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Approach to Cholesterol Management: 2001 National Cholesterol Guidelines

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In May 2001, the National Cholesterol Education Program (NCEP) released the third report of the Adult Treatment Panel (ATP III) for the management of high blood cholesterol in the United States (1). These clinical guidelines were directed to health care professionals. ATP III represents the third installment of ATP reports going back to 1988. A brief review of the major features of these reports may be useful to provide perspective to the evidence base for management of high blood cholesterol among adults.

ATP I was published in 1988 (2). It provided a guideline for management of patients in whom cholesterol levels were definitely elevated. Its goal was the long-term, clinical prevention of coronary heart disease (CHD) in patients with hypercholesterolemia. Treatment of hypercholesterolemia was considered to be the clinical extension of the public health approach to preventing CHD. The primary evidence base for ATP I came from results of the Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT), which was reported in 1984 (3,4). This trial showed that reduction of low density lipoproteins (LDL) with a bile acid sequestrant, cholestyramine, will reduce the incidence of major coronary events in patients with primary hypercholesterolemia. This "proof of concept" was considered to be sufficient for initiating both NCEP and ATP I. However, in ATP I, the use of drug therapy was downplayed. Recommendations instead focused on use of dietary therapy, specifically, reduced intakes of saturated fats and cholesterol, to lower blood cholesterol levels.

Five years later, ATP II was released (5). Between ATP I and ATP II, a meta-analysis of secondary prevention trials of cholesterol-lowering therapy had been performed (6). This analysis, which combined the data from a series of earlier trials, demonstrated that cholesterol lowering significantly reduces the risk for major coronary events in patients with established CHD. In addition, HMG CoA inhibitors (statins), which are powerful cholesterol-lowering drugs, became widely available for use in clinical practice (7). Based on the meta-analysis (6) and the availability of statin drugs, ATP II added an emphasis on secondary prevention (prevention of CHD in patients with established CHD), but continued to support long-term, primary prevention in hypercholesterolemic persons.

The third report (ATP III) (1) ratified the prior programs of long-term prevention in persons with elevated cholesterol levels and intensive secondary prevention. But it added a new emphasis, namely, more intensive primary prevention in high-risk persons. Thus ATP III extended primary prevention to at least some persons who have only mildly elevated serum cholesterol. The ATP III panel had the benefit of knowing the results of five major clinical trials of statin therapy. Three were secondary prevention trials (8,9,10), and two were for primary prevention (11,12). All of these trials demonstrated a marked reduction of major coronary events accompanying intensive cholesterol-lowering therapy. Overall, ATP III greatly expands the use of intensive cholesterol lowering in primary prevention to prevent the development of new-onset CHD. This paper will review the major features of ATP III.

Lipoprotein Targets in Cholesterol Management

Low density lipoprotein (LDL) as primary target of therapy. Several lines of evidence indicate that LDL is the major atherogenic lipoprotein (1,2,5). This evidence is derived from animal studies, prospective epidemiological studies, genetic forms of hypercholesterolemia, and controlled clinicali trials. LDL particles consist of two major components, namely, a surface coat containing apolipoprotein B-100 (apo B) and a core containing mainly cholesterol esters. A simple clinical measure is the cholesterol content of the LDL fraction (LDL cholesterol). Because of the association of LDL cholesterol with CHD risk and ease of measurement, NCEP guidelines identified elevated serum LDL cholesterol as the primary target of lipid-lowering therapy for clinical practice.

Limitations of LDL cholesterol in general. Some investigators however question whether LDL cholesterol is the *ideal* risk identifier and/or target of therapy. There are two arguments in favor of other LDL parameters: (a) LDL particles can be heterogeneous in size, and some LDL particles may be more atherogenic than others; and (b) the LDL particle number may be a better indicator of the atherogenic potential of the LDL fraction than is LDL cholesterol concentration. Each of these arguments and alternative approaches to the clinical evaluation of LDL can be considered.

Regarding the first, one proposed approach to LDL assessment is to measure LDL particle size and to identify patients who have an excess of small LDL particles. Several studies indicate that high levels of small LDL particles are accompanied by increased risk for CHD (13-19). When an excess of small LDL particles is found, the LDL-cholesterol level probably *underestimates* the atherogenic potential of the LDL fraction. There are two reasons for this underestimation. First, the LDL-cholesterol level fails to reflect the total number of LDL particles in the circulation; and second, smaller LDL particles may be more atherogenic than larger LDL particles (13-20).

A direct estimate of the number of LDL particles is made available by measurement of LDL-apolipoprotein B (apo B) levels. Since each LDL particle contains one apo B molecule per particle, the LDL-apo B concentration gives a precise measure of the number of LDL particles in circulation. Unfortunately, it is difficult to routinely measure LDL-apo B levels, so alternative approaches have been sought. For example, it has been postulated that the number of apo B particles in the LDL fraction can be accurately estimated by nuclear magnetic resonance (NMR) (21-23). If the accuracy of this method can indeed be confirmed by independent means, estimation of LDL particle number by NMR should represent a step forward in the determination of the atherogenecity of the LDL fraction.

Limitations of LDL cholesterol in patients with hypertriglyceridemia. The greatest discrepancies among LDL-cholesterol levels, LDL particle number, and LDL particle size occur in patients who have elevated serum triglycerides. For this reason, it may be acceptable to focus on alternatives to measuring LDL cholesterol in clinical practice primarily on those patients in whom triglycerides are elevated. Moreover, beyond the LDL fraction, many patients with elevated triglycerides appear to have an excess of atherogenic remnant lipoproteins. Methods are being developed for measuring these remnants (24-27). To date these methods are not widely available for routine

practice. As an alternative, several investigators have proposed that total apo B is the preferred indicator of the total atherogenic potential contained in combined LDL plus VLDL. The essential concept is that most apo B-containing lipoproteins are atherogenic; and since both LDL and VLDL contain apo B, the total apo B level will encompass all of these lipoproteins. Several reports indeed suggest that the total apo B level is a better "predictor" of CHD than is the LDL-cholesterol level (28-39). Such in fact has not been proven by large prospective studies; nonetheless, the concept of total apo B as an indicator of all atherogenic lipoproteins combined with suggestive preliminary data make for an attractive hypothesis.

One of the limitations at present for measurement of total apo B in clinical practice is a lack of wide availability in routine clinical chemistry. The method could be more widely employed, but also, routine assessment of total apo B would confer costs above that of usual lipoprotein lipid analysis. These facts led the NCEP to identify a parameter in routine lipoprotein analysis that can serve as a "surrogate" for total apo B (1). This is non-HDL cholesterol, which includes cholesterol in LDL and VLDL. This measure is obtained by subtracting HDL cholesterol from total cholesterol. In patients with elevated triglycerides, the non-HDL cholesterol includes cholesterol in atherogenic remnant lipoproteins as well as LDL cholesterol. Furthermore, non-HDL-cholestrerol concentrations are highly correlated with total apo B levels (40-41). Recent investigators and/or research reports have added support for use of non-HDL cholesterol as an alternative target for lipid-lowering therapy (42-46). To the present, few data are available to indicate that total apo B is a better predictor of major coronary events than is non-HDL cholestetrol. Thus, for the reasons of availability and costs, the NCEP ATP III report recommends that non-HDL cholesterol be a secondary target of cholesterol-lowering therapy in patients with elevated triglyceride (triglyceride $\geq$ 200 mg/dL).

Although many researchers have emphasized the "predictive power" of one lipoprotein fraction over another (e.g. LDL cholesterol vs. small LDL vs. non-HDL cholesterol vs. total apo B), the primary attention of ATP III is on lipoprotein goals for therapy, and not a prediction. Selection of patients for therapy depends on many factors, beyond the lipoprotein fraction. For this reason, the essential questions to ask are: (a) which lipoprotein fraction should be the target of therapy? and (b) what should be the goal of therapy for this fraction? ATP III maintains that LDL cholesterol should remain the *primary* target of lipid-lowering therapy. However, for patients with elevated triglycerides, the recommendation is for non-HDL cholesterol to be a secondary target of therapy. Should accurate apo B measurement be available, total apo B could be an alternate secondary target of therapy—instead of non-HDL cholesterol. The specific goals of therapy for these categories will be described in more detail later in this article. Further, the implications for choice of therapy for each of these targets will be discussed later as well.

Atherogenic dyslipidemia as alternate target of therapy. One way to simplify the lipoprotein abnormalities for clinical practice is to divide them into (a) elevated LDL cholesterol, and (b) atherogenic dyslipidemia. The latter includes:

- Elevated triglyceride ($\geq$ 150 mg/dL)
- Small, dense LDL (LDL pattern B)
- Non HDL cholesterol ($\geq$ 130 mg/dL)
- Low HDL cholesterol (< 40 mg/dL in men; < 50 mg/dL in women)

These four abnormalities frequently, but not always, go together. They are commonly present in patients with the *metabolic syndrome* (discussed below). Each abnormality of pattern probably contributes independently to atherogenesis; and it represents a valid second target for lipid-lowering therapy (after LDL cholesterol) (1). ATP III puts priority on non-HDL cholesterol the first target for therapy in atherogenic dyslipidemia, but a low HDL cholesterol and small LDL particles can be considered as additional targets of treatment.

Metabolic Syndrome

ATP III recognized the *metabolic* syndrome as a major contributor to CHD risk beyond elevated serum LDL (1). This syndrome is complex disorder characterized by the presence of multiple borderline risk factors in one individual (Table 1). When these borderline risk factors combine in one person their risk adds up to that of at least a major risk factor. The quantitative contribution of each borderline risk factor is uncertain, but growing evidence suggests that each of the abnormalities shown in Table 1 contributes independently to risk. In some patients, borderline risk factors become categorically elevated, i.e., high-normal blood pressure $\rightarrow$ categorical hypertension and/or impaired fasting glucose $\rightarrow$ type 2 diabetes; when this occurs, risk is increased even more. ATP III developed the diagnostic criteria for the metabolic syndrome shown in Table 2. When a patient has three of five of the factors shown in Table 2, a clinical diagnosis of the metabolic syndrome can be made. ATP III placed increased emphasis on the appropriate management of the metabolic syndrome in patients who are undergoing clinical lipid management.

Table 1
Risk Factors of the Metabolic Syndrome

- Atherogenic dyslipidemia
  - Elevated triglycerides (≥ 150 mg/dL)
  - Small LDL particles (LDL pattern B)
  - Elevated non-HDL cholesterol (≥ 130 mg/dL)
  - Low HDL cholesterol (< 40 mg/dL in men; < 50 mg/dL in women)
- High-normal blood pressure (130-139/15-89 mmHg)
- Insulin resistance
- ± impaired fasting glucose (110-126 mg/dL)
- Proinflammatory*
- Prothrombotic state†

*Indicated by one or more of elevated hs-CRP (> 3.0 mg/L), homocysteine (≥ 15 micromol/L) or lipoprotein a [Lp(a)] (≥ 30 mg/dL), and fibrogen. Elevated hs-CRP appears tobe the most reliable indicator of proinflammatory state. Lp(a) can be elevated on a genetic basis.

† Indicated by elevated PAI-1, elevated fibroinogen, or clotting factor VIIc.

Table 2

Clinical Diagnosis of the Metabolic Syndrome – Any 3 of the Following:

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

** Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients 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.

. A recent report examined the prevalence of the metabolic syndrome among US adults (47). This report reviewed a random sample of 8814 men and women of the Third National Health and Nutrition Examination Survey (NHANES III) covering the years 1988-1994. In all adults over age 20, the overall prevalence of the metabolic syndrome was about 23%. The prevalence rises progressively throughout life reaching a level over 40% by age 60. African American women and Mexican American women have a particularly high frequency, undoubtedly related to a high prevalence of obesity. All told, approximately 47 million US residents have the metabolic syndrome.

Current Concepts of Development of CHD

ATP III attempted to integrate its treatment regimen into current concepts of development of CHD. Views on the pathogenesis of CHD have evolved rapidly over the past decade (48). The current paradigm of causation of CHD can be outlined briefly. Three key steps are identified:

(a) development of stable atherosclerotic plaques
(b) transformation of stable plaques into unstable plaques
(c) plaque rupture leading to acute coronary syndromes

The first step, development of stable plaques, is a long-term process. Atherosclerosis in the coronary arteries develops slowly but relentlessly. Elevated atherogenic lipoproteins are the initiating and driving force in plaque build-up. Moreover, in the presence of elevated atherogenic lipoproteins, other risk factors--cigarette smoking, hypertension, low HDL, and diabetes--accelerate atherogenesis. Even so, in populations that have very low levels of serum cholesterol, CHD rates are relatively low even when other risk factors are common (49). A major goal of public health intervention is to slow the development of atherosclerosis, which ultimately will reduce the incidence of CHD in the general population.

In some persons, coronary atherosclerosis advances to the point that it impairs blood flow to the myocardium. The result will be stable angina pectoris. In a portion of these patients, coronary artery intervention (angioplasty or by-pass) may be required to reduce angina symptoms. Delaying the development of atherosclerosis certainly would reduce the prevalence of angina pectoris in our society.

The second stage of atherogenesis is the transformation of stable plaques into unstable plaques. The latter consist of localized regions of stable plaques that are prone to rupture. The mechanisms responsible for formation of unstable plaques are not fully understood, but they seemingly involve enhanced inflammatory changes in certain areas of the plaque (50). Stable plaques result from a process of very low grade chronic inflammation. Unstable plaques contain regions of more active inflammation. Atherogenic lipoproteins are proinflammatory agents, and apparently contribute to development of unstable plaques. It is clear that a heavy burden of stable plaque is commonly accompanied by regions of unstable plaque. Results of recent clinical trials

are consistent with the view that that LDL-lowering therapy reduces the prevalence of unstable plaques even when the bulk of stable plaques is not decreased (51).

The third step in development of CHD is plaque rupture leading to acute coronary syndromes (unstable angina and myocardial infarction). Sometimes areas of unstable plaques become so fragile that plaques rupture or rode. When this occurs, a thrombogenic surface is exposed to the blood stream and coronary thrombosis occurs. The resulting thrombosis is the basis of acute coronary syndromes. The rationale for chronic aspirin therapy is to reduce the size of thrombosis that occurs at times of plaque rupture; the benefit of aspirin therapy will be a decrease in severity of acute coronary syndrome.

A better understanding of the later steps of plaque development leads to a more rational approach to prevention. When persons have advanced coronary atherosclerosis, the goal of intervention shifts to short-term prevention of plaque rupture and thrombosis, hence acute coronary syndromes. Clinical trials reveal that LDL-lowering therapy will reduce the frequency of acute coronary syndromes (8-12). The same is true for aspirin therapy. Thus, several lines of evidence indicate that aggressive LDL lowering combined with aspirin therapy will stabilize unstable plaques and reduce the incidence of acute coronary syndromes in patients with advanced atherosclerotic disease.

Modalities of Risk-Reduction Therapy

ATP III recognizes two major approaches to therapy: (a) therapeutic lifestyle changes (TLC), and (b) drug therapy. For both approaches, the primary goal of therapy is to reduce LDL levels; but in addition, both lifestyle changes and drugs can be prescribed to lower risk for CHD in other ways. Lifestyle recommendations for LDL lowering are two: (a) reduced intakes of saturated fats and cholesterol, and (b) use of LDL-lowering adjuncts [plant stanol/sterols (2g/day) and increased viscous fiber (10-25 g/d)]. These two dietary changes together will lower LDL-cholesterol levels up to 25% (1). Two other lifestyle therapies are weight reduction and increased physical activity. Weight reduction in overweight/obese persons will enhance the lowering of LDL that is brought about by other dietary changes. Weight reduction and increased physical activity furthermore will induce other metabolic alterations that lower the risk for CHD.

Four categories of drugs are available for lipid management (Table 3). The primary drugs used for LDL lowering are statins and bile acid sequestrants. Statins are first-line therapy for most patients. Bile acid sequestrants are less powerful LDL-lowering drugs than statins, but are useful to enhance LDL lowering when combined with statin therapy. Two other drug categories--nicotinic acid and fibric acids--can mildly reduce LDL levels, but they have greater effects on other lipoproteins (VLDL and HDL). These latter drugs may incrementally decrease risk when combined with LDL-lowering drugs.

Table 3. Drugs for Lipid Management

Drug Class, Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications	Clinical Trial Results
Bile acid Sequestrants*	LDL-C ↓15-30% HDL-C ↑3-5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: dysbeta-lipoproteinemia TG >400 mg/dL Relative: TG >200 mg/dL	Reduced major coronary events and CHD deaths
HMG CoA reductase inhibitors (statins)†	LDL-C ↓18-55% HDL-C ↑ 5-15% TG ↓ 7-30%	Myopathy Increased liver enzymes	Absolute: Active or chronic liver disease Relative: Concomitant use of certain drugs‡	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Nicotinic acid¥	LDL-C ↓ 5-25% HDL-C ↑15-35% TG ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: Chronic liver disease Severe gout Relative: Diabetes Hyperuricemia Peptic ulcer disease	Reduced major coronary events, and possibly, total mortality
Fibric acids§	LDL-C ↓ 5-20% (may be increased in patients with high TG) HDL-C ↑10-20% TG ↓10-50%	Dyspepsia Gallstones Myopathy	Absolute: Severe renal disease Severe hepatic disease	Reduced major coronary events. Increased non-CHD mortality (in 2/5 clinical trials)

* Cholestyramine (4-16 g), colestipol (5-20 g), colesevelam (2.6-3.8 g)

† Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg); standard starting doses of statins are lovastatin (40 mg), pravastatin (40 mg), simvastatin (20 mg), fluvastatin (40 mg), and atorvastatin (10 mg).

‡ Cyclosporine, gemfibrozil (or niacin), macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors

¥ Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g).

§ Gemfibrozil (600 mg BID), fenofibrate (200 mg), clofibrate (1000 mg BID)

Risk Assessment: Key to Patient Selection for Therapy

With the development of effective therapies to reduce risk for CHD, a critical question is: how to select individuals for clinical intervention? The selection of patients for clinical therapy is ideally based on an assessment of the risk for future CHD events. This selection is made on the basis of risk determinants called *risk factors*. Three categories of risk factors are identified by ATP III: (a) major, independent risk factors, (b) underlying risk factors, and (c) emerging risk factors.

Major risk factors. These factors include cigarette smoking, hypertension, elevated LDL, low HDL, hyperglycemia, family history of premature CHD, and aging. The major risk factors are defined categorically in Table 4; this table also shows which risk factors are counted in defining a patient's risk category. Each of them, except for aging, has a direct causative role in atherogenesis. The relationship between aging and CHD risk can be explained by the fact that the burden of atherosclerosis increases with age. The greater the coronary plaque burden, the greater will be the incidence of acute coronary syndromes. The major risk factors provide the foundation for the risk-assessment algorithm developed by the Framingham Heart Study (52).

Table 4

Categorical Classification of Major Risk Factors

Cigarette smoking (any smoking in past year)
Hypertension (BP $\geq$ 140/90 mmHg or on antihypertensive medication)
[High LDL Cholesterol $\geq$ 160 mg/dL]*
Low HDL cholesterol (< 40 mg/dL)†
[High plasma glucose $\geq$ 126 mg/dL]‡
Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first degree relative < 65 years)
Age (men $\geq$ years; women $\geq$ 55 years)

* High LDL cholesterol is not included in the "risk factor" count in ATP III because it is the target of therapy based on other risk factors.

† HDL cholesterol $\geq$ 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

‡ High plasma glucose is not included in the "risk factor" count in ATP III because its presence identifies a patient as having diabetes, which is counted as a CHD risk equivalent (see Table 5)

Underlying risk factors. These factors are overweight/obesity, physical inactivity, and an atherogenic diet. By and large they raise the risk for CHD indirectly by enhancing other risk factors. The underlying risk factors are not used in quantitative (Framingham) risk assessment; rather they are direct targets of medical intervention. Weight loss therapy for the overweight/obese patient is described by the National Institutes of Health Obesity Education Initiative (OEI) (53). The U.S. Surgeon General has issued a report on clinical approaches to healthy physical activity (54). Recommendations for weight loss and physical activity are summarized in ATP III (1).

Emerging risk factors. These are factors that have been found to be associated with CHD but do not have the robust relationship to CHD that is present for the major, independent risk factors. To date these factors have not been incorporated into quantitative risk assessment algorithm. Expert opinion differs as to their quantitative and independent contribution to CHD risk. Their use therefore in patient selection for risk-reduction therapies depends on clinical judgment rather than on formalized risk-assessment equations.

Many of the emerging risk factors are biomarkers. Examples include lipid markers [elevated triglycerides, lipoprotein subfractions, apolipoproteins Lp(a)], homocysteine, prothrombotic factors (fibrinogen and PAI-1), proinflammatory factors (C-reactive protein), and genotypes. Another category of emerging risk factors falls under the heading of subclinical atherosclerosis. The presence of advanced subclinical atherosclerosis (plaque burden) is a predictor of major coronary events. Subclinical atherosclerosis can be detected in several ways: ankle/brachial blood pressure index (ABI), coronary calcium, and carotid intimal medial thickening (55). Integrating subclinical atherosclerosis into "global" risk assessment is a challenge for future research.

Framingham risk assessment. ATP III adopted Framingham risk scoring to estimate 10-year risk for CHD. The end point for this assessment is risk for *hard* CHD, which includes myocardial infarction and coronary death. The parameters included in Framingham scoring are the total cholesterol, HDL cholesterol, blood pressure, smoking status, and age. In ATP III separate algorithms are made available for men and women (1).

Identification of Risk Categories

ATP III identifies three major categories of risk: (a) high-risk, (b) intermediate risk, and (c) lower risk. A combination of clinical status, the number of major risk factors, and the estimated 10-year risk determine risk for hard CHD (determined by Framingham risk scoring). Each category of patients will be described briefly.

High-risk Patients. An expanded category for high-risk status requiring intensive LDL-lowering therapy is one of the major new features of ATP III. The classification of patients at high risk is shown in Table 5. Two high-risk categories are (a) established CHD and (b) *CHD risk equivalents*. The former includes patients with a history of acute coronary syndrome (myocardial infarction and unstable angina), stable angina, coronary procedures (angioplasty and by-pass), and myocardial ischemia documented by exercise testing or imaging. A positive exercise electrocardiogram in a middle-aged man with multiple risk factors conveys a risk for major coronary events equal to that of patients with established CHD.

Table 5
High-Risk Patients

- Established coronary heart disease (CHD)
  - History of acute coronary syndromes (unstable angina or myocardial infarction)
  - History of angina pectoris
  - History of coronary artery procedures (coronary angioplasty or by-pass surgery)
  - Demonstration of myocardial ischemia

- CHD risk equivalents
  - Non-coronary forms of clinical atherosclerotic disease
    - Peripheral arterial disease
    - Abdominal aortic aneurysm
    - Carotid artery disease (carotid transient cerebral attack, carotid stroke, > 50% obstruction of carotid artery)
  - Diabetes mellitus
  - Multiple risk factors
    - 10-year risk for CHD > 20% (Framingham scoring)
    - 2+ risk factors + advanced subclinical coronary atherosclerosis (e.g. coronary calcium > 75th percentile for age in men)

The category of *CHD risk equivalent* denotes an absolute risk for major coronary events as high as that of patients with established CHD. Introduction of the concept of CHD risk equivalent is a substantial addition to ATP III that will greatly expand the number of patients who are candidates for intensive LDL-lowering therapy. One group of patients in this category are those with non-coronary clinical atherosclerotic disease. Included are patients with peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks of carotid origin, carotid strokes, and > 50% stenosis of a carotid artery). A second group of patients with CHD risk equivalent include those with clinical diabetes. ATP III separated diabetes out of the risk factor category and put it into CHD risk equivalent category because of a relatively high 10-year risk for new CHD events and because of a poor prognosis of patients with diabetes at time of acute coronary syndromes and/or following myocardial infarction. The last group high-risk patients are those who are currently asymptomatic but who have a 10-year risk for CHD of > 20%. These patients can be identified in either of two ways. First, if a patient with multiple (2+) risk factors has a 10-year risk for CHD of > 20%, this patient is designated as having a CHD risk equivalent. Alternatively, if a patient with 2+ risk factors has advanced subclinical atherosclerosis (e.g. coronary calcium score > 75th

percentile for age in men), he/she likewise can be said to have a CHD risk equivalent (56).

Intermediate-risk patients. These patients have 2 or more major risk factors, but a 10-year risk of ≤ 20% by Framingham scoring. Intermediate-risk patients are divided into *moderately high-risk patients* and *moderate-risk patients.* Three types of patients can be identified as being at *moderately high risk* by any of the following characteristics in addition to 2+ risk factors:

- 10-year risk for CHD of 10-20% (Framingham scoring)
- Metabolic syndrome
- High sensitivity (hs) C-reactive protein (CRP) ≥ 3.0 mg/L

If a person with 2+ risk factors *but* without the metabolic syndrome or elevated hs-CRP has a 10-year risk for CHD < 10%, this person is said to be at *moderate risk.* He/she is not considered to be a high, short-term risk, but may still be at higher long-term risk for CHD.

Lower risk persons. Persons at lower risk have zero or one major risk factor. They are not likely to develop CHD over the next 10 years, but if they have an elevated LDL cholesterol (≥ 160 mg/dL), they can still be at higher lifetime risk for CHD.

Goals of Therapy for LDL Cholesterol

LDL cholesterol is the primary target therapy for therapy of lipoproteins. The goals of therapy for each risk category are shown in Table 6. The LDL goals for the three risk categories—high, intermediate, and lower—are < 100 mg/dL, < 130 mg/dL, and < 160 mg/dL, respectively.

Table 6
LDL Cholesterol Goals in Each Risk Category

Risk Category	LDL-Cholesterol Goal
High risk*	< 100 mg/dL
Intermediate risk (2+ risk factors)	< 130 mg/dL
Lower risk (0-1 risk factor)	< 160 mg/dL

* See Table 4 for patients included in the high-risk category

Therapeutic Options for LDL-Lowering Therapy

High-risk patients. The goal for LDL cholesterol for high-risk patients is < 100 mg/dL. When baseline LDL-cholesterol is ≥ 130 mg/dL, an LDL-lowering drug can be started simultaneously with therapeutic lifestyle changes. The usual first drug is a statin. If baseline (or on treatment) LDL cholesterol level is the range of 100 to 129 mg/dL,

several options for LDL-lowering therapy are available: (a) intensify reduction of saturated fatty acids and cholesterol, (b) add LDL-lowering dietary adjuncts (plant stanols/sterols) or increased viscous fiber), (c) start an LDL-lowering drug (or increase drug dosage), and (d) if necessary, add a second LDL-lowering drug (e.g. bile acid sequestrant). At present, further LDL-lowering therapy is not recommended when LDL cholesterol levels are < 100 mg/dL. Patients with both CHD and CHD risk equivalents are treated similarly.

Intermediate-risk patients. Patients in this risk category have multiple (2+) risk factors. The goal for LDL cholesterol is < 130 mg/dL. When LDL-cholesterol levels are ≥130 mg/dL, therapeutic lifestyle changes are required for in all patients. An LDL-lowering drug can be added for any patient when the LDL-cholesterol level is ≥160 mg/dL on dietary therapy. In addition, consideration can be given to adding an LDL-lowering drugs when the LDL cholesterol level is 130-159 mg/dL on dietary therapy when a patient is at *moderately high risk*, i.e., under the following circumstances:

- 10-year risk for CHD of 10-20% (Framingham risk scoring)
- Metabolic syndrome is present
- HS-CRP is ≥ 3.0 mg/L

Among the latter three circumstances, ATP III specifically identifies the first for routine management. The latter two are recognized as clinical options based on clinical judgment.

Lower risk patients. These patients have 0-1 risk factor. Their LDL-cholesterol goal is <160 mg/dL. When LDL cholesterol is ≥ 160 mg/dL, therapeutic lifestyle changes are indicated in all patients. When baseline LDL-cholesterol levels are persistently ≥ 190 mg/dL, an LDL-cholesterol lowering drug generally is indicated. When the baseline (or on-treatment) LDL-cholesterol level is in the range of 160-189 mg/dL, initiation (or intensification) of drug therapy is optimal. The goal is to reduce lifetime risk for CHD, and if the patient is deemed to be at higher lifetime risk, use of an LDL-lowering drug is warranted.

Therapeutic Options for Metabolic Syndrome

The primary approach to management of the metabolic syndrome includes treatment of the underlying causes (i.e., obesity and physical inactivity); in addition, it is often necessary to separately or treat the metabolic risk factors as needed to achieve the goal for each. ATP III considers the metabolic syndrome to be a secondary target of therapy after elevated LDL cholesterol in patients undergoing lipid management. Considerations will be given to management of each of these risk factors.

Underlying causes. The two major acquired causes of the metabolic syndrome are obesity and physical inactivity. Patients with abdominal obesity are particularly likely to develop this syndrome. Both obesity and physical activity inactivity appear to be independent risk factors for CHD (53,57,58). For these two causes, the essential

approach is weight loss and increased physical activity. Unless intervention is made on these underlying causes, it is unlikely that all of the risk factors associated with this syndrome can be normalized. Genetic factors also contribute to the syndrome. Some genetic factors apparently have generalized actions that predispose to the whole syndrome. Others seemingly affect only one or another of the risk factors. Currently there is interest in the development of drugs to modify the whole syndrome. Although the appropriate target for such therapy is not known, one class of promising drugs are the thiazolidinediones. Another is metformin. To date, however, these drugs are not recommended for treatment of the metabolic syndrome in patients who do not have type 2 diabetes.

Atherogenic dyslipidemia. This lipoprotein phenotype appears to enhance risk for CHD over and above that of elevated LDL cholesterol (1). Thus, atherogenic dyslipidemia is one potential target of therapy among the risk factors of the metabolic syndrome. First-line therapy for atherogenic dyslipidemia is management of the underlying causes—obesity and physical inactivity, i.e., weight reduction and increased exercise. Also, very low fat (high-carbohydrate) diets should be avoided to prevent accentuation of hypertriglyceridemia (1). In addition, two drug categories improve the lipoprotein profile in patients with atherogenic dyslipidemia. These are nicotinic acid and fibric acids. It must be remembered that even in patients with atherogenic dyslipdemia, LDL cholesterol is the primary target of lipid-lowering therapy. Therefore, if either nicotinic acid or a fibric acid is employed, it usually is given together with an LDL-lowering drug. The combination of a statin + nicotinic acid generally is safe, although it carries the side effects commonly accompanying nicotinic acid. On the other hand, the combination of stain + fibrate imparts an increased risk for myopathy. For this reason, appropriate selection of patients for this combination is necessary. Conditions in which combination statin + fibrate therapy generally should be avoided are:

- Patients requiring high doses of statins
- Older patients (> 70 years; especially women with small body frames and frailty)
- During acute illnesses (e.g. infections and peri-operative periods)
- Patients with multi-system diseases (e.g. chronic renal failure due to diabetes)
- Patients receiving certain drugs [e.g. cyclosporine, azole antifungals, itraconazole and ketoconazole, microlide antibiotics, erythromycin and clarithromycin, HIV protease inhibitors, Nefazodone (antidepressant), varapamil]
- Patients who consume large amounts of grapefruit juice (>1 quart per day)

For patients with atherogenic dyslipidemia, the LDL cholesterol remains the primary target of therapy. However, the secondary target could be total apo B. Table 7 compares the goals for LDL cholesterol, non-HDL cholesterol, and total apo B for patients with atherogenic dyslipidemia. A low HDL level can be a third target for treatment, and efforts to raise HDL levels are warranted. Even so, no specific goals for HDL-raising therapy are set in ATP III.

Table 7

Comparison of LDL Cholesterol, Non-HDL Cholesterol, and Total Apo B Goals for Three Risk Categories

Risk Category	LDL-C Goal	Non-HDL-C Goal	Total Apo B Goal
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100 mg/dL	<130 mg/dL	< 90 mg/dL
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130 mg/dL	<160 mg/dL	< 110 mg/dL
0-1 Risk Factor	<160 mg/dL	<190 mg/dL	< 130 mg/dL

Elevated blood pressure. The blood pressure is variously elevated with the metabolic syndrome. A pressure ≥ 130/85 mmHg is one of the diagnostic criteria for the syndrome. Therapeutic blood pressure lowering definitely reduces risk for CHD (59,60). Treatment of the underlying causes will lower the blood pressure in many patients, as will reducing sodium intakes, increasing potassium, and increasing consumption of fruits and vegetables. Nonetheless, patients with categorical hypertension (≥ 140/90 mmHg after dietary therapy), blood pressure lowering medication often will be required in addition to lifestyle changes.

Insulin resistance (± impaired fasting glucose). Insulin resistance typically is present in patients with abdominal obesity who exhibit the metabolic syndrome. A portion of these patients will have impaired fasting glucose. First-line therapy for both is management of obesity and physical inactivity. Insulin sensitizers (e.g. metformin and thiazolidinedione) hold potential, but their value for reducing risk for CHD has not been validated by clinical trial. A recent clinical trial yet to be published nonetheless showed that metformin therapy in patients with impaired fasting glucose will reduce the risk for type 2 diabetes.

Prothrombotic state. Weight reduction and increased physical activity in obese patients will mitigate the prothrombotic state. Furthermore, it may be prudent to provide chronic low-dose aspirin therapy to patients with the metabolic syndrome, even for primary prevention. Recent meta-analyses of aspirin trials show that low-dose aspirin reduces major coronary events by at least one-fourth.

Proinflammatory state. This risk factor is most readily recognized by the presence of an elevated hs-CRP (> 3 mg/L). Weight reduction and increased physical activity should reduce the prothrombotic state. Statin therapy has been reported to reduce hs-CRP levels (57,58), as has vitamin E (59). Whether these therapies will reduce the proinflammatory state has not been determined.

Summary

One of the fundamental concepts behind treatment of the multiple risk factors of the metabolic syndrome is that benefit of therapy is cumulative. This potential benefit is illustrated in Table 8. Each form of therapy produces independent reduction in relative risk. To estimate total risk reduction, relative risk reductions are multiplied as shown in Table 8. Treatment of all risk factors should reduce risk for acute coronary syndromes by about 75%.

Table 8
Potential Benefit of Intensive Treatment of Metabolic Syndrome

Risk Reduction Therapy	Relative Risk Reduction (Individual Therapies)	Cumulative Relative Risk (on Therapies)
LDL lowering (statins)	- 30%	0.70
Aspirin	-25%	0.52
Blood pressure control	-20%	0.42
Fibrates/nicotinic acid	-20%	0.34
Weight loss/exercise	-20%	0.27
Vitamin E	-10% (?)	0.25

ATP III represents a major increment in the management of lipids and lipoproteins to prevent CHD. It is an evidence-based report in which the recommendations have been greatly bolstered by a series of robust clinical trials. LDL cholesterol remains the primary target of lipid-lowering therapy. However, new lipid targets are admitted under certain circumstances, e.g. hypertriglyceridemia and atherogenic dyslipidemia. Patients with established CHD continue to receive priority of therapy; but adding CHD risk equivalents has expanded the high-risk category. Moreover, more intensive LDL-lowering therapy is introduced for moderately high-risk patients. The latter include patients with the metabolic syndrome. ATP III considers the metabolic syndrome to be a major risk-enhancing metabolic disorder that deserves increased attention in clinical management of patients at risk for CHD.

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