative (before age 55 in men or age 65 in women), diabetes, smoking, or hypertension. Screening is not recommended in males younger than 35 years or in females younger than 45 years in the absence of unusual family history of coronary events or existence of other non-lipid CV risk factors (e.g., hypertension, smoking) (Pignone et al., 2001).

Screening Lipid Profile in the Elderly

At a population level, patients of any age may benefit from general lifestyle recommendations to curtail dietary saturated fat and to perform aerobic exercise several times per week, regardless of the results of lipid screening. Targeted lipid screening of males aged 35 to 75 years and females aged 45 to 75 years is recommended in the primary prevention setting, based on the results of RCTs of lipid interventions. For every given age, the CVD risk for a female is the same as that for a male 10 years her junior.

The recommendation for screening up to age 65 is based on strong clinical and epidemiologic evidence. The AFCAPS/TexCAPS trial results (Downs et al., 1998) suggest that treating patients aged 65-73 is beneficial. Epidemiologic evidence suggests benefit in ages 65 to 75. The association of cholesterol and mortality weakens in elderly patients. However, screening should be performed if the patient has multiple CVD risk factors, established CVD, *or* a history of revascularization procedures *and* good quality of life with no other major life-limiting diseases.

EVIDENCE

	Recommendation	**Source**	**QE**	**Overall Quality**	**R**
1	Fasting lipid profile should be obtained in men ≥age 35 and women ≥age 45	NCEP ATP-III, 2002 USPSTF, 2001	I	Good	A
2	Fasting lipid profile should be obtained in patients with family history or clinical evidence of familial hyperlipidemia	NCEP ATP-III, 2002	I	Good	A
3	Consider screening fasting lipid profile in young adults with other risk factors (family history of premature CVD, HTN, or smoking)	NCEP ATP-III, 2002 Pignone et al., 2001 USPSTF, 2001 The Lovastatin Study Group, 1993	I	Fair	B
4	Fasting lipid profile should be obtained for patients with increased waist circumference (men >40 inches , women >35 inches) to aid in assessment of metabolic syndrome	NCEP ATP-III, 2002	I	Good	B
5	Persons with average or below average CV risk should be screened every five years	Working Group Consensus	III	Poor	I
6	Elderly patients age > 75 should be screened if they have multiple CVD risk factors, a history of CVD *and* good quality of life with no other major life-limiting diseases	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

F. Obtain a Fasting Lipid Profile

OBJECTIVE

Screen appropriate patients for the presence of dyslipidemia.

BACKGROUND

Lipid levels are preferably obtained in a fasting state. However, if the testing opportunity is nonfasting, only the values for TC and HDL will be usable. In otherwise low-risk persons (0–1 risk factor), further testing is not required if the HDL-C level is > 40 mg/dL and TC is <200 mg/dL. For persons with multiple (2+) risk factors, LDL-C levels are needed as a guide to clinical management.

The most common method for assessing serum lipid levels involves measuring TC, HDL-C and TG levels and then using the Friedewald formula to calculate the LDL-C [LDL =TC – HDL – (TG/5)]. TG concentrations, however, are affected by recent food intake and will affect the calculation of LDL-C (see Annotation G). Although nonfasting values may still provide useful information, treatment of dyslipidemia requires measurement of lipids in the fasting state. Therefore, patients should be fasting for at least 9-14 hours prior to lipid profile determinations to ensure an accurate LDL-C value.

Box 4. Lipid Screening Test

- Ensure test obtained in fasting state (9 to 14 hour fast)
- TC, TG, and HDL-C are measured directly
- LDL-C is calculated, therefore, TG level should be considered

(If TG > 400 mg/dL, try to reduce with diet and exercise, or consider direct measurement of LDL-C)

RECOMMENDATIONS

1. A complete fasting lipid profile should be obtained in an individual with other risk factors for coronary disease. [A]
2. Clinical decisions should be based upon lipid profiles done 1 to 8 weeks apart (fasting) with an LDL-C or TC difference of <30 mg/dL. [I]
3. Lipid profiles should not be obtained within 8 weeks of acute hospitalization, surgery, trauma, or infection unless they are obtained within 12-24 hours of the event to ensure accuracy. [I]
4. Lipid profiles should not be measured in pregnant women until three to four months post partum. [I]

DISCUSSION

LDL-C is routinely estimated from measurements of TC, TG, and HDL-C in the fasting state. If the TG level is below 400 mg/dL, this value can be divided by five to estimate the VLDL-C level. Since TC is the sum of LDL-C, HDL-C, and VLDL-C, a calculated level of LDL-C can be estimated by using the Friedewald (1972) formula as follows:

LDL-C = TC – HDL-C – TG/5 (Friedewald et al., 1972).

Intra-individual cholesterol measurement may vary up to 14 percent from an individual's average value (Cooper et al., 1992). The standard deviation of the differences in measured cholesterol values increases as the average cholesterol level increases. Therefore, some guidelines recommend that clinical decisions should be based upon lipid profiles done 1 to 8 weeks apart (fasting or no fasting) with an LDL-C or TC difference of less than 30 mg/dL. If the second result differs by more than 30 mg/dL, repeat again or calculate the average of the results.

Measurement of any lipid is preferably performed with the patient in a baseline stable condition, in the absence of acute illness. Recent acute hospitalization, MI, stroke, surgery, trauma, or infection may temporarily lower cholesterol levels up to 40 percent. Some medications can have an incidental negative impact on a patient's lipid profile. Progestins, estrogens, androgens, anabolic steroids, corticosteroids, cyclosporine, diuretics, protease inhibitors, and retinoids may raise cholesterol and/or TG levels.

If a lipid profile cannot be obtained immediately (within 12 to 24 hours of the event), a lipid profile can be obtained no less than 8 weeks post-event to obtain an accurate reading. Cholesterol levels increase by as much as 20 to 35 percent during pregnancy and should not be measured until three to four months after delivery.

EVIDENCE

	Recommendation	Source	QE	Overall Quality	R
1	A complete fasting lipid profile should be obtained in individuals with other risk factors for CAD	USPSTF, 2001	I	Good	A
2	Clinical decisions should be based upon lipid profiles done 1 to 8 weeks apart (fasting or no fasting) with an LDL-C or TC difference of less than 30 mg/dL	Working Group Consensus	III	Poor	I
3	Lipid profiles should not be obtained within 8 weeks post-acute hospitalization, surgery, trauma, or infection unless they are obtained within 12-24 hours of the event to ensure accuracy	Working Group Consensus	III	Poor	I
4	Lipid profiles should not be measured in pregnant women until three to four months post partum	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

G. If TG >400 mg/dL, Apply Diet and Exercise to Reduce TG; Consider Direct Measurement of LDL-C

OBJECTIVE

Identify patients whose LDL-C is confounded by secondary /modifiable causes of hypertriglyceridemia.

BACKGROUND

When TG levels are very high (over 400 mg/dL), the estimation of LDL-C using the Friedewald formula is not accurate. A direct measurement of the LDL-C can be performed using specialized laboratories. In addition, patients with significant elevated TG need further evaluation (see Annotation T).

In the management of dyslipidemia, therapy targeted at lowering LDL-C levels is the first priority to lower CVD risk. However, since many institutions continue to rely upon the calculated LDL value, and LDL-C can be affected by conditions which raise TGs, it is important to address the common, easily modifiable causes of hypertriglyceridemia with simple interventions (e.g., diet and exercise).

RECOMMENDATIONS

1. If TG levels can be brought to <400 mg/dL by dietary or other interventions, then Friedewald's formula can be used to calculate a more exact LDL-C level. [C]

2. If TGs cannot be brought to levels less than 400 mg/dL, then consider measuring LDL-C directly, or estimate the LDL-C using the following equation: [I]

   Estimated LDL-C = (TC – HDL) – 30
3. Screen and treat common causes of elevated TGs: fatty diet, high carbohydrate diets, alcohol use, hypothyroidism, and hyperglycemia. [B]
4. In the absence of secondary causes, the first-line therapy for elevated TGs should be therapeutic life-style changes. [C]

DISCUSSION

The Friedewald calculation [LDL-C = total cholesterol - (HDL-C + TG/5] yields an unacceptable inaccurate estimation of the LDL-C in patients with TGs >400. Also, simple reversible processes, which raise triglycerides, also raise LDL-C. When resolutions of these causes of hypertriglyceridemia are addressed, the LDL-C may also be modified. In the absence of reversible causes of hypertriglyceridemia there are three options to obtain an accurate LDL-C measurement: 1) Perform a direct LDL-C measurement using a specialized laboratory, 2) Estimate the LDL-C using the adjusted non-HDL equation, or 3) Attempt to modify the triglycerides using therapeutic lifestyle changes (TLC) and estimate the LDL-C when the triglyceride level is <400.

Since non-HDL-C levels tend to be approximately 30 mg/dL greater than estimated LDL levels, the estimated LDL from this equation will be approximately 30 points lower and LDL goals need to be interpreted accordingly. Estimated LDL-C = (TC – HDL) – 30 mg/dL.

Hypertriglyceridemia can be caused by or exacerbated by an underlying medical disorder. When secondary disorders of hyperlipidemia are appropriately treated, TG levels can greatly improve or, in some cases, even return to the normal range. For other conditions associated with high level of TG see Annotation L1, Table 1)

EVIDENCE

	Recommendation	**Source**	**QE**	**Overall Quality**	**R**
1	Use Friedewald's formula to calculate LDL-C – when TG levels can be brought to <400 mg/dL by dietary or other interventions	Friedewald et al., 1972 NCEP ATP-III, 2002	III	Fair	C
2	If TGs are >400 consider directly measuring LDL-C	Friedewald et al., 1972 NCEP ATP-III, 2002 Stone & Blum, 2002	III	Poor	I
3	Screen and treat common causes of elevated TGs	Cleeman, 1998 Friedewald et al., 1972 NCEP ATP-III, 2002 Stone & Blum, 2002	II-3	Fair	B
4	In the absence of secondary causes, the first-line therapy for elevated triglycerides should be therapeutic life-style changes	Cleeman, 1998 Friedewald et al., 1972 NCEP ATP-III, 2002 Stone & Blum, 2002	II-3	Poor	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

H. Is Lipid Profile Abnormal?

OBJECTIVE

Identify patients who require further evaluation and/or therapy for dyslipidemia.

BACKGROUND

In the VA/DoD guideline for Dyslipidemia (1999), initial classification for primary prevention was based on measurement of TC and HDL-C. This guideline recommends measurement of LDL-C for screening purposes. This measurement requires a fasting lipid analysis that includes total cholesterol, HDL-C, TG and estimation of LDL-C. Classifications of these serum lipids are shown in Box 5. Persons with very high LDL-C concentrations can have one of several familial forms of hypercholesterolemia.

Classification of Serum Lipids

Numerous epidemiological studies and clinical trials have shown a link between CVD and dyslipidemia, particularly elevated TC and LDL-C. Some evidence indicates that HDL-C protects against the development of atherosclerosis, and serum levels inversely correlate with risk for CVD. Although controversial, there is also some evidence that increasing levels of TG may be a risk for cardiovascular disease. (See Annotation U)

Box 5. Classification of Serum Lipids

Total Cholesterol (TC) mg/dl (mmol/L)	**Category**
< 200 (< 5.2)	Normal
200 - 239 (5.2 - 6.1)	Borderline high
≥ 240 (≥ 6.2)	High
LDL- Cholesterol mg/dl (mmol/L)	
< 100 (< 2.6)	Normal
100 - 129 (2.6 - 3.3)	Above, near optimal
130 - 159 (3.4 - 4.0)	Borderline high
160 - 189 (4.1 - 4.8)	High
≥ 190 (≥ 4.9)	Very high
HDL- Cholesterol mg/dl (mmol/L)	
< 40 (<1.0)	Low
≥ 60 (≥ 1.6)	High
Triglycerides (TG) mg/dL (mmol/L)	
<150 mg/dL (< 1.7)	Normal
150 - 199 mg/dL (1.7 - 2.2)	Borderline High
200 – 499 mg/dL (2.3 - 5.6)	High
≥ 500 mg/dL (≥ 5.6)	Very High

RECOMMENDATIONS

1. Patients with LDL >130 mg/dL, HDL <40 mg/dL, or TG >200 mg/dL should be assessed for further management of dyslipidemia. [C]

DISCUSSION

Epidemiological studies have shown a direct relationship between elevated cholesterol and the incidence of CVD (Law et al., 1994; Law, 1999). Elevated LDL-C is the most significant lipid abnormality for determining treatment goals, as many clinical trials have consistently shown that lowering LDL results in a reduced incidence of CVD. Recent studies with statins indicate that a 1 percent decrease in LDL-C reduces the risk for CVD by 1 percent (See Appendix F). LDL-C levels <100 mg/dl are associated with a very low-risk for CVD in the population and therefore, are considered optimal. Patients without known CVD who have an LDL lower than 130 mg/dL have a relatively low incidence of cardiovascular events therefore levels of 100 – 129 mg/dl are

considered near, but above optimal (Kannel, 1995). At borderline high LDL-C levels, 130-159 mg/dl, atherogenesis proceeds at a significant rate and accelerates as LDL-C increases, with a very high-risk at levels ≥190 mg/dl. Low HDL-C is inversely associated with an increased risk for CVD. Although no threshold for low HDL has been identified, an arbitrary value of <40 has been set as being low by the NCEP ATP-III (2002), and appears to be a reasonable set point. Elevated TG levels may be associated with increased risk for CVD and are commonly associated with other lipid and nonlipid risk factors. In persons with no CVD risk factors TG levels are typically less than 100 mg/dl. Epidemiological studies suggest when TG levels are ≥ 200 mg/dl; the presence of increased quantities of atherogenic lipoproteins can heighten CVD risk beyond that predicted by LDL-C alone. However, there are no trials focusing on treatment of elevated triglycerides alone to lower adverse coronary events.

EVIDENCE

	Recommendation	Source	QE	Overall Quality	R
1	Classify Serum Lipid levels based on degree of elevation of LDL, TG, or low HDL	NCEP ATP-III, 2002	II-2	Good	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

I. Encourage Healthy Lifestyle

OBJECTIVE

Promote lifestyle changes that will decrease the risk of CVD.

BACKGROUND

A healthy lifestyle is the foundation of primary prevention of CVD. A healthy lifestyle also decreases the risk of developing other co-morbid conditions that increase the risk of CVD such as diabetes, elevated blood pressure, and depression.

RECOMMENDATIONS

1. All adults should be encouraged to adopt healthy lifestyles that may reduce the risk of cardiovascular disease, to include:
    a. Tobacco cessation interventions offered to all smokers [A]
    b. Eat a healthy diet [B]
    c. Engage in 30 minutes or more of moderate intensity physical activity on most days of the week. [B]

DISCUSSION

Smoking, diet, and exercise, habits are prominent modifiable risk factors to be considered in prevention efforts. Clinical trials, as well as epidemiologic studies, support the association of a high-fat/cholesterol diet, sedentary lifestyle, and obesity with increased risk of CVD. All patients should be advised on lifestyle changes as a matter of general health (NCEP ATP-III, 2002), and appropriate referral for counseling may be advisable. There is evidence that CVD risk can be reduced with lifestyle modifications.

Smoking Cessation

Smoking cessation is one of the most effective ways to reduce risk for CVD and other atherosclerotic diseases. Research demonstrates that the physician's advice to stop smoking increases quit rates compared with the absence of such advice (USDHHS, 2004). Furthermore, there is substantial evidence that even brief smoking cessation treatments can be effective. All physicians should strongly advise every patient who smokes to stop smoking, as their advice is often a key factor in patient’s decision to stop.

The USPSTF Update to the Preventive Services guideline 2003 stated:

- The USPSTF strongly recommends that clinicians screen all adults for tobacco use and provide tobacco cessation interventions for those who use tobacco products

- Brief tobacco cessation counseling interventions, including screening, brief counseling (3 minutes or less), and/or pharmacotherapy, have proven to increase tobacco abstinence rates, although there is a dose-response relationship between quit rates and the intensity of counseling. Effective interventions may be delivered by a variety of primary care clinicians.

For detailed analyses of the evidence and recommendations, see the VA/DoD Clinical Practice Guideline for Tobacco Use – Update 2003

Physical Activity

A sedentary lifestyle is associated with a twofold increase in CVD risk (Blair, 1994). Clinicians should advise patients of all ages to follow a well-balanced exercise plan consisting of stretching, aerobic activity, and strengthening (Mazzeo et al., 1998). Although the exact exercise parameters for optimal CVD prevention have been difficult to determine, research clearly demonstrates a dose-response relationship to risk reduction with increasing activity and caloric expenditure (Pate et al., 1995; Joint British recommendations, 1998). Therefore, current exercise guidelines for the general population are that every adult in the United States accumulate 30 minutes or more of moderate intensity aerobic physical activity on most (and preferably all) days of the week (Pate et al., 1995; ACSM, 1995; Pollock & Wilmore, 1990; Spate-Douglas et al., 1999). Patients who need specialized exercise programs may be referred to an exercise professional.

Healthy Diet

Healthy eating habits contribute to lowering risk factors for CVD. Therefore, patients should be encouraged to maintain healthy eating habits that include intake of a variety of fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, and sources of protein low in saturated fat (e.g., poultry, lean meats, plant sources). Patients should limit saturated fat intake to <10 percent of calories, limit cholesterol intake to <300 mg/dL, and limit intake of trans fatty acids (NCEP ATP-III, 2002).

Maintaining a healthy weight also contributes significantly to lowering CVD risk. Clinicians should encourage maintenance of a healthy weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated, to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference <40 inches for men and <35 inches for women.

Weight loss, Excessive Alcohol Intake, Stress

Many experts also recommend the following additional lifestyle modifications:
- Limitation of alcohol intake to one or two drinks per day
- Stress management

EVIDENCE

	Recommendation	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	Advise patients to stop smoking	PHS, 2000 Silagy & Stead, 2001 USPSTF, 1996 & 2003	I	Good	A
2	Provide tobacco cessation interventions to smokers	PHS, 2000	I	Good	A
3	Provide interventions to	Beresford et al., 1997	I	Fair	B

	encourage a healthy diet	McCarron et al., 1997 USPSTF, 1996			
4	Encourage 30 minutes or more of moderate intensity aerobic physical activity on most days of the week	Pate et al., 1995 ACSM, 1995 Pollock & Wilmore, 1990 Spate-Douglas et al., 1999	I IIa	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

J. Repeat Dyslipidemia Evaluation in 1 to 5 Years

OBJECTIVE

Provide appropriate clinical follow-up for patients initially at low-risk for CVD.

RECOMMENDATIONS

1. Patients with average or below average risk for atherosclerotic events should be screened for dyslipidemia every five years. [B]

DISCUSSION

If the initial dyslipidemia screening reveals a TC <200 mg/dL or LDL-C <130 mg/dL AND HDL-C >40 mg/dl, the patient—in the absence of other risk factors—will be of average or below average risk for atherosclerotic events over a five-year period.

Because TC and LDL-C tends to increase with advancing age, patients at initially average risk for CVD events may, over time, become patients at above-average risk or may develop concurrent health conditions (nephrotic syndrome, hypothyroidism, and diabetes) that can present as dyslipidemia. Re-assessment of the lipid profile five years after an initially favorable dyslipidemia screening permits timely identification and treatment of such individuals.

EVIDENCE

	Recommendation	**Source**	**QE**	**Overall Quality**	**R**
1	Patients with average or below average risk for atherosclerotic events should be screened for dyslipidemia every five-year period	NCEP ATP-III, 2002 The Lovastatin Study Group, 1993	III	Fair	B

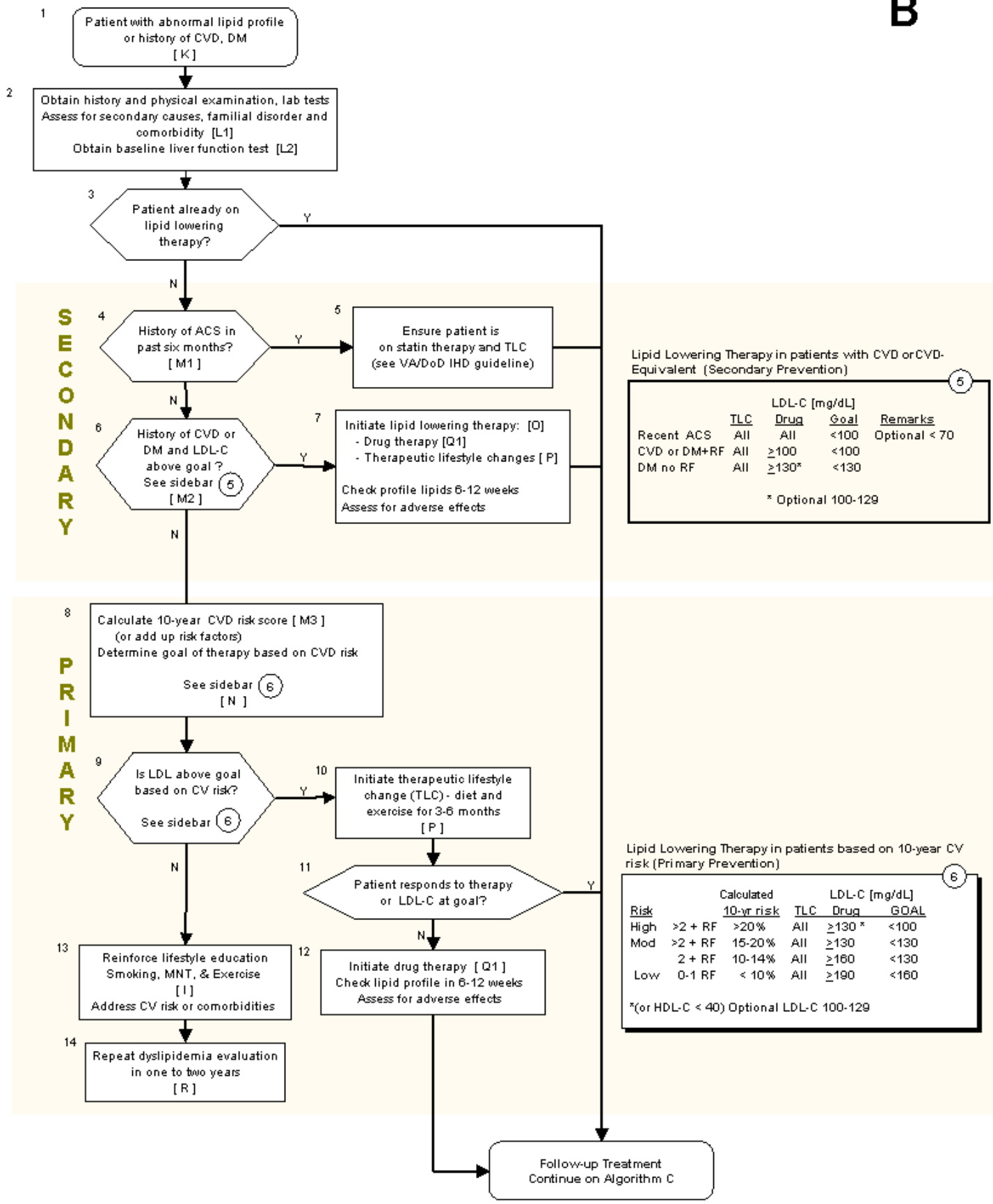
QE = Quality of Evidence; R = Recommendation (see Appendix A)

Management of Dyslipidemia

Module B: Initiation of Therapy

2/3/2006

B



CVD - Cardiovascular disease ; DM - Diabetes Mellitus; MNT -Medical Nutrition Therapy; TLC - Therapeutic Lifestyle Changes; HDL-C - High density lipoprotein cholesterol; LDL-C - Low density lipoprotein cholesterol; TG - Triglycerides; RF - Risk Factor

ANNOTATIONS

K. Patient with Abnormal Lipid Profile or History of CVD or Diabetes

DEFINITION

Patients managed by this guideline algorithm have abnormal lipid profiles (dyslipidemia) or evidence of cardiovascular disease (CVD) or diabetes.

L1. Obtain History, Physical Examination, and Laboratory Tests. Assess for Secondary Causes, Familial Disorders, and Comorbidities

OBJECTIVE

Detect and if needed treat health disorders that present with an elevated LDL-C or TG, low HDL-C, or metabolic syndrome.

BACKGROUND

Several underlying conditions may influence lipid levels. Addressing these underlying conditions can improve or normalize underlying lipid abnormalities. Failure to address these can render therapy sub-optimal or ineffective. When treating potential causes of secondary hyperlipidemia, the provider should follow up the lipid levels at a reasonable time, usually six to eight weeks, following correction of any such underlying disorder. Even with successful treatment of a secondary cause of hyperlipidemia, intervention with appropriate pharmacologic agents to lower cholesterol and/or triglycerides TG levels may be required. Initial laboratory tests will also provide the baseline values for any lipid lowering therapy that may be initiated.

RECOMMENDATIONS

1. Adults with abnormal lipid profiles (dyslipidemia) should be assessed for secondary causes, familial disorders, and other underlying conditions that may influence lipid levels. [I]

2. Assessment for secondary causes should be based on medical history, physical examination and laboratory tests:

    2.1. Measurement of serum thyroid-stimulating hormone (TSH), BUN/creatinine, liver function tests (LFTs), and a dipstick urinalysis should be obtained to exclude hypothyroidism, chronic renal failure, obstructive liver disease, and nephrotic syndrome conditions. [I]
    2.2. If dipstick urine protein is >1+ (detected in two urine tests), nephrotic syndrome as a secondary cause of elevated LDL-C should be ruled out. [I]
    2.3. Serum lipids should be assayed six to eight weeks post-TSH normalization to determine the need for additional treatment. [I]
    2.4. Patients with hypertriglyceridemia should be evaluated for alcohol use, diabetes, and hypothyroidism. Addressing these underlying conditions can improve or normalize triglyceride levels, and failure to address these can render therapy ineffective. [I]
    2.5. Lipid levels in patients treated for secondary hyperlipidemia should be repeated six to eight weeks post correction of the underlying disorder.
    2.6. Family members of patients presenting with very severe hypercholesterolemia should be screened to detect other candidates for therapy.
    2.7. Consider consulting with a specialist to assist the primary care clinician in co-managing patients with familial disorders who do not respond to therapy. [I]

Table 1. Secondary Causes of Lipid Abnormalities

Disorder/Patient Characteristic	Effect on Lipids	Laboratory Test
Chronic renal failure/ post renal transplantation	↑ TG, ↑ TC, ↓ HDL-C	S_{Cr}
DM	↑ TG, ↑ TC, ↓ HDL-C	Glucose, HbA1c
Ethanol use	↑ TG, ↑ HDL-C	--
HIV/AIDS Wasting	↑ TG, ↓ TC, ↓ HDL-C, ↓ LDL-C	--
HIV/AIDS (HAART)	↑ TG, ↑ TC, ↑ LDL-C	--
Hypothyroidism	↑ TG, ↑ TC, ↑ LDL-C	TSH
Inactivity	↓ HDL-C	--
Nephrotic syndrome	↑ TC, ↑ LDL-C	Urinalysis, serum albumin
Obesity	↑ TG, ↓ HDL-C	--
Obstructive liver disease	↑ TC	LFTs (Alkaline phosphatase, total bilirubin)
Estrogen therapy	↑ TG, ↓ LDL, ↑ HDL	--
Medications	Variable	--

AIDS = acquired immune deficiency syndrome; DM = diabetes mellitus; HAART = highly active antiretroviral therapy; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; LFTs = liver function tests; S_{Cr} = serum creatinine; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.

DISCUSSION

Consider and Treat Secondary Causes of Elevated LDL- C

Hypothyroidism raises serum LDL. A normal serum TSH level adequately rules out the common condition of primary hypothyroidism. TSH alone cannot exclude the rare condition of secondary hypothyroidism (hypothalamic or pituitary insufficiency). If there is any clinical suspicion of this condition, serum thyroxine (T_4) should be measured. Normal TSH and normal T_4 effectively rule-out the possibility of secondary hypothyroidism.

Treatment of severe hypothyroidism (manifested by very high TSH and/or very low T_4) with oral L-thyroxine replacement often lowers elevated LDL to the normal range; treatment of mild, or subclinical, hypothyroidism has considerably less impact on the serum LDL. In either case, serum lipids should be assayed six to eight weeks after normalization of the serum TSH (or T_4, in the case of secondary hypothyroidism) to see if any additional treatment is needed (Stone et al., 1997; NCEP III, 2002).

Nephrotic syndrome is a secondary cause of dyslipidemia (Stone et al., 1997; NCEP III, 2002). Nephrotic syndrome is characterized by excessive urinary protein excretion, which may be detected by routine dipstick urine testing. If the dipstick test is positive, then a spot urine-protein creatinine ratio should be obtained. If an abnormal ratio (≥3g/day) is discovered, referral to a nephrologist for further evaluation and management is appropriate.

Consider and Treat Secondary Causes of Hypertriglyceridemia

Hypertriglyceridemia can be caused by or exacerbated by an underlying medical disorder. When secondary disorders of hyperlipidemia are appropriately treated, TG levels can greatly improve or, in some cases, even return to the normal range. Hypertriglyceridemia has been associated with obesity and alcohol use/abuse. The

need to screen for underlying alcohol use, together with a critical review of dietary habits, cannot be overemphasized (Oberman et al., 1992). Diabetes mellitus (especially suboptimally controlled), and hypothyroidism, have also been documented as potential causes for hypertriglyceridemia (See Table 1).

Consider Medication

Some medications can have an incidental negative impact on a patient's lipid profile. Progestins, estrogens, androgens, anabolic steroids, corticosteroids, cyclosporine, protease inhibitors, diuretics, and retinoids may raise cholesterol and/or TG levels. A thorough review of the patient's chart and previous lipid panels may support the possibility of a drug side effect as the etiology for the lipid abnormality, or a trial of the suspected agent may be required for confirmation. Of note, oral estrogens have been associated with significant hypertriglyceridemia, which resolved with the discontinuation of the oral preparation. Many of these patients appear to be able to tolerate estrogen patch therapy without recurrence of the TG elevations. Progestins have been shown to decrease HDL, thereby counteracting the HDL-raising effects of estrogen therapy.

Familial Hypercholesterolemia

Most severe forms of hypercholesterolemia are the result of genetic disorders. Hypercholesterolemia is characterized by severe elevations of LDL-C (>200 mg/dL), tendinous xanthomas and xanthelasmae on physical examinations, and premature CVD. Familial combined hyperlipidemia is characterized by elevations of TC, TG, or both, in different members of the same family, and is associated with premature CVD. Family members of patients presenting with very severe hypercholesterolemia should undergo screening to detect other candidates for therapy. A consultation with a specialist is recommended to assist the primary care clinician in co-managing these patients.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Detect and treat secondary cause of dyslipidemia	NCEP ATP-III, 2002 Stone et al., 1997 Stone & Blum, 2002	III	Poor	I
2	Refer familial hypercholesteremia to specialist	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

L2. Obtain Baseline Serum Transaminase (ALT/AST) Prior to Starting Lipid Lowering Therapy

OBJECTIVE

Establish baseline transaminase monitoring parameters prior to initiating lipid lowering therapy.

BACKGROUND

Asymptomatic increases in transaminases to greater than three times the upper limits of normal (ULN) on two consecutive lab tests is estimated to occur 0.1 - 2 percent in patients receiving lipid-lowering drug treatment (incidence is similar to patients treated with placebo). In case of statins, elevations are usually transient and may normalize even with continued therapy or may not reoccur even with reintroduction of the same statin dose. Nonetheless, patients should be monitored until the transaminase has normalized.

RECOMMENDATIONS

1. Baseline serum transaminase (ALT/AST) should be obtained prior to starting lipid-lowering therapy. [I]

2. Levels of serum transaminase (ALT/AST) should be obtained in patients on statin, 6-12 weeks after starting statin therapy, and/or change in dose or combination therapy, then annually or more frequently, if indicated. [I]
3. Levels of serum transaminase (ALT/AST) should be obtained in patients on niacin, 6-12 weeks after reaching a daily dose of 1,500 mg and 6-12 weeks after reaching the maximum daily dose, then annually or more frequently, if indicated. [I]

DISCUSSION

Statins are tolerated well by most persons. It is reported that elevated hepatic transaminases generally occur in 0.5 percent to 2 percent of cases and are dose dependent (Hsu et al., 1995, Bradford et al., 1991). It has not been determined whether transaminase elevation with statin therapy constitutes true toxicity. Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with re-challenge or selection of another statin. No specific evidence exists showing exacerbation of liver disease by statins; however, statin use is contraindicated in patients with cholestasis and active liver disease (Cressman et al., 1988; Hunninghake, 1990).

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Statins— Evaluate ALT/AST initially, approximately 6-12 weeks after starting, then annually or more frequently, if indicated	NCEP ATP-III, 2002	III	Poor	I
2	Nicotinic Acid— Evaluate ALT/AST initially, 6-12 weeks after reaching a daily dose of 1,500 mg, 6-12 weeks after reaching the maximum daily dose, then annually or more frequently, if indicated	NCEP ATP-III, 2002	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

M1. History of Acute Coronary Syndrome in Past 6 Months?

OBJECTIVE

Identify patients with recent acute coronary syndrome (ACS) for whom there is a compelling need for statin therapy regardless of current lipid levels.

BACKGROUND

Patients with ACS are at high-risk for suffering recurrent coronary events in the near term. Based on recent studies it is recognized that moderate- to high-dose statins are a key element of the post-ACS management strategy regardless of the lipid profile at the time of the event (see Annotation N for target levels of therapy).

RECOMMENDATIONS

1. A lipid panel should be drawn at the time of admission for all patients with suspected acute coronary syndrome (ACS). [C]
2. Initiating a moderate- to high-dose statin therapy prior to hospital discharge may be considered in patients admitted with ACS irrespective of their lipid profile. [B]
3. Patients with recent ACS (within the past 6 months) should be on a moderate dose of statin therapy to reduce LDL-C level below 100 mg/dL. [A]

4. A lower target (70 mg/dL) may be considered for very high-risk patients. [B]

DISCUSSION

Patients with ACS are at very high-risk for early recurrence of coronary events. Several large registries (Swedish and German post-MI registries, Mayo Clinic Registry), have demonstrated an increased risk for recurrent AMI in patients who were discharged without a statin. The only randomized study, The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Trial (2001), confirmed that intensive LDL-lowering did reduce recurrent events for up to 18 months. The PROVE-IT (2004) trial also supports the evidence for early initiation of statin therapy in the post-ACS population. Therefore, moderate- to high-dose statins should be a key element of the post-ACS management strategy regardless of the lipid profile at the time of the event.

The update to NCEP-ATP III (Grundy, 2004) suggested, based on both HPS and PROVE IT, that additional benefit may be obtained by reducing LDL levels to substantially below 100 mg/dL. This likelihood is enhanced by the finding that intensive lowering of LDL-C to well below 100 mg/dL will reduce progression of coronary atherosclerotic lesions.

EVIDENCE

	Recommendation	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	For patients admitted with ACS, a lipid panel should be drawn at the time of admission	Working Group Consensus	III	Poor	C
2	Patients should be started on moderate- to high-dose statins prior to hospital discharge and irrespective of their lipid profile	Bybee et al., 2002 Lorenz et al., 2005 Stenestrand & Wallentin, 2001	I	Good	B
3	If not started on a statin prior to hospital discharge, then one should be started within 6 months post-ACS	A to Z, 2004 PROVE-IT, 2004	I	Good	A
4	An optional lower target for LDL-C may be considered for post-ACS patients	PROVE-IT, 2004	I	Good	B

QE = Quality of the Evidence; R = Strength of Recommendations (see Appendix A)

M2. History of CVD or DM and LDL-C Above Goal?

(See Module A, Annotations B and C)

M3. Calculate 10-Year Risk Score for CVD

OBJECTIVE

Determine short-term risk (i.e., over ten years) as the basis for determining the type and intensity of interventions.

BACKGROUND

The magnitude of efficacy of interventions for dyslipidemia in preventing CVD is dependent upon the absolute risk for coronary heart disease as determined by a compilation of major risk factors. The higher the

risk, the greater the absolute risk reduction associated with dyslipidemia interventions. Determining short-term risk (i.e., over ten years) serves as the basis for determining the type and intensity of interventions.

RECOMMENDATIONS

1. A global 10-year risk for CVD should be calculated to assess the short-term (10-year) absolute risk of a CVD event. [A]
2. The Framingham Risk Calculator should be used, as it is the most commonly used and readily available calculator validated in numerous populations. [I]
   http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof
3. Other risk markers or measure of atherosclerotic burden may be useful to adjust the risk category, if they have been validated to have independent prognostic value. [C]

DISCUSSION

Using conventional risk factors (age, male gender, blood pressure, tobacco smoking, and cholesterol level) to derive a composite measure of absolute risk for CVD in the subsequent 10 years is now recommended by the AHA and NCEP as an initial step to determine the type and intensity of lipid interventions (NCEP ATP-III, 2002; Sheridan et al., 2003; Grundy et al., 1999; Wilson et al., 1998; Bethesda Conference, 1996; Grundy et al., 2001; Grundy et al., 1999). There are several risk prediction tools, all of which use conventional risk factors (Sheridan et al., 2003). The most commonly used calculator is derived from the Framingham Study that has been validated in multiple U.S. and international populations (Sheridan et al., 2003; Grundy et al., 1999; Wilson et al., 1998). Its limitations include overestimation of risk in younger (<age 40) populations and certain ethnic groups (e.g., Japanese and Hispanic) as well as potentially creating a false sense of reassurance in young populations with high relative risk but low absolute risk, since age is the strongest variable in predicting CVD risk. There are no clinical trials that have determined the clinical outcomes impact of using a risk calculator for lipid intervention decision-making. However, since all of the lipid trials have proven efficacy only in patients at high absolute risk, it is rational to use a systematic tool to accurately define whether a patient meets the characteristics of the populations in whom lipid-lowering therapies have proven effective.

Risk Score Calculation and Validity of Scoring Tools

Strategies that explicitly consider CVD risk factors in addition to lipid levels are more accurate than those that measure only lipid levels. Grover et al. found that a Framingham-based coronary risk model was a better predictor of CVD mortality compared to LDL-C/HDL-C ratio, TC/HDL-C ratio, or TC alone (Grover et al., 1995).

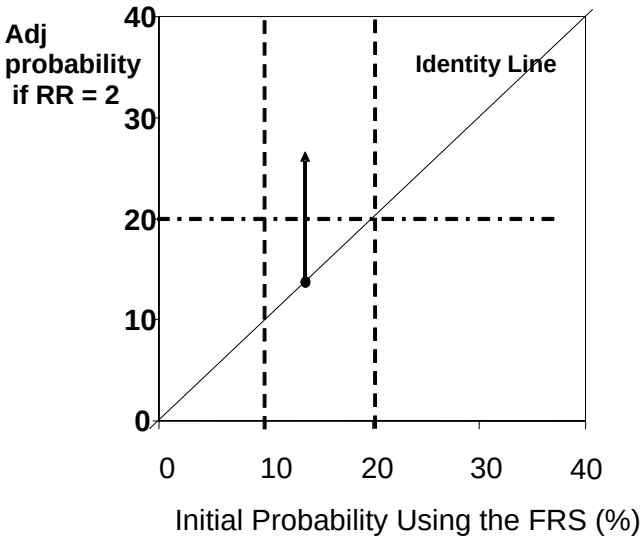
In a later study, Grover et al. (2000) found that the Framingham risk equations were more accurate than counting risk factors for predicting coronary artery disease (CAD) risk. Risk counting was a particularly poor method for predicting risk for women. Calculating risk using risk equations is a more accurate method to identify people at high-risk for CVD than counting the number of risk factors present, especially for women.

There is emerging evidence that genetic, serologic, physiologic, psychosocial, and anatomic markers of CHD risk can add prognostic value to the Framingham Risk Score (FRS) (Ridker, 2001; Pearson et al., 2003; O'Donnel et al., 2004; Ford et al., 1998; Greenland et al., 2000 & 2004; Pletcher et al., 2004). The risk markers with proven independent prognostic value are: High Sensitivity C-reactive Protein (hsCRP) (>3mg/dL), first degree family history of premature CAD, metabolic syndrome, elevated carotid intima-media thickness, decreased brachial artery reactivity, history of major depressive disorder, coronary artery calcification (>75percent for age and gender), and microalbuminuria with impaired renal function.

Although there is insufficient evidence at this time to recommend routine screening for these risk markers, it may be useful in the intermediate risk patient for whom it is less convincing that drug therapy would have a meaningful impact on outcomes. If any of this information is in the abnormal range, it would be reasonable to multiply the predicted ten-year risk calculated from the FRS by the adjusted relative risk associated with the abnormal risk marker, and then base dyslipidemia management on the resulting category of risk. (See Figure 1

for a schematic on how to adjust risk based on new information from new independent prognostic information). However, at this time such a strategy of risk determination for the purposes of guiding lipid management has never been proven to be associated with improved outcomes.

Figure 1. Incorporating New Test Information to Determine Risk of CHD



Schematic to help adjust the 10-year risk associated with new test information (e.g., C-reactive protein [CRP] or high coronary artery calcium [CAC] scores on electron beam computed tomography [EBCT]) that has incremental prognostic value, independent of conventional risk factors (i.e., FRS). One should first determine the 10-year risk using the FRS to determine the x-axis point on the identity line, and then use the adjusted relative risk associated with the new information to multiply the 10-year FRS. For example, if the FRS indicates a 10-year risk of 13 percent, and the patient has a high CRP (>3mg/L) which has an approximate adjusted relative risk of 2, then the adjusted 10yr risk would be 13 percent x 2 = 26 percent (i.e., a CHD risk equivalent). While a rational approach, such a strategy of refining risk has not been sufficiently validated in prospective studies, but can be helpful in guiding care in the face of uncertainty surrounding new prognostic test information.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	A global 10-year risk for CVD should be calculated to assess the short-term (10 years) absolute risk of a CVD event	Grover et al., 1995 & 2000 Grundy et al., 2004	I	Good	A
2	The Framingham Risk Calculator is the most commonly used and readily available calculator validated in numerous populations	Grundy et al., 1999 Sheridan et al., 2003 Wilson et al., 1998	III	Poor	I
3	Other risk markers or measures of atherosclerotic burden may be useful to adjust	Ford et al., 1998 Greenland et al., 2000 & 2004 O'Donnel et al., 2004	III	Fair	C

	the risk category	Pearson et al., 2003 Pletcher et al., 2004 Ridker, 2001			

QE = Quality of Evidence; R = Recommendation (see Appendix A)

N. Determine Risk for CVD and Establish the Goal for Interventions

BACKGROUND

Once a 10-year risk has been calculated, the goals of therapy can be determined based upon the absolute 10-year risk. Risk calculation is not necessary for patients with documented CVD or CVD equivalent, and secondary prevention for these patients is appropriate.

Table 2. Goals of Lipid Lowering Therapy

	Risk Category	Number of Risk Factors (RF)	10-Year Risk	LDL-C Goal * mg/dL	Remarks
1	Recent ACS	N/A	N/A	<100	Option <70 mg/dL
2	CHD or equivalent (DM with other risk factors)	N/A	N/A	<100	Optional <130 for DM with no other risk factors
3	High	2 + RF	≥ 20%	<100	--
4	Intermediate	2 +RF	15 - 20%	<130	--
5			10 - 14% **	<130	--
6	Low	0-1 RF	N/A	<160	--

N/A = Not applicable

* Recommendations are based on quality of evidence for improving CVD outcomes.

** There is insufficient evidence at this time to recommend routine screening for other risk markers not included in the risk index (e.g., FH, hsCRP, metabolic syndrome, depression), or evidence of significant atherosclerotic burden (e.g., high coronary artery calcification scores, intima medial thickness, abnormal brachial reactivity, or abnormal ankle-brachial index). These risk markers have independent prognostic value whereby abnormal values can shift risk percent upward across treatment thresholds with more robust evidence for efficacy. Therefore, they may be useful in the intermediate risk patient for whom it is less convincing that drug therapy would have a meaningful impact on outcomes. Example: Patient with a 10-year risk of 13 percent in whom an abnormal test with a proven adjusted relative risk of >2 would shift the patient to a high-risk category (across a 20 percent, 10-year risk threshold).

RECOMMENDATIONS

1. Goals of lipid lowering therapy should be tailored to risk level and based upon the balance between benefits, risks, and patient preferences. [C]

Goals of Therapy for Secondary Prevention

2. LDL-C should be lowered to <100 mg/dL for patients with a recent ACS. [A]
3. An optional lower target for LDL-C (<70 mg/dL) may be considered for very high-risk post-ACS patients. [B]
4. LDL-C should be lowered to <100 mg/dL for patients with previous documented CHD or CVD equivalent (DM with other major risk factors) for secondary prevention. [A]
5. LDL-C should be lowered to <130 mg/dL for patients with DM without other major risk factors for secondary prevention. [C]

Goals of Therapy for Primary Prevention

6. LDL-C should be lowered to <100 mg/dL for patients with high 10-year risk >20 percent. [B]
7. LDL-C should be lowered to <130 mg/dL for patients with intermediate 10-year risk (15-20 percent). [B]

8. LDL-C should be lowered to <130 mg/dL for patients with intermediate 10-year risk (10-14 percent). [C]
9. LDL-C should be lowered to <160 mg/dL for patients with low 10-year risk. [I]
10. LDL-C reduction of 30-40 percent from baseline may be considered an alternative therapeutic strategy for patients who can not meet the above goal.

DISCUSSION

Targeting therapy to risk is based on the findings from multiple intervention trials that the magnitude of benefit is closely related to the short-term predicted risk of a CHD event (Wilson et al., 1998; Grundy, 2004). Other than the Post-Coronary Artery Bypass (CABG) trial (1997) and the recent (TNT) trial (2005), there are no published clinical outcomes trials that have used LDL goals as a pre-specified target of therapy. Thus, determining LDL goals for therapy is based on limited objective data.

Prospective epidemiologic evidence indicates that the incidence of CHD is proportional to serum TC and LDL-C. Thus, it is theoretically rational that the lowering of CVD risk will be directly related to the lowering of cholesterol. Whether this relationship continues to be linear at very low LDL levels (<100 mg/dL) is a subject of continuing research.

Secondary Prevention

In ACS, there are several trials among patients who derived improved outcomes from aggressive LDL lowering to mean LDL levels well below 100 mg/dL (PROVE-IT, 2004; MIRACL, 2001; REVERSAL, 2004). In PROVE-IT, ACS patients randomized to high dose atorvastatin with an LDL goal of less than 70 mg/dL achieved fewer major cardiovascular events compared to patients treated to a goal of less than 100 mg/dL on pravastatin. There appeared to be a threshold effect where benefits were most pronounced among patients with a baseline LDL 125 mg/dL or greater (Absolute Risk Reduction [ARR] 8.5 percent) than those with baseline LDL of less than 125 mg/dL (ARR 2.1 percent). Thus, most benefit will occur in patients with higher starting LDL levels who achieve at least a goal of <100 mg/dL. Given the overall nature of the PROVE-IT trial to achieve a goal of <70 mg/dL, it may be reasonable to pursue an optional therapeutic goal of LDL-C <70 mg/dL in patients with ACS (Grundy et al., 2004).

Numerous secondary prevention high quality randomized trials using statin medications have shown reduction in CHD morbidity and mortality. The mean "on-treatment" LDL-C of the cohorts in these trials was well below <120 mg/dL (HPS, 2002; PROVE-IT, 2004; A to Z, 2004; TNT, 2005; CARE, 1996). While several of these trials had mean on-treatment LDL levels <100 mg/dL, and NCEP recommends a goal of <100 mg/dL in such patients, such a threshold has not been sufficiently proven in stable CHD patients or primary prevention high-risk cohorts. However, more recently there have been two trials that showed benefit to more aggressive treatment in stable high-risk secondary prevention patients. LDL-C was lowered in HPS from 130 to 89 mg/dL and in TNT from 99 to 78 mg/dL. Both trials showed significant improvements in multiple cardiovascular outcomes. In HPS, there was no threshold effect for starting therapy, with equal relative risk benefit among the tertiles of baseline LDL. More research is needed to confirm the efficacy and safety of aggressive LDL-lowering therapy to levels below 100 mg/dL in stable CHD patients.

Primary Prevention

Among patients without a history of CVD but who have high predicted risk (typically men over age 50 and women over age 60 who have multiple other risk factors), which is comparable to those with a history of clinical CHD, it is rational to treat such patients as aggressively as one would for those with CHD (i.e., goal <100 mg/dL) (NCEP III, 2002; ASCOTS-LLA, 2003 [which had patients with HTN with three other risk factors]; Haffner et al., 1998).

Several primary prevention statin trials (which included only patients with LDL-C >130 mg/dL) demonstrated significant CHD risk reduction among intermediate- and high-risk patients without a history of CVD. All these trials had baseline LDL levels greater than 130 mg/dL, and achieved on-treatment LDL levels in the low 100s mg/dL. The AFCAPS/TexCAPS trial (1998) achieved a mean LDL-C of <120 mg/dL, the WOSCOPS

study (1995) ~140 mg/dL, and the ASCOT-LLA ~130 mg/dL (2003). Sub-group analyses of the primary prevention trials indicates that a vast majority of the improved outcome occurred in patients whose 10-year risk exceeded 20 percent, and correlated with reduction in LDL. There was less improvement (but statistically significant) in those with 10-year risk in the 15-20 percent category, and there was no statistically significant risk reduction among those with 10-year risk <15 percent.

Although the short-term risk may be low in those with a 10-year FRS <10 percent, the long-term relative risk associated with high LDL-C (>160 mg/dL) is high enough that lipid lowering interventions to lower the LDL-C to <160 mg/dL would be reasonable to modify long-term risk.

Goals: Specific LDL Absolute Values Versus Percent LDL Reduction

Some experts argue that it is the percentage drop in LDL, not the absolute LDL achieved that is important in achieving benefit. In HPS, there was similar risk reduction in those who received a standard dose of simvastatin, regardless of final LDL. Specifically, reduction of CHD events was similar for those with final LDL of 116, 116-135, and those greater than 135 mg/dL. This strategy recognizes that significant clinical benefit occurs with 30-40 percent LDL reduction regardless of final LDL, and attempting to drive LDL down further with higher doses of statins or combination therapy may expose patients to additional adverse events without proven efficacy. The SEARCH and the IDEAL trials currently underway may give additional insight into whether aggressive treatment with statins will address the value of LDL absolute values or percent reduction as the more valid strategy.

Why Does the VA/DoD Guideline Differ from NCEP in their LDL Goals?

Most NCEP recommendations are consensus statements designed to guide the broad clinical field of dyslipidemia. Many of the recommendations are based on observational studies with rational inferences based on biologic plausibility. Clinical practice guidelines have to guide practical decision-making in real world practice among patients for whom there are most often no applicable clinical trials, and in whom there is an intricate balance of patient preferences, co-morbidities, medication interactions, and other psychosocial factors. Therefore, the VA/DoD Dyslipidemia Guidelines Working Group was tasked to design a rigorous evidence-based guideline whereby recommendations were based on high quality clinical data (typically randomized controlled trials [RCT] using hard outcomes). The Guideline Working Group's knowledge of the DoD and VHA clinical practice settings allows for adaptation of these recommendations to our specific system of care. This is the basis upon which there are differences between NCEP and the VA/DoD CPG recommendations. The decisions on treatment will always be guided by clinical judgment of the providers who may strive to achieve lower LDL-C goals for their individual patient.

Most high-risk patients (those with CVD or CVD equivalent) will benefit from statin therapy, regardless of baseline LDL. However, patients with very high baseline LDLs may have difficulty in achieving LDL of less than 100 despite moderate to high dose statin therapy (greater than 25 percent reduction in LDL-C). Most recent studies achieving very low treatment LDLs started with low baseline LDL (mean LDL-C in HPS was 131 mg/dL; median LDL-C in PROVE-IT was 106 mg/dL) opposed to 188 mg/dL in 4S. Thus, in those patients with a high LDL baseline, the full risk-benefit of combination drug therapy or even high dose statin therapy is unknown, especially among patients with significant disease comorbidities or concomitant drug therapy. The data from meta-analyses of the major statin RCTs indicate that an LDL-C reduction of 30-40 percent from baseline may be considered a therapeutic strategy for patients who can not meet the above goal.

EVIDENCE

	Recommendation	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	Target lipid lowering therapy to risk	Bethesda Conference, 1996 Grundy et al., 2004	I	Good	C
	Secondary Prevention				
2	Goal <100 mg/dL for recent ACS patients	MIRACL, 2001 PROVE-IT, 2004	I	Good	A

		REVERSAL, 2004			
3	An optional lower target for LDL-C may be considered for severe post-ACS patients	PROVE-IT, 2004	I	Good	B
4	Goal <100 mg/dL for patients with previous documented CHD or CVD or CVD equivalent = DM	CARE, 1996 HPS, 2002 TNT, 2005	I	Good	A
5	Goal <130 mg/dL for patients with DM without other major risk factors	Haffner et al., 1998 NCEP Consensus	III	Poor	C
	Primary Prevention				
6	Goal <100 mg/dL for high-risk group	ASCOT-LLA, 2003 HPS, 2002 WOSCOPS, 1995	I	Fair	B
7	Goal <130 mg/dL for patients with intermediate 10-year risk (15-20%).	AFCAPS, TexCAPS, 1998	I	Fair	B
8	Goal <130 mg/dL for intermediate-risk group 10-14%	NCEP ATP-III, 2002	III	Poor	C
9	Goal <160 mg/dL for low-risk group	Consensus Group	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

O. Initiate Lipid Lowering Therapy to Achieve Goal

OBJECTIVE

Select an appropriate therapy based on LDL-C baseline level and other risk factors for CVD.

BACKGROUND

Two approaches to therapy are available: lifestyle changes and drug therapy:

> Lifestyle changes are the first step of treatment dyslipidemia. These include dietary changes, smoking cessation, weight loss (if overweight), and exercise. These changes may reduce cardiovascular disease risk independent of their influence on lipid levels.
>
> Drug therapy should be reserved for those with known CVD and those patients at increased CVD risk failing to reach LDL-C targets with lifestyle modifications. Statins have been shown to be cost-effective in both these populations.

RECOMMENDATIONS

Non-Pharmacologic Therapy

1. Therapeutic lifestyle changes (TLC) should be recommended for ALL patients with dyslipidemia, regardless of risk or baseline LDL-C level. [C]

Drug Therapy for Secondary Prevention:

2. All patients with a recent ACS should be on at least a moderate dose of statin therapy. [A]
3. Statin drug therapy should be initiated for patients with previous documented CHD or CVD equivalent (diabetes with other major risk factors) if baseline LDL-C is ≥100 mg/dL. [A]
4. Statin drug therapy should be initiated for patients with documented DM with no major risk factors if baseline LDL-C is ≥130 mg/dL. [C]

5. Statin drug therapy may be considered optional for all patients with CHD or CVD equivalent (diabetes with other major risk factors) regardless of LDL-C baseline. [B]

Drug Therapy for Primary Prevention:

6. Drug therapy should be initiated for high-risk patients (>20%) if baseline LDL is ≥130 mg/dL. [B]
7. Drug therapy is optional to consider in high-risk patients (>20%) if baseline LDL is 100-129 mg/dL. [B]
8. Drug therapy may be offered to patients with high-intermediate risk (15-20 percent) if baseline LDL is ≥130 mg/dL. [B]
9. Drug therapy may be offered to patients with low-intermediate risk (10-14 percent) if baseline LDL is ≥160 mg/dL. [C]
10. Drug therapy may be offered to low-risk patients (<10 percent) if baseline LDL is ≥190 mg/dL. [I]

The following table summarizes the lipid lowering strategy for patients in primary prevention. Individual management of cardiovascular risk should be informed mainly by the probable absolute magnitude of treatment benefits. Lowering absolute risk involves modification of multiple risk factors/co-morbidities, not only LDL-C levels. Therefore, these goals should serve as a general guide and clinical judgment should be used to modify the goals as appropriate for each patient.

Table 3. Dyslipidemia Therapy Thresholds And Goals

	Risk Category	Disease Status or Risk Factors	Calculated 10-Year Risk	TLC	LDL-C Level for Considering Statin Drug Therapy	LDL Goal of Therapy
Secondary Prevention	Very high	Recent ACS	N/A	All	All	<100 mg/dL <70 optional
		CHD or DM with other risk factors	N/A	All	≥100 mg/dL	<100 mg/dL
		DM with no other risk factors	N/A	All	≥130 mg/dL 100-129 optional	<130 mg/dL
Primary Prevention	High	More than 2 RF	≥ 20%	All	≥130 (or HDL <40) 100-129 optional	<100 mg/dL
	Intermediate	More than 2 RF	15-20%	All	≥ 130 mg/dL	<130 mg/dL
			10-14 % *	All	≥ 160 mg/dL	<130 mg/dL
	Low	0 or 1 RF	N/A	All	≥190 mg/dL	<160 mg/dL
LDL-C reduction of 30-40 percent from baseline may be considered an alternative therapeutic strategy for patients who can not meet the above goals.						

N/A = Not applicable; TLC = Therapeutic Lifestyle Changes; RF = Risk Factor

* There is insufficient evidence at this time to recommend routine screening for other risk markers not included in the risk index (e.g., FH, hsCRP, metabolic syndrome, depression), or evidence of significant atherosclerotic burden (e.g., high coronary artery calcification scores, intima medial thickness, abnormal brachial reactivity, or abnormal ankle-brachial index). These risk markers may be useful in the intermediate risk patient for whom it is less convincing that drug therapy would have a meaningful impact on outcomes.

DISCUSSION

Initial Therapy: In one prospective secondary prevention trial, the CARE study, a post-hoc analysis found no outcomes benefit when high-dose pravastatin was initiated at a baseline LDL-C <125 mg/dL (Sacks et al., 1996). However, evidence clearly supports initiation of pharmacotherapy when LDL is >130 mg/dL in patients with CHD. In the Heart Protection Study (HPS), the initial LDL-C was approximately 130 mg/dL

(HPS, 2002). Furthermore, in a post-hoc analysis of HPS, those patients presenting with a pretreatment LDL-C of less than 100 mg/dL also achieved a similar benefit in reduction of coronary events with treatment of simvastatin (HPS, 2002). Based on consensus opinion and post-hoc analysis of HPS it is recommended that statins be initiated for LDL ≥100 mg/dL for secondary CHD prevention.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Therapeutic lifestyle changes should be recommended for ALL patients	NCEP ATP-III, 2002	III	Fair	C
2	For recent ACS patients, moderate to high-dose statins should be given prior to hospital discharge; If not started prior to discharge, then statin therapy should be started within 6 months post ACS	A to Z, 2004 MIRACL, 2001 PROVE-IT, 2004	I	Good	A
3	Initiate drug therapy in all patients with previous documented CHD or CVD equivalent (DM with other major risk factors) if baseline LDL-C is ≥100 mg/dL	CARE, 1996 4S, 1994 HPS, 2002 LIPID, 1998 PROSPER, 2002 TNT, 2005	I	Good	A
4	Drug therapy should be initiated for patients with DM and NO major risk factors) if baseline LDL-C is ≥130 mg/dL	NCEP Consensus of experts	III	Poor	C
5	Drug therapy may be considered for all patients with DM and other risk factors regardless of LDL baseline	CARDS, 2004 TNT, 2005	I	Fair	B
6	Drug therapy should be initiated for high-risk patients (10-year risk > 20%) if baseline LDL is ≥130 mg/dL	AFCAPS/TexCAPS, 1998 ASCOT-LLA, 2003 WOSCOPS, 1995	I	Good	A
7	Consider drug therapy in high-risk patients if baseline LDL is 100-129 mg/dL	HPS, 2002	I	Fair	B
8	Offer drug therapy for high-and intermediate-risk (15-20%) if baseline LDL is ≥130 mg/dL	ASCOT-LLA, 2003 AFCAPS/TexCAPS, 1998 WOSCOPS, 1995	I	Fair	B
9	Offer drug therapy for low-intermediate risk (10-15%) patients if baseline LDL is ≥160	NCEP ATP-III, 2002	III	Poor	C
10	Offer drug therapy for low-risk patients (<10%) if baseline LDL is ≥190 mg/dL	NCEP ATP-III, 2002	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

P. Therapeutic Lifestyle Change

BACKGROUND

In 2002, the National Cholesterol Education Program (NCEP) Expert Panel on Deletection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recommended Therapeutic Lifestyle Change (TLC) is a clinically focused, multifactorial approach to reducing risk for CVD. Components of TLC include: promoting reduced intakes of saturated fat and cholesterol, adding therapeutic dietary components for enhancing LDL-C lowering (plant stanols/sterols and soluble fiber), weight reduction, and an increase in physical activity. TLC is indicated in all patients with dyslipidemia and represents a shift from the two-step dietary approach recommended in the second report of the Adult Treatment Panel. The Step 1 diet, recommending dietary cholesterol intake of less than 300 mg/day and saturated fat intake of 8-10 percent of total calories, has now become the general recommendation for a healthy diet. The Step II diet, recommending cholesterol intake of less than 200 mg/day and saturated fat intake of less than 7 percent of total calories has become the basis for the current TLC dietary recommendations.

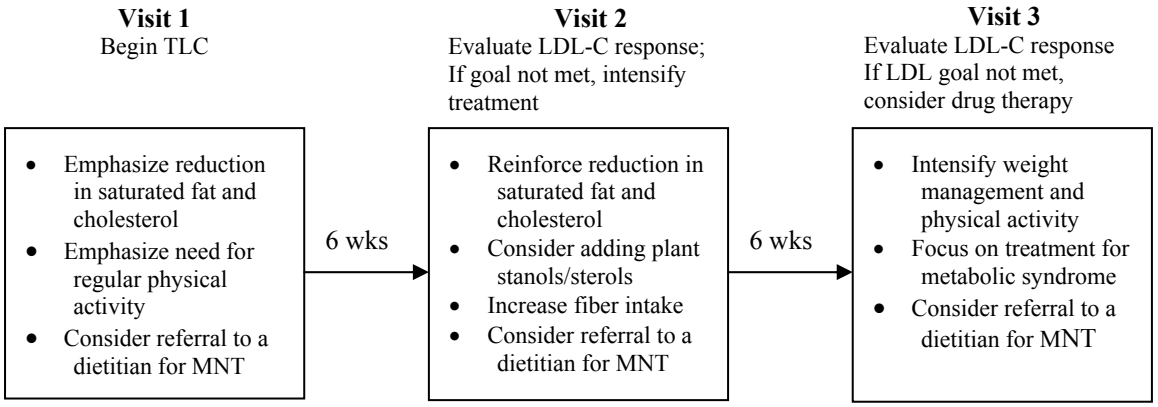
The priority of treatment for reducing CAD risk remains focused on LDL-C reduction. Once a patient's LDL-C goal has been achieved, management of metabolic syndrome and other lipid abnormalities may be emphasized. At any and every stage of dietary therapy, effective dietary modification will be facilitated by consultation with a registered dietitian or other qualified nutritionist for Medical Nutrition Therapy (MNT).

For secondary prevention of recurrent CVD events, non-pharmacologic therapy is always indicated, but should not delay appropriate pharmacotherapy.

For primary prevention of CVD, emphasis on TLC is an important component and is effective in reducing CVD risk by lowering LDL-C and blood pressure. Ample time should be given (3-6 months) for patients to improve their LDL-C and total lipid profile prior to starting lipid-lowering medication. Patients failing primary clinician efforts may benefit from MNT provided by a registered dietitian or other qualified nutritionist (see Appendix C, *Medical Nutrition Therapy*).

TLC is provided in a step-wise approach focused on initiating TLC components and followed by subsequent evaluation of the effect on LDL-C and moving to intensify MNT as indicated.

Figure 2: Step Wise Care Approach (NCEP ATP-III, 2002)



P1. Medical Nutrition Therapy

OBJECTIVE

Improve dyslipidemia using medical nutrition therapy (MNT).

BACKGROUND

Dietitians and nutrition professionals can provide MNT for patients to lower CVD risk and treat dyslipidemia through diet and lifestyle improvement. In fact, the most cost-effective approach to prevention of CHD is TLC including diet modification, exercise, and weight control, combined with smoking avoidance/cessation. The American Dietetic Association Evidence-Based Guidelines for the Treatment of Hyperlipidemia are consistent with those more specific requirements of the TLC diet (NCEP ATP-III, 2002). MNT incorporates the provision of dietary education and TLC in addition to assessment/reassessment of clinical and anthropometric measurements. It is important to note that providing effective MNT is time intensive and requires approximately one hour during initial consultation, and 30-45 minutes for follow-up assessment (American Dietetic Association, 2001).

RECOMMENDATIONS

1. Diet intervention should be the first step in lipid lowering therapy. [B]
2. Patients whose initial treatment is TLC should be given 3-6 months of dietary therapy prior to beginning medication and longer, if lipids are improving and nearing LDL thresholds. [B]
3. Initial diet should focus on reduction of saturated fats to <7 percent of total calories and dietary cholesterol to <200 mg/day similar in composition to the TLC diet (formerly Step II diet). [B]

    a. The range of 25-35 percent of total calories from fat is to be paired with keeping saturated fats and trans-fatty acid percents of total calories low.
    b. Advise 10 percent monounsaturated fat, <7 percent saturated fat, <200 mg cholesterol diet.
    c. If TGs are elevated, ensure that blood glucose is under control, limit alcohol and simple sugars, and evaluate need for weight loss. Emphasis should be placed on weight reduction and physical activity.
    d. Limit foods with trans fatty acids (e.g., stick margarine, shortening, and commercially baked products and processed food).
    e. Select >5-6 servings/day fruits and vegetables and six servings/day whole-grain products.

4. Patient's specific diet should be individualized based on nutrition assessment, other CVD risk factors, other disease conditions, and patient's lifestyle. [I]
5. Patients should be evaluated 4-6 weeks after their initial consultation. A lipid profile and anthropometric data should be analyzed. Further dietary intervention may include:

    a. Increase soluble (viscous) fiber to 10-25 g/day to lower LDL-C. [B]
    b. Increase plant sterols/stanols to 2 g/day to lower LDL-C. [B]
    c. Include nuts such as walnuts and almonds (1 oz. ~5 times/week) and soy protein (25g/day or 8 oz. of tofu) to lower LDL-C. [B]
    d. Select fatty fish (average of 7 oz./week) (fish oil) to lower TG. [B]

6. Weight management for overweight and obese patients should be encouraged to lower LDL-C and TG and to reduce CV risk. [B]
7. Patients in whom triglycerides >500 mg/dL should receive strict diet therapy including avoidance of alcohol, restriction of dietary fat, and avoidance of concentrated carbohydrates (sweets). For triglycerides >1000 mg/dL a very low fat diet should be instituted quickly to reduce chylomicronemia and risk of acute pancreatitis.
8. Patients with evidence of metabolic syndrome should receive MNT that incorporates the additional protocol for weight management with increased physical activity. [B]

DISCUSSION

Nutritional Counseling

A focused strategy of intensive nutrition counseling to reduce serum cholesterol is effective (Henkin et al., 2000; Delahanty et al., 2001 & 2002) and cost beneficial (Delahanty et al., 2001; Sikand et al., 2000). A systematic review of 19 randomized control trials using individualized dietary advice to modify fat intake concluded that individualized dietary advice for reducing cholesterol concentration is modestly effective (Tang et al., 1998). The authors note that failure to comply fully with the dietary recommendations was the likely explanation for this limited effectiveness.

Therapeutic Lifestyle Change (TLC)

Cholesterol and saturated fat are primary LDL-raising dietary constituents and are the focus of the TLC model. A diet low in saturated fat is effective in lowering LDL-C. The Boeing Employees Fat Intervention Trial (beFIT) showed that a diet together with TLC can lower LDL-C from 7.6–8.8 percent and this reduction occurs whether individuals have high cholesterol or high cholesterol combined with high TGs (Walden et al., 1997). The relationship between dietary fat and CVD continues to be a central component of strategies for risk reduction in individuals following a fat restricted diet. Although many observational studies and systematic reviews support the relationship between dietary fat and CVD, studies of dietary interventions are less convincing. A Cochrane report suggests that reduction of dietary fat intake results in reductions in CV events, but only in trials of at least two years duration (Hooper et al., 2001).

In the DELTA study, investigators reduced dietary saturated fatty acids from 15 percent to 6.1 percent and found a concurrent 11 percent reduction in LDL-C (Ginsberg et al., 1998). Indeed, the dose-response relationship between reduction in saturated fat intake and serum cholesterol have been well documented; for every 1 percent reduction in saturated fat, a 2 percent reduction in serum cholesterol is seen (Mensink & Katan, 1992).

In a systematic review of Step 1 and Step 2 diets reported by Yu-Poth et al. (1999), the Step 1 diet lowered LDL-C by an average of 12 percent and the Step 2 diet (the predecessor to the TLC diet guidelines) by 16 percent. Jenkins and colleagues (2003) reported a 12 percent decrease in LDL-C with a Step 2 diet, and Lichtenstein and colleagues (2002) reported an 11-12 percent decrease in LDL-C. The TLC diet requires a dietary saturated fat restriction of <7 percent of total calories and <200 mg/dL of dietary cholesterol (NCEP ATP-III, 2002). Additionally, total fat calories should not exceed 25-35 percent of total energy intake (Lichtenstein et al., 2002). This is not a recommendation to increase total fat, rather a guideline to reduce saturated fat (animal, dairy fat, coconut, and palm kernel oils) in conjunction with an overall reduction in total dietary fat calories.

In the U.S., mean trans fatty acid intake is approximately 2.6 percent of total energy compared to saturated fat intake of approximately 11 percent. Major sources include: partially hydrogenated oils such as those in baked products, crackers, cookies, doughnuts, breads, and French fries. Trans fatty acids raise serum LDL-C levels similar to saturated fats and dietary intake should be kept as low as possible (Liechtenstein et al., 1999).

Intensive dietary modification promoted within the TLC model incorporates more than a reduction in saturated fat intake. Additional dietary modifications that may promote reduction in LDL-C, and overall CHD risk reduction are outlined in Table 4 (Essential components of Therapeutic Lifestyle Changes), and Table 5 (Macronutrient Recommendations for the TLC Diet).

Table 4. Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day
****Trans fatty acids are another LDL-raising fat that should be kept at a low intake.*	

Table 5. Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories
****ATP-III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrates to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.* *† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.*	

Intensifying Diet Therapy

The NCEP ATP-III report introduces the concept of therapeutic options for patients who are close to LDL-C goals and might attain them by increasing specific diet constituents including viscous (soluble) fiber, soy protein, and plant stanol/sterol esters. Viscous fiber, notably psyllium, pectin, and β-glucan and as components of whole grains, fruits, vegetables, nuts, oats and legumes can further lower LDL. A meta-analysis concluded that for every 1-gram increase of soluble dietary fiber, expected LDL decrease would be 2.2mg/dl (Brown et al., 1999). In addition to fiber, 2-3 grams/day of plant stanol/sterols have been shown to lower LDL-C by 6-15 percent in patients with hypercholesterolemia (Christiansen et al., 2001), and those already eating a low fat diet (Maki et al, 2001). When dietary LDL-C reducing options were compared to statin therapy, Jenkins and colleagues (2005) reported a similar reduction in LDL-C between a group consuming a diet high in viscous fiber, soy protein, nuts, and plant stanols/sterol esters compared to the statin therapy group (Jenkins et al., 2005).(See appendix C-3 for sources of fiber, soy protein and other diets)

Plant sterols consumed in normal diets (stanols are less abundant in nature) and in increased amounts by vegetarians, are poorly absorbed, and appear to interfere with the absorption of dietary cholesterol (Heinemann et al, 1991). A meta-analysis of stanols/sterols effects on health suggest that average LDL-C reduction by consumption of 2 g/d of sterols/stanols is 9–13 percent (and this effect was greater with increased age). A cautionary note by the American Heart Association suggests that plant stanol/sterol products may reduce the absorption of carotenoids and thus stanol/sterol supplements should not be consumed in conjunction with fruits and vegetables (Lichtenstein & Deckelbaum, 2001).

Nuts are rich in alpha-linolenic acid (a plant omega-3 fatty acid), fiber, and micronutrients, and produce significant total and LDL-C lowering properties when incorporated into diets in amounts from 50-100 grams/day (NCEP, 2001). Effects on body weight and HDL-C have been mixed (Sabate et al., 2003; Lovejoy et al., 2002). However, the American Heart Association in a scientific statement issued by the Nutrition Committee recommended increasing the amount of omega-3 fatty acids in the diet both from plant and marine sources based on evidence for beneficial effects on risk reduction of CVD (Krauss et al., 2000).

Soy protein has mild cholesterol lowering effects, especially when replacing animal protein in the diet and especially in patients with hyperlipidemia. Consumption of 25g/day or more of soy protein in a diet low in saturated fat and cholesterol lowers LDL-C by approximately 5 percent (Jenkins et al., 2000).

Moderate **fish consumption** has been associated with cardioprotective effects, including a decrease in sudden death, decreased risk of arrhythmias and decreased platelet aggregation. Fish are an excellent source of

omega-3 (n-3) fatty acids. The American Heart Association recommends at least two servings/week of fish together with an increase in plant n-3 food sources (Kris-Etherton, Harris, et al., 2002). In the Diet and Reinfarction Trial (DART), men recovering from myocardial infarction who were randomized to receive dietary advice to increase fatty fish consumption had a 29 percent reduction in all-cause mortality at 2-year follow-up (Burr et al., 1989). In the large GISSI prevention study, patients randomized to receive n-3 fatty acid supplements (1g/day) had a significant 14 percent reduction in total death and a 17 percent reduction in cardiovascular death (GISSI investigators, 1999). Although the mechanism by which n-3 fatty acids might reduce coronary events is unknown, higher intakes of n-3 fatty acids reduce risk for coronary events and coronary mortality.

DASH and Mediterranean Diet

One randomized controlled trial investigating the DASH diet (Dietary Approaches to Stop Hypertension) reported a 9 percent reduction in LDL-C compared with controls. The DASH diet contained 27 percent fat, 7 percent saturated fat and 141 mg of dietary cholesterol and has also been shown to reduce hypertension (Obarzanek et al., 2001).

Several trials have examined the relationship between a Mediterranean-type diet (high in monounsaturated fat and n-3 fatty acids) and the risk of heart disease. The n-3 fatty acids are found in fatty fish (e.g., salmon, trout, sardines, and tuna) and in some plant sources such as walnuts, flaxseed, and various vegetables (Curtis & O'Keefe, 2002). In the Lyon Diet Heart Study, patients randomized to receive a Mediterranean-type diet including high monounsaturated fat had significant reductions at 1 and 4 year follow up (mean 27 months) in combined primary endpoints of death from cardiovascular causes including: nonfatal acute myocardial infarction (73 percent), cardiac mortality (76 percent), and total mortality (70 percent) (Kris-Etherton et al., 2001).

Weight Loss

NCEP ATP-III emphasizes weight reduction as part of an LDL-lowering therapy. Unlike previous recommendations (NCEP II), ATP-III recommends delaying the focus on weight reduction until after dietary measures to lower LDL-C are introduced. The delay prevents patients from receiving excessive amounts of dietary information. After approximately 3 months of TLC, the major focus should shift to weight reduction and management of metabolic syndrome (see Figure 2). In addition to dietary strategies, regular physical activity is central to successful weight management.

A small decrement in weight can improve risk factors for CHD. A long-term strategy is more difficult and will require regular physical activity to maintain the reduced weight. Many health professionals miss a valuable opportunity in weight management by not emphasizing the goal of preventing further weight gain. This is particularly true in situations such as medication use that promotes weight gain (steroids, certain anti-depressants or anti-diabetic agents) or injury (fractures that cause immobilization). The goal of weight loss should focus on reduction of body weight in the short term, maintain lower body weight for the long term and, at a minimum, prevent further gain (NHLBI, 1998). A goal of 10 percent reduction in body weight over 6 months requires a sustained effort, and usually translates to reducing body weight by 1-2 lbs per week. There is considerable variation in individual response to weight-loss regimens and patient success may be enhanced by participation in self-help groups.

Metabolic Syndrome

Patients with dyslipidemia and evidence of metabolic syndrome (see Annotation W for definition of the Metabolic Syndrome) benefit from the additional components of weight management during MNT, which includes the goals of increasing exercise and a calorie controlled meal plan (NCEP ATP-III, 2002; Nieman et al., 2002, Sartorio et al., 2003).

In those with metabolic syndrome who have abdominal obesity, high TGs, low HDL-C, glucose intolerance, and/or elevations of blood pressure, it may be useful to increase the amount of unsaturated oil as either monounsaturated or polyunsaturated fatty acids (for example, canola oil) to allow less carbohydrate and hence

better glucose control. A meta-analysis by Garg (1998) showed that in Type 2 diabetes, a high–monounsaturated fat diet can improve lipoprotein profiles as well as glycemic control. Moreover, there was no evidence that high–monounsaturated fat diets induce weight gain in patients with Type 2 diabetes provided that energy intake is controlled.

The Finnish Diabetes Prevention Study, (Tuomilehto et al., 2001) looked at 522 middle-aged overweight men and women with glucose intolerance. Subjects were randomized to two groups. The intervention group had individualized counseling. The intervention group achieved significant improvements in five lifestyle behavioral areas as contrasted with the control group (reduce weight (>5 percent body weight), reduce fat and saturated fat in diet, and increase fiber (>15 g/10000 kcal) and physical activity (.4 hrs/week). The benefits were highly significant, as after 4 years, the risk of DM was reduced by 58 percent. This suggests that lifestyle change can reduce risk for CHD.

EVIDENCE

	Recommendation	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	Use MNT for lowering LDL-C.	Delahanty et al., 2001 & 2002 Sikand et al., 2000 Yu-Poth et al., 1999	I	Good	B
2	Recommend 3-6 months of diet therapy prior to pharmacotherapy, if needed	NCEP ATP-III, 2002	I	Fair	B
3	Recommend a low saturated fat, low cholesterol diet	Dietary Guidelines for Americans, 2005 NCEP ATP-III, 2002	II	Good	B
4	Reduce saturated fats to less than 7% of total calories	Dietary Guidelines for Americans, 2005 Hooper et al., 2001 Krauss et al., 2000 Lichtenstein et al., 2002 NCEP, 2001	I	Fair	B
5	Provide individualized dietary counseling with reinforcement during follow-up	NCEP ATP-III, 2002 Tang et al., 1998	I	Fair	B
6	Consume viscous fiber (at least 10-25 grams/day)	Brown et al., 1999 Kris-Etherton, Taylor et al., 2002	I	Fair	B
	Eat plant sterols/stanol esters (2-3g/day)	Christiansen et al., 2001 Jenkins et al., 2003 & 2005 Lichtenstein & Deckelbaum, 2001 Maki et al., 2001	I	Fair	B
	Eat 5 ounces of nuts per week	Jenkins et al., 2003 Krauss et al., 2000 Lovejoy et al., 2002 Sabate, 2003	I	Fair	B
	Eat 25 grams/day of soy protein	Anderson et al., 1995 Erdman, 2000 Merritt, 2004 Meyer et al., 2004	I	Fair	B

	Eat at least two servings of fish per week	Kris-Etherton, Harris et al., 2002 NCEP ATP-III, 2002	I	Fair	B
7	Reduce caloric intake and increase physical activity to maintain desirable body weight	Krauss et al., 2000 NCEP ATP-III, 2002	I	Fair	B
8	Low fat diet for TGs >500mg/dL; Very low fat diet if TGs >1000 mg/dL	ADA, 2001 NCEP ATP-III, 2002	I	Fair	B
9	Recommend MNT for management of metabolic syndrome	ADA, 2001 NCEP ATP-III, 2002 Nieman et al., 2002 Sartorio et al., 2003	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

P2. Physical Activity / Exercise and Weight Control

BACKGROUND

Researchers generally agree that physical activity provides substantial cardiovascular benefits for men and women. However, there is still debate on the duration, frequency, and intensity of physical activity required for optimal health.

The Surgeon General, the Centers for Disease Control (CDC), and the American Heart Association (AHA) recommend a regular program of moderate-to-vigorous intense physical activity for an accumulated time of 30 minutes or more per day. In addition to the aerobic component (complete with stretching and proper warm-up/cool down activities), studies demonstrate that all patients could benefit from adding proper and safe resistance training to their routine.

Many health professionals are not aware that increasing physical activity can be achieved by emphasizing lifestyle activities as well as scheduled forms of physical activity (e.g., climbing stairs, walking for errands, parking the car further away in the parking lot, and housework or gardening. It has been demonstrated that multiple short bursts of physical activity can be as effective in promoting weight loss and improving cardiovascular risk factors as a single continuous period of exercise. Physical activity achieved by changes in lifestyle in the home or work environment can be as effective as structured exercise activity in a gym or health club. Engaging patient preferences may also help to lower perceived barriers to regular exercise.

For additional discussion of the health benefits of physical activity see Appendix D

RECOMMENDATIONS

1. Moderate intensity levels of physical activity should be performed for at least 30 minutes most, preferably all, days of the week. [B]
2. In patients with CVD, aerobic exercise should not precipitate angina.
3. Increased physical activity through lifestyle change should be encouraged, as it is equally as effective as structured exercise in reducing body fat, improving cardiorespiratory fitness and improving cardiovascular risk factors. [B]
4. Physical activity, through lifestyle change or structured exercise, should be encouraged to maintain weight control (or weight loss if overweight or obese), to improve insulin resistance, and increase HDL-C. [B]

DISCUSSION

The longstanding belief that physical activity must be vigorous to be healthful has been overturned in the last decade by epidemiologic studies indicating otherwise. In 1995, the CDC and the American College of Sports Medicine (ACSM) recommended that adults engage in 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week (Pate et al., 1995). This has also been the standard endorsed by the U.S. Surgeon General since 1996. The Surgeon General's report, *Physical Activity and Health* (U.S. DHHS, 1996), clearly outlines the goal for persons of all ages and emphasizes that regular physical activity may be more beneficial than a few days of intense workouts.

In 2002, the Institute of Medicine (IOM) concurred that moderately intense activity is beneficial; however, that one half-hour is not sufficient to maintain a healthy weight or to achieve maximal health benefits. Therefore, IOM recommended a 60-minute standard that was included as part of a report focused on diet and nutrition goals for the American public (http://www.nap.edu/books/0309085373/html/).

Physical activity guidelines issued by the American Heart Association (AHA) and endorsed by the ACSM support the 30-minute goal for the prevention of CVD, as does the AHA's February 2004 CV prevention guidelines specifically targeted to women. The World Health Organization also included the 30-minute recommendation in its 2004 global blueprint for fighting these and other chronic diseases.

Effect of Exercise on Lipid Profile

Moderate dose-response relationships between exercise intensity and blood lipids—specifically, HDL-C and TGs—have been reported in observational studies (Rankinen & Bouchard, 2002). Based on data from 51 individual studies (including 28 RCTs) with exercise training programs of 12 weeks, the most common lipid change (40 percent of the studies) was an increase of HDL-C (4.6 percent on the average) in both men and women. Reductions in LDL-C and TG levels were also reported, although less frequently than changes in HDL levels (Leon & Sanchez, 2001).

An eight-month trial (Kraus et al., 2002) that assigned overweight middle-aged women and men to various exercise regimens or to a non-exercising control group found that, although improvements in lipids profile were far more striking among the "high-amount/high intensity" exercise group than among either the "low-amount/ high-intensity" and "low-amount/moderate-intensity" groups, a comparison of the latter two groups showed that they experienced similar improvements in lipid profiles.

The investigators concluded that lipid profiles are related more strongly to the amount, rather than the intensity, of exercise. Brisk walking (three 50-minute sessions per week) was also found to have favorable effect on blood lipids in a 10-week randomized trial (Fahlman et al., 2002). In these trials, the beneficial effects of exercise occurred in the absence of concurrent dietary change.

A Cochrane meta-analysis (Halbert et al., 1999) identified 31 randomized, controlled trials of aerobic and resistance exercise training which were conducted over a minimum of four weeks and involved measurement of one or more of the following: TC, HDL-C, LDL-C and TGs. A total of 1,833 hyperlipidemic and normolipidemic participants were included. In trying to determine the effectiveness of exercise training (aerobic and resistance) in modifying blood lipids, the analysis has shown that aerobic exercise training resulted in small but statistically significant decreases of 0.10 mmol/L (95 percent: 0.02, 0.18), 0.10 (95 percent confidence interval (CI): 0.02, 0.19), 0.08 mmol/L (95 percent CI: 0.02, 0.14), for TC, LDL-C, and TG, respectively, with an increase in HDL-C of 0.05 mmol/L (95 percent CI: 0.02, 0.08). Comparisons between the intensities of the aerobic exercise programs produced inconsistent results; but more frequent exercise did not appear to result in greater improvements to the lipid profile than exercise three times per week. The evidence for the effect of resistance exercise training was inconclusive. The author concluded that the results appear to indicate that aerobic exercise training produced small but favorable modifications to blood lipids in previously sedentary adults. Caution is required when drawing firm conclusions from this study given the significant heterogeneity with comparisons.

Effect of Diet and Exercise on Lipid Profiles

Stefanick and colleagues (1998) tested the effects of diet alone or exercise combined with the NCEP diet on LDL levels. Dietary intake of fat and cholesterol decreased during the one-year study (P<0.001), as did body weight, in women and men in either the diet group or the diet-plus-exercise group, as compared with the controls (P<0.001) and the exercise group (P<0.05), in which dietary intake and body weight were unchanged. Changes in HDL-C and TG levels and the ratio of total to HDL-C did not differ significantly among the treatment groups, for subjects of either sex. The serum level of LDL-C was significantly lower in the diet-plus-exercise group, as compared with the control group (women 2.5+/-16.6 mg/dL, men 4.6+/-21.1 mg/dL).

The reduction in LDL-C in men in the diet-plus-exercise group was also significant as compared with that among the men in the exercise group (decrease of 3.6 mg/dL, P<0.001). In contrast, changes in LDL-C levels were not significant among the women or the men in the diet group, as compared with the controls. The NCEP Step 2 diet failed to lower LDL-C levels in men or women with high-risk lipoprotein levels who did not engage in aerobic exercise. This finding highlights the importance of physical activity in the treatment of elevated LDL-C levels.

Scranton et al., (2004) examined predictors of a change in TC/HDL ratio over a period of 14 years among 4,451 men free of CVD from the Physicians' Health Study. After a mean follow-up of 14 years, mean TC decreased by 7 mg/dL, HDL increased by 1 mg/dL, and the ratio decreased by 0.37. In multivariate logistic analyses, the physicians studied were more likely to have a TC/HDL ratio equal or greater than 5 at follow-up if they maintained a BMI of 25 kg/m2 or more (OR, 1.69 [1.35-2.12]), gained weight (OR, 2.01 [1.55-2.62]), or became inactive (OR, 1.43 [1.11-1.83]). However, older physicians in the study group and those who consumed alcohol or received treatment for hyperlipidemia were more likely to have a ratio of less than 5. Although pharmacologic treatment for hyperlipidemia had the greatest favorable impact on the ratio over time, data also show that maintaining an ideal weight and exercise have beneficial effects.

Cardiovascular Benefit of Physical Activity

Findings from epidemiologic studies strongly support the recommendation of 30 minutes per day of moderate-intensity activity to reduce the risk of CVD. For example, among nearly 74,000 postmenopausal women aged 50 to 79 years participating in the Women's Health Initiative, walking briskly for at least 2 1/2 hours per week (i.e., a half-hour five times per week)—or expending an equivalent amount of energy through more vigorous exercise—was associated with a 30 percent reduction in CV over three years of follow-up (Manson et al., 2002). The protective effect of walking was observed in women who were white and black, middle-aged and older, and lean or overweight.

The CV benefits of walking—the most common leisure activity among U.S. adults—have also been demonstrated in other studies of women. In the Nurses' Health Study, which followed 72,000 healthy middle-aged female nurses for eight years, women who walked briskly for 3 hours per week or, alternatively, exercised more vigorously for 1.5 hours per week, had a 30 to 40 percent lower incidence of heart attack than did sedentary women (Manson et al., 1999). In the Women's Health Study, a 7-year follow-up of 39,000 healthy, middle-aged female health professionals, walking at least 1 hour per week was associated with a 50 percent reduction in CVD risk in women reporting no vigorous physical activity (Lee et al., 2001). Among 1,564 middle-aged University of Pennsylvania alumnae followed for 30 years, walking 10 or more blocks per day as compared with walking less than 4 blocks per day was associated with a one-third reduction in CVD incidence (Sesso et al., 1999).

Activity of light and moderate intensity levels has been observed to be protective of subsequent CHD in cohort studies of subjects with CHD at baseline (Wannamethee et al., 2000). Similarly, cardiac rehabilitation studies, although usually multifactor in nature, have supported the suggestion that physical activity reduces the risk of subsequent CHD (Deedwania et al., 1997). A Cochrane review, (Jolliffe et al., 2003) based on randomized, controlled trials reviewed a total pooled patient population of 7,683. The study revealed a 27 percent reduction in all-cause mortality in the exercise-only intervention group (odds ratio, 0.73; 95 percent confidence interval [CI], 0.54-0.98). Total cardiac mortality was reduced by 31percent (odds ratio, 0.69; 95 percent CI, 0.51-0.94), but there was no effect of either exercise only or comprehensive cardiac rehabilitation on the occurrence of nonfatal myocardial infarction. A recent review from the European Society of

Cardiology (Giannuzzi et al., 2003) broadly supports this view and also provides age-specific recommendations for exercise.

Metabolic Equivalent

Duration refers to how long one exercises and frequency refers to how often. Intensity refers to how "hard" one exercises and is typically measured in kilocalories (kcal) burned per minute or in a unit called the metabolic equivalent (MET). One MET is the amount of energy (oxygen) that the body expends while sitting quietly, and is taken as a constant of 1 $kcal.kg^{-1}.hr^{-1}$. A 2-MET activity expends twice the energy of sitting quietly; a 3-MET activity expends three times the energy of sitting quietly, etc. Moderate-intensity activities, such as brisk walking, are those that burn 3.5 to 7 kcal per minute (for a 70-kg person) or, equivalently, those that expend 3 to 6 METs. Vigorous activities, such as running, are those that burn more than 7 kcal per minute or expend more than 6 METs.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Increase physical activity to improve lipid profile	Fahlman et al., 2002 Halbert et al., 1999 Kraus et al., 2002 Stefanick et al., 1998	I	Fair	B
2	Engage in moderate levels of exercise/physical activity for at least 30 minutes, on most days of the week	AHA, ACSM 2002 Pate, 1995 U.S. DHHS, 1996	I	Fair	B
3	Increase physical activity is just as effective as structured exercise in reducing body fat, improving cardiorespiratory fitness	Lee et al., 2001 Manson, 1999 & 2002 Wannamethee et al., 2000	II	Fair	B
4	Exercise should be encouraged to maintain weight control (or weight loss if overweight or obese)	NHLBI, 1998 Scranton et al., 2004	II	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

Q1. Pharmacotherapy: Monotherapy

OBJECTIVE

Reduce the risk of CVD events and achieve lipid goals through the use of optimal pharmacotherapy.

BACKGROUND

There is good evidence supporting lipid-lowering therapy for primary and secondary prevention of CVD, based on LDL-C and CVD risk. Patients with known CVD or multiple risk factors require more aggressive treatment.

NCEP ATP-III identifies the landmark trials that continue to support the benefits of aggressive therapy with statins to reduce lipid levels for both primary and secondary prevention. An update to this report (Grundy et al., 2004) reviews the clinical trials on current and novel therapies that emphasize the importance of intensifying lipid-lowering treatment to improve outcomes. It further highlights the current gap in CHD treatment that exists in hospital and outpatient settings; recognizes the significant number of eligible patients not receiving therapy; and correlates this with the significant opportunity for reduced morbidity and mortality with proper treatment.

NCEP ATP-III emphasizes that aggressive drug therapy may slow, stabilize, and cause regression of plaque growth, and notes that an emerging body of evidence suggests that statin therapy has a salutary benefit for raising HDL-C and lowering LDL-C to synergistically reduce CHD risk. ATP-III also reviews the anti-inflammatory and pleiotropic effects of statins, and their benefits beyond LDL-C reduction in reducing CHD risk, and emphasizes the increasing importance and clinical relevance of the measurement of non-HDL-C and inflammatory markers in evaluating and treating CHD risk. Since LDL-C is the primary target of therapy in the primary and secondary prevention of CVD, statins are the first line therapy for most patients. Statins have the advantage of potency, ease of use, and tolerability over other cholesterol lowering agents.

Table 6 summarizes the recommended choice of drugs for dyslipidemia.

Table 6. Dyslipidemia Drug Therapy

	Drug	Expected Change in Lipoprotein *	
↑ LDL-C			
		LDL-C	
Initial	Statins	-22 to -60%	
Alternate	Niacin	-15 to -25%	
	Bile acid resin	-10 to -27%	
	Ezetimibe	-18% to –20%	
↑ LDL-C and ↑ TG			
		LDL-C	**TG**
Initial	Statins	-22 to -60%	-6 to -30%
	Niacin	-15 to -25%	-20 to -50%
Alternate	Fibrates	+10 to -35%	-20 to -50%
↑ LDL-C and ↓ HDL-C			
		LDL-C	**HDL-C**
Initial	Statins	-22 to -60%	+2 to +12%
	Niacin	-15 to -25%	+15 to +30%
Alternate	Fibrates	+10 to -20%	+10 to +20%

*** Considerations**

Statins Statins are contraindicated in active liver disease, in those persons with persistent elevation of liver transaminases, and in pregnancy.

Niacin Niacin is contraindicated in hepatic disease and relatively contraindicated in gout or history of complicated/active peptic ulcer disease (PUD). Use niacin with caution in patient with diabetes, since it may alter glucose control.

Resins Resins may increase TG and can reduce the absorption of many drugs. Therefore, other drugs should be administered 1 hour before or 4-6 hours after administration of the resin.

Fibrates Fibrates are contraindicated in severe renal or hepatic disease, including primary biliary cirrhosis and preexisting gallbladder disease.

Ezetimibe Maximum LDL-C lowering effect should be apparent within 2 weeks of initiation of treatment.

For information on dosing, administrations, and adverse effects of the pharmacologic agents, see Appendix E.

RECOMMENDATIONS

1. Pharmacologic treatment of dyslipidemia should be individualized and dictated by lipid levels. [B]

Elevated LDL-C

2. Statins are first line agents in primary and secondary prevention of CVD regardless of HDL-C or TG level. [A]
3. Moderate doses of formulary statins (to achieve an LDL-C reduction of 25 percent or greater) should be initiated unless a patient is considered to be at greater than usual risk for adverse events from statins (e.g., myopathy). [A]
4. For patients who cannot tolerate statins, niacin or resins should be considered for treatment. [A]
5. There is insufficient clinical outcome evidence to recommend ezetimibe monotherapy for reduction of CV risk. [I]
6. Ezetimibe can be considered for lowering LDL-C in patients who are unable to tolerate other lipid-lowering drugs. [A]
7. The dose of statin should be adjusted at 6 to 12 week intervals until individual LDL-C goals are achieved or statin doses have been maximized. [I]

Isolated Hypertriglyceridemia

8. Niacin, fibrates, or fish oil supplements may be used in treatment of hypertriglyceridemia. [B]

Isolated Low HDL-C

9. For secondary prevention, gemfibrozil or niacin may be used in patients with isolated low HDL-C and normal LDL-C. [A-Gemfibrozil; B-Niacin]

Safety and Follow-Up

10. Patients treated with statins or fibrates should be educated regarding the importance of recognizing and reporting any unexplained muscle tenderness, pain, or weakness. [I]
11. Lipid profiles should be repeated 6-12 weeks after initiation of therapy and/or change in dose and/or combination therapy. [B]
12. Liver function tests (LFTs) should be performed prior to and after 12 weeks following initiation of treatment, any elevation in dose, and periodically thereafter in those receiving statins, fibrates, or niacin. [I]
13. Creatine kinase (CK) levels should be obtained in patients who develop muscle pain, weakness, or tenderness after institution of statin or fibrate therapy. [I]

DISCUSSION

There are a large number of clinical trials evaluating pharmacotherapy of dyslipidemia. These trials can be separated into several categories: lipid lowering studies, primary prevention trials, and secondary preventions. The prevention trials can be further divided into trials that examine hard clinical outcomes (such as death, MI, and other CV events) and studies that have intermediate outcomes (such as angiographic studies). This guideline gives priority to studies with hard clinical outcomes. A detailed discussion of the important clinical trials for primary and secondary prevention can be found in Appendix F.

Pharmacotherapy for Primary and Secondary Prevention (Monotherapy)

It should be emphasized that all clinical trials demonstrating beneficial clinical outcomes with statins have utilized doses that result in a LDL-C lowering of at least 25 percent (see Appendix F). In order to achieve LDL-C lowering of this magnitude, moderate doses of statins are usually required (See Table 7). Since none of these trials used a target LDL-C to guide dose of statin, the emphasis on treatment of dyslipidemia for primary prevention should focus on providing a statin to lower LDL-C at least 25 percent.

Furthermore, no primary prevention trial has demonstrated lowering of clinical outcomes in patients at low 10-year risk for events. Thus, there is insufficient evidence to recommend pharmacotherapy in low-risk patients, although prudence would suggest following NCEP (2002) recommendations for those individuals with very high LDL-C levels.

Primary Prevention

Lipid-lowering treatment has been shown to reduce CHD events, cardiovascular mortality, and total mortality in patients without known CHD, although these trials have focused on patient populations with significant 10-year risk for events.

Treatment should be based on risk, which varies widely in this group of patients. Drug therapy is indicated for the primary prevention of CVD in patients at moderate to high-risk for CHD who remain above LDL-C thresholds with non-pharmacologic measures.

Secondary Prevention

Lipid-lowering treatment has been shown to reduce CHD events, CV mortality, and total mortality in patients with CHD.

Patients with CHD or CVD or those with diabetes should have statins initiated when LDL-C level remains above 130 mg/dL despite diet and exercise.

Special Populations

White males have been studied most frequently in clinical trials for the prevention of CAD. However, there is evidence that women, non-whites, and elderly patients all benefit from lipid lowering therapy based on the presence of other risk factors. Women have been included in most lipid lowering trials, albeit in small numbers for some studies. A meta-analysis of clinical trials found a significant reduction in CHD events in women and the elderly similar to the reductions observed with men and those younger than 65 years of age (LaRosa et al., 1999). A second, more recent meta-analysis of clinical trials of women treated with lipid-lowering drugs did not find a statistical difference in CHD events in women without known CHD but did find a significant reduction in CHD events in women with known CHD (Walsh & Pignone, 2004). However, the authors comment that some of the analyses were limited because of the low number of CHD events in the available trials. Some larger clinical trials had adequate numbers of women enrolled to demonstrate a decrease in clinical outcomes (CARE, 1996; 4S, 1994; HPS, 2002; PROVE-IT, 2004), while other trials did not show statistically significant benefit (LIPID, 1998; AFCAPS/TexCAPS, 1998; ASCOT-LLA, 2003; A to Z, 2004) likely related to inadequate statistical power. Older age patients also benefit from lipid-lowering therapy, based on risk factors. Nearly all the clinical trials have shown benefit in patients older than 60-65 years of age (4S, 1994; CARE, 1996; LIPID, 1998; WOSCOPS, 1995; ASCOT-LLA, 2003; etc). Indeed, in HPS and PROSPER, there was clinical benefit observed in patients age 70 and above.

Although African Americans have high rates of CHD mortality, they are significantly under-represented in most dyslipidemia clinical trials. Most large clinical trials do not report non-white race as a demographic feature; of the few studies that list race, results of benefit based on race are not reported. We are unaware of any meta-analysis or study that has demonstrated benefits of lipid-lowering therapy in non-white patients. However, although not based on evidence, we concur with the recommendations of ATP-III that non-white patients should obtain similar treatment for dyslipidemia, based on risk factor assessment.

STATINS

Primary Prevention

The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are considered first line agents in most cases because of their effectiveness in reducing LDL-C, their safety and tolerability, and because of their demonstrated ability to reduce CV morbidity and mortality in clinical primary

prevention trials (WOSCOPS-Shepherd, 1995; AFCAPs/TexCAPS-Downs et al., 1998; ASCOT-LLA-Sever, 2003). Only statins have been demonstrated to lower mortality for primary prevention. Other agents have been shown to reduce major CHD events (fatal or nonfatal MI or CHD death) but were not powered statistically to determine their impact on total mortality.

The efficacy of statins to decrease incidence of important clinical outcomes (death, MI, revascularization, stroke, etc.) varies among primary prevention trials, likely the result of differences in baseline lipid abnormalities, patient populations, and LDL-C lowering of statin interventions. Thus, the number needed to treat (NNT) to avoid a major coronary event ranges from 31 to 91; these are higher NNTs than found in secondary prevention (NNT to avoid a major coronary event was 12 in the 4S Trial) trials involving statins.

Secondary Prevention

There are an impressive number of clinical trials demonstrating a consistent benefit with statins for the secondary prevention of cardiovascular events. The 4S, CARE, and LIPID studies were published prior to 1999 and consisted of patients with documented CHD. In each of these studies, statin therapy significantly reduced the incidence of major coronary events, including CHD death and overall mortality in LIPID and 4S. The risk of stroke was also reduced in CARE and 4S. Since 1999, there have been two additional secondary prevention trials evaluating the effect of statins on clinical endpoints and four evaluating statins after an acute coronary syndrome or percutaneous coronary intervention (MIRACL, LIPS, HPS, PROSPER, PROVE IT, and A to Z trials). These studies have convincingly shown that statins are beneficial for secondary prevention in patients with high as well as normal LDL-C, younger as well as older patients, and in stable coronary artery disease as well as acute coronary syndromes. Finally, numerous angiographic trials have demonstrated that statins slow the progression of atherosclerosis as measured by serial coronary angiography resulting in a trend towards reduced CHD events.

Thus, statins are the preferred pharmacotherapy for secondary prevention because of their effectiveness in reducing LDL-C, their safety and tolerability, and because of their demonstrated ability to reduce cardiovascular morbidity and mortality.

Moderate or high-dose statins have been associated with the best clinical results, regardless of baseline lipid levels, with LDL-C lowering in the range of 25-50 percent. Consequently, the emphasis on treatment of dyslipidemia for secondary prevention should focus on providing a statin to lower LDL-C at least 25 percent.

Table 7. Doses of Currently Available Statins Required to Attain an Approximate 30% to 40% Reduction of LDL-C Levels (Standard Doses)*

Drug	Dose, mg/day	LDL Reduction, %
Atorvastatin	10†	39
Lovastatin	40†	31
Pravastatin	40†	34
Simvastatin	20–40†	35–41
Fluvastatin	40–80	25–35
Rosuvastatin	5–10‡	39–45

* Estimated LDL reductions were obtained from U.S. Food and Drug Administration (FDA) package inserts for each drug.
† All of these are available at doses up to 80 mg. For every doubling of the dose above standard dose, an approximate 6% decrease in LDL-C level can be obtained.
‡ For rosuvastatin, doses available up to 40 mg; the efficacy for 5 mg is estimated by subtracting 6% from the FDA–reported efficacy at 10 mg. (Jones et al., 1998)

Considerations-Statins

At this time, there is no convincing evidence that one statin is superior to another when administered in equally potent doses. When statins are provided in doses that are approximately equivalent, a similar percent reduction in LDL-C and percentage of patients meeting their LDL-C goals can be achieved. With regard to lowering TGs or elevating HDL-C, there does not appear to be major differences between agents.

Evidence exists for reducing CHD events with all of the currently available statins excluding rosuvastatin. The choice of statin may depend upon degree of desired LDL-C lowering (see Appendix E for dose and expected LDL-C reduction). Rosuvastatin should be reserved for those patients unable to achieve their LDL-C goals with maximally tolerate doses of other statins that possess clinical outcome and long-term safety data.

Titration and Follow-up

Prior to initiation of statin pharmacotherapy, the ACC/AHA/NHLBI Clinical Advisory Panel recommends determination of baseline liver function, with repeat testing at approximately 6-12 weeks and then annually or more frequently, if indicated (Pasternak et al., 2002). This is based on manufacturer recommendations and the relative contraindication of these agents in patients with underlying liver disease. Routine follow-up liver testing is not based on evidence but rather consensus. In the A to Z trial, significant elevations of liver enzymes were unusual (0.5 percent absolute increase in simvastatin 40/80 mg over placebo/simvastatin 20 mg) and most events occurred within the first 6 months of therapy (de Lemos et al., 2004). On the other hand, in PROVE-IT (2004), atorvastatin (80 mg) was associated with a statistically significant greater risk for elevation in liver enzymes compared to pravastatin (40 mg) (3.3 percent vs. 1.1 percent, $P<0.001$).

Muscle toxicity (myopathy and rhabdomyolysis) has been reported with all of the available statins. The ACC/AHA/NHLBI clinical advisory panel identified certain factors that may predispose or place a patient at increase risk for developing muscle toxicity while receiving statins. Some of those factors include, but are not limited to, advanced age (especially >age 80), female gender, frailty, renal insufficiency, polypharmacy, heavy alcohol use, and hypothyroidism. Baseline measurement of CK is not routinely recommended, however, it should be determined in patients who develop muscle soreness, tenderness, or pain. All patients receiving statins should be educated regarding the recognition and reporting of any unexplained muscle pain, tenderness, or weakness.

The dose of statin should be adjusted at 6 to 12 week intervals until individual LDL-C goals are achieved, or statin doses have been maximized.

FIBRATES

Primary Prevention

Unlike the statins, relatively little evidence supports clinically relevant outcomes associated with the fibrates for primary prevention. The best evidence for benefit is with gemfibrozil; it is not clear whether all fibrates possess a similar cardioprotective effect.

In the Helsinki Heart Study (HHS) (1987), there was a 34 percent relative risk reduction in cardiac outcomes (ARR 1.4percent, NNT=71), but no difference in death. Clofibrate was studied in the World Health Organization (WHO) Cooperative Trial (1984). Although there was a decrease in major CHD events, overall mortality was higher in the clofibrate group. Fenofibrate is currently being studied in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial; results are expected in 2005.

The fibrates have relatively modest effect on LDL-C lowering; greater benefit is seen with triglyceride lowering, and increases in HDL-C. Thus, until further evidence becomes available, the use of the fibrates in primary prevention should probably be limited to patients who are not good candidates for statin therapy, particularly for patients with high TGs or low HDL-C.

Secondary Prevention

Several studies have examined use of fibrates for secondary prevention. One study (Coronary Drug Project, 1975) found no significant decrease in any clinical endpoints with use of clofibrate compared to placebo. Two trials of bezafibrate (BIP and LEADER trials; bezafibrate is not available in U.S.) did not find benefit in primary outcomes (fatal and no-fatal CHD events), although in LEADER there was a benefit in non-fatal CHD events. Likewise, a sub study of the Helsinki Heart Study (1993) also found no benefit of gemfibrozil in preventing clinical outcomes. However, the VA-HIT study of gemfibrozil found a significant decrease in combined MI and CV death in patients with low HDL (≤40 mg/dL) and moderately elevated LDL-C (≤140 mg/dL). This trial is of significance to VA and DoD in that it was performed entirely within VA, and the relative risk reduction in hard clinical outcomes was similar to that of statin trials. The newest fibrate, fenofibrate, has been studied in one small trial (DAIS) not statistically powered to detect clinical outcomes, although there was a decrease in atherosclerotic progression. The FIELD study of fenofibrate therapy in diabetics should be available in 2005. Although there is evidence to support a reduction in CHD events with gemfibrozil, it is not clear whether all fibrates possess a similar cardioprotective effect.

Considerations-Fibrates

As noted above, only VA-HIT has demonstrated a significant decrease in a primary endpoint of CHD events. Thus, given the preponderance of consistent benefit of statins, and equivocal results in all fibrate studies other than VA-HIT, statins are preferred therapy over fibrates for secondary prevention of CHD events. However, patients with low HDL-C who are not candidates or intolerant for statins, should be given consideration for gemfibrozil. Results of FIELD may offer additional evidence for benefit of fibrates in diabetic patients.

Fibrates are contraindicated in patients with severe liver or renal impairment including primary biliary cirrhosis. They are also contraindicated in patients with preexisting gallbladder disease, since all fibrates may increase cholesterol excretion into the bile increasing the risk for cholelithiasis. If cholelithiasis is suspected, gallbladder studies should be performed and the fibrate discontinued if gallstones are found.

It is recommended that LFTs be measured prior to initiation of fibrate therapy and periodically during treatment, since clinically significant elevation of these tests has been reported. In addition, periodic monitoring of the complete blood count is recommended during the first 12 months of fibrate therapy since rare cases of serious hematologic abnormalities (leukopenia, thrombocytopenia, anemia, etc.) have been reported. In patients with serum creatinine values >2 mg/dL, administration of fibrates may worsen renal insufficiency, therefore, consideration of alternative therapy or of a lower dose is recommended. Myopathy and rhabdomyolysis have been reported with fibrate monotherapy, especially in those patients with impaired renal function. As a result, patients receiving monotherapy with fibrates should be educated regarding recognition and reporting of any unexplained muscle pain, tenderness, or weakness.

NIACIN

Primary Prevention

Niacin has the ability to reduce LDL-C and TGs and raise HDL-C, thus making it an attractive agent for primary prevention of CHD. However, there are no clinical trials conducted in a primary prevention population to support a reduction in CHD events with niacin when used alone.

Secondary Prevention

Although niacin has been studied in several drug combination trials for secondary prevention, there is only one trial using niacin monotherapy. In the Coronary Drug Project (1975), patients receiving niacin had a significant decrease in nonfatal MI (Relative Risk Reduction [RRR] rate 27 percent, ARR 3.6 percent, NNT 28) and all stroke (RRR 24 percent, ARR 2.7 percent, NNT 37), but no benefit in overall mortality.

Niacin-Considerations

Niacin can be considered as second line treatment for the primary or secondary prevention of CHD in patients that are not candidates for or are intolerant of statins. They also may be considered as add-on therapy for

patients not meeting their lipid goals (LDL-C, HDL-C, and TG) with statins alone. (See combination treatment in Annotation Q2.)

Niacin is contraindicated in patients with significant liver impairment, active liver disease, unexplained transaminase elevations, active peptic ulcer disease, or arterial bleeding.

The primary limitation of niacin is the flushing side effects which can occur with any niacin products but can be minimized by giving low dose aspirin 30 minutes or a nonselective nonsteroidal anti-inflammatory drug (NSAID; e.g., ibuprofen) prior to niacin. Higher doses of niacin may raise glucose or uric acid concentrations. Two trials demonstrated the safety and efficacy of niacin in patients with diabetes. In the first study, an extended release niacin product (1500 mg/dL) was administered to diabetics managed by diet, oral hypoglycemics, or insulin (ADVENT, 2002). In the second study, up to 3 grams daily of crystalline niacin was administered to patients with diabetes and peripheral arterial disease (ADMIT, 2000). In either study, glycemic control was not clinically significantly changed in patients receiving niacin versus placebo.

Serious liver toxicity has been reported in patients receiving sustained release niacin in doses of >2 grams daily and less often in patients on crystalline niacin. Providers choosing to switch crystalline niacin to extended release niacin or niaspan should begin at a low dose of the extended release product and titrate to the desired response. Liver function should be measured prior to initiation of treatment, at 6-12 weeks and then periodically thereafter. Niacin may cause rash and gastrointestinal (GI) symptoms.

BILE ACID SEQUESTRANTS OR RESINS

Primary Prevention

Bile acid sequestrants (BAS) have the ability to reduce LDL-C and slightly raise HDL-C; however, they may increase TG concentrations. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT, 1984) decreased CHD death and nonfatal MI (RRR 19 percent, ARR 1.6 percent, NNT 62), but there was no overall mortality benefit compared to placebo.

Secondary Prevention

There are no published trials evaluating the effect of resins (as monotherapy) on clinical endpoints in patients with CVD. Resins have the ability to reduce LDL-C 10-27 percent, no effect on HDL-C, and either no effect or may increase triglyceride concentrations. They may be considered as add-on therapy for those not achieving their LDL-C goals on niacin or moderate to maximum daily doses of statins (See combination therapy-Annotation Q2).

Considerations-BAS or Resin

The major limitations of resins **a**re their poor tolerability (GI adverse effects), potential for drug interactions (if taken with other medications), and potential to further increase TGs in patients with elevated TG levels.

Resins may be considered as second-line therapy in patients unable to tolerate statins or other lipid-lowering treatments. Resins may also be considered in combination with statins or other lipid-lowering drugs if LDL-C goals are not achieved with monotherapy (see combination therapy-Annotation Q2).

EZETIMIBE

Ezetimibe (Zetia®) is the first in a new class of cholesterol lowering agents called the cholesterol absorption inhibitors. It acts by selectively inhibiting absorption of cholesterol (dietary and biliary) at the brush border of the small intestine.

Aside from LDL-C lowering, there is no evidence to support a reduction in CHD events with ezetimibe when used alone for primary or secondary prevention of CHD. However, it can be considered for lowering LDL-C

in those patients either unable to tolerate and/or having an inadequate LDL-C lowering response to other lipid-lowering agents.

Considerations

When combined with statins, ezetimibe may increase the risk of elevated transaminases. It should not be used with gemfibrozil, fenofibrate, or enofibrate micronized.

FISH OIL SUPPLEMENTS (N-3 Polyunsaturated Fatty Acids or N-3 PUFA or Omega-3 Fatty Acids)

In NCEP ATP-III, the use of fish oil supplementation or -3 PUFAs is discussed briefly. As part of the report, n-3 PUFAs (e.g., fish, fish oils, or high linolenic acid oils) in lower doses (1-2 g/day) are mentioned for the prevention of CHD. ATP-III concluded that the strength of the available clinical trial evidence for this use was moderate and states that more definitive clinical trials are needed prior to routinely recommending n-3 PUFAs for primary or secondary prevention of CHD (NCEP ATP-III, 2002; DART-Burr et al., 1989; Singh et al., 1997; GISSI, 1999).

Based upon the evidence from two systematic reviews (Harris, 1997; Farmer et al., 2001) and several other randomized controlled trials (Harris, 1997; Nordoy et al., 2001; Durrington et al., 2001; Stalenhoef et al., 2000), n-3 PUFAs, in doses of 3-4 grams per daily are safe and efficacious in lowering TGs and are an alternative to fibric acids (gemfibrozil or fenofibrate) or nicotinic acid for the treatment of hypertriglyceridemia.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Pharmacologic treatment of dyslipidemia should be individualized and is dictated by lipid levels	NCEP ATP-III, 2002	I	Fair	B
2	Statins are first line agents in primary and secondary prevention regardless of baseline TG or HDL-C level	Primary Prevention: AFCAPS/TexCAPS, 1998 ASCOT-LLA, 2003 CARDS, 2004 WOSCOPS, 1995 Secondary Prevention: CARE, 1996 4S, 1994 HPS, 2002 LIPID, 1998 PROSPER, 2002	I	Good	A
3	Moderate doses of formulary statins (to achieve an LDL-C reduction of 25% or greater) should be initiated (unless greater than usual risk for adverse events)	Primary Prevention: AFCAPS/TexCAPS, 1998 WOSCOPS, 1995 Secondary Prevention: CARE, 1996 4S, 1994 HPS, 2002 LIPID, 1998 LIPS, 2002 PROSPER, 2002 PROVE-IT, 2004	I	Good	A
4	Consider treatment with other lipid lowering agents (niacin or	Primary Prevention: HHS, 2002	I	Good	A

	resins) for patients who cannot tolerate statins	LRC-CPPT, 1984 Secondary Prevention: CDP, 1975 LEADER, 2002 VA-HIT, 1999			
5	Use of ezetimibe monotherapy for preventing CVD	Working Group Consensus	III	Poor	I
6	Ezetimibe can be considered for lowering LDL-C in patients who are unable to tolerate other lipid-lowering drugs	Bays et al., 2001 Knopp,Dujovne, et al., 2003 Knopp, Gitter, et al., 2003 Sudhop et al., 2002	I	Good	A
7	Aggressive early treatment with a moderate dose of statins for all patients with recent ACS	PROVE-IT, 2004 REVERSAL, 2004	I	Good	A
8	Dose of statin should be adjusted at 6 to 12 week intervals until individual LDL-C goals are achieved or statin doses have been maximized	Working Group Consensus	III	Poor	I
	Isolated Hypertriglyceridemia				
9	Consider niacin, fibrates, or fish oil supplements to lower TGs	Niacin: NCEP ATP-III Fibrates: NCEP ATP-III Fish Oils: Harris 1997 & Farmer et al., 2001	I	Fair	B
	Isolated Low HDL-C				
10	Gemfibrozil	VA-HIT, 1999	I	Good	A
11	Niacin to increase HDL-C	King et al., 1994 Lavie et al., 1992 Miller et al.,1993 Miller et al., 1995 Vega & Grundy, 1989	I	Fair	B
	Safety and Follow-Up				
12	Provide patients with education about unexplained muscle tenderness, pain, or weakness	ACC/AHA/NHLBI, 1998 NCEP ATP-III, 2002	III	Poor	I
13	Repeat lipid profile in 6-12 weeks after initiation of therapy and/or change in dose and/or with combination therapy	Benner et al., 2004 NCEP ATP-III, 2002	II	Fair	B
14	LFT should be performed prior to and after 6-12 weeks following initiation/change of dose, and periodically thereafter in those receiving statins, fibrates, or niacin	NCEP ATP-III, 2002	III	Poor	I
15	Obtain CK levels in patients who develop muscle pain, weakness, or tenderness after institution of statin or fibrate therapy	NCEP ATP-III, 2002	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

Q2. Pharmacotherapy: Combination Therapy

OBJECTIVE

Achieve lipid goals through the use of combination pharmacologic agents.

BACKGROUND

Occasionally, a statin alone is insufficient to reach a patient's LDL goal. When this occurs, a more potent statin or higher dosage may be prescribed, or other lipid lowering agents may be added to the regimen. If the choice is to combine agents, the achieved reduction in LDL will be the sum of the lowering provided by each drug.

To date, there have been no large, published clinical endpoint trials evaluating the benefits of combination pharmacologic therapies for dyslipidemia. There are, however, angiographic and LDL-C lowering trials demonstrating benefit with certain drug combinations. As a result of the lack of clinical outcome data to support an advantage of combination drug therapy over monotherapy with statins, careful consideration must be given to the risk of toxicity in individual patients before exposing them to combination therapy.

Some lipid-lowering treatments (e.g., statins plus fibrates) are known to be associated with an increased risk for muscle toxicity when used in combination. Several factors have been identified as increasing an individual's risk for muscle toxicity with statins and fibrates including drug interactions, advanced age, impaired renal function, female gender, alcoholism, and hypothyroidism. Furthermore, since the risk of adverse events increases with higher doses of statins, combination of these agents should be limited to the lowest possible dose of statins needed to achieve lipid goals.

Despite the lack of clinical outcome data, NCEP ATP-III recognizes that some individuals may require combination therapy to achieve their lipid goals. Examples of these individuals may include those needing additional LDL-C lowering (not achieved with monotherapy), those with very high TG levels (≥500 mg/dL) and those with mixed dyslipidemias (low HDL-C, high TGs and elevated LDL-C).

It should be emphasized that the available clinical trials, evaluating certain lipid-lowering combinations, do not necessarily represent the patients identified by NCEP ATP-III as being potential candidates for combination therapy. For example, there has never been a randomized clinical trial evaluating combination lipid-lowering agents in patients with very high TG levels. However, consideration of combination lipid-altering treatments in these individuals is based upon clinical reasoning.

Table 8. Potential Combination Pharmacological Treatments for Dyslipidemia

Drug Combination	Expected Change in Lipoproteins (%)			Outcome DATA
	LDL	HDL	TG	
↑ LDL-C When Monotherapy is Inadequate				
Statin + Resin	-30 to -60	-	+10	No Data
Statin + Niacin	-25 to -57	-13 to -36	-19 to -38	No Data
Statin + Ezetimibe	-34 to -60	-3 to -9	-11 to -24	No Data
Niacin + Resin	-32 to -43	-37 to -43	-27 to -29	No Data
Statin + Resin or Ezetimibe + Niacin	No Data			No Data
↑ LDL-C and ↑ TG (≥500 mg/dL)				
Statin + Niacin * **	-25 to -57	-13 to -36	-19 to -38	No Data

Statin + Fibrate	-	-19 to -22	-41 to -53	No Data
Statin + Fish Oil	-	-	-20 to -30	No Data
Niacin + Fibrate	No Data TC -13	- 45	-20	No Data
Ezetimibe + Niacin **Ezetimibe + Fish Oil**	No Data			No Data
Very High TG and/or Low HDL-C Without Elevated LDL-C*				
Statin + Niacin *** **Statin + Fibrate** **Statin + Fish Oil** **Fibrate + Niacin**	See above for effect on lipids. No data in patients with TG >400 mg/dL.			No Data
Fibrate or Niacin + Fish Oil	No Data			No Data
Fibrate + Niacin + Fish Oil	No Data			No Data
Low HDL-C, high LDL-C and high TG)*				
Statin + Niacin	See Above			No Data
Statin + Fibrate	See Above			No Data
Fibrate + Niacin + Resin	26	36	50	No Data

(Guyton 1999, Worz & Bottorff, 2003, NCEP ATP-III, 2002), *Combination studies did not include patients with very high TG (≥500 mg/dL).
- =No additional benefit with combination, N=niacin, NR=not reported, R=resin, S=statin, TC=total cholesterol. The manufacturers of ezetimibe recommend avoiding the combination of ezetimibe plus fibrates (Fibrates can increase cholesterol excretion into the bile. In a dog study, ezetimibe also increased cholesterol excretion into the bile). There is no data on the combination of ezetimibe plus fish oils.
*** No clinical trial data in patients with TG >400 mg/dL

RECOMMENDATIONS

LDL-C Lowering Combination Therapy [ONLY FOR SECONDARY PREVENTION]

1. For patients not at goal, monotherapy should be titrated until goal is achieved or maximum tolerable dose has been reached. [C]
2. Combination therapy to achieve LDL-C goal may be considered for carefully selected patients who do not achieve the LDL-C goal with maximally tolerated monotherapy. [I]
3. Combination lipid-lowering therapy should include a statin unless the patient is unable to tolerate statins. [A]
4. Addition of a resin to the statin can be considered for secondary prevention in patients not meeting their LDL-C goals on maximally tolerated doses of statins. [B]
5. Addition of niacin or a resin to the statin can be considered in patients not meeting their LDL-C goals to further reduce the LDL-C level. [B]
6. Addition of ezetimibe to the statin can be considered in patients not meeting their LDL-C goals on maximally tolerated doses of statins and unable to tolerate niacin or a resin to reduce the LCL-C level. [I]
7. In patients unable to tolerate statins and not achieving their LDL-C goals with niacin or resins, a combination of both resin and niacin may be considered. [B]
8. In any combination therapy the lowest possible dose of statin should be used to achieve lipid goals. When combined with fibrates (greatest risk), niacin or possibly ezetimibe, the risk of adverse events with statins (e.g., muscle toxicity) appears to increase with increasing statin doses. [C]

Elevated LDL-C and Very High Triglycerides (>500 mg/dL)

If non-HDL goals cannot be achieved with a statin (or other LDL-lowering regimen) alone, a TG-lowering drug may be added to the statin. Choices are niacin, a fibrate, and fish oils.

9. Combination therapy with statins and niacin, fish oils or fibrates can be considered for the secondary prevention of CVD in patients with elevated LDL-C and very high TGs. [C]

10. Combination therapy with niacin and fibrates can be considered for the secondary prevention of CVD in patients with elevated LDL-C and very high TGs in patients unable to tolerate statins. [C]

Very High Triglycerides and/or Low HDL-C Without Elevated LDL-C

11. For secondary prevention of CVD in patients with either low HDL-C or very high triglycerides and no elevation of LDL-C levels, combination therapy with statin plus niacin, fibrate or fish oil may be considered. [C]
12. Combination therapy with niacin and fibrates and/or fish oils can be considered in patients unable to tolerate statins. [C]

DISCUSSION

Combination Pharmacotherapy

There is increasing interest in combination pharmacologic therapy for managing dyslipidemia. Several explanations for the interest include the "optional" more aggressive LDL-C lowering goal in the very high-risk patient who is unable to reach their LDL-C goal with statin monotherapy, increasing recognition of the importance of addressing atherogenic dyslipidemia frequently associated with metabolic syndrome and management of mixed dyslipidemias not optimized with statins alone. Although it seems reasonable to address and improve the total lipid profile, there are no large randomized clinical endpoint trials examining the benefit of combination therapy. There are, however, several angiographic and many LDL-C lowering trials demonstrating benefit in those surrogate endpoints.

Bile acid sequestrants, niacin, and ezetimibe combined with a low dose statin can produce similar LDL-C lowering as quadruple the statin dose (e.g., simvastin 10 mg + ezetimibe 10 mg = simvastin 80 mg daily). However, since most of the large health outcome statin trials utilized higher statin doses (20-40 mg/d), it is not known whether the same clinical benefit will be seen if a low dose statin is combined with another lipid-lowering agent.

The risk of toxicity from combining certain lipid-lowering treatments (e.g., statin + fibrates) must be carefully considered prior to initiating therapy. Furthermore, since the risk of adverse events increases with higher doses of statins, combination of these agents should be limited to moderate dose statins.

Box 6. Key Elements in Management of Combination Therapy

1. Treatment of LDL and non-HDL should focus on statin therapy alone.
2. Reserve combination therapy for high-risk patients (secondary prevention or familial hypercholesterolemia)
3. Discuss the risks and unproven clinical benefits of statin-fibrate therapy with the patient and document it in the patient's medical record.
4. Prescribe the lowest effective dosages of the statin and fibrate to achieve treatment goals.
5. Use caution in patients with the following characteristics: advanced age, female gender, compromised renal function, heavy alcohol use, frailty and hyperthyroidism.
6. Be cautious about use of drugs that could interfere with the metabolism of the statin, or are known potent CYP 3A4 inhibiting medications (e.g., macrolides, azole antifungals, protease inhibitors, cyclosporine, etc.)
7. Obtain a baseline CK level and repeat the measurement during therapy, if the patient reports symptoms consistent with myopathy.
8. Teach patients to recognize and report generalized muscle weakness, tenderness, or pain; be prepared to evaluate those who experience these symptoms. (Evaluate CK and UA.)
9. Discontinue therapy for myopathic symptoms and elevated CK
10. If TG-lowering drug is added to a statin, caution is required due to particularly higher risk of myopathy. Fibrate and niacin combinations with statin may be more toxic than combination with fish oil.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Combination lipid-lowering therapy should include a statin unless the patient is unable to tolerate statins	CARDS, 2004 HPS, 2004	I	Substantial	A
2	In combination therapy with a statin, the lowest possible dose of statin should be used to achieve lipid goals and minimize complications	Work Group Consensus	III	Poor	C
3	Combination therapy should be reserved for patients on secondary prevention	Work Group Consensus	III	Poor	I
4	Addition of niacin to the statin can be considered in patients on secondary prevention not meeting their LDL-C goals on maximally tolerated doses of statins	HATS, 2004	I	Good	B
5	Addition of a resin to the statin can be considered in patients not meeting their LDL-C goals on maximally tolerated doses of statins	Brown et al., 1990	I	Good	B
6	Addition of ezetimibe to the statin can be considered for lowering LDL-C levels in patients not meeting their LDL-C goals on maximally tolerated doses of statins and unable to tolerate niacin or a resin	Gagne, Bays et al., 2002	I	Good	I
7	Combination of resin and niacin can be considered in patients unable to tolerate statins and not achieving their LDL-C goals with niacin or resins alone	Blankenhorn et al., 1987 Brown et al, 1990	II	Good	B
8	Combination of statins and niacin, fish oils, or fibrates can be considered in patients with elevated LDL-C and very high TGs	Working Group Consensus based upon clinical reasoning	III	Poor	C
9	Combination of niacin and fibrates can be considered in patients with elevated LDL-C and very high TGs who are unable to tolerate statins	Working Group Consensus based upon clinical reasoning	III	Poor	C
10	Combination of statin and niacin, fibrate or fish oil may be considered in patients who have achieved	Working Group Consensus based upon clinical reasoning	III	Poor	C

	their LDL-C goal or are without elevated LDL-C, and have either low HDL-C or very high TGs				
11	Combination of niacin and fibrates and/or fish oils can be considered in patients with elevated LDL-C and very high TGs who are unable to tolerate statins	Working Group Consensus based upon clinical reasoning	III	Poor	C

QE = Quality of Evidence; R = Recommendation (see Appendix A)

R. Repeat Dyslipidemia Evaluation in 1 to 2 Years (Patients *not* on Therapy)

OBJECTIVE

Provide appropriate clinical follow-up for patients not on therapy.

BACKGROUND

Because lipids tend to increase with advancing age, patients at initially low-risk for CVD events may over time, become patients at above-average risk or may develop concurrent health conditions (nephrotic syndrome, hypothyroidism, and DM) that can declare as dyslipidemia. Periodic reassessment of serum cholesterol and TGs permits timely identification and treatment of such individuals.

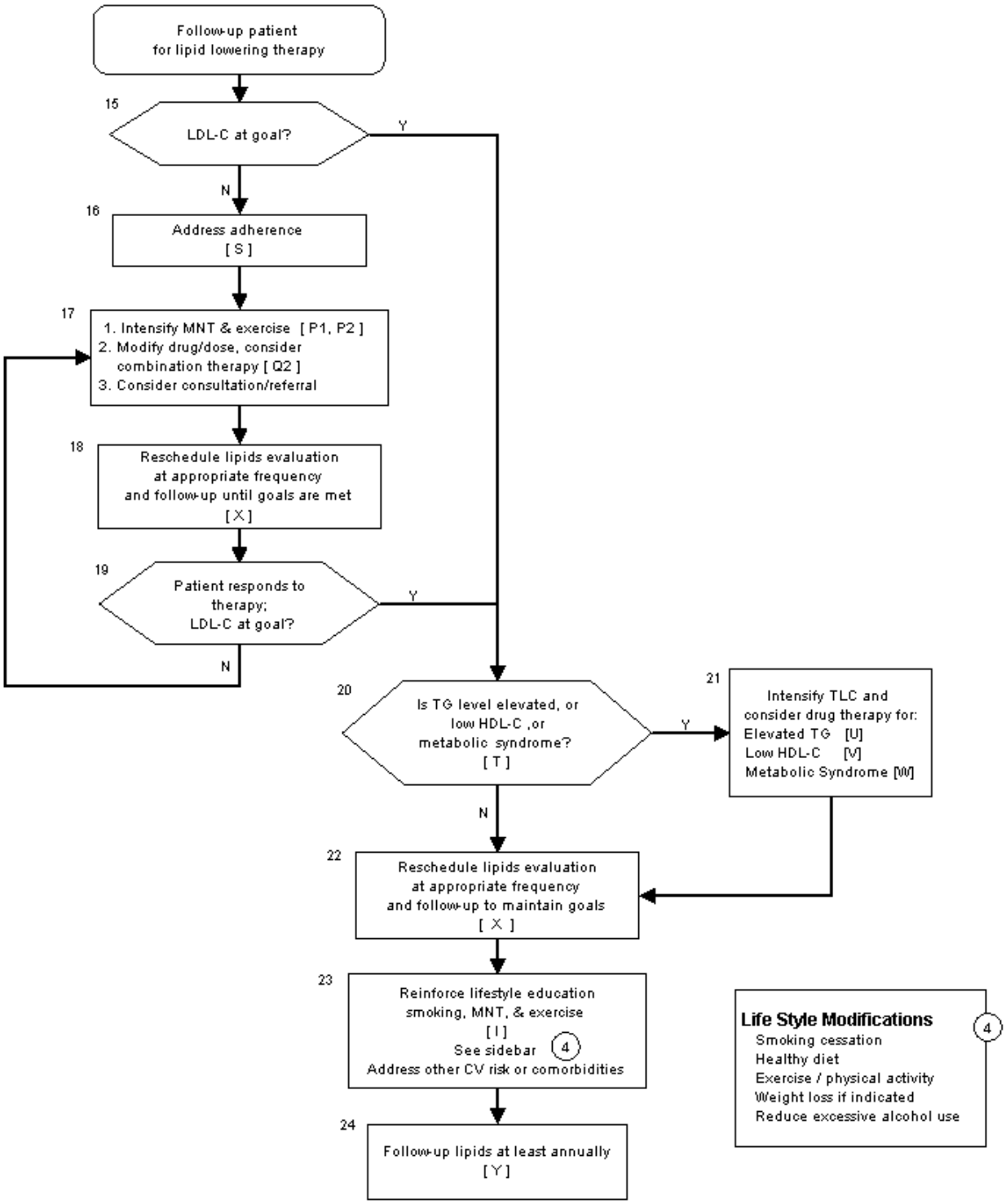
RECOMMENDATIONS

1. If the initial dyslipidemia screening reveals TC >200 mg/dL, or fasting LDL-C >130 mg/dL or HDL-C <40 mg/dL, but LDL-C level is under the recommended goal level based upon CV risk, the patient will be at low-risk for lipid-related events over a one to two-year period and thus, should be reevaluated for dyslipidemia in one to two years.

11/20/2005

Management of Dyslipidemia
Module C: Follow-up Treatment

C



CVD - Cardiovascular disease ; DM - Diabetes Mellitus; MNT -Medical Nutrition Therapy; TLC - Therapeutic Lifestyle Changes;
HDL-C - High density lipoprotein cholesterol; LDL-C - Low density lipoprotein cholesterol; TG - Triglycerides

ANNOTATIONS

S. Address Adherence to Therapy

OBJECTIVE

Identify causes of inadequate response to therapy following dose or stepwise titration.

BACKGROUND

Poor adherence can limit the effectiveness of lipid lowering therapies. In asymptomatic conditions such as dyslipidemia, this can be especially problematic. The selection of patients, close monitoring, and educational efforts of providers lead to a higher adherence to therapy in clinical trials. In general practice, long-term adherence to drug therapy is estimated to be only 50 percent. Adherence to drug therapy should be assessed in any individual taking medications before assuming that a lack of response is attributed to simple inadequacy of the chosen agent. The NCEP ATP-III guidelines acknowledge the challenge in implementing and maintaining patient adherence to both lifestyle changes and pharmacotherapy regimens.

Factors associated with poor adherence to medication include:

- Number of drugs: Complexity, and frequency of drug administration
- Medication adverse effects: Particularly an issue for niacin and resins, although statins may cause myalgias and nonspecific gastrointestinal symptoms
- Incomplete patient education: Asymptomatic patients may not understand the benefit of medication or need for long-term therapy
- Cost and psychosocial factors: Patients may not be able to obtain medications.

Factors associated with poor adherence to diet and exercise include:

- Incomplete patient effort and self-motivation: Some patients are unable or unwilling to comply with strict dietary changes, such as a TLC diet, and a regular exercise regimen
- Suboptimal social support: Family and lifestyle may not be conducive to strict dietary changes. Patients may not have access to exercise facilities or safe environment (e.g., safe neighborhood in which to walk)
- Incomplete patient education: Some patients may not have received adequate information because of missed visits or inadequate time for counseling
- Cost: Patients may perceive that dietary interventions increase costs, although this is generally not the case. Patients unable to walk may not have access to other exercise options (swimming, stationary bike/machines, etc.).

RECOMMENDATIONS

1. Adherence to therapy should be assessed at every visit, through history, pill count, and/or administrative records especially if therapeutic goals have not been reached. [I]
2. Adherence to lipid-lowering medication regimens may be improved by a multi-pronged approach [I] including:
    a. Evaluation of medication side effects
    b. Simplifying medication regimens to incorporate patient preference
    c. Addressing barriers for obtaining the medications (administrative, economic, etc.)
    d. Coordination with other healthcare team members to improve monitoring of adherence with prescriptions of pharmacological and lifestyle modification
    e. Patient and family education about their disease/treatment regimens
    f. Evaluation for depression.

DISCUSSION

Numerous reasons for poor medication adherence have been suggested including long-term therapy, cognitive impairment, number of medications prescribed, frequency of administration, complexity of the drug regimen, cost of medications, side effects, and other factors such as acceptance of the disease, perceived severity, and satisfaction with healthcare providers, etc.(Eraker et al., 1984). Adherence to medication regimens may also be impacted by patient and/or caregiver education on the disease and its management, education of the healthcare practitioner on patient communication, patient involvement in self-care, and health professional medication monitoring.

It is difficult to apply patterns of medication adherence to various diseases due to different belief models or motivating factors for adherence (e.g., acute life-threatening disease, symptomatic illness vs. asymptomatic condition). For example, the use of statins in controlled studies such as the Heart Protection Study was high (85 percent) over multiple years (HPS, 2002). In practice, two-year compliance may be as low as 40 percent in the elderly (Jackevicius et al., 2002; Benner et al., 2002). Comorbidity of major depression and diabetes is associated with less physical activity, unhealthy diet, and lower adherence to oral hypoglycemic, anti-hypertensive, and lipid-lowering medications. Adverse effects (more common in individuals on multiple agents), may also affect adherence.

EVIDENCE

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Assess medication adherence at each visit through history, pill count, or medical record review	Working Group Consensus	III	Poor	I
2	Consider a multi-pronged approach to improve adherence to medication regimens	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

T. Does The Patient Have Elevated TG Level, or Low HDL-C Level, or Metabolic Syndrome?

BACKGROUND

Elevated LDL-C level is considered the primary target of lipid-lowering therapy. Epidemiologic and clinical studies have shown that a high blood TG level is an independent risk factor for CVD (Austin et al., 1998; Krauss, 1998). However, when triglyceride levels are >200 mg/dL, the ATP-III cautions that the presence of increased quantities of atherogenic remnant lipoproteins can raise the risk of CHD far beyond what an LDL-C level alone can predict. The atherogenic lipoproteins include small, dense LDL, very-low-density lipoprotein (VLDL), and intermediate-density lipoprotein (IDL), which are cholesterol-enriched particles that have many of the same properties as LDL-C. The risk for CVD is higher in patients who have elevated levels of both, LDL-C and TG.

It is common to find low HDL-C levels in patients who have high levels of TG. In addition, these low levels often accompany insulin resistance. A low HDL-C level is considered an independent CHD risk factor and is clearly linked to increased CHD morbidity and mortality. Various epidemiologic studies have shown that for every 1 percent decrease in HDL-C, there is a 2 to 3 percent increase in CHD risk.

Patients with high TG and low HDL-C often have several other CVD risk factors, including central obesity, impaired glucose tolerance, and HTN. This constellation of findings is referred to as syndrome X, Reavan's syndrome, dysmetabolic syndrome, and, most recently defined by NCEP ATP-III as metabolic syndrome.

The goal of dyslipidemia management is ultimately to decrease CV risk, and the evidence is best at reducing such risk through LDL-C lowering therapies. LDL-C remains the treatment priority, and should be addressed regardless of the TG level. Once the LDL-C goal has been reached, treatment attention may shift to obtain optimal lipoprotein profiles.

U. Evaluation and Treatment of High Triglycerides

OBJECTIVE

Evaluate and treat TG levels above 200 mg/dl.

BACKGROUND

In the management of dyslipidemia, therapy targeted at LDL lowering is the first priority to lower CVD risk. Some dyslipidemic disorders manifest with significantly elevated TG levels. Although there are no clinical trials that have shown that reducing TG levels reduces CV risk, there are situations when emphasis needs to be placed on reducing the serum TG level. Patients with very high levels of TGs are at risk for the development of acute pancreatitis, and some authorities recommend TG level ≥ 500 mg/dL as a threshold for treatment to prevent pancreatitis. Accurate measurement of TG requires fasting for 9-12 hours prior to the test. Thus, for TG levels >400 mg/dL the first step would be to ensure that it was done in a fasting state, and repeat the measurement, if not.

Box 7. Treatment for Hypertriglyceridemia		
TG >200 – 499 mg/dL	**TG ≥500 mg/dL**	**TG >1000 mg/dL**
• Lifestyle management • Weight loss • Alcohol cessation • Secondary causes	• Very low fat diet • Low concentrated carbohydrate diet • Alcohol cessation • Secondary causes • Consider drugs, if no response to above • Consider referral	• Strict MNT (avoidance of alcohol, fat, and restrict calories) • Secondary causes • Drug therapy, if no response to above • Consider referral

RECOMMENDATIONS

1. Patients with elevated TG (≥200 mg/dL) should have a repeat fasting lipid profile, and if persistent receive intensive MNT, an appropriate exercise program, and be screened for underlying causes. [B]
2. Drug therapy may be considered in patients with very high TG levels (≥ 500 mg/dL) that do not respond to lifestyle interventions and the treatment of underlying causes of elevated TG, for the purpose of preventing pancreatitis. [I]
3. Effective drugs for lowering hypertriglyceridemia include: fibrates, niacin, and fish oil. [B]

Table 9. Drug Treatment for Hypertriglyceridemia

TG 500-1000 mg/dL		
	Drug	**Efficacy (Expected % Reduction in TG)**
Initial	Fibrates	-20 to -50
Alternate	Niacin	-20 to -35
	n-3 PUFA Supplements, Omega-3 Fatty Acids/Fish Oils	-20 to -30

- Fibrates are contraindicated in severe renal disease.

- Niacin is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active peptic ulcer disease (PUD).

DISCUSSION

Since the goal of the management of dyslipidemia is ultimately to decrease CV risk, and the evidence is best at reducing such risk through LDL-C lowering therapies, LDL-C remains the treatment priority, and should be addressed regardless of the TG level.

Pancreatitis is typically seen with TG levels ≥1,000 mg/dl, but patients with TG levels ≥500 mg/dL may develop a rapid elevation in the TG level (e.g., after a high-fat meal) resulting in acute pancreatitis. Therefore, some recommend lowering very high TG levels (>500 mg/dL) to prevent acute pancreatitis.

Patients with hypertriglyeridemia will often have an acquired or secondary condition responsible for the TG elevation. Acquired causes of elevated TG include: obesity, excess alcohol intake, physical inactivity, cigarette smoking, and high carbohydrate intake. Secondary causes of elevated TG may also include poorly controlled DM, chronic renal failure, Cushing's syndrome, pregnancy, and various drugs (beta blockers, thiazide diuretics, oral estrogens, tamoxifen, protease inhibitors, and retinoids).

The primary treatment for elevated TG is lifestyle modification and the treatment of underlying causes. In many instances, life style modification and treatment of secondary conditions will correct the hypertriglyceridemia. Poorly controlled DM and alcohol abuse are common conditions responsible for very high TG value, and therefore, assessment and treatment of these conditions if present, should always be a priority in the management of very high TG levels. Drug therapy should be considered in patients with very high levels (>500 mg/dL) that does not respond to other measures. Drugs that are known to lower TG levels include fibrates, nicotinic acid, fish oil (omega-3 fatty acids), and statins.

EVIDENCE

	Recommendation	Source of evidence	QE	Overall Quality	R
1	Elevated TG should receive intensive MNT, exercise, and screening for underlying causes	NCEP ATP-III, 2002 Stone & Blum, 2002	II-3	Fair	B
2	Consider drug therapy to prevent pancreatitis	Cleeman, 1998 NCEP ATP-III, 2002 Stone & Blum, 2002	III	Poor	I
3	Use of fibrates, niacin, and fish oil to lower hypertriglyceridemia	Farmer et al., 2001 Harris, 1997	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

V. Evaluation and Treatment of Low HDL-C

OBJECTIVE

Reduce risk of CVD through raising the level of HDL-C.

BACKGROUND

Causes of low HDL-C include genetic factors, elevated serum TGs, overweight and obesity, physical inactivity, cigarette smoking, very high carbohydrate intake, diabetes, and certain drugs (NCEP ATP-III, 2002).

Large epidemiologic trials have shown that a low HDL-C is associated with an increased risk for CHD, and thus, it is classified as a major risk factor for CHD. Despite these observations, the independent contribution of

low HDL-C to CHD risk is complex, as it is usually associated with other metabolic factors such as diabetes, metabolic syndrome, and other atherogenic dyslipidemias that also increase CHD risk. In addition, clinical trials targeting low HDL-C also affect other lipid parameters that influence CHD risk. Nonetheless, patients with low HDL-C should have non-pharmacologic as well as pharmacologic interventions aimed at increasing its level, depending on underlying risk for CHD events.

RECOMMENDATIONS

1. Patients with CVD who have low HDL-C (<40 mg/dL), TG >200 mg/dL and normal levels of LDL-C may benefit from gemfibrozil therapy. [A]
2. Lifestyle modifications, including weight loss, exercise, and smoking cessation should be given high priority in the therapeutic plan for patients with low HDL-C. [B]
3. CVD patients with low HDL-C (<40 mg/dL), may be considered for treatment with niacin. [B]

Table 10. Drug Treatment for Isolated Low HDL-C

LDL-C <130 and Low HDL-C		
Drug	**Efficacy (Expected % Reduction in TG)**	
Gemfibrozil	**LDL-C** **+10 to –35**	**HDL-C** **+2 to 34**

DISCUSSION

Multiple epidemiologic studies, including the Framingham Study, have observed an inverse relationship between HDL-C levels and risk for CVD, where a difference of one mg/dL is associated with a 2-3 percent change in risk (Gordon et al., 1989). In the Framingham Study, for instance, men with an HDL lower than 25 mg/dL had an incidence of CHD of 176.5/1000, compared to an incidence of 100/1000 in men with an HDL-C of 25 to 34 mg/dL. Likewise, women with an HDL-C of 25 to 34 mg/dL had an incidence of CHD of 164.2/1000, compared to 54.5/1000 in women with an HDL of 35 to 44 mg/dL. The importance of low HDL as a risk factor for developing CHD was borne out in the AFCAPS/TexCAPS trial, in which the most significant benefit was seen in patients treated with an entry HDL lower than 35 mg/dL (Downs et al., 1998). Just as a low HDL level is inversely linked to an increased risk for developing CHD, a high HDL level is inversely linked to a decreased risk for developing CHD (Wilson et al., 1998). It has been established that the protective effect of a high HDL is present even in the setting of a high LDL (Kannel, 1995).

There are relatively few trials targeting low HDL-C. Most important is VA-HIT (Robins et al., 1999), which randomized patients with established CVD, and HDL-C <40 mg/dL, and LDL-C <140 mg/dL to either gamfibrozil, or placebo. Mean entry HDL-C was 32 mg/dL, and LDL-C was 111 mg/dL. After a mean follow-up of five years, the gemfibrozil treatment arm had a 22 percent relative risk reduction in the combined end-point of nonfatal MI or death due to CVD, and a 25 percent reduction in stroke. The study was not statistically powered to detect overall mortality benefit. Subgroup analysis of VA-HIT strongly suggests that CHD patients with low HDL-C, TGs >200 mg/dL, HTN, or impaired glucose tolerance were particularly likely to benefit from gemfibrozil therapy.

More recently, a small study of U.S. military retirees with known CHD assessed a strategy aimed at increasing HDL-C (Whitney et al., 2005). The intervention of a 3-drug regimen of gemfibrozil, niacin, and cholestyramine was associated with a 26 percent decrease in a composite endpoint of all CV endpoints. However, in addition to a 36 percent increase in HDL-C, there was a 26 percent decrease in LDL-C level, thus confounding the interpretation of the benefit associated with increasing the levels of HDL-C.

Niacin reduces LDL-C by up to 25 percent in a dose-dependent manner. To reduce the risk of hepatotoxicity, the dose of extended- and sustained-release forms of niacin is limited to 2g/d, which reduces LDL-C by 15-20 percent. Immediate-release niacin can be titrated to 3 g/d (or more) and can reduce LDL-C in the 20-25 percent range. While niacin's LDL-C lowering is linear, its effect on TGs and HDL-C is curvilinear. Modest doses of niacin can significantly alter these two lipid levels. For example, one g/d of immediate-release niacin can increase HDL-C by 25-30% and reduce TGs by a similar margin. Niacin is the most effective drug available for raising HDL-C. It also lowers lipoprotein (a) by about 30 percent.

The effect of various agents on HDL-C was evaluated in other randomized, placebo-controlled trials involving patients with isolated low HDL-C. In an 8-month study of 22 normolipidemic men with reduced HDL-C levels, Vega and Grundy (1989) reported a 9 percent increase in HDL-C (from 0.78 to 0.85 mmol/L) with gemfibrozil therapy, which was significantly different from placebo. In a 3-month study of 14 men with low levels of HDL-C but desirable TC, Miller et al. (1993) reported a 9 percent increase in HDL-C with gemfibrozil versus placebo. In a report by Lavie and colleagues (1992), 3 months of treatment with sustained-release niacin resulted in a 27 percent increase in HDL-C compared with placebo in 19 men with coronary artery disease (CAD) and very low levels of HDL-C (<35 mg/dL). Unmodified (crystalline) niacin given for 12 weeks achieved a 31 percent increase in HDL-C compared with controls (no treatment) in 15 men with low HDL-C. (King et al., 1994). Three months of treatment with phenytoin in 37 male and 2 female nonepileptic subjects with low HDL-C levels resulted in a 12 percent increase in HDL-C versus dietary baseline (Miller et al., 1995).

Lifestyle Modification to Raise HDL-C

Nonpharmacologic interventions should be attempted in all patients with low HDL-C. HDL-C levels are affected by lifestyle modifications, including weight reduction, smoking cessation, and exercise. Weight loss, exercise, and smoking cessation should be given high priority in the therapeutic plan for all these patients.

Aerobic exercise, such as running, increases HDL-C levels in a dose-dependent manner. Studies have shown that regular exercise is associated with increased levels of HDL-C (Haskell et al., 1988; Kokkinos et al., 1995; Superko & Haskell, 1987). A clear dose-response relationship was observed between aerobic exercises (running) and HDL-C concentrations (Wood et al., 1991). Comparing six groups of runners based on the mean number of miles run per week (0, 5, 9, 12, 17, and 31) the mean HDL-C level was found to increase by 0.308 mg/dL with each 1-mile increase in running distance. Furthermore, mean HDL-C levels were significantly higher in those who ran 12 or 17 miles per week versus nonrunners and those who ran 5 miles per week, and were significantly higher in those who ran 31 miles per week versus all of the other groups.

HDL-C levels in smokers are 7 to 20 percent lower than those in nonsmokers (Cullen et al., 1998). In one small RCT (Moffatt, 1988) subjects who stopped smoking for 60 days raised HDL-C levels by 5.7 mg/dL by day 30 and by an additional 6.8 mg/dL by day 60, reaching 63.9 mg/dL. In contrast, HDL-C levels in re-smokers (stopped smoking for 30 days and resumed smoking thereafter) returned to pre-cessation values (50.7 mg/dL) by day 60. Before smoking cessation, all smoker had HDL-C levels that were 15 to 20 percent lower than those of the nonsmokers. Other studies, however, have shown less of an effect of smoking on HDL-C levels, e.g., the Münster Heart Study [PROCAM; 1998], in which mean HDL-C levels were reduced by 6.4 percent in male smokers and by 6.7 percent in female smokers versus nonsmokers.

Dattilo and colleagues meta-analysis of 70 studies (published between 1966 and 1989) found a consistent linear association between weight loss and HDL-C concentrations in both men and women. For every 3 kg (7 lb) of weight loss, HDL-C levels increased 1 mg/dL when weight reduction was maintained (Dattilo & Kris-Etherton, 1992). Wood and colleagues (1988) demonstrated in a 1-year randomized controlled study that losing fat weight through dieting, or through exercise (primarily running) significantly increases plasma concentrations of HDL-C and decreases levels of LDL-C but not significantly so.

Dietary modifications also affect HDL-C levels. Low-fat diets, in addition to reducing LDL-C levels, lower HDL-C levels in all patients. Alcohol use increases HDL-C in a dose-dependent manner, whereas caloric restriction acutely lowers HDL-C concentrations. Although there continues to be debate about the optimal dietary and lifestyle modifications necessary to reduce coronary heart disease, there is a consensus that smoking cessation, exercise, weight reduction, and a reduction in saturated fat intake will benefit most individuals.

EVIDENCE

	Recommendation	Source of Evidence	QE	Overall Quality	R
1	CVD patients with HDL-C <40 mg/dL, triglycerides >200 mg/dL, benefit from gemfibrozil therapy	VA-HIT, 1999	I	Good	A
2	Lifestyle modifications, including weight reduction, smoking cessation, and exercise improve HDL-C level. Aerobic exercise Weight loss	Dattilo & Kris-Etherton, 1992 Haskell et al., 1988 Kokkinos et al., 1995 Superko & Haskell, 1987 Wood et al., 1991	II	Fair	B
3	CVD patients with low HDL-C, may benefit from niacin	King et al., 1994 Lavie et al., 1992 Miller et al., 1993 Miller et al., 1995 Vega & Grundy, 1989	I	Fair	B

QE = Quality of Evidence; R = Recommendation (see Appendix A)

W. Evaluation and Treatment of Metabolic Syndrome

OBJECTIVE

Identify therapeutic treatment options for individuals with metabolic syndrome.

BACKGROUND

A recent study assessing the magnitude of the association between the NCEP ATP-III (2002) definition of metabolic syndrome and CVD found that individuals without diabetes or CVD, but with metabolic syndrome, are at increased risk for long-term CV outcomes, although statistical models suggested that most of that risk was accounted for by the Framingham Risk Score (FRS). Nevertheless, identification of individuals with metabolic syndrome may provide opportunities to intervene earlier in the development of shared disease pathways that predispose individuals to both CVD and diabetes (McNiell et al., 2005).

Specific recommendations for the management of lipid disorders in those with metabolic syndrome have been described in NCEP ATP-III (2002). The recommendations emphasize lifestyle management (weight loss, physical activity, dietary fat restriction). Medications can potentially favorably alter low levels of HDL-C and high level of TG and in theory, reduce the risk of CVD in individuals with metabolic syndrome. However, specific treatment targets and recommendations have not been fully clarified, particularly with regards to drug therapy, largely on the basis of a lack of hard outcomes data from clinical trials. Further clinical trial data will be required before more specific recommendations regarding the treatment of low levels of HDL and high levels of TGs in metabolic syndrome can be made. These issues will be addressed in detail in future revisions of the guidelines as more definitive data become available.

RECOMMENDATIONS

1. TLC should be initiated for patients diagnosed with metabolic syndrome. [B]
2. Lifestyle modification for weight reduction through diet and increased physical activity is indicated for patients diagnosed with metabolic syndrome. [B]
3. Drug therapy to alter insulin resistance or low HDL-C or elevated TG has not been demonstrated to improve CVD outcomes in patients with metabolic syndrome and as such, clinicians will have to individualize therapy. [I]

DISCUSSION

Metabolic syndrome is a diagnosis that has evolved since the late 1980s when "Syndrome X" was first described by Dr Gerald Reaven as a constellation of abnormalities including glucose intolerance, hyperinsulinemia, elevated TG, low HDL and HTN. Often coexisting with "Syndrome X" was central obesity. In 2002, NCEP ATP-III Guidelines defined the metabolic syndrome (see Box 8) and noted the root causes to be overweight/obesity, physical inactivity, and genetic factors. Metabolic syndrome is closely associated with insulin resistance, which can be either a genetic predisposition or acquired.

Regardless, insulin resistance and metabolic syndrome increase the risk for CVD in diabetic and non-diabetic patients and at any given level of LDL-C. Most patients with metabolic syndrome are overweight or obese; clinical studies have noted a high correlation between abdominal obesity and factors characteristic of metabolic syndrome (elevated TG, low HDL-C, insulin resistance, and high blood pressure).

Closely associated with abdominal obesity is an elevation of serum TGs. A higher TG level is usually accompanied by lower HDL-C concentrations. HDL-C levels <40 mg/dL occur commonly in men with insulin resistance. Further, moderate reductions of HDL-C levels are observed commonly in women with the syndrome; thus for women, HDL-C <50mg/dL counts as an indicator of the presence of metabolic syndrome. A moderately strong association exists between insulin resistance and hypertension. Insulin resistance also is associated with high-normal blood pressure or pre-HTN (Chobanian et al, 2003).

Impaired fasting glucose (110–125 mg/dL) usually is an indicator of insulin resistance and is frequently accompanied by other metabolic risk factors. A portion of persons with impaired fasting glucose will eventually develop Type 2 diabetes, which further enhances risk for CVD. Other components of the metabolic syndrome (proinflammatory state and prothrombotic state) are not easily identified by routine clinical evaluation. However, in the presence of abdominal obesity, they often are present. For practical purposes, metabolic syndrome is identified by the presence of three or more of the following components:

Box 8. Criteria for Identifying Metabolic Syndrome

Risk Factor	Defining Level
Abdominal Obesity	**Waist Circumference**
Men†	**>40 in (>102 cm)**
Women	**>35 in (>88 cm)**
Triglycerides	**≥150 mg/dL**
HDL Cholesterol	
Men	**<40 mg/dL**
Women	**<50 mg/dL**
Blood Pressure	**≥130/85 mmHg**
Fasting Glucose	**≥110 mg/dL**

NCEP ATP-III, 2002

† *Some male persons can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Treatment

The full effect of risk reduction in a patient treated for high LDL-C will be lost if metabolic syndrome is ignored. In fact, the presence of metabolic syndrome accentuates CVD risk accompanying any given level of LDL. To achieve maximal benefit from modification of multiple metabolic risk factors, the underlying insulin

resistant state must become a target of therapy. The most well-studied, effective, and preferred means to reduce insulin resistance is weight reduction in overweight/obese persons with or without increased physical activity. (For the management of obese patient see the VA/DoD Guideline for Management of Obesity.)

Drug treatment of several individual components of metabolic syndrome will reduce CVD risk. Risk reductions by lowering blood pressure with anti-hypertensive drugs and treating the prothrombotic state with aspirin are well documented. However, lowering serum glucose or reducing insulin resistance with drugs in patients with metabolic syndrome has not yet been documented to reduce risk for CVD. Similarly, while there may be a strong trend toward reduced CVD risk with drug treatment for atherogenic dyslipidemia (low HDL and elevated TG), there are no CV outcomes studies to date that have been completed (nor designed) to specifically answer this question. Clinicians will have to individualize treatment for any given patient when contemplating drug treatment for insulin resistance or dyslipidemia associated with metabolic syndrome.

The presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-C goals are set with the major risk factors. Primary emphasis nonetheless, should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with metabolic syndrome.

EVIDENCE

	Recommendation	Source	QE	Overall Quality	R
1	TLC should be initiated for patient in which metabolic syndrome is indicated	NCEP ATP-III, 2002	III	Fair	B
2	Lifestyle modification for weight reduction through diet and increased physical activity is indicated for obese patients (BMI is ≥30)	NCEP ATP-III, 2002	III	Fair	B
3	Individualize drug therapy for modification of insulin resistance or dyslipidemia in the presence of metabolic syndrome using clinical judgment	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (see Appendix A)

X. Reschedule Lipids Evaluation at Appropriate Time and Follow-Up To Maintain Goals

OBJECTIVE

Measure the efficacy of prescribed therapy for hyperlipidemia after allowing sufficient time to reach a new steady state.

BACKGROUND

Nadir values of LDL-C and TGs may not be achieved until after three to six months of TLC. Pharmacotherapy likewise, may not result in lower lipid values until after at least 6-12 weeks of treatment. Remeasurement of serum lipids after at least 6-12 weeks of drug therapy, or after at least three months of dietary therapy, allows for the documentation of efficacy, the identification of unfavorable effects of treatment, and the dose titration of medication. The frequency of lipid evaluation is based on the interval used in randomized controlled studies to assess response to therapy.

RECOMMENDATIONS

1. Lipid profiles should be reevaluated after at least 6-12 weeks of drug therapy or change in dose or after at least three to six months of dietary therapy to document efficacy, identify adverse effects, and to titrate medication dose. [I]
2. Follow-up visits should [I] include:
    - Patient history
    - Physical exam
    - Laboratory tests
    - Documentation of adverse events]
3. Once the goal is achieved, therapy for dyslipidemia should be continued to maintain the goal. Treatment of dyslipidemia is a lifelong process; however, adjustments may be necessary if the patient develops medical conditions that affect the severity of comorbidity or life expectancy.

DISCUSSION

Follow-up visits should include:

- Patient history, including compliance with nonpharmacologic measures such as diet, compliance with medication, need for changes in drug therapy regimen, presence of symptoms suggesting adverse drug reactions, adherence to exercise program if prescribed, and reevaluation of the modifiable cardiovascular risk factors.

- Physical exam, including weight and blood pressure, symptoms and severity of co-morbid health conditions.

- Laboratory tests, including periodic fasting lipid profile, and creatine kinase (CK) if symptoms of myopathy are present. For patients on gemfibrozil, statins, niacin, or zetia check transaminases (AST, ALT); laboratory tests are indicated at 6-12 week intervals initially, and at least every 6 to 12 months for patients on a stable maintenance regimen. For patients on niacin, check uric acid and fasting blood sugar. For patients on zetia who are taking wafarin check INR and recheck 2 to 3 months after initial treatments.

- Adverse events to be considered include: hyperglycemia, hyperuricemia (for patients on niacin), significant (>3 times the upper limit of normal) elevations of transaminases (with niacin, statins, or gemfibrozil) and myalgias (with gemfibrozil or statins). Side effects include: GI symptoms (for patients on BAS) and rash and GI symptoms (for patients on niacin).

EVIDENCE

	Recommendation	**Source**	**QE**	**Overall Quality**	**R**
1	Reevaluate serum lipids after at least 6-12 weeks of therapy or after at least three to six months of TLC	Working Group Consensus	III	Poor	I
2	Follow-up visits should include: patient history, physical exam, lab tests, and adverse event documentation	Working Group Consensus	III	Poor	I

Y. Follow Up, Repeat Lipid Evaluation At Least Annually

OBJECTIVE

Ensure that patients initially treated for dyslipidemia receive periodic reassessment of the efficacy of treatment.

BACKGROUND

When dyslipidemia is identified and the care provider and patient undertake dietary and/or pharmacologic treatment, it is pertinent clinically and economically to periodically repeat measurement of serum lipids to ensure that desirable response to therapy continues. TC and LDL-C tend to increase with advancing age, even in intensively treated patients. Thus, an initially favorable response to treatment may not be maintained over time.

RECOMMENDATIONS

1. Lipid evaluations should be repeated at least annually. [I]

DISCUSSION

Secondary Prevention

Patients known to be at high-risk for CVD based on multiple risk factors other than hyperlipidemia are candidates for early and aggressive dietary and pharmacologic therapy; thus annual reevaluation of serum lipid status is prudent and cost-effective.

Primary Prevention

New medical conditions, such as hypothyroidism, nephrotic syndrome, and diabetes, can appear at any time. The dyslipidemias associated with these conditions may exacerbate pre-existing primary hyperlipidemia and thwart previously effective dietary and/or pharmacologic therapy. Marked change in serum lipids may prompt timely diagnosis and treatment of such concurrent health conditions.

EVIDENCE

	Recommendation	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	Perform periodic follow up	NCEP ATP-III, 2002	III	Poor	I

APPENDICES

Updated Version 2.0 – 2005
PENDING APPROVAL

APPENDIX A

Guideline Development Process

Development of the 1999 Guideline for the Management of Dyslipidemia in Primary Care

In 1994, a guideline for the Treatment of Cardiovascular Disease was developed for the VHA. The initial guideline was the product of a research and consensus building effort among professionals from throughout the VHA that included: cardiologists, social workers, nurses, administrators, primary care physicians, external peer review physicians and expert consultants in the field of guideline and algorithm development. A process to update the guideline for the Management of Dyslipidemia in Primary Care was started in mid-1999, as a collaborative effort between the Department of Veterans Affairs and the Department of Defense. A companion guideline, the Management of Ischemic Heart Disease (IHD) in Primary Care was also launched during the same timeframe.

The Guideline for the Management of Dyslipidemia represented hundreds of hours of diligent effort on the part of participants from the DoD, VHA, academia, and a team of private guideline facilitators. An experienced moderator facilitated a multidisciplinary panel that included internists, family practitioners, cardiologists, nurses, pharmacists, medical nutrition therapists, and rehabilitation specialists (see Appendix H for a list of participants). Policy-makers and civilian practitioners joined these experts from the DoD and VHA. The process was evidence-based whenever possible. Where evidence is ambiguous or conflicting, or where scientific data were lacking, the panelists' clinical experience guided the development of consensus-based recommendations to improve patient outcomes.

The goal in developing this guideline was to incorporate information from several existing, national recommendations into a format that would maximally facilitate clinical decision-making (Woolf, 1992). This effort drew heavily from the following sources:

> Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Journal of the American Medical Association 2001, 285 (19), 2486-2497.
>
> NCEP ATP-III, 2002: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002, 106, (25), 3143-421.
>
> The U.S. Preventive Services Task Force Guide to Clinical Preventive Services. Second Edition 2001.
>
> Pharmacy Benefits Management—Medical Advisory Panel. The pharmacologic management of hyperlipidemia. VHA PBM-SHG Publication. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs.

Development of the 2005 Guideline for the Management of Dyslipidemia - Update (Version 2.0)

The development of the 2005 Dyslipidemia Guideline Update (version 2.0) was initiated in September 2004 and continued through November 2005. The development process followed the steps described in "Guideline for Guideline," an internal working document of VHA's National Clinical Practice Guideline Council, which requires an ongoing review of the work in progress. The 1999 VA/DoD Dyslipidemia Guideline represented a "seed document" that was updated and adapted by the joint VA/DoD Dyslipidemia Working Group. As with the original Working Group, the charge of the VA/DoD group was to provide evidence-based action recommendations whenever possible; hence, major clinical randomized controlled trials (RCTs) and observational studies published from August 1999 through August 2004 in the areas of diagnosis and treatment of dyslipidemia.

Target Audience

This guideline is designed for primary care providers. While the screening module is designed for use by primary care providers in an ambulatory care setting, the treatment modules can also be used to coordinate and standardize care within subspecialty teams and as a teaching tool for students and house staff.

Guideline Development Process

The Offices of Quality and Performance and Patient Care Service, in collaboration with the network Clinical Managers, the Deputy Assistant Under Secretary for Health, and the Medical Center Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD that formed the Guideline Development Working Group. Working Group members included representatives of the following specialties: internal medicine, cardiology, endocrinology, medical nutrition therapy, social work, family practice, nursing, pharmacy, and rehabilitation medicine.

At the start of the update process, the clinical leaders, guideline Working Group members, outside experts, and experts in the field of guideline and algorithm development were consulted to determine which aspects of the 1999 guideline required updating. These consultations resulted in the following recommendations that guided the update efforts: (1) update any recommendations from the original guideline likely to be affected by new research findings; (2) provide information and recommendations on health systems changes relevant to dyslipidemia screening and treatment; (3) address content areas and models of treatment for which little data existed during the development of the original guideline; and (4) review the performance and lessons learned since the implementation of the original guideline.

The Working Group participated in an initial face-to-face meeting to reach consensus about the guideline algorithm and recommendations and to prepare a draft document. The draft continued to be revised by the Working Group at-large through numerous conference calls and individual contributions to the document. Following the initial effort, an editorial panel of the Working Group convened to further edit the draft document. Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes the following:

- Determination of appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction.
- Literature review to determine the strength of the evidence in relation to these criteria.
- Formulation of the recommendations and grading of the level of evidence supporting the recommendation.

Experts from the VA and DoD internal medicine, cardiology and primary care reviewed the final draft. Their feedback was integrated into the final draft. This document will be updated every two years, or when significant new evidence is published to ensure that VA and DoD healthcare delivery remains on the cutting edge of the latest medical research.

Formulating of Questions

The Working Group developed researchable questions and associated key terms after orientation to the seed guideline and to goals that had been identified by the Working Group. The questions specified: (adapted from the Evidence-Based Medicine (EBM) toolbox, Centre for Evidence-Based Medicine, (http://www.cebm.net):

- **P**opulation – Characteristics of the target patient population
- **I**ntervention – Exposure, diagnostic, or prognosis
- **C**omparison – Intervention, exposure, or control used for comparison
- **O**utcome – Outcomes of interest

These specifications served as the preliminary criteria for selecting studies. Research questions focused on the following areas of inquiry: screening, risk assessment, strategies, metabolic syndrome, non-drug therapy, drug monotherapy, drug combination therapy, and adverse effects.

Selection of Evidence

Published, peer-reviewed, RCTs were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, scientifically sound basis for judging comparative efficacy. The Working Group made this decision recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. Evidence-based systematic reviews were considered to be the strongest level of evidence as well as meta-analyses that included randomized controlled studies. The evidence selection was designed to identify the best available evidence to address each key question and ensured maximum coverage of studies at the top of the hierarchy of study types: evidence-based guidelines, meta-analyses, and systematic reviews. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and EPC reports.

The search was performed using the National Library of Medicine's (NLM) MEDLINE database. The term "hyperlipidemia" was used together with the following Boolean expressions and terms:

- Epidemiology
- Screening
- Diagnosis
- Primary Care
- Protocols
- Therapy
- Patient Education
- Economics

In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials (CCTR). For Medline/PubMed searches, limits were set for language (English), date of publication (1999 through August 2004) and type of research (RCT and meta-analysis).

Once definitive reviews or clinical studies that provided valid relevant answers to the question were identified, the search ended. The search was extended to studies/reports of lower quality (observational studies) only if there were no high quality studies.

Exclusion criteria included reviews that omitted clinical course or treatment. Some retrieved studies were rejected on the basis of published abstracts, and a few were rejected after the researchers scanned the retrieved citation for inclusion criteria. Typical exclusions included studies with physiological endpoints or studies of populations that were not comparable to the population of interest (e.g., studies of dyslipidemia in children). The bibliographies of the retrieved articles were hand-searched for articles that may have been missed by the computer search. Working Group members also contributed articles as part of the evidence gathering process.

The results of the search were organized and evidence reports as well as copies of the original studies were provided to the Working Group for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal healthcare system. Recommendations were based on consensus of expert opinions and clinical experience only when scientific evidence was unavailable. Although the Strenght of Recommendation (SR) rating was influenced primarily by the science, other factors were taken into consideration when assigning a SR rating such as: the burden of suffering imposed on the patient.

Literature Review and Inclusion Criteria

As a result of the original and updated literature reviews, articles were identified for possible inclusion. These articles formed the basis for formulating the guideline recommendations. The following inclusion criteria were used for selecting randomized controlled trial studies:

- Articles published between 1999 and 2004, with some exceptions
- English language only
- Full articles only
- Age limited to adults >18 years
- Minimum study size of 100 patients per arm
- Randomized controlled trials only; no cross-over trials
- Minimum 1 year for CVD outcomes (MIs, mortality, strokes, etc.)
- Minimum 12 weeks for intermediate outcomes (TC, LDL, HDL, TG)
- Baseline LDL levels reported
- Sufficient information to identify patient risk level
- Key outcomes cited

For some questions, special inclusion criteria (mostly related to minimum clinical trial size) were developed based upon research question content and available literature.

The literature search for the guideline update was validated by: (1) comparing the results to a search conducted by the independent research and appraisal team; (2) a review of the database by the expert panel; and (3) requesting articles pertaining to special topics from the experts in the Working Group. It is important to note that due to application of article screening criteria in the updated guideline, some of the studies that were included in the original guideline were not included in the updated analyses.

Preparation of Evidence Tables (Reports) and Evidence Rating

A group of research analysts, with experience in evidence-based appraisal, independently read and coded each article that met inclusion criteria. The research team prepared a brief summary of the critical appraisal of each article that included the following components:

- Description of patient population
- Interventions
- Comparisons
- Outcomes
- Summary of results
- Analysis of findings
- Evidence Appraisal
- Clinical significance

Quality of evidence ratings were assigned for each source of evidence using the grading scale presented in Table A-1 [USPSTF, 2001). The quality rating procedure used in this update was different from the rating scale used in the development of the original guideline in 1999. Where adjustments to the update process were made, articles from the original process were re-graded to reflect the changed rating scale (e.g., the SR was assigned for each evidence, based on study design and significance of the quality of the evidence).

Recommendation and Overall Quality Rating

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group received an orientation and tutorial on the evidence USPSTF 2001 rating process, reviewed the evidence and independently formulated Quality of Evidence ratings (see Table A-1), a rating of Overall Quality (see Table A-2), and a Net Effect of the Intervention (see Table A-3) and a Final Grade of Recommendation (see Table A-4).

Evidence Rating System

Table A-1: Quality of Evidence (QE)	
I	At least one properly done RCT
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality	
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

Table A-3: Net Effect of the Intervention	
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering; or an infrequent condition with a significant impact on the individual patient level.

Table A-4: Final Grade of Recommendation

	The net benefit of the intervention			
Quality of Evidence	**Substantial**	**Moderate**	**Small**	**Zero or Negative**
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

A	A strong recommendation that the clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, or poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

Lack of Evidence – Consensus of Experts

The majority of the literature supporting the science for these guidelines is referenced throughout the document and is based upon key RCTs and longitudinal studies published from 1999 through 2004. Following the independent review of the evidence, a consensus meeting was held to discuss discrepancies in ratings and formulate recommendations. Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus."

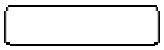
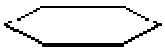
Algorithm Format

The goal in developing the guideline for dyslipidemia was to incorporate the information from several existing, national consensus, and evidence-based guidelines into a format that would maximally facilitate clinical decision-making. The use of the algorithm format was chosen because of the evidence that such a format improves data collection, diagnostic and therapeutic decision-making and changes patterns of resource use. However, few guidelines are published in such a format. To enhance continuity of care, the Dyslipidemia Guideline was designed to encompass a broad spectrum of outpatient care to detect and treat persons with dyslipidemia. This required incorporating multiple published guidelines into a single, unified document.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken.

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (Society for Medical Decision-Making Committee [SMDMC], 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

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Men

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Women

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

APPENDIX B

APPENDIX C

Medical Nutrition Therapy

BACKGROUND

At any and every stage of dietary therapy, effective dietary modification will be facilitated by consultation with a registered dietitian or other qualified nutritionist for medical nutrition therapy (MNT). The term nutrition professional refers to a registered dietitian or qualified nutritionist (NCEP ATP-III, 2001). MNT refers to clinical nutrition assessment and provision of appropriate nutrition therapy and is an effective, low-cost approach to the management of patients with hypercholesterolemia (McGehee et al., 1995). MNT integrates information on food, nutrients, and meal preparation consistent with cultural background, socioeconomic status, and desired clinical outcomes (Medical Nutritional Therapy Across the Continuum of Care, 1998). It is a reasonable investment of resources resulting in improved lipid profile, diet, activity, weight, and satisfaction outcomes (Delahanty et al, 2001). MNT has demonstrated effectiveness for many diagnoses and has shown to be associated with a decrease in utilization of health services, lowered morbidity, and progress towards positive health outcomes (DCCT, 1993; Sikand et al., 1996; Sikand et al., 1997, The Cost of Covering MNT under TRICARE, 1998). MNT is an intrinsic component of clinical practice and a shared responsibility of the healthcare team.

Medical Nutrition Therapy and Therapeutic Lifestyle Change

The American Dietetic Association MNT Protocol for Dyslipidemia recommends three to four sessions, each session 30 to 60 minutes in length. The MNT protocol was designed for nutrition professionals and requires an intensive time commitment between the provider and patient. Similarly, TLC, as proposed in ATP-III, requires multiple provider patient encounters, time-commitment, and periodic evaluation of goals.

Based upon ATP-III guidelines for TLC and the MNT Protocol for Dyslipidemia, key treatment components include:

1) Focus on reduction of LDL by adjusting dietary LDL-raising constituents (i.e., saturated fats and cholesterol). The Dietary CAGE questionnaire (See Table C-2) included in the ATP-III guidelines is a valuable tool for physicians to assess a patient's intake of saturated fat and cholesterol.
2) Encourage additional dietary options for improving LDL (i.e., consumption of plant stanols/sterols and viscous (soluble) fiber (See Table C-3).
3) Modify dietary practices by making healthier food choices (See Table C-4).
4) Weight control and increased physical activity is a key component of lifestyle change for overweight patients and those with metabolic syndrome (but remains secondary to meeting LDL cholesterol goal).

Table C-1. Medical Nutrition Therapy Prescriptions for High Blood Cholesterol

Nutrient	Therapeutic Lifestyle Changes (TLC) Diet
Saturated Fat*	Less than 7% of total calories
Polyunsaturated Fat	Up to 10% of total calories
Monounsaturated Fat	Up to 20% of total calories
Total Fat	25-35% of total calories
Carbohydrate+	50-60% of total calories
Fiber	20-30 g/day (Viscous [soluble] fiber: 10-25 g/d)
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total Calories (energy)≠	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

Adapted from NCEP ATP-III, 2002

*Trans fatty acids are another LDL-raising fat that should be kept as low as possible.

+Carbohydrates should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables. Viscous fiber intake (goal 10-25 g/day) can be increased by emphasizing certain foods: cereal grains, fruits, vegetables, dried beans, peas, and legumes.

≠Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

It is important to provide ongoing support and reinforcement to patients undertaking significant dietary changes, such as follow-up visits, telephone calls, and postcards. Encourage patients through the plateaus and regressions that occur as a normal part of efforts at long-term change (USDHHS, Clinician's Handbook, 1998).

Table C-2. Dietary CAGE Questions for Assessment of Intakes of Saturated Fat and Cholesterol

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

Adapted from NCEP III, 2002

Table C-3. Food Sources of Viscous (Soluble) Fiber (NCEP ATP-III, 2001)

Food Source	Soluble Fiber (g)	Total Fiber (g)
Cereal Grains (1/2 cup cooked)		
Barley	1	4
Oatmeal	1	2
Oat Bran	1	3
Psyllium Seeds, Ground (1Tbsp)	5	6
Fruit (1 medium fruit)		
Apples	1	4
Bananas	1	3
Blackberries (1/2 cup)	1	4
Citrus Fruit (orange, grapefruit)	2	2-3
Nectarines, Peaches	1	2
Pears	2	4
Plums	1	1.5
Prunes (1/4 cup)	1.5	3
Legumes (1/2 cup cooked		
Black Beans	2	5.5
Kidney Beans	3	6
Lima Beans	3.5	6.5
Navy Beans	2	6
Northern Beans	1.5	5.5
Pinto Beans	2	7
Lentils (yellow, green, orange)	1	8
Chick Peas	1	6
Black Eyed Peas	1	5.5
Vegetables (1/2 cup cooked)		
Broccoli	1	1.5
Brussels Sprouts	3	4.5
Carrots	1	2.5

Table C-4. TLC Recommended Food Choices

Food Group	Choose	Decrease
Lean meat, poultry, and fish ≤5 ounces per day	Beef, pork, lamb – lean cuts (loin, round, leg) well trimmed before cooking; extra lean hamburger Poultry without skin Fish, shellfish Processed meats prepared from lean meats, e.g., lean ham, lean frankfurters, lean meat with soy protein or carrageenin	Regular hamburger, fatty cuts of beef, spare ribs, t-bone steak, bacon, organ meats (liver, brain, sweetbreads) Poultry with skin, fried chicken Fried fish, fried shellfish Regular luncheon meat (bologna, salami, sausage, frankfurters)
Eggs <2 egg yolks per week	Egg whites, cholesterol-free egg whites	Egg yolks (if more than the recommended); includes eggs used in baking and cooking
Low-fat dairy products 2-3 servings per day	Fat free (skim), ½% or 1% fat milk and buttermilk (fluid, powdered, evaporated) Yogurt – non-fat or low-fat yogurt or yogurt beverages	Whole milk (fluid, evaporated, condensed), 2% milk, imitation milk Whole milk yogurt
Dairy products	Cheese: low-fat natural or processed cheese Cottage cheese: low-fat, nonfat, or dry curd (0% to 2%) Frozen dairy dessert: ice milk, frozen yogurt (low-fat or nonfat) Low-fat coffee creamer Low-fat or nonfat sour cream	Regular cheeses (American blue, Brie, cheddar, Colby, Edam, Monterey Jack, whole-milk mozzarella, Parmesan , Swiss), cream cheese, Neufchatel cheese Cottage cheese (4% milk fat) Ice cream Cream, half & half, whipping cream Non-dairy creamer, whipped topping, sour cream
Fats and Oils (Amount adjusted to caloric level to maintain or achieve desirable weight) ≤6-8 teaspoons per day Stanol/sterol-containing margarines recommended	Unsaturated oils: sunflower, corn, soybean, cottonseed, canola, olive, peanut Margarines: -made from unsaturated oils listed above, especially soft or liquid forms Salad dressings – made with unsaturated oils, low-fat or fat-free Seeds and nuts: – peanut butter, other nut butters	Coconut oil, palm kernel oil, palm oil Butter, lard, shortening, bacon fat, stick margarine Dressings – made with egg yolk, cheese, sour cream, whole milk Macadamia, cashews, brazil nuts and pine nuts (not heart healthy nuts) Coconut
Breads and cereals >6 servings per day; adjusted to caloric needs	Breads-whole-grain bread, English muffins, bagels, buns, low fat corn or flour tortilla Viscous (soluble) fiber sources: barley, oats, psyillium, dried beans and peas Cereal – whole grain oat, wheat, corn, multigrain Whole grain pasta, brown rice Baked potatoes Crackers, low-fat – animal type, graham, soda crackers, breadsticks, melba toast	Bread in which eggs, fat, and/or butter are a major ingredient; croissants Regular tortillas Most granolas High-fat crackers, potato chips, tortilla chips, corn chips Commercial baked pastries, muffins, biscuits, doughnuts, butter rolls, sweet rolls, Danish, cakes, pies, coffee cakes, cookies Avid fried potatoes

	Homemade baked goods using unsaturated oil, skim or 1% milk, and egg substitute—quick breads, biscuits, cornbread muffins, bran muffins, pancakes, waffles	
Soups	Reduced or low-fat and reduced sodium varieties, e.g., chicken or beef noodle, minestrone, tomato, vegetable, potato; reduced-fat soups made with skim milk	Soup containing whole milk, cream, meat fat, poultry fat, or poultry skin
Vegetables 3-5 servings per day	Fresh, frozen, or canned, without added fat, sauce, or salt Viscous (soluble) fiber vegetable sources: broccoli, Brussels sprouts, carrots	Vegetables fried or prepared with butter, cheese, or cream sauce
Fruits 2-4 servings per day	Fruit-fresh, frozen, canned or dried Viscous (soluble) fiber fruit sources: apples, berries, bananas, citrus, nectarines, pears, plums, prunes Fruit juice: fresh, frozen or canned	Fried fruit or fruit served with butter or cream
Sweets and modified fat desserts Use cautiously if weight loss is recommended or with hypertriglyceridemia	Beverages: fruit – fruit-flavored drinks, lemonade, fruit punch Sweets: sugar, syrup, honey, jam, preserves, candy made without added fat (candy corn, gumdrops, hard candy), fruit flavored gelatin Cocoa powder Frozen dessert: low-fat and nonfat yogurt, ice milk, sherbet, sorbet, fruit ice, popsicles Cookies, cake, pie, pudding: prepared with egg whites, egg substitutes, skim milk or 1% milk, and unsaturated oil or margarine; ginger snaps, fig and other fruit bar cookies, fat-free cookies (e.g. meringue cookies), angel food cake	Chocolate Candy made with milk chocolate, coconut oil, palm kernel oil, palm oil Ice cream and frozen treats made with ice cream Commercial baked pies, cakes, doughnuts, high-fat cookies, cream pies

From USDHHS, Clinician's Handbook, 1998

Note: Careful selection of processed foods is necessary to stay within the sodium guideline (<2,400 mg) (USDHHS, JNC 7, 2003). These represent general guidelines that will need to be individualized for patients based on lipid profile, co-morbidities, and treatment goals.

Specific Foods as Non-pharmacologic Therapy

Consumers and healthcare professionals alike are increasingly interested in the use of functional foods (nutritious foods that contain specific ingredients that aid with specific physiological functions). Below is a summary of selected nutrients regarding potential benefit and practical application.

Vitamins/antioxidants: Folic acid and vitamins B6 and B12 play a role in the metabolism of homocysteine, however, there are no published randomized controlled clinical trials to indicate whether decreasing homocysteine through dietary supplements of B Vitamin/Folate intake will reduce CHD Risk (NCEP ATP-III, 2001). In addition, clinical trials of antioxidant supplements have also failed to demonstrate CHD risk reduction.

Alcohol: Moderate intakes of alcohol in middle-aged and older adults may reduce risk for CHD. No more than two drinks/day for men and one drink/day for women are recommended (NCEP ATP-III, 2001). A drink is defined as 5 ounces of wine, 12 ounces of beer or 1.5 ounces of distilled spirits, such as 80 proof whiskey.

Dietary sodium, potassium and calcium: Many individuals with hypercholesterolemia also have hypertension. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a sodium intake of <2400 mg/day and further recommends adequate intakes of dietary potassium and enough dietary calcium and magnesium for good health (USDHHS, JNC 7, 2003). ATP-III affirms these recommendations for individuals undergoing cholesterol management (NCEP ATP-III, 2001).

Herbal or botanical dietary supplements: Despite widespread promotion of several herbal or botanical dietary supplements for prevention of CHD, there is scarce data on product standardization, controlled clinical trials for efficacy, and long-term safety and drug interactions. Clinical trial data are not available to support the use of herbal and botanical supplements in the prevention or treatment of heart disease. Healthcare professionals should ask patients to determine if dietary supplements are being used because of the potential for drug interaction (NCEP ATP-III, 2001).

Plant Stanols/Sterols: Plant stanols/sterols should be utilized as substitutes for foods of similar fat content, such as plant stanol margarine to replace vegetable oil margarine. The recommended dose is 2 g/day and research has demonstrated a 10-15% reduction in LDL cholesterol levels. This recommended intake can be achieved by consumption of one tablespoon of plant sterol margarine (cannot be utilized in cooking or baking as heat breaks down the sterols) or one and one-half tablespoons of margarine spread made from plant stanol esters, which can also be utilized in cooking or baking.

Soy Protein: Soy protein included in a diet low in saturated fats and cholesterol can lower levels of total cholesterol and LDL cholesterol in individuals with hypercholesterolemia. High intakes of soy protein, between 25-40 g/day, can cause small reductions in LDL cholesterol, especially when it replaces animal food products. The allowed health claim for soy protein products states that one serving must provide at least 6.25 grams of soy protein. To achieve the recommended intake of 25 grams of soy protein, an individual would need 4 servings of day. Some soy foods contain much higher amounts than 6.25 grams. Tofu provides 13 grams of soy protein in a 4-oz serving; ¼ cup of soy nuts provides 19 grams; an 8-oz serving of soymilk provides 10 grams; soy sausage products provide 6 grams; soy burgers provide 10-12 grams; soy protein bars provide 14 grams of soy protein.

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Nutrition Guidelines to Reduce Your Cardiovascular Risk

Your Risk Factors

(Check all that apply.)

☐ **High Blood Pressure.** You have high blood pressure. Blood pressure is the force of blood against the walls of arteries. Blood pressure greater than 120/80 is considered high. Self-monitoring and control of your blood pressure is extremely important because high blood pressure increases your chance (or risk) for getting heart disease and/or kidney disease, and for having a stroke.

☐ **High Blood Cholesterol.** You have high blood cholesterol. Cholesterol is a waxy, fat-like substance that occurs naturally in all parts of the body and that your body needs to function normally. If you have too much cholesterol in your bloodstream, the excess is deposited in arteries, including the coronary arteries, where it contributes to the narrowing and blockages that cause the signs and symptoms of heart disease. Components of your blood cholesterol, such as low density lipoproteins (LDL) and high density lipoproteins (HDL) are also important indicators of heart disease risk. Desirable levels are based on your estimated risk. Total blood cholesterol levels >200 mg/dl are considered high. An LDL-cholesterol level >130 mg/dl is generally considered high and HDL-cholesterol level <40 mg/dl is considered low; both are risk factors for heart disease.

☐ **High Blood Triglycerides.** You have high blood triglycerides. Triglycerides are a form of fat carried in the bloodstream. High triglyceride levels often seen in combination with lower HDL (and sometimes diabetes) can raise your risk for heart disease. Desirable levels are based on your estimated risk. Your goal is either <150 mg/dl or <200 mg/dl, depending on your risk level.

☐ **Overweight.** You are overweight. If you are overweight, losing as few as 10 pounds can make a difference! Achieving and maintaining a desirable body weight is important in improving your overall health. Excess weight may increase blood cholesterol, triglycerides and blood pressure, raising your risk of cardiovascular disease.

Strategies for Reducing Your Risk

(Check all that apply.)

☐ **Maintain a Healthy Weight.** To estimate your calorie needs to lose or maintain your weight, see below. If you are overweight, reduce your total calorie intake by watching your portion sizes. Limit excess fat and sweets intake and start or increase exercise.

How many calories should you eat?

To Lose Weight: 10 x body weight in pounds = _____

To Maintain Weight (moderate activity level): 13 x body weight in pounds = _____

To Maintain Weight (high activity level): 15 x body weight in pounds = _____

⇒ For More Info: http://airforcemedicine.afms.mil/shapeyourfuture (Shape Your Future...Your Weight! Weight Gain Prevention Community Website).

☐ **Eat a Well Balanced Diet**. Increase your fruit and vegetable intake. Limit excessive sweets by limiting portion sizes and frequency of sweetened drinks, desserts and snacks. The DASH diet may help you guide your food choices and may also help you to lower your blood pressure and reduce the risk of heart disease and stroke.

⇒ For More Info: See the 24-page DASH booklet "*Facts About the DASH Eating Plan*" in your Cardiovascular Risk Assessment packet and additional info available at www.nhlbi.nih.gov.

⇒ The AF community website http://airforcemedicine.afms.mil/shapeyourfuture has several tools available: 1) Diet & Nutrition Mini-Profile 2) How's Your Diet? And 3) How Does Your Diet Stack Up?

☐ **Limit Fats and Cholesterol.** Consumption of too much saturated fat, trans fat, and dietary cholesterol raises "bad" cholesterol levels and raises cardiovascular risk. Saturated fats are solid at room temperature and found in beef, pork, chicken skin, whole milk, butter, and cheese. To reduce your total fat, saturated fat and cholesterol intake, select lean meats, fish, skim or non-fat dairy products and reduce fried foods. Reduce the number of egg yolks to 2-3 per week and limit high fat snacks and desserts. Plant stanols and sterols (2 grams/day) substituted for foods of similar fat content, such as margarines, can lower cholesterol levels an additional 10-20%.

Guidelines for Fat Consumption

⇒ Between 25%-35% of your calories should come from total fat, with emphasis on unsaturated fats.
⇒ Less than 7% of your calories should come from saturated fat.
⇒ Limit cholesterol in foods to <200 mg per day.

Below are basic guidelines which depend on your calorie level

Calorie Level Per Day	Total Fat Gram Target	Saturated Fat Gram Target
1200-1400 calories	33-38 grams	9-11 grams
1400-1600 calories	38-45 grams	11-13 grams
1600-1800 calories	45-50 grams	13-14 grams
1800-2000 calories	50-55 grams	14-15 grams
2000-2200 calories	55-61 grams	15-17 grams
2200-2400 calories	61-67 grams	17-19 grams
2400-2600 calories	67-72 grams	19-20 grams
2600-2800 calories	72-78 grams	20-22 grams
2800-3000 calories	78-83 grams	22-23 grams

*Note: If you have high triglycerides (>400 mg/dL), you will need to reduce your total fat intake to 20% of your calories. To do this, divide your calorie level by 9 (calories in a gram of fat) and multiply that number by 0.20 (e.g., 2000 calories divided by 9 = 44 grams fat)

⇒ For More Information:
- o http://www.americanheart.org (American Heart Association)
- o www.nhlbi.nih.gov (National Heart Lung and Blood Institute)

☐ **Limit Sodium**. Excess sodium intake may increase blood pressure. Decrease sodium (salt) in your diet to less than 2,400 mg per day. You can do this by limiting salt added to food and used in cooking and by limiting consumption of salt preserved foods, packaged and convenience foods and snacks. Check with your provider regarding use of salt substitutes, such as potassium chloride.

⇒ More information:
- o http://www.nhlbi.nih.gov/health/public/heart/index.htm#hbp;
- o http://www.nhlbi.nih.gov/health/hbp/index.html (interactive web guide)
- o http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm (Handout with menus and recipes)

☐ **Increase Fiber**. Add more dried beans, peas, lentils, and more fruits, vegetables, and whole grains to your diet. Increasing your fiber intake, particularly viscous (soluble) fiber such as those found in oatmeal, oat bran, dried beans/peas and apples, will help lower cholesterol levels and has other important health benefits as well. Aim for 20-30 grams of fiber daily, with 10-25 grams from foods providing viscous or soluble fiber.

⇒ For More Information:
- o http://www.dietsite.com/dt/diets/eatingwell/fiber/highfiber/asp
- o http://www.americanheart.org (American Heart Association)
- o http://eatright.org (American Dietetic Association)

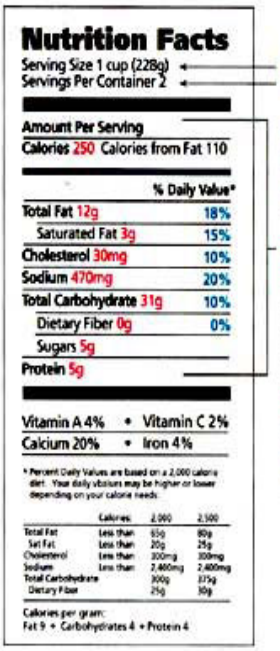
☐ **Exercise**. Exercise has been shown to lower blood pressure, improve blood cholesterol levels and promote weight loss and weight maintenance of a healthy weight. Walk briskly, jog, swim, cycle or do another aerobic activity 30-45 minutes a day at least three times per week. Check with your physician or healthcare team before starting an exercise program.

⇒ For More Information:
- o http://www.fitwatch.com (Fit Watch)
- o http://www.justmove.org (Just Move)
- o http://www.smallstep.gov (SmallStep.gov)
- o http://www.mavc.10kaday.com (10K a Day)

☐ **Limit Alcohol**. Alcohol consumption may elevate your blood pressure and blood triglycerides. If you drink, limit your alcohol intake to one drink per day for women and two drinks for men. A drink is equivalent to 12 oz beer or 4 oz wine or 1.5 oz. distilled spirits.

☐ **Nutrition Counseling Referral**. You may need more help incorporating the above recommendations into your lifestyle. Call your local Nutrition Clinic at _____ *(phone number)* to schedule an appointment.

Reading Food Labels



- Serving size
- Number of servings
- Calories
- Total fat in grams
- Saturated fat in grams
- Cholesterol in milligrams

Here, the label gives the amounts for the different nutrients in one serving. Use it to help you keep track of how much fat, saturated fat, cholesterol, and calories you are getting from different foods. Pay attention to the actual amounts (in grams or milligrams). *Don't use the percents shown* (percent daily value) because they are not geared to the TLC diet.

Reading Food Labels

Reading food labels can be challenging. Important tips are to look at serving sizes and the number of servings in the container. The total fat, saturated fat, cholesterol, sodium and fiber contents are important to review for people trying to eat to reduce cardiovascular disease risk.

APPENDIX D

Exercise

Most studies demonstrate that an exercise program serves as a valuable nonpharmacologic means of improving lipid profiles in patients with dyslipidemia (including those with concurrent CHD/CVD, and/or DM). [2-6,8,10-11,20] Exercise parameters explored vary considerably, and researchers have yet to establish the exact levels for maximally increasing HDL, lowering LDL and triglycerides, and for slowing or reversing coronary atherosclerosis.[1,3-7,10-11,13,15,18,20,23-24] Researchers consistently demonstrate a dose response relationship to CHD/CVD risk reduction and improved lipid profiles with increasing total activity time and caloric expenditure[1,7,13,19,23-24]

Additionally, it has been shown that diet and exercise have a synergistic effect when combined, and both aerobic and resistance training are helpful for improving dyslipidemia.[2-4,9] Therefore, exercise and diet should be prescribed together, and the current exercise guidelines for the general population would also be beneficial for patients with dyslipidemia (with/without DM and/or CHD/CVD). [2-6,8-9,11,22,24]

The following specific exercise guidelines have not been assessed in a well-designed study to see if they produce the absolute optimal impact on dyslipidemia management but are a synthesis of various studies, prior exercise consensus panels, and an effort to use the positive dose relationship of exercise in improving dyslipidemia.[6-7,12-13,15,22,24]

The exercise guideline goal is to accumulate 30 minutes or more of moderate intensity physical activity on most (and preferably all) days of the week.[14,17-18,24] In addition to the aerobic component (complete with stretching and proper warm-up/cool), studies demonstrate that all patients could benefit from adding resistance training to their routine. The following are recommended: 2-3 sets of 8-12 repetitions, moderate weight, of at least 8-10 major muscles, 2-3 times per week.[**15-16**] Exercise testing and risk stratification may be appropriate when sedentary individuals over the age of 40 with CHD/CVD risk factors or established disease first begin an exercise program.[25,29] Recent studies show that such patients can ultimately progress to the same goals, if exercise is titrated appropriately—below symptomatic threshold, and with supervision (if indicated). [26-28,30]

Attached is an example of a handout that may help to encourage participation in the prescribed exercise program. Consider referring patients to a physical therapist or to a cardiac rehabilitation program when monitoring or supervision is indicated. [**21,27**] (See also VHA/DoD Guideline for IHD - Cardiac Rehabilitation Module.)

Exercise Handout

How to improve your health, cardiovascular fitness and reduce body fat

What can being physically active do for you?

Here are some of the specific benefits of regular physical activity:

Heart Health:	Can cut the risk of heart disease almost in half, and also may help prevent major risk factors, such as obesity and high blood pressure.
Cholesterol Control:	Can improve blood cholesterol profiles by raising HDL levels (good cholesterol) and lowering triglycerides, another fat carried in the blood.
Muscling Out Fat:	Improves the body's muscle-to-fat ratio by building or preserving muscle fat mass, which, in turn, increases calorie-burning efficiency to reduce body fat.
Bone Support:	Seems to slow the bone loss associated with advancing age—a major cause of fractures in later life.
Insulin Enhancement:	Enables the body to use insulin more efficiently, helping to control adult-onset diabetes.
Cancer Check:	By combating obesity, appears to lower the risk of certain cancers, particularly cancers of the breast, colon and uterus.
Aerobic Improvement:	Slows the decline in aerobic capacity (the maximum volume of oxygen the body can consume) that is associated with aging, helping to improve cardiorespiratory health.
Weight Control:	When combined with proper nutrition, can help control weight and prevent obesity, a major risk factor for many diseases.
Attitude Adjustment:	Reduces anxiety and depression, improves self-esteem, and helps you better manage stress.

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APPENDIX E

E-1: DRUG THERAPY INFORMATION

Statins

Drug	Dose
Atorvastatin	10-80mg daily
Fluvastatin	20-80 mg daily (divided qpm-bid); XL 80mg qpm
Lovastatin	10-80mg daily pm with food (80mg given as 40mg bid)
Pravastatin	10-80mg daily pm
Simvastatin	5-80mg daily pm
Rosuvastatin †	5-20 mg/day, although 40 mg is the maximum daily dose.

†In those patients on 40 mg daily, baseline and periodic urinary and renal function monitoring are recommended. If unexplained, persistent proteinuria is noted in a patient receiving rosuvastatin 40 mg daily, the manufacturer recommends reducing the dose of rosuvastatin.

Potential Adverse Effects:

- Abdominal pain, constipation, diarrhea, dyspepsia, nausea, myopathy (<0.2%; 5% in combination with gemfibrozil; 2% in combination with niacin), rhabdomyolysis
- Increase in LFTs >3 x the upper limit, and CPKs >10 x the upper limit

Precautions/ Contraindications/ Comments:

- Hypersensitivity
- Caution in hepatic disease
- LFT monitoring is recommended by drug manufacturers within 3 months of initiation or changing dosage, and then periodically
- Avoid in pregnant/lactating women
- Caution in severe renal impairment, use lowest dose in moderate renal impairment
- Evening/bedtime dosing may improve efficacy
- Increased risk for myopathy when any statin is combined with fibrates or niacin (≥1 gm daily). The risk is also increased if combining with atorvastatin, lovastatin or simvastatin with potent inhibitors of CYP 3A4 (azole antifungals, macrolide antibiotics, immunosuppressives, protease inhibitors or delavirdine, grapefruit juice, nefazodone, diltiazem, verapamil, or amiodarone)

Bile Acid Resins

Drug	Dose
Colestipol powder	5-30gm/day (daily or divided bid-tid)
Colestipol tablets	2-16gm/day (daily or divided bid-tid)
Cholestyramine powder	4-8 gm bid
Colesevelam tablets (NF)	3.75 gm (daily or divided bid)

bid=twice daily; NF=nonformulary; tid=three times daily

Potential Adverse Effects:

- Nausea, bloating, constipation, flatulence
- May increase TG

Precautions/ Contraindications/ Comments:

- Complete biliary obstruction
- Caution if active PUD due to GI irritation
- Moderate doses are most well tolerated
- Take other medications 1 hour prior or 4-6 hour after resin to avoid drug-drug interactions

Fibrates

Drug	Dose
Gemfibrozil	1200mg/day (divided bid before meals)
Fenofibrate	160-200 mg/day

Potential Adverse Effects:

- GI symptoms, nausea, vomiting, diarrhea, rash, hepatitis, gallstones, and myopathy and rhabdomyolysis

Precautions/ Contraindications/ Comments:

- Gallbladder disease
- Monitor LFTs throughout therapy; contraindicated in hepatic disease
- Reduce dose in modest renal insufficiency; contraindicated in severe renal dysfunction
- Risk of myopathy/rhabdomyolysis increases when combined with statins
- Monitor INR; may need to adjust warfarin dosage to prevent bleeding complications

Niacin

Drug	Dose
Niacin ER	500mg-2gm daily at bedtime
Niacin IR	1.5-3gm/day (divided tid); Start IR 50-100mg bid-tid; increase dose by 300mg/day per week

Potential Adverse Effects:

- Flushing, blurred vision, GI distress, itching, headache, hepatotoxicity, hyperglycemia, hyperuricemia

Precautions/ Contraindications/ Comments:

- Hepatic disease; persistent elevation of LFTs
- Monitor LFTs at baseline; 6-12 weeks after start or dosage change; monitor every 6-12 months thereafter
- Active peptic ulcer disease (PUD). Avoid in patients with a documented history of PUD
- Arterial bleeding
- May causes glucose intolerance; caution in DM

- Decreases urinary secretion of uric acid, caution with gout. Avoid in patients with documented history of gouty attacks. If CrCl is 1050 ml/min give 50% of dose; if <10 ml/min give 25%
- Take with food to avoid flushing or GI upset
- ASA 30 minutes prior to dose may minimize flushing.

Cholesterol Absorption Inhibitors

Drug	Dose
Ezetimibe (Zetia®)	10 mg

Potential Adverse Effects:

- LFT elevation when combined with statins
- Reports of myopathy after adding ezetimibe to high dose statins
- Diarrhea
- Abdominal pain
- Hepatitis
- Pancreatitis
- Angioedema
- Thrombocitopnea
- Rhabdomyolysis (rare)

Precautions/ Contraindications/ Comments:

- Possible drug unteraction : Cyclosporine, fibrates, bile acid sequestrants, statins (LFT elevation)
- Combination with statins may result in LFT elevation
- Myopathy has been reported in a subgroup of patients given ezetimibe alone or when added to high dose statins
- Avoid with moderaste to severe hepatic insufficiency
- Monitor INR when combined with wafarin
- The manufacturer of ezetimibe has recommended that ezetimibe not be routinely combined with fibrates until more data are available in humans
- Until more data are available on the myopathic risk of ezetimibe, instruct patients to report any unexplained muscle tenderness pain or weakness when ezetimibe is combined with statins.

ONEGA-3 Polyunstaurated Fatty Acid

Drug	Dose
Omega-3 fatty acid (Omacor®, various)	Elevated LDL-C: 1 gram daily or divided Elevated TG: 2-4 grams daily or divided

Potential Adverse Effects:

- GI including nausea, eructation and taste perversion or fishy taste
- LDL-C elevation (especially in those with very high TG and no concomitant statin)
- ALT elevation

Precautions/ Contraindications/ Comments:

- Drug to drug interactionAnticoagulants
- ALT should be checked at baseline and 6-12 weeks after initiation of fish oils and periodically thereafter.
- Lipid panel, including TG and LDL-C should be checked within 6-12 weeks of initiation of treatment.

E-2: Drug Interactions with Bile Acid Resins, Fibrates, and Niacin[1]

The combination of a bile acid resin and statin can further reduce the LDL-C. Combining fibrates with statins may provide additional increases in HDL-C and reductions in TG; however, the potential benefit must be balanced against an increased risk of myopathy.

Niacin combined with a statin also raises HDL-C and lowers triglycerides. It is associated with an increased risk of myopathy; however, the risk is lower than with fibrates and may be less than previously believed. The risk for muscle toxicity, observed with lipid-lowering combinations, is increased with increasing statin doses.

INTERACTIVE AGENT(S)		CLINICAL MANIFESTATIONS
Bile acid resins (resins) Cholestyramine Colestipol	Digoxin Levothyroxine Warfarin	May decrease the absorption of many drugs; take other drugs 1 hour before or 4-6 hours after resin May impair absorption of fat soluble vitamins
	Amiodarone	May increase the elimination of amiodarone; follow for increased dosage requirements of amiodarone
Fibrates Fenofibrate Gemfibrozil (May also occur with clofibrate)	Glyburide	May cause hypoglycemia; may occur with other sulfonylureas
	Statin	Myopathy including rhabdomyolysis reported in up to 5% of lovastatin patients[2]; interaction also reported with atorvastatin[3] and cerivastatin[4] Avoid combination if patient is on another agent that can affect CYP3A4 metabolism Check pretreatment LFTs Monitor for musculoskeletal symptoms (CK normal range 21-235 U/L[5], look for 10x upper limit if patient is symptomatic). There is no evidence that checking baseline CK can reduce the risk for myopathy with lipid-lowering agents. However, if a patient has any unexplained muscle pain, tenderness or weakness, patients should discontinue treatment and a CK level is indicated.
	Warfarin	Risk of ↑ anticoagulant activity
Niacin	Statins	Myopathy has been reported in 2% of lovastatin patients with or without rhabdomyolysis but more recent data question this increased risk. Caution if patient is on another agent that can affect CYP3A4 metabolism Check pretreatment LFTs; recheck after initiation and dosage changes Monitor for musculoskeletal symptoms
Statins	Azole antifungals (fluconazole, ketaconazole, itraconazole)	Inhibits metabolism of 3A4 metabolized statins (atorvastatin, lovastatin, simvastatin) and may increase risk for myopathy/rhabdomyolysis
	Immunosuppressives (cyclosporin, tacrolimus)	Can increase risk of myopathy/rhabdomyolysis

INTERACTIVE AGENT(S)		CLINICAL MANIFESTATIONS
	Macrolide antibiotics (clarithromycin, erythromycin)	Inhibits metabolism of 3A4 metabolized statins (atorvastatin, lovastatin, simvastatin) and may increase risk for myopathy/rhabdomyolysis
	Protease inhibitors (ritonavir, saquinavir)	Inhibits metabolism of 3A4 metabolized statins (atorvastatin, lovastatin, simvastatin) and may increase risk for myopathy/rhabdomyolysis
	Anticoagulants	Case reports of increased INR with all statins
	Niacin/Fibrates	Increased risk of myopathy
	Calcium channel blockers (diltiazem, verapamil)	Increased risk of myopathy

THIS TABLE INCLUDES SIGNIFICANT DRUG INTERACTIONS (TO DATE) AND MAY NOT ENCOMPASS ALL POSSIBLE AGENTS

_____

[1] Bays, H., Dujovne, C. (1998). Drug interactions of lipid lowering drugs. Drug Safety. 19(5), 355-371.

Farmer, J. A., Gotto, A. M. (1994). Antihyperlipidaemic agents: Drug interactions of clinical significance. Drug Safety. 11(5), 301-309.

Garnett, W. R. (1995). Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. American Journal of Health-Systems Pharmacy. 52, 1639-1645.

Hansten, P. D., & Horn, J. R. (1997). Drug Interaction Analysis and Management. Vancouver: Applied Therapeutics.

[2] Garnett, W. (1995). Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. American Journal of Health-Systems Pharmacy.52, 1639-1645.

[3] Duel, P. B., Connor, W. E., & Illingworth, D. R. (1998). Rhabdomyolysis after taking atorvastatin with gemfibrozil. American Journal of Cardiology. 81, 368-9.

[4] Pogson, G. W., Kindred, L. H., & Carper, B. G. (1999). Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy. American Journal of Cardiology. 83, 1146.

[5] CK normal range may vary among laboratories, and is affected by age, race, exercise/muscle mass, and comorbid conditions.

[6] Guyton, J. R., & Capuzzi, D. M. (1998). Treatment of hyperlipidemia with combined niacin-statin regimens. American Journal of Cardiology. 82, 82U-84U.

[7] Curtis, A., ed. (1999). Physicians' Desk Reference. 53rd ed. Montvale, NJ: Medical Economics Company.

E-3: Drug Therapy Summary [1, a-d]

DRUG	LDL-C	HDL-C	TG	DOSE	CAUTIONS/MONITOR[e]
Resin Cholestyramine 4 g powder/LIGHT colestipol 5 g powder/1 g tablet	↓ 10-20%[f]	± 3%[b]	↑ 3-10%[b]	• Cholestyramine 4 gm bid and colestipol 5 gm bid are usual and best tolerated doses. • Take other meds 1 h prior or 4-6 h after or take with dinner	• May ↑ TG • Caution if active PUD due to GI irritation • GI intolerance
Niacin 100, 250, 500 mg IR tablet IR at 1.5-3g/day 500 mg, 750 mg, 1 g ER tablets ER at 1.5 g/day[g]	↓ 13-21% ↓ 13%	↑ 10-24% ↑ 19%	↓ 19-24% ↓ 10%	• Start IR 50-100 mg bid-tid & ↑ dose by 300 mg/d per week (refer to Appendix E-3 for *NIACIN DOSE PACK*); ER use titration pack • Usual maximum daily dose IR 3 g/d; ER 2 g/d • Take w/meals to avoid flushing or GI upset	• LFTs at baseline, 6 weeks after start or dosage change; monitor every 6-12 months thereafter • May causes glucose intolerance - caution in DM • Avoid in patients with documented history of PUD. • Decreases urinary secretion of uric acid, caution with gout • Avoid in patients with documented history of gouty attacks • Contraindicated in hepatic disease • If CrCl is 10-50 ml/min give 50% of dose; if <10 ml/min give 25%[h]
Fibrates Gemfibrozil 600 mg tab	+/- 10%[i]	↑ 10%[i]	↓ 43%[i]	600 mg bid	• Monitor LFTs throughout therapy; contraindicated in hepatic disease • Reduce dose in modest renal insufficiency • Risk of myopathy with statin • Monitor INR; may need to adjust Warfarin dosage to prevent bleeding complications
fenofibrate 67 mg capsule	↓ 17-35%[j]	↑ 2-34%[j]	↓ 32-53%[j]	67-201 mg/d	Same cautions as gemfibrozil
Statins atorvastatin 10, 20, 40 mg, 80 mg fluvastatin 20, 40 mg, 80 mg XL lovastatin 10, 20, 40 mg tab rosuvastatin 5, 10, 20 and 40 mg simvastatin 5, 10, 20, 40, 80 mg tab	↓ 22-60%[k]	↑ 2-12%[k]	↓ 6-37%[k]	• Lovastatin (VA National Formulary agent) 10-80 mg/day q p.m. (80 mg given as 40 mg BID) • Simvastatin (DoD BCF/VA National Formulary agent) 5-80 mg/day q p.m. • Evening/bedtime dosing may improve efficacy	• LFT elevation monitor LFTs within 6-12 weeks of initiation and after dosage increases, then periodically • Myopathy <0.2%[l] 5% in combination with gemfibrozil; 2% in one study and less in others in combination with niacin • Caution in hepatic disease • Caution in severe renal impairment, use lowest dose in moderate renal impairment and monitor

[l] Adapted from PBM-MAP, 1997

[a] ac = before meals; ALT = alanine aminotransferase; ASA = aspirin; AST = aspartate aminotransferase; BAR = bile acid resin; CrCL = creatinine clearance; DM = diabetes mellitus; GI = gastrointestinal; HDL = high-density lipoprotein cholesterol; Hct = hematocrit; Hbg = hemoglobin; HMG-CoA RI = HMG CoA reductase inhibitors; IR = immediate release; LDL = low-density lipoprotein cholesterol; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; PUD = peptic ulcer disease; pwdr = powder; SR = sustained release; TC = total cholesterol; TG = triglyceride; TIA = transient ischemic attack; WBC = white blood (cell) count.

[b] McKenney, J. M. Dyslipidemias. In: Koda-Kimble, M. A., Young, L. Y., eds. Applied Therapeutics: The Clinical Use of Drugs. 6th ed. Vancouver: Applied Therapeutics Inc., 1995:9-1-9-26.

[c] Talbert, R. L. Hyperlipidemia. In: DiPiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., Posey, L. M., eds. (1997). Pharmacotherapy: A Pathophysiologic Approach. 3rd ed. Stamford, CT: Appleton & Lange:459-489.

[d] Antihyperlipidemic Agents. In: Hebel, S. K., ed. Drug Facts and Comparisons. St. Louis: Facts and Comparisons Inc.; 1998:171f-72p.

[e] Refer to Appendix E-2 for drug interactions.

[f] At 1 year follow-up on an average dose of 4 packets/day. The Lipid Research Clinics Coronary Primary Prevention Trial. (1984). Journal of the American Medical Association.;251:351-74.

[g] Knopp, R. H., Alagona, P., Davidson, M., et al. (1998). Equivalent of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. Metabolism, 47, 1097-1104.

[h] Bennett, W. M., Aranoff, A. R., Morrison, G., et al. (1983). Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. American Journal of Kidney Diseases 3(3), 155-187.

[i] Frick, M. H., Elo, M. O., Haapa, K., et al. (1987). Helsinki Heart Study. New England Journal of Medicine. 317, 1237-1245.

[j] Adkins, J. C., Faulds, D. (1997). Micronised fenofibrate. Drugs. 54, 615-633.

[k] Depending on specific agent and dose, refer to product package inserts.

[l] Bradford, R. H., Shear, C. L., Chremos, A. N., et al. (1994). EXCEL Study Results: Two year efficacy and safety follow-up. American Journal of Cardiology. 74, 667-673.

E-4: Statin Dose Charts

Statin Dose Charts
Treat to Goal Chart

The PEC has developed a chart to assist prescribers to 'Treat to Goal' by matching statin doses and baseline LDL levels. The chart 'does the math' by identifying the best starting statin dose given a baseline LDL and the patient's LDL goal. It also contains additional information which may be helpful: descriptions of CHD risk factors and patient risk groups, common prescribing information, and typical non-formulary statin request information.

Treat To Goal

- Treat to Goal Chart - Adobe Acrobat version (pdf file) - for easy distribution.
  http://www.pec.ha.osd.mil/Updates/0201web/Statin_Files/Treat_to_Goal_Chart.pdf

- Treat to Goal Chart - MS Excel 95 version - can be customized by facilities that would like to include site-specific information. Please note that this file contains separate versions of the front page for color vs. black and white printing.
  http://www.pec.ha.osd.mil/Updates/0201web/Statin_Files/Treat_to Goal_Chart_95.xls

E-5: Drug Selection Based on Required LDL-C Reduction

% LDL-C Reduction Required	Pravastatin	Fluvastatin	Lovastatin	Simvastatin	Rosuvastatin	Atorvastatin
18	10 mg	20 mg	10 mg	5 mg		10 mg
19						
20						
21	20 mg					
22						
23		40 mg	20 mg			
24				10 mg		
25						
26						
27		80 mg				
28	40 mg		40 mg			
29						
30						
31				20 mg		
32						
33			80 mg			
34						
35						
36				40 mg		20 mg
37						
38						
39						
40					5 mg	
41				80 mg		
42						
43						
44						40 mg
45						
46						
47						
48						
49						
50						
51					10 mg	
52					20 mg	80 mg
53					40 mg	
54						
55						
56						
57						
58						

Adapted from the DoD Pharmacoeconomic Center (PEC) Publication, July, 1999.

LDL-C Reduction-Point Estimates - The point estimates provided were derived from the information obtained from the product package insert and published randomized studies. To establish an efficacy (versus effectiveness) estimate of LDL-C reduction for each drug and strength, studies and/or Product Package Inserts (PPI) must have met the following criteria: 1) published in a peer reviewed journal (not applicable to PPI) or provided in the FDA approved PPI, 2) subjects must have been randomized to treatment, 3) number of study subjects receiving each dosage strength clearly stated, and 4) duration of therapy and timing of LDL-C measurement provided. To estimate efficacy, LDL-C reductions must have been obtained at baseline and again between six and twenty-four weeks of initiation of "statin" therapy. The final point estimate for each drug and strength is a weighted average based upon the number of study subjects evaluated in each study.

APPENDIX F

PHARMACOLOGIC THERAPY
SUMMARY OF SUPPORTING STUDIES

F-1 Monotherapy

Primary Prevention

Treatment should be based on risk, which varies widely in this group of patients. Coronary heart disease risk increases with increasing risk factors, and can be easily calculated (Wilson et al., 1998, or http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof). Lowering LDL-C has been shown to reduce the incidence of CHD, with each 1 percent reduction in LDL-C reducing relative risk for major CHD events by 1 percent (Grundy et al., 2004). However, in patients with low absolute risk for developing CHD, even this impressive relative risk reduction results in a small change in the absolute risk or total event rate. The National Cholesterol Education Program (NCEP) guidelines recommend LDL targets based on number of CHD risk factors, as well as 10-year calculated risk of developing clinical CHD (myocardial infarction or cardiac death) (NCEP ATP-III, 2002).

Table F-1.1 Primary Prevention Clinical Endpoint Trials Involving Statins

Clinical Trial	Baseline LDL-C Mean (mg/dL)	LDL-C Change Mean (%)	Major Coronary Events (RRR, ARR, NNT)	Fatal or Nonfatal MI (RRR, ARR, NNT)	Revascular-ization (RRR, ARR, NNT)	Stroke (RRR, ARR, NNT)	CHD Death (RRR, ARR, NNT)	Total Mortality (RRR, ARR, NNT)
WOSCOPS 1995 N=6,595 men, 4.9 years, pravastatin 40 mg vs. placebo	192	26%	RRR 31% ARR 2.2% NNT 44	Nonfatal MI: RRR 31% ARR 1.9% NNT 54	RRR 37% ARR 0.9% NNT 112	NS	RRR 32% ARR 0.7% NNT 142	NS
AFCAPS/TexCAPS - 1998 N=6,605, men and women, 5.2 years, lovastatin 20-40 mg vs. placebo	150	25%	RRR 37% ARR 2% NNT 49	RRR 40% ARR 1.2% NNT 86	RRR 33% ARR 1.5% NNT 65	NR	NS (not enough fatal CHD events reported)	NS
ALLHAT-LLT-2002 N=10,355, 4.8 years, pravastatin 40 mg vs. usual care (unblinded)	129	28%-prava, 11% usual care	NS	NS	NR	NS	NS	NS
ASCOT-LLA 2003 N=10,305, median 3.3 years, atorvastatin 10 mg vs. placebo	131	35% -1 year, 29%-end of study	RRR 36% ARR 1.1% NNT 91	RRR 38% ARR 1% NNT 100	NR	RRR 27% ARR 0.7% NNT 143	CVD Death: NS	NS
CARDS 2004 N=2838 Type 2 DM, median 3.9 years, atorvastatin 10 mg vs. placebo	117	40%	RRR 37% ARR 3.2% NNT 31	ARR 2% NNT 50	NS	RRR 48% ARR 1.3% NNT 77	Not analyzed (24 CHD events placebo vs. 18 atorva)	NS

Results were included if the differences were statistically significant ($p<0.05$ or less), +Post-hoc analysis, NR=not reported, NS=not significant, PCI=percutaneous coronary intervention

Summary of Clinical Endpoint Trials-Primary Prevention

Statins (published since 1999)
Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs. Usual Care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998-3007.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (**ALLHAT-LLT**-2002), 10,355 patients were randomized to receiving non-blinded pravastatin 40 mg daily or usual care for a mean follow up duration of 4.8 years. Although, 14% of patients in this trial had known CHD, it has been included in the primary prevention section of this guideline because the majority of participants simply had one or more risk factors for CHD. The primary endpoint was all-cause mortality with nonfatal MI or fatal CHD combined, cause-specific mortality or cancer being considered as secondary endpoints. There were no differences in total mortality or CHD events between groups. Some have speculated that the non-differences between groups may be explained in part by the small difference observed in LDL-C reduction between groups (16.7%) and by the use of lipid-lowering drugs in the approximately one-third of those in the usual care group.

Sever PS, Dahlof, B, Poulter NR, et al. Prevention of Coronary and Stroke Events With Atorvastatin in Hypertensive Patients Who Have Average or Lower-Than-Average Cholesterol Concentrations, in The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A Multicentre Randomised Controlled Trial. Lancet 2003;361:1149-1158.

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (**ASCOT-LLA**-Sever 2003) evaluated atorvastatin 10 mg vs. placebo for primary prevention in a large hypertensive population with 3 or more CHD risk factors (translating into a 10-year CHD risk of >20%). Average LDL-C pretreatment was 132 mg/dl, with follow up of 3.3 years (halted prematurely due to attainment of pre-specified outcomes of nonfatal MI and CHD death). Although there was a non-significant trend towards a reduction in total mortality (13%, p=0.16), there were significant reductions in nonfatal MI plus fatal MI (37%, p=0.0005, ARR 1.1%, NNT 90), total coronary events (29%, p=0.0005, ARR 1.4%, NNT 71) and stroke (27%, p=0.02, ARR 0.6, NNT 167). Cardiovascular mortality did not differ between groups (p=0.51).

Colhoun HM, Betteridge DJ, Durrington RN, et al. Primary Prevention of Cardiovascular Disease With Atorvastatin in Type 2 Diabetes Mellitus in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicenter Randomized Placebo-Controlled Trial. Lancet 2004;364:685-696.

In the Collaborative Atorvastatin Diabetes Study (**CARDS**-Colhoun-2004), 2838 patients with type 2 diabetes mellitus were randomized to receive atorvastatin 10 mg or placebo for a median follow up period of 3.9 years. The trial was stopped prematurely because the prespecified early stopping rule for efficacy had been met. Patients randomized to atorvastatin experienced a 37% relative risk reduction in the primary endpoint (MI, unstable angina, CHD death, resuscitated cardiac arrest, coronary revascularization or stroke) and a nonsignificant trend towards reduced total mortality.

Fibric Acid Derivatives (Fibrates)

Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-Prevention Trials With Gemfibrozil in Middle-Aged Men With Dyslipidemia. Safety of Treatment, Changes in Risk Factors, And Incidence of Coronary Heart Disease. N Engl J Med 1987;317:1237-1245.
WHO Cooperative Trial in The Primary Prevention of Ischaemic Heart Disease Using Clofibrate. Report from the Committee of Principal Investigators. British Heart J. 1978;40:1069-1118.

In the Helsinki Heart Study (**HHS**), 4,081 asymptomatic men with primary dyslipidemia were randomized to receive gemfibrozil 600 mg twice daily or placebo for 5 years. The primary outcome was a reduction in the risk for cardiac outcomes (fatal and nonfatal myocardial infarction and cardiac death). At 5 years, there was a 34% relative risk reduction in cardiac outcomes (ARR 1.4%, NNT=71). (HHS-Frick, 1987) In the World Health Organization **(WHO**) Cooperative Trial, males with elevated cholesterol without coronary artery disease were randomized to either clofibrate (1.6 grams daily) or placebo and followed for a mean of 5.3 years. The primary endpoint was the incidence of major CHD events (including fatal and nonfatal MI) and overall mortality. The incidence of major CHD events occurred significantly less often in the clofibrate group vs. placebo (RRR 20%), but was confined to a reduction in nonfatal MI. Death due to cardiac causes was not different between groups. Overall mortality was higher in the clofibrate group vs. placebo (162 vs. 127, $p<0.05$). The increased incidence of death in the clofibrate group was attributed to diseases of the liver, intestines and gallbladder and not due to an increased rate of death from IHD. The authors concluded that because of the possibility for serious adverse events with clofibrate, aside from a potential reduction in IHD, that only those patients with the highest risk for IHD and the highest cholesterol levels be considered candidates.
The Fenofibrate Intervention and Event Lowering in Diabetes (**FIELD**) Study was designed to determine whether treatment with fenofibrate reduces cardiovascular mortality in type 2 diabetics. Eligibility criteria include patients with or without prior ASCVD. To date, 9,795 diabetics have been enrolled and will be followed for 5-7 years. Results from FIELD are expected in 2005.

Bile Acid Sequestrants (BAS or Resins)

Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in the incidence of coronary heart disease. JAMA 1984;251:351-364.

The Lipid Research Clinics Coronary Primary Prevention Trial (**LRC-CPPT**) evaluated the incidence of CHD death or nonfatal MI in 3,806 asymptomatic men taking cholestyramine vs. placebo for 7.4 years. There was an overall statistically significant 19% reduction in the risk of the primary endpoint of CHD death or nonfatal MI in favor of the cholestyramine group. The cumulative seven-year incidence of CHD death or nonfatal MI occurred in 7% of the cholestyramine vs. 8.6% of the placebo group (ARR 1.6%, NNT 62) (LRC-CPPT-1984).

Secondary Prevention

In the 2002 NCEP ATP-III update, certain groups of patients, without known CHD, are recognized as having a similar 10-year risk for MI or CHD death (hard CHD) as those patients with established CHD. These patients are referred to as having a "CHD risk equivalent". Individuals identified as having "CHD risk equivalents" include patients with diabetes mellitus and those at high-risk for CHD due to multiple risk factors. All of these individuals are at high-risk for first or recurrent coronary events translating into a 10-year risk in excess of 20%. As a result, treatment recommendations for these high-risk individuals (known CHD or CVD or CHD risk equivalents) should be the same. ATP-III has indicated that the Framingham 10-year risk scoring method for determining CHD risk in adult patients (without CHD or diabetes) is the most reliable and is readily accessible online. (http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof)

Table F-1.2 Secondary Prevention Clinical Endpoint Trials Involving Statins

Clinical Trial	Mean Base-line LDL-C (mg/dL)	Mean LDL-C Change (%)	Major Coronary Events (RRR, ARR, NNT)	Fatal or Nonfatal MI (RRR, ARR, NNT)	Revascular-ization (RRR, ARR, NNT)	Stroke (RRR, ARR, NNT)	CHD Death (RRR, ARR, NNT)	Total Mortality (RRR, ARR, NNT)
SECONDARY PREVENTION CLINICAL ENDPOINT TRIALS								
4S-1994 N=4444 5.4 years Simvastatin 20 mg (37% on 40 mg daily) vs. placebo	188	35%	RRR 35% ARR 9% NNT 12	Nonfatal: RRR 37% ARR 6.7% NNT 15	RRR 37% ARR 5.9% NNT 17	RRR 30% + ARR 1.3% NNT 77	RRR 42% ARR 3.5% NNT 28	RRR 30% ARR 3.3% NNT 30
CARE-1996 N=4159 5 years Pravastatin 40 mg vs. placebo	139	27%	RRR 24% ARR 3% NNT 33	RRR 25% ARR 2.4% NNT 41	RRR 27% ARR 4.7% NNT 41	RRR 31% ARR 1.1% NNT 86	(NS)	(NS)
LIPID-1998 N=9014 6.1 years Pravastatin 40 mg vs. placebo	150	25%	RRR 24% ARR 3.5% NNT 28	RRR 29% ARR 2.8% NNT 36	RRR 20% ARR 3% NNT 34	RRR 19% (p=0.048)) ARR 0.8% NNT 127	RRR 24% ARR 1.9% NNT 52	RRR 22% ARR 3% NNT 33
HPS-2002 N=20,536 5 years Simvastatin 40 mg vs. placebo	131	29.5%	RRR 27% ARR 3.1% NNT 32	Nonfatal: RRR 38% ARR 2.1% NNT 47	RRR 24% ARR 2.6% NNT 38	RRR 25% ARR 1.37% NNT 72	RRR 17% ARR 1.5% NNT 65	RRR 13% ARR 1.75% NNT 57
PROSPER-2002 N=5804 (70-82 yrs) 3.2 years Pravastatin 40 mg vs. placebo	146	34%	Major CV Events: RRR 15% ARR 2.1% NNT 48	RRR 19% ARR 2.1% NNT 48	(NS)	(NS)	RRR 24% ARR 0.9% NNT 111	(NS)
TNT-2005 N=10,001 (35-75 yrs) Median 4.9 years Atorvastatin 10 mg vs. 80 mg in stable CHD (LDL 101 vs. 77, respectively)	152 (98 after active run-in phase)	35% after 8 week run-in with atorva 10	RRR 22% ARR 2.2% NNT 45	**Nonfatal:** RRR 22% ARR 1.3% NNT 77	(NR)	RRR 25% ARR 0.8% NNT 125	(NS) 127 vs. 101 in favor of high dose	(NS) 155 vs. 183 in favor of low dose
STATUS-POST ACUTE CORONARY SYNDROME/PCI CLINICAL ENDPOINT TRIALS								
MIRACL-2001 N=3086 16 weeks Atorvastatin 80 mg vs. placebo	124	40%	RRR 16% (P=0.048) ARR 2.6% NNT 38	(NS)	(NS)	RRR 50% ARR 0.8% NNT 125	(NS)	(NS)
PROVE IT-TIMI		Statin-	Major CV					

22-2004 N=4162 2 years Atorvastatin 80 mg vs. pravastatin 40 mg	106 (median)	naïve: 22% prava, 51% atorva (median)	Events: RRR 16% ARR 3.9% NNT 26 (Results favor atorvastatin)	(NS)	RRR 14% ARR 2.5% NNT 40	(NS)	(NS)	(NS)
A to Z-2004 N=4497 2 years Simvastatin 40 mg for 1 month followed by 80 mg vs. placebo for 4 months followed by Simvastatin 20 mg	111-112 (median)	24 months Simva 80: 41% Simva 20: 27 % (median)	Major CV Events: (NS)	(NS)	(NS)	(NS)	RRR 25% (p=0.05) ARR 1.3% NNT 77	(NS)
LIPS-2002 N=1677 3.9 years Fluvastatin 40 mg twice daily vs. placebo after PCI	131	27% (median)	RRR 22% ARR 5.3% NNT 19	(NS)	(NR)	(NR)	(NS)	(NS)

Results were included if the differences were statistically significant (p<0.05 or less), +Post-hoc analysis
NR=not reported, NS=not significant, PCI=percutaneous coronary intervention

Summary of Clinical Endpoint Trials-Secondary Prevention

STATINS (published since 1999)

MRC/BHF Heart Protection Study (HPS) of Cholesterol Lowering With Simvastatin in 20,536 Individual: A Randomized Placebo-Controlled Trial. Lancet 2002,360:7-22.

In **HPS**, more than 20,000 men and women between the ages 40-80 years who were considered to be at high-risk for coronary heart disease were enrolled. This study is unique in that it targeted individuals in whom the risk and benefits of cholesterol lowering had been uncertain (women, those over 70 years, diabetics, those with non-coronary vascular disease and those with average or below average cholesterol). Patients were randomized to simvastatin 40 mg daily or placebo for an average of 5 years. Over the 5-year period, there were significant reductions in overall mortality, death from CHD, nonfatal myocardial infarction, coronary revascularization, stroke and major vascular events. These reductions were observed in women, individuals over and under 70 years, TC <200 mg/dl and LDL-C <120 mg/dL. Of further interest, in HPS, risk of major cardiovascular events was reduced similarly regardless of baseline LDL-C. The subgroup of patients whose mean baseline LDL-C was less than 100 mg/dl and mean treatment LDL-C was 65 mg/dl (1.7 mmol/L) versus those on placebo (mean LDL-C 97 mg/dl), experienced a risk reduction nearly as great as those with higher baseline LDL-C. However, when evaluating the effect of the degree of LDL-C lowering, the reduction in cardiovascular events was similar regardless of degree of prerandomization LDL-C response (e.g. those with an LDL-c reduction of <38% on simvastatin experienced a similar risk reduction as those achieving a ≥48% response).

Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): A Randomized Controlled Trial. Lancet 2002;360:1623-1630.

In **PROSPER**, 5,802 men and women between the age of 70 and 82 years with a history of or risk for vascular disease were randomized to receive pravastatin 40 mg daily or placebo for an average follow up duration of 3.2 years. There was a significant reduction in major coronary events, fatal and nonfatal MI, and CHD death in favor of pravastatin versus placebo. There were no differences in risk for revascularization, stroke or overall mortality. An unexpected statistically significant increase in cancer diagnoses was observed in the pravastatin vs. placebo group (p=0.02).

LaRosa JC, Grundy SM, Waters MD, et al. Intensive Lipid Lowering With Atorvastatin in Patients with Stable Coronary Artery Disease. NEJM 2005;352: (published online 3-05) http://content.nejm.org/cgi/reprint/NEJMoa050461v1.pdf

In **TNT**, 15,464 men and women (aged 35-75, LDL-C 130-250 mg/dL and TG ≤600 mg/dL) with known CAD entered an 8-week run-in phase with open label atorvastatin 10 mg daily. Patients were randomized to atorvastatin 10 or 80 mg daily for a mean duration of 4.9 years if their LDL-C level was <130 mg/dL after the open-label run-in phase. The primary outcome measure was an occurrence of a major cardiovascular event (e.g. death from CHD, nonfatal MI, resuscitated cardiac arrest and fatal or nonfatal stroke). Secondary outcomes included major coronary event, CVA, hospitalization for heart failure, peripheral artery disease and death from any cause including cardiovascular or coronary causes. Mean LDL-C in the low dose group was 101 mg/dL and 77 mg/dL in the high dose group. A primary event occurred in 434 patients (8.7%) on high dose atorvastatin versus 548 patients (10.9%) in the group receiving 10 mg of atorvastatin ($p<0.001$, 95% CI 0.69-0.89, RRR 22%, ARR 2.2%, NNT 45). There were also significant reductions in favor of the high dose group for nonfatal MI and fatal or nonfatal stroke. There were no statistical differences in the rates of CHD death (127 atorva 10 vs. 101 atorva 80, $p<0.09$), non-CHD death (155 atorva 10 vs. 183 atorva 80) or overall mortality (282 atorva 10 vs. 284 atorva 80, $p=0.92$).

It is important to point out that in a separate paper outlining the study design of TNT, there was a prespecified subgroup analysis of concomitant medications to determine if observed differences could be explained by a disparity in other medications known to reduce the risk for cardiovascular outcomes (e.g. aspirin, beta-blockers, calcium channel blockers, and hormone replacement therapy). In the published results, the authors only acknowledge that the pattern of use of concomitant medications was similar between groups. However, a list of important medications and the percentage of patients receiving them in both groups is lacking from the baseline characteristics. In addition, there is no discussion of this prespecified subgroup analysis and whether there were differences at the end of the study. These omitted data are very important information in determining that the observed differences were solely due to differences in LDL-C (Waters, et al. AJC 2004;93:154-158).

Adverse events related to treatment group were reported significantly more often in the high vs. low dose group (406 vs. 289, 8.1% vs. 5.8%, respectively. $p<0.001$). Treatment withdrawal due to adverse events was also significantly higher in the high dose group (7.2% vs. 5.3%, respectively. $p<0.001$). Persistent, clinically significant elevation in liver function tests (LFTs) was reported in 9 patients receiving low dose atorvastatin and 60 receiving high dose atorvastatin (0.2% vs. 1.2, $p<0.001$, NNH 100). There were no differences with regard to reports of myalgias or the number of cases of rhabdomyolysis between groups.

The authors conclude from their data that there is an important incremental benefit to reducing LDL-C to less than 80 mg/dL with atorvastatin 80 mg beyond what is achieved with 10 mg daily. However, in an accompanying editorial, the author notes that although there were differences in cardiovascular events in favor of atorvastatin 80 mg, there were no differences in overall mortality. Although, there was a numerical reduction in CHD death in favor of high dose atorvastatin, there was a numerical increase in non-CHD death in the high dose group. The editorialist concludes that until the safety and effectiveness of 80 mg of atorvastatin are established, the benefits of reduced cardiovascular events with the risk of an increase in the risk of death from noncardiovascular causes need to be carefully considered.

Clinical Endpoint Trials Involving Statins Conducted in Patients Status-Post Acute Coronary Syndromes or Percutaneous Coronary Interventions (published since 1999)

Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes. (MIRACL Study) JAMA 2001;285:1711-1718.

In **MIRACL**, patients with acute coronary syndromes (unstable angina or non-Q wave MI) were randomized to receive atorvastatin 80 mg or placebo for a period of 16 weeks. The primary endpoint

was a composite of major CV events (e.g. death, nonfatal MI, cardiac arrest with resuscitation, or recurrent myocardial ischemia requiring rehospitalization). A significant difference in the primary endpoint between atorvastatin 80 mg and placebo was reported (p=0.048) in favor of atorvastatin There was no difference between groups in risk for cardiac death, nonfatal MI, or cardiac arrest. However, there was a difference in favor of atorvastatin in the risk for recurrent myocardial ischemia requiring rehospitalization and stroke. Also noted in MIRACL was a significantly greater risk for clinically important elevations in liver function tests (LFTs) in the atorvastatin versus placebo groups (2.5% vs. 0.6%, p<0.001).

Cannon CP, Braunwald E, McCabe CH, et.al. Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE-IT). N Engl J Med 2004;350.

In **PROVE-IT-TIMI-22** trial, investigators set out to determine whether lowering LDL-C to 100 mg/dL with pravastatin versus an LDL-C of 70 mg/dL with atorvastatin resulted in a difference to time to occurrence of death or major cardiovascular events (MI, unstable angina requiring hospitalization, revascularization and stroke) in patients with ACS. PROVE-IT was an event-driven trial and follow up continued until 925 events had occurred for a mean follow up of 24 months. There was a significant reduction in risk for occurrence of major cardiovascular events in favor of atorvastatin (26.3% vs. 22.4%, p=0.005, 95% CI 5-26%).

Among individual components of the primary endpoint, the only statistically significant difference favoring atorvastatin were in the need for revascularization and recurrent unstable angina. A reduction in occurrence of all individual components of the primary endpoint were seen in favor of the atorvastatin vs. pravastatin group with the exception of stroke which favored pravastatin slightly.

Of interest, in those patients with baseline LDL-C 125 or greater, there was a much greater reduction in the hazard ratio of 34% (20.1% vs. 28.2%= ARR 8.1% NNT 12) compared to those patients with a baseline LDL-C of less than 125 mg/dL with a RRR of 7% (23.5 vs. 25.6=ARR 2.1%, NNT 47). Additionally, there were no differences in the primary outcome between treatment groups in the 25% of patients receiving statins prior to enrollment in the study.

In PROVE-IT, withdrawal for adverse events did not differ between groups. However, the number of patients experiencing clinically significant elevation in liver function tests (LFTs) was significantly greater in the atorvastatin vs. pravastatin group (3.3 vs. 1.1%, p<0.001). There was no difference in creatine kinase (CK) elevations and no patients developed rhabdomyolysis. Finally, 30-33% of patients in each group withdrew from the study.

de Lemos JA, Blazing MA, Wiviott SD, et al. Early Intensive vs. a Delayed Conservative Simvastatin Strategy in Patients With Acute Coronary Syndromes. Phase Z of the A to Z Trial. JAMA 2004;292:1307-1316.

In **A to Z**, investigators compared an early aggressive intervention in patients presenting with ACS beginning with simvastatin 40 mg daily and increasing to 80 mg after one month versus a delayed conservative approach to determine if there were differences in the composite primary endpoint of major cardiovascular events (cardiovascular death, nonfatal MI, readmission for ACS and stroke). The delayed conservative approach involved placebo for the first four months followed by simvastatin 20 mg daily. Based upon several assumptions, a sample size of 4500 patients was determined to yield 970 cardiovascular events within one year with a planned follow-up of two years. There was no difference in the primary endpoint which occurred in 14.4% of the early aggressive group vs. 16.7% of the delayed conservative group. (p=0.14, 95% CI 0.76-1.04).

Among individual components of the primary endpoint, cardiovascular death occurred in 4.1% vs. 5.4% in the early aggressive vs. the delayed conservative groups, respectively (p=0.05, 95% CI 0.57-1, ARR 1.3%, NNT 77). No differences were seen in other secondary endpoints with regard to nonfatal MI, readmission for ACS, revascularization or stroke. There was a statistically significant difference in new onset congestive heart failure (CHF) occurring more often in the delayed conservative group.

Interestingly, a post-hoc analysis demonstrated no difference between groups during the first 4 months (placebo phase) of the trial. However, when the investigators evaluated the time from 4 to 24 months, there was a statistically significant benefit in favor of the early aggressive group (6.8% vs. 9.3%, p=0.02, 95% CI 0.6-0.95, ARR 2.5%, NNT 40) for the primary composite endpoint.

In A to Z, clinically significant elevation in LFTs was not different between groups. However, 9 patients in the early aggressive group experienced myopathy (CK >10 times the upper limit of normal with associated muscle symptoms) while only 1 patient while in the placebo phase of the delayed conservative group experienced myopathy. Of the 9 cases of myopathy (0.4%), 3 patients developed rhabdomyolysis. One of those patients was receiving a medication known to interact with simvastatin (verapamil) while another patient had contrast-induced renal failure. There were no cases of myopathy in patients receiving 20 mg or 40 mg of simvastatin. Similar to PROVE-IT, 32-34% of patients in both groups withdrew from the study.

Serruys PW, Feyter P, Macaya C, etal. Fluvastatin for Prevention of Cardiac Events Following Successful First Percutaneous Coronary Intervention. A randomized controlled trial. JAMA 2002;287:3215-3222.

In **LIPS**, 1677 patients who had undergone percutaneous coronary intervention (PCI) were randomized to receive fluvastatin 80 mg daily or placebo for 3 to 4 years. The primary outcome in this trial was a composite endpoint of major coronary adverse events (MACE) including cardiac death, non-fatal myocardial infarction, or reintervention procedure. In this trial, fluvastatin was associated with a statistically significant reduction in MACE (21.4% vs. 26.7%, p=0.01) compared to placebo.

Fibric Acid Derivatives (Fibrates)

Clofibrate

Clofibrate and Niacin in Coronary Heart Disease. The Coronary Drug Project Research Group. JAMA 1975;231:360-381.

In the Coronary Drug Project (**CDP**), 8,341 men having one or more myocardial infarctions were randomized to 1 of 6 treatment groups. Three of those treatment groups were stopped early due to increased events (e.g. nonfatal MI, death, thromboembolism and cancer) compared to placebo. These included both estrogen groups and the dextrothyroxine group. The remaining 3 groups included clofibrate 1.8 grams daily, niacin 3 grams daily and placebo. The primary endpoint was total mortality. Secondary endpoints included cardiac and noncardiac mortality and nonfatal events (e.g. MI, angina, CHF, stroke, pulmonary embolism and arrhythmias). The trial had a planned follow up of 5 years but actual follow up ranged from 5-8.5 years. For overall mortality, there was no significant difference between clofibrate and placebo (20% vs. 20.9 %, respectively, no statistics provided). There was also no difference between clofibrate and placebo in definite nonfatal MI or cardiac death combined with nonfatal MI (p-values not provided). Although there was no difference in total mortality in the niacin vs. placebo groups, there was a significantly lower risk for nonfatal MI in favor of niacin vs. placebo.

Gemfibrozil

Frick, MH, Heinonen OP, Huttunen JK, et al. Efficacy of Gemfibrozil in Dyslipidemic Subjects With Suspected Heart Disease. An Ancillary Study in The Helsinki Heart Study Frame Population. Ann Med 1993;25:41-45.

A sub study of the Helsinki Heart Study (**HHS**) was conducted in males excluded from the primary prevention cohort due to a history of myocardial infarction, angina or prior ECG changes. There were 628 subjects enrolled in the secondary prevention component of the study who received either gemfibrozil or placebo for 5 years. The primary outcome in this study was cardiac events (combined fatal and non-fatal MI and sudden cardiac death). There was no difference in the primary endpoint

between gemfibrozil and placebo (p=0.14, 95% CI 0.88-2.48). The authors concluded that because of missing key prognostic factors (e.g. extent of coronary artery obstruction, degree of left ventricular dysfunction, true prevalence of CHD, etc.) the results are considered to be less conclusive.

Robins SJ, Collins D, Rubins HB. Relation of baseline lipids and lipid changes with gemfibrozil to cardiovascular endpoints in the VA-high density lipoprotein intervention trial (VA-HIT). Circulation 1000 (1999);100:1238.

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (**VA-HIT**), 2,531 men with CHD, low HDL-C (≤40 mg/dL) and moderately elevated LDL-C (≤140 mg/dL), were randomized to receive gemfibrozil 600 mg twice daily or placebo for 5 years. Participants were included if their triglyceride level was ≤300 mg/dL or 3.38 mmol/L. The primary outcome in this trial was nonfatal myocardial infarction or death of cardiac origin. A primary event occurred in 21.7% of those receiving placebo versus 17.3% receiving gemfibrozil for a relative risk reduction of 22% (95% CI 7-35, p=0.006, ARR 4.4%, NNT 23). The relative risk reduction for combined cardiac events (nonfatal MI, death from coronary causes or stroke) with gemfibrozil was 24% compared to placebo (95% CI 11-36, p<0.001). There was no difference between groups in the rates of coronary revascularization, hospitalization for unstable angina, overall death or cancer. The authors concluded that raising HDL-C and lowering triglycerides with gemfibrozil, without lowering LDL-C, reduced major CHD events.

Fenofibrate

Effect of Fenofibrate on Progression of Coronary-Artery Disease in Type 2 Diabetes: The Diabetes Atherosclerosis Intervention Study, A Randomized Study. Lancet 2001;357:905-910.

Investigators, in the Diabetes Atherosclerosis Intervention Study (**DAIS,** 2001), randomized 418 type 2 diabetics to fenofibrate 200 mg or placebo daily for a minimum of 3 years. All eligible patients had to have at least one visible coronary lesion so that both progression and regression could be determined. The primary endpoint of DAIS was angiographic progression. Lipid entry criteria were as follows: LDL-C 135-174 mg/dL and triglycerides of <450 mg/dL or LDL-C ≤174 mg/dL and triglycerides of 150-460 mg/dL plus total cholesterol to HDL-C ratio of 4 or greater. Although clinical outcomes were measured, DAIS was not powered to observe a reduction in clinical outcomes. Patients on fenofibrate experienced less atherosclerotic progression (e.g. smaller increase in percent diameter stenosis and smaller decrease in minimum lumen diameter p=0.02, p=0.029, respectively) in the fenofibrate versus the placebo group. Clinical events occurred in 38 patients receiving fenofibrate versus 50 on placebo. The difference in events was not statistically significant.

The Fenofibrate Intervention and Event Lowering in Diabetes (**FIELD**) Study was designed to determine whether treatment with fenofibrate reduces cardiovascular mortality in type 2 diabetics. Eligibility criteria include patients with or without prior ASCVD. To date, 9,795 diabetics have been enrolled and will be followed for 5-7 years. Results from FIELD are expected in 2005.

Bezafibrate (not available in the U.S.)

Secondary Prevention by Raising HDL Cholesterol and Reducing Triglycerides in Patients With Coronary Artery Disease. The Bezafibrate Infarction Prevention (BIP) Study. Circulation 2000;102:21-27.

The bezafibrate infarction prevention (**BIP**) study was designed to investigate whether treatment with bezafibrate would reduce the risk of nonfatal myocardial infarction or cardiac death in patients with coronary heart disease. Inclusion lipoprotein values were as follows: cholesterol 180-250 mg/dL, HDL-C ≤45 mg/dL, triglycerides ≤300 mg/dL and LDL-C ≤180 mg/dL In BIP, 3,122 patients were randomized to bezafibrate 400 mg or placebo daily and followed for a mean of 6.2 years. A primary event occurred in 13.6% on bezafibrate versus 15% on placebo (p=0.26) and was not statistically significant. However, a post hoc analysis revealed a significant reduction in the risk of a primary endpoint occurring in patients with higher baseline triglyceride levels (≥200 mg/dL) (p=0.02). This

difference was restricted to nonfatal MI occurring less often in the treatment group. Total and noncardiac death was similar between groups.

Jamshidi Y, Flavell DM, Hawe E, MacCallum PK, Meade TW, Humphries SE. Genetic determinants of the response to bezafibrate treatment in the lower extremity arterial disease event reduction (LEADER) trial. Atherosclerosis. 2002 Jul;163(1):183-92

A second trial involving bezafibrate was the lower extremity arterial disease event reduction (LEADER-Meade 2002) study. In **LEADER,** men with lower extremity arterial disease were randomized to bezafibrate 400 mg daily or placebo for a median follow up period of 4.6 years. The primary outcome measure in the LEADER trial was a composite of all fatal and nonfatal CHD events and all strokes. Secondary endpoints included analysis of individual CHD events (fatal and nonfatal) and stroke. For the primary endpoint, there was no difference between treatment groups in the incidence of combined fatal and nonfatal CHD events and stroke (n=150 vs. 160 events, bezafibrate vs. placebo, respectively, p=0.72, 95% CI 0.76-1.21). As for the secondary endpoint of individual CHD events and stroke, the only difference was in nonfatal CHD events occurring less often in the bezafibrate group (n=26 vs. 46 events, bezafibrate vs. placebo, respectively, p=0.05, 95% CI 0.36-0.99). Upon further review of the event data, the reduction in nonfatal CHD events was noted primarily in patients less than 65 years of age. The authors do not provide specific data but comment that the subgroup of patients, who experienced a reduction in nonfatal MI with bezafibrate in BIP (those with elevated triglycerides), did not experience a similar benefit in LEADER.

Niacin

Clofibrate and Niacin in Coronary Heart Disease. The Coronary Drug Project Research Group. JAMA 1975;231:360-381.

In the Coronary Drug Project **(CDP**), 8,341 men having one or more myocardial infarctions were randomized to 1 of 6 treatment groups. Three of those treatment groups were stopped early due to increased events (e.g. nonfatal MI, death, thromboembolism and cancer) compared to placebo. These included both estrogen groups and the dextrothyroxine group. The remaining 3 groups included clofibrate 1.8 grams daily, niacin 3 grams daily and placebo. The primary endpoint was total mortality. Secondary endpoints included cardiac and noncardiac mortality and nonfatal events (e.g. MI, angina, CHF, stroke, pulmonary embolism and arrhythmias). The trial had a planned follow up of 5 years but actual follow up ranged from 5-8.5 years. Niacin significantly reduced the 5-year rate of nonfatal MI by 27% (ARR 3.6%, NNT 28) and fatal and nonfatal stroke by 24% (ARR 2.7%, NNT 37) versus placebo. There were no statistically significant differences in rates of death due to cardiovascular causes or overall mortality between the niacin and placebo groups.

F-2 EVIDENCE SUPPORTING COMBINATION THERAPY

Table F-2.1 Potential Combination Pharmacologic Treatments for Dyslipidemia

Drug Combination	Expected Change in Lipoproteins (%)			Angiographic Results	Considerations
	LDL (↓)	HDL (↑)	TG (↓)		
Additive Effects for reducing LDL-C when mono-therapy is inadequate					
1. Statin + Resin	30-60	--	↑10	(Brown 1990) Lova-colestipol: Less progression and more regression than placebo	Drug-drug interaction (take other drugs 1 hr before or 4-6 hrs after resin)
2. Statin + Niacin	25-57	13-36	19-38	(HATS 2001)-less progression and less clinical events, (Arbiter-2 2004) (NS), (Hecht 2005)-(NS)	Risk of LFT abnormalities, especially with extended-release niacin products ≥2 g/day.
3. Statin + Ezetimibe	34-60	3-9	11-24	None	IMPROVE-IT ezetimibe10 + simva 40 vs. simva 40 in 10,000 ACS patients is announced
4. Niacin + Resin	32-43	37-43	27-29	(Blankenhorn 1987, Brown 1990) Less progression in both studies and reduced clinical events.	Drug-drug interaction (take other drugs 1 hr before or 4-6 hrs after resin)
5. Statin + Resin or Ezetimibe + Niacin				None	Addition of resins to S+N partially reversed TG and HDL benefit of S+N (Pasternak, 1996)
Additive Effect for reducing very high TG (≥500 mg/dL) in the presence of elevated LDL-C*					
1. Statin + Niacin	See above for effect on lipids. No clinical trial data in patients with TG >400 mg/dL.				
2. Statin + Fibrate	--	19-22	41-53	None	Risk of myopathy is increased. See cautions/recommendations in discussion section
3. Statin + Fish Oil	--	--	20-30	None	
4. Niacin + Fibrate	NR TC 13	45	20	None	36% reduction in CAD death, p<0.01 Lipid results based upon 1-2 studies (Carlson 1988)
5. Ezetimibe + Niacin or Fish Oil	No Data				
Additive benefit for reducing very high TG and/or low HDL-C without elevated LDL-C*					
1. Statin + Niacin or Fibrate or Fish Oil	See above for effect on lipids. No clinical trial data in patients with TG >400 mg/dL.				
1. Fibrate + Niacin	See above. No clinical trial data in patients with TG >400 mg/dL.				
2. Fibrate or Niacin + Fish Oil	No Data				
3. Fibrate + Niacin + Fish Oil	No Data				
Mixed Dyslipidemias (low HDL-C, high LDL-C and high TG)*					
1. Statin + Niacin	See Above				
2. Statin + Fibrate	See Above				
3. Fibrate + Niacin + Resin	26%	36%	50%	(Whitney et al., 2005)-Coronary stenosis was reduced 0.8% in treatment vs. an increase of 1.35% in placebo (p=0.04)	Major CV events occurred in 9 treatment vs. 19 placebo participants (p=0.04). No difference in individual clinical events.

(Guyton 1999, Worz 2003, NCEP ATP-III), *Combination studies did not include patients with very high TG (≥500 mg/dL).
-=No additional benefit with combination, N=niacin, NR=not reported, R=resin, S=statin, TC=total cholesterol. The manufacturers of ezetimibe recommend avoiding the combination of ezetimibe plus fibrates (Fibrates can increase cholesterol excretion into the bile. In a dog study, ezetimibe also increased cholesterol excretion into the bile). There is no data on the combination of ezetimibe plus fish oils.

DISCUSSION

Statins plus Bile Acid Sequestrants (BAS or Resins)

To date, there have been no outcome or atherosclerotic progression studies comparing statins alone to combination therapy with statins and resins. Over the past 15 years, there have been numerous randomized clinical trials evaluating the additive LDL-C lowering benefit of combining a statin with a resin. In these trials, combination of a resin with a statin resulted in an additional 11-20% LDL-C reduction over that achieved with statin mono-therapy. The combination is safe and effective in lowering LDL-C and may be considered in those patients not achieving their LDL-C goal with moderate to high doses of statins.

In one small study (Brown NEJM 1990;323:1289), 146 men with documented coronary artery disease (and elevated apolipoprotein B) underwent baseline quantitative arteriography and then were randomly assigned to placebo or more intensive management with lovastatin (20 mg twice daily) plus colestipol (10 g three times daily) or niacin (4 g daily) plus colestipol (10 g three times daily) for 2.5 years. Clinical outcomes (death, MI or revascularization) and lipid values were monitored and arteriography was repeated at the end of the study. Clinical outcomes occurred significantly less often in the combination groups compared to placebo (RR 0.27, 95% CI 0.10-0.77) Significantly less patients experienced progression and more experienced regression in the combination group compared to placebo. Low-density lipoprotein cholesterol was reduced 46% and HDL-C increased 15% in the statin-colestipol group.

Although resins may not affect the LDL-C lowering ability of statins, it is prudent to recommend patients take other drugs, including statins, either one-hour before the resin or 4 to 6 hours after the resin to avoid interference of absorption of other concomitant medications. Risk for adverse effects is not additive with the combination.

Statins plus Niacin

The addition of niacin to statins can be an attractive option for some patients because of their complementary lipid-altering effects. In a review of 9 trials evaluating the effect of the combination on lipids, niacin (1-3 grams) added to statins (fluvastatin 20 mg, lovastatin or pravastatin 20-40 mg) resulted in a LDL-C lowering of 25-57%, HDL-C was increased 13-36% and triglycerides were reduced by 19-38 (Guyton, Am J Cardiol 1998, 82U-84U, Guyton Current Cardiology Reports 1999;1:244-250).

To date, there have been three trials evaluating the benefit of statin-niacin combinations on atherosclerotic progression (Table F-2.2). In two trials (Brown 1998-HATS NEJM, Taylor 2004-Arbiter-2-Circulation), patients with known CAD were randomized to receive statins plus niacin. In the third, patients without known CAD received the combination of statins plus niacin and were compared to those on statins alone. In this particular study, the patient's treating physician chose the lipid-lowering agent and dose based upon clinical considerations that were not dictated by the study. As a result, significantly more patients on combination therapy had lower HDL and higher triglycerides than those receiving statin mono-therapy. The authors concluded that statin mono-therapy was associated with similar electron beam tomography (EBT) determined calcified plaque progression in those with normal HDL and TG compared to statin-niacin combination in those with elevated TG and low HDL (e.g. statin alone in patients with controlled lipids=statin+niacin in those with high TG and low HDL).

Table F-2.2 Statin+Niacin Atherosclerotic Progression Trials

Clinical Trial	HATS 2001	Arbiter-2-2004	Hecht, HS 2005
N	160-RCT	167-RCT	162-Observational study
Population	Men <63, Women <70, known CAD, HDL<35 men, <40 women, LDL <145, TG <400	Men and women >30, known CVD, LDL <130, HDL <45 **on statins**, mostly simva ≥20 mg/day	Men and women **w/o** known CAD but evidence of subclinical atherosclerosis
Intervention	**Simva 10-20+Niacin 2g** or Antioxidant vits, the combination or placebo	Addition of Niaspan 1 g or placebo to background statins	Statins (atorva, simva or prava) or statins + Niaspan 1897 mg/day (mean)
Duration	3 years	1 year	1.2 years
Method Measuring Progression	Arteriography: left and right coronary arteries	Carotid B-mode ultrasound (intima-media thickness)	Electron Beam Tomography - (EBT) calcified plaque
Progression/Regression	Regressed 0.4% in simva-niacin (p<0.001) vs. placebo	Increase in CIMT niacin vs. placebo (p=0.08). Post-hoc subgroup=those on niacin w/o insulin resistance, IMT progressed less (p=0.026)	NS
LDL/HDL/TG (change from baseline)	-42%/+26%/-36%	-3%/21%/13%	-41%/+25%/-26.5%
Outcomes (Death CHD or other, MI, Revascul-arization, stroke	Simva-niacin RRR 90% reduction in clinical events (p=0.03)	NS with addition of niacin vs. placebo (p=0.20)	NR
Comments	Antioxidant vitamins lessened the benefit of simva-niacin combo.	149/167 were included in endpoint analysis	HDL was significantly lower and TG significantly higher in the combo group.

NR=not reported, NS=not significant, w/o=without

Earlier studies demonstrated a higher risk for myopathy when niacin was combined with a statin. However, more recent evidence questions this increased risk. The major limitation of the statin-niacin combination is primarily the ability of patients to tolerate the adverse effects of niacin (flushing, etc).

The addition of niacin to a statin can be considered if the LDL-C goal is not achieved with moderate (at least 25% reduction in LDL-C) dose statins.

Statins plus Ezetimibe

There have been numerous studies evaluating the effect of ezetimibe combined with statins on lipid levels (Worz, 2003, Gagne Circ and Am J Cardiol 2002). The addition of ezetimibe to statin therapy generally results in an additional 15-20% reduction in LDL-C, 7-13% reduction in triglycerides and an increase in HDL-C of 1-5%. To date, there have been no published clinical outcome trials or atherosclerotic progression trials examining the cardiovascular benefit of the combination. However, the IMPROVE-IT trial has recently been announced. The Improved Reduction of Outcomes: VYTORIN (ezetimibe 10/simvastatin 40) Efficacy International Trial or IMPROVE-IT will evaluate, over a 2-year period, the combination of ezetimibe plus simvastatin versus simvastatin 40 mg alone in 10,000 recent ACS patients. The primary endpoint is the composite of death, MI, rehospitalization for ACS or revascularization. In February 2005, the design and rationale for Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regressions (ENHANCE) trial was published. In ENHANCE, the combination of ezetimibe plus simvastatin (10/80) will be compared to simvastatin 80 mg to determine if there are greater benefits with combination therapy with regard to reducing carotid artery intima-media thickness. This trial will follow patients for 2 years.
Similar to the BAS and niacin, ezetimibe combined with a low dose statin can produce similar LDL-C lowering as quadruple the statin dose (e.g. simva 10 mg + ezetimibe 10 mg = simva 80 mg daily). However, since most of the large health outcome statin trials utilized higher statin doses (20-40 mg/d), it is not known whether the same clinical benefit will be seen if a low dose statin is combined with ezetimibe or another agent.

The combination of ezetimibe plus statins appears to be safe. However, in clinical trials comparing ezetimibe in combination with statins versus statins alone, clinically significant elevation in LFTs occurred in 1.3% of patients receiving combination therapy vs. 0.4% in those receiving statins alone. As a result, LFTs should be performed prior to addition of ezetimibe to statin therapy, after 6-12 weeks and periodically thereafter.

Recently, a letter was published in the Annals of Internal Medicine reporting two cases of suspected myopathy occurring soon after the addition of ezetimibe. One of those patients was receiving atorvastatin 80 mg and the other fluvastatin 80 mg. A response to this letter (Phillips, Ann Intern Med 2004) stated that they had observed a similar experience. Furthermore, they report evaluating 300 patients in their system with intolerance to lipid-lowering therapies. They describe a group of patients with common features suggesting impaired fatty acid oxidation as a possible mechanism for an increased susceptibility to myopathic symptoms. Thirty of these patients were given ezetimibe mono-therapy and 18 experienced a recurrence of their myopathic symptoms. Many patients in this group could not tolerate statins, niacin or fibrates. The authors of this letter suggest further study of impaired fatty acid oxidation as a possible mechanism for statin-associated myotoxicity.

Statins plus Fibrates

There are no published clinical trials examining the effect of combination therapy with fibrates and statins on reducing CHD outcomes. There are however, several studies demonstrating an improvement in lipids with combined statins and fibrates (Wierzbicki AS, et al., Curr Med Res Opin 2003;19:155-168, Shammas NW, et al., Preventative Cardiol 2003;189-194.)

The Lipids in Diabetes Study (LDS) was designed to compare cerivastatin and fenofibrate for primary prevention in 5000 diabetic subjects followed for 5 years. Additionally, 1,250 of those subjects would have been on both ceriviastatin and fenofibrate. However, this trial was stopped due to the withdrawal of cerivastatin in August 2001 and as a result no outcomes were reported.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) is a large trial with plans to enroll 10,000 type 2 diabetics to determine the effects of aggressive versus standard glycemic control and blood pressure or blood lipid control on cardiovascular risk in diabetics in the presence of good glycemic control. The lipids portion of the trial will include 5,800 patients and will compare the cardiovascular risk of a statin plus a fibrate (fenofibrate plus simvastatin) versus a statin alone (simvastatin). Participants will be followed for 5.5-8.5 years with the study concluding in June 2009.

Despite the lack of health outcome data with combination therapy, NCEP ATP-III recognizes use of these combinations in high-risk patients with mixed dyslipidemias including those with “metabolic syndrome”.

Many experts believe that the lipid-lowering benefit of combining a statin with a fibrate outweighs the risk in patients with mixed dyslipidemia at high-risk for coronary events. However, risk for muscle toxicity with combination therapy is greater than that for either statins or fibrates alone and should therefore be used with caution (Shepherd 1995). Certain factors can also increase an individual’s risk for muscle toxicity with the combination including drug-drug interactions, advanced age, impaired renal function, female gender, alcoholism and hypothyroidism. The benefit to risk ratio in the case of combination therapy with statins and fibrates is difficult to determine since the benefit of the combination has not been fully elucidated.

In the summer of 2004, the VA Pharmacy Benefits Management Group and the Medical Advisory Panel created an evidence report http://www.vapbm.org/Safety%20Reports/87ry38statin-fibrate-Final.pdf evaluating the combination of statins and fibrates. Based upon this report and recommendations from NCEP ATP-III, the following should be considered when debating this combination:

A) Since there is a lack of health outcome evidence to support using the statin-fibrate combination but there is a known increased risk of serious muscle toxicity, the combination cannot be routinely recommended. However, although there are no data to support a “treatment” triglyceride level in which patients would obtain the most benefit, several authors have recommended the statin-fibrate combination be considered in a patient with mixed dyslipidemia (LDL-C >100 mg/dl, HDL-C<40 mg/dl and/or TG in excess of 500 mg/dl) at high-risk for CHD events. While patients with triglyceride

levels >500 mg/dL were not enrolled in outcome studies of fibrates (e.g., VA-HIT, 1999), the risk of pancreatitis may be increased in these patients. In addition, while NCEP ATP-III recognizes the combination in patients with elevated LDL-C and atherogenic dyslipidemia, they do state that objective data are not available to support their recommendation.

B) NCEP ATP-III and other experts also recommend the combination be considered **only** if the patient has normal liver, renal and thyroid function. Furthermore, the combination should be avoided in patients receiving known potent CYP 3A4 inhibiting medications (e.g. macrolides, azole antifungals, protease inhibitors, cyclosporine, etc.) or other medications known to alter statin metabolism.

C) Prior to adding a fibrate to statin therapy, consideration should be given to other available less toxic options such as n-3 polyunsaturated fatty acids (n3 PUFAs, a.k.a. fish oils) or niacin combined with statins. Triglyceride reduction is in the range of 20-30% with fish oils and 20-50% with niacin. In addition, niacin can increase HDL-C by 15-35%. However, like the statin-fibrate combination, there is a lack of health outcome evidence demonstrating a greater benefit of these combinations versus a statin alone (with the exception of niacin in one small study-HATS).

D) If the statin-fibrate combination is selected, the lowest effective statin dose should be used when combined with gemfibrozil or fenofibrate.

E) Providers choosing to prescribe statin-fibrate therapy, regardless of specific statin or fibrate used, should discuss the risks and benefits of such therapy with their patient. This discussion should be clearly documented in the patient's medical record. Patients should be educated to report any unexplained muscle pain, tenderness or weakness to their providers immediately.

F) When a statin-fibrate combination is used, NCEP ATP-III recommends a baseline creatine kinase (CK) level prior to initiation of combination therapy. Measurement of CK is repeated if the patient reports muscle symptoms resembling myopathy. NCEP ATP-III recommends discontinuing combination therapy (both statin and fibrate) if CK is greater than 10 times the upper limit of normal associated with muscle symptoms (tenderness, pain or weakness). Then, wait for symptoms to resolve completely and CK to normalize prior to restarting either drug and begin with a lower dose of the drug (s).

Statins plus Fish Oils

There are no clinical endpoint trials examining the combination of statins plus fish oils. In doses of 3-4 grams of fish oil per day, triglyceride reduction in the range of 20-30% can be achieved (Harris 1997, Farmer 2001). There does not appear to be additive toxicity with the combination of statins and fish oils. As a result, the combination can be considered in those patients with elevated LDL-C and triglycerides in $\geq$500 mg/dL and appears to be a safer alternative than statin plus fibrates.

Niacin plus Bile Acid Sequestrants (BAS or Resins)

Table F-2.3 Niacin + Bile Acid Sequestrants-Angiographic Evidence

Clinical Trial	CLAS 1987	FATS 1990
N	162-RCT	140-RCT
Population	Nonsmoking men 40-59 years s/p CABG	Men <62 years, known CAD
Intervention	Niacin 3-12 g + Colestipol 30 g vs. placebo	Niacin 4 g + Colestipol 30 g, Lovastatin 40 mg + Colestipol 30 g vs. placebo
Duration	2 years	2.5 years
Method Measuring Progression	Coronary angiography	Quantitative coronary arteriography
Progression/Regression	P<0.01 net regression in favor of combination vs. placebo	Progression was significantly less frequent in the combination groups vs. (Placebo 43%, N+C 25%, L+C 21%) and regression was also more frequent in the combination groups vs. placebo (p=0.005)
LDL/HDL/TG (change from baseline)	-43%/+37%/-27%	-32%/+43%/-29%
Outcomes (Death CHD or other, MI, Revascul-arization, stroke	Deterioration in overall coronary status was significantly less in combination group vs. placebo (p<0.001)	Clinical events were significantly more frequent in the placebo vs. N+C or L+C groups (10/52, 2/48, 3/46, respectively)

CLAS=cholesterol-lowering atherosclerosis study, FATS= Familial Atherosclerosis Treatment Study NR=not reported, NS=not significant, s/p CABG=status post coronary artery bypass graft, w/o=without

As summarized in Table F-2.3, there are two published atherosclerotic progression trials evaluating the benefit of niacin plus resins (Blankenhorn JAMA 1987, Brown NEJM 1990). In both trials, lipid levels were improved and progression was lower in the combination versus placebo groups. In addition, clinical endpoints were reduced in one of the trials.

The limitation of this combination may be the ability to tolerate the bothersome adverse effects of either product, especially at higher doses. This combination can be considered in patients unable to tolerate statins and requiring two drugs to achieve their lipid goals.

Niacin plus Fibrates

The combination of niacin and clofibrate was examined in the Stockholm Ischemic Heart Disease trial of 555 men and women (Carlson LA Acta Med Scand 1988). In this trial, consecutive patients surviving a MI were randomized to a control group (n=276) or treatment with clofibrate and niacin for a period of 5 years. All cause mortality was significantly lower in the combination versus control group (RRR 26%, ARR 7.9%, NNT 13, p<0.05) and death due to ischemic heart disease was also significantly reduced (RRR 36%, p<0.01) in the combination group. Investigators performed subgroup analysis and attributed the benefit to the triglyceride lowering ability of the combination (-20%).

NCEP ATP-III states that the combination has not been largely studied but may be an appealing combination for those with atherogenic dyslipidemia. Since the combination has not been evaluated in a large number of individuals, the adverse effects of the combination are unknown.

Statins or Fibrates plus Niacin and Bile Acid Sequestrants (BAS or Resins)

At this time, there are no large studies evaluating the effect of more than two lipid-lowering agents on clinical endpoints. There is at least one study evaluating the stepped care approach in modifying lipid levels. In a study by Pasternak, et al., (Ann Intern Med 1996), 91 patients with CAD were randomized to stepped care with pravastatin 40 mg, niacin 1.5-3 g, cholestyramine 4-24 g and gemfibrozil in an attempt to meet lipid goals.

Pravastatin 40 mg reduced LDL-C by 32%, triglycerides by 15% and increased HDL-C by 8%. Addition of 1.5 g and then of 3 g of niacin resulted in an additional reduction of LDL-C by 11 and 14%, respectively, TG by 10 and 13%, respectively and elevation in HDL-C of 8 and 6%, respectively. Addition of cholestyramine resulted in no change in LDL-C, an increase in TG of 46% and reduced HDL-C by 8%. Finally, the addition of gemfibrozil to pravastatin, niacin and cholestyramine restored the damage done to the lipid profile by the resin in that it reduced TG by 37% and increased HDL-C 12%.

In a more recent study (Whitney et al., 2005), 143 military retirees were randomized to receive gemfibrozil (600 mg/day), niacin (titrated to 3 grams/day) and cholestyramine (titrated to 16 grams/day) or their corresponding placebos for a period of 30 months. Patients had angiographic evidence of coronary heart disease, low HDL-C (mean 34 mg/dL), and were no older than 76 years of age and received aggressive dietary and lifestyle interventions. A 6-8 month dietary run-in phase was conducted in order to determine a participant's adherence to dietary intervention. A significantly greater number of patients in the active treatment group either did not have progression of their CAD or had improvement (70%) versus those in the placebo group (50%) ($p=0.03$) as assessed by comparing baseline and end of study angiography. Overall, coronary stenosis progressed 1.4% in the placebo group vs. being reduced by 0.8% in the treatment group. Clinical events (e.g. death, hospitalization for angina, CVA or TIA, or revascularization) occurred in 9 patients in the treatment vs. 19 patients in the placebo group ($p=0.04$). However, there were no statistical differences between groups when individual clinical events were evaluated. Although the group was considered to be at high-risk for CAD, there were no MIs during the 30-month study duration and only 1 death in the placebo group attributed to CAD.

APPENDIX G

ACRONYM LIST

ACS	Acute Coronary Syndrome
ACSM	American College of Sports Medicine
AHA	American Heart Association
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AMI	Acute Myocardial Infarction
ARR	Absolute Risk Reduction
ASCVD	Atherosclerotic Cardiovascular Disease
ATP	Adult Treatment Panel
BAS	Bile Acid Sequestrants
BMI	Body Mass Index
CABG	Coronary Artery Bypass
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CDC	Centers for Disease Control
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CPG	Clinical Practice Guideline
CRP	C- Reactive Protein
CV	Cardiovascular
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
EBCT	Electron Beam Computed Tomography
FRS	Framingham Risk Score
GI	Gastrointestinal
HbAlc	Glycosylated Hemoglobin A_1C
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HMG-CoA	Hydroxyl Methylglutaryl Coenzyme A
HsCRP	High Sensitive C- Reactive Protein
HTN	Hypertension
IDL	Intermediate-Density-Lipoprotein
IOM	Institute of Medicine
LDL-C	Low Density Lipoprotein Cholesterol
LFT	Liver Function Tests
MET	Metabolic Equivalent
MI	Myocardial Infarction
MNT	Medical Nutrition Therapy
NNT	Number Needed To Treat
PUD	Peptic Ulcer Disease
RCT	Randomized Control Trial

RRR	Relative Risk Reduction
RF	Risk Factor
SCr	Serum Creatine
TC	Total Cholesterol
TG	Triglycerides
TLC	Therapeutic Lifestyle Change
TSH	Thyroid - Stimulating Hormone
ULN	Upper Limits Of Normal
V-LDL	Very High, Low Density Lipoprotein

APPENDIX H

Participant List

Janetta R. Blackmore M.S., R.D., L.D. Captain
Senior Clinical Dietitian, Nutrition Care Division
William Beaumont Army Medical Center
5005 N. Piedras St
El Paso, TX 79920
Phone: (915) 569-1544 DSN 979
Fax: (915) 569-1198
Email: janetta.blackmore@amedd.army.mil

David R. Bretzke, PharmD
Clinical Pharmacy Analyst
DoD Pharmacoeconomic Center
2421 Dickman Rd, St 81
Ft. Sam Houston, TX 78234-5081
Phone: (210)-295-1271
Fax: (210)-295-2789
Email: David.Bretzke@amedd.army.mil

Bruening Wendy PhD
Research Analyst
ECRI
5200 Butler Pike
Plymouth Meeting
PA 19462
Phone: (610)-825-6000
Email: wbruening@ECRI.org

Vincent F. Carr, Col, USAF, MC, CFS
DO, MSA, FACC
Chief Consultant for Internal Medicine Services
AFMSA/SGOC
Bolling AFB
110 Luke Ave, Room 405
Washington, DC 20032
Phone: (202) 767-4060
Fax: (202) 404-4043
Email: vincent.carr@pentagon.af.mil

Carla Cassidy RN, MSN, NP
Clinical Quality Program Specialist
Department of Veterans Affairs
810 Vermont Avenue
Washington, DC 20420
Phone: (202)-273-6954
Fax: (202)-273-9030
Email: carla.cassidy@hq.med.va.gov

Martha D'Erasmo MPH
Independent Consultant
4550 North Park Ave 505
Chevy Chase, MD 20815
Phone: (301) 654-3152
Email: Marty@hqiinc.com

John R. Downs, MD
Section Chief, General Internal Medicine
Research /Verdict
Audie L. Murphy Memorial Veterans Hospital Division
7400 Merton Minter Blvd
San Antonio TX 78229
Phone: (210)-617-5238
Fax: (210)-567-4423
Email:rdowns@verdict.uthscsa.edu

Rosalie Fishman RN, MSN, CPHQ
President
HQI Inc.
2300 Shady Grove Rd. Suit 350
Rockville, MD 20850
Phone: (301) 351-9959
Fax: (301) 330-0740
Email Rosalie@hqiinc.com

Vincent P. Fonseca LtCol, MD, MPH
Physician/Epidemiologist
AFMSA/SGOZ
2509 Kennedy Circle
Brooks AFB , TX 78235-5116
Phone: (210) 536-6661
Fax: (210) 536-6290
Email: Vincent.Fonseca@brooks.af.mil

Connie Foster RN, MSN, APRN
Advanced Practice RN
Colmery O'Neil VAMC
2200 SW Gage Blvd.
Topeka, KS 66622
Phone: (785) 350-3111 ext. 2824
Fax: (785) 350-4486
Email: connie.foster@med.va.gov

Carl A. Gibson, LTC, MD
Asst. Chief Endocrine Service
Medical Director Diabetes Care Center
Madigan Army Medical Center
Endocrine Service/Dept. of Medicine
Tacoma, WA. 98431-1100
Phone: (253) 968-0438
Fax: (253) 968-0448
Email: carl.gibson@nw.amedd.army.mil

Chester B. Good, MD, MPH
Associate Professor of Medicine
Pittsburgh VAMC
University Drive C
Pittsburgh, PA 15240
Phone: (412) 688-6477
Fax: (412) 688-6527
Email: Chester.good@med.va.gov

Teresa M. Hoos, MS, RD
Clinical Dietician: Nutrition & Food Service
Portland VAMC
PO Box 1034
Portland, OR 97207-1034
Phone: (503) 220-8262 Ext 55502
Fax: (503) 721-1050
Email: Teresa.Hoos@med.va.gov

Zoë C. Hawes, Capt, RN, MSN, ACNP USAF, NC
Nurse Practitioner, Cardiology/Internal Medicine
Malcolm Grow Medical Center
89 MDOS/SGOMC
1050 W. Perimeter Rd
Andrews AFB, MD 20762
Phone: (240) 857 -3293
Fax: (240)-857-4535
Email: zoe.Hawes@andrews.af.mil

Margaret Hawthorne LTC
Chief, Evidence-Based Practice
USAMEDCOM
2050 Worth Road, Suite 26
Fort Sam Houston, TX 78234-6026
Phone: (210) 221-8297
Fax: (210) 221-8478
Email: Margaret.Hawthorne@amedd.army.mil

Robert L. Jesse, MD, PhD
National Program Director, Cardiology, VHA
VACO & VAMC
1201 Broad Rock Road; Cardiology (111J)
Richmond, VA 23249
Phone: (804)-675-5419
Fax: (804)-675-5420
Email: Robert.jesse@med.va.gov

Catherine L. Kelley, Pharm.D
Clinical Pharmacy Specialist
Veterans Affairs: PBM-SHG
First Ave, 1 block north of Cermak Road
Bldg. 37, Rm. 139
Hines, Illinois 60141
Phone: (708)-786-7862
Fax: (708)-786-7891
Email: cathykelley@cox.net

Angela V. Klar, MSN, RN, ANP-CS
Clinical Practice Guideline Coordinator
US Army MEDCOM Quality Management
2050 Worth Road, Bldg 2792, Suite 26
FT. Sam Houston, TX 78234
Phone: (210)-221-8740(DSN 471)
Fax: (210)-221-8478
Email: Angela.Klar@cen.amedd.army.mil

Acquanetta Lancaster, MS, NP, CDE
Nurse Practitioner
Baltimore VAMC
10 North Green Street, 2C140
Baltimore, MD 21201
Phone: (410) 605-7000 Ext 6409
Fax: (410) 605-7930]
Email: acquanetta.lancaster@med.va.gov

Patrick G. O'Malley MD, MPH, LTC
Chief, General Internal Medicine WRAMC
Walter Reed Army Medical Center
6900 Georgia Ave
Washington DC 20307-5001
Phone: (202)-782-5638
Fax: (202)-782-4845
Email: patrick.omalley@na.amedd.army.mil

Leonard Pogach, MD, MRA
National Program Director, Diabetes, VHA
VA New Jersey Health Care System
385 Tremont Avenue
East Orange, New Jersey 07018
Phone: (973) 676-1000 ext. 1693
Fax: (973) 305-7111
Email: Leonard.Pogach@med.va.gov

Oded Susskind, MPH
Medical Educational Consultant
Brookline MA 02446
Phone: (617) 232-3558
Fax: (775) 370-3470
Email: oded@tiac.net

Charlie Turkelson PhD
Chief Research Analyst
ECRI
5200 Butler Pike
Plymouth Meeting PA 19462
Phone: (610) 825-6000
Email: CTurkels@ecri.org

Zingeser Pamela
Independent Consultant
7612 Epsilon Dr.
Rockville, MD 20855
Email: pzingeser@aol.com

APPENDIX I

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