

Diagnosis and Treatment of Metabolic Syndrome in Menopausal Women

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Metabolic syndrome is a disorder of combined lipid and glucose metabolism in a genetically susceptible individual with sufficient visceral adiposity to provoke adipose tissue dysfunction. This adipose tissue dysfunction also results in hypertension, glucose intolerance, and a proinflammatory, prothrombotic state. Physiologic features of menopause—such as decreased insulin sensitivity, estrogen deficiency, shift to an android body habitus and weight gain, as well as lack of physical activity—contribute to the development and risk of metabolic syndrome in menopause. Age itself remains a predominant risk factor for metabolic syndrome.

Endocrinologist Gerald Reaven, who helped to draw attention to the metabolic syndrome concept, is quoted as having said, “All obese people are not created equal—insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals.”¹ Previously thought of as a “pre-diabetes” syndrome, metabolic syndrome is now more properly viewed as a “pre-coronary syndrome” because of the associated increased risk of cardiovascular events. Cardiovascular disease remains the leading cause of morbidity and mortality among menopausal women, and despite preventive efforts we have been less successful in reducing this risk in women than in men.^{2,3} Early and accurate risk prediction and aggressive prevention would seem to be what is needed.

The Controversy

A diagnosis of metabolic syndrome has been the subject of controversy. This controversy has several facets.^{4,7} There are multiple definitions of metabolic syndrome, which has led to some confusion as to whether or not the syndrome describes an actual biological entity or whether it is simply a construct. Small changes in the cut points used in the definition of metabolic syndrome will likely impact its specificity and sensitivity in the prediction of cardiovascular risk. Some have questioned whether or not the risk of atherosclerotic cardiovascular disease (ASCVD) associated with metabolic syndrome is greater than that of the sum of its risk factors. However, the risk of ASCVD rises geometrically rather than linearly with the addition of metabolic syndrome risk factors, and the increased incidence of type 2 diabetes mellitus (T2DM) additionally increases long-term risk.³ There is also controversy concerning the clinical utility of the metabolic syndrome, as no prospective trials yet exist demonstrating that the diagnosis of the metabolic syndrome and implementation of specific therapeutic regimens would affect the

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morbidity or mortality from ASCVD or from T2DM. (*Post hoc* analysis does reveal that patients with metabolic syndrome derive incremental benefit from intensified statin therapy⁸).

Regardless of whether metabolic syndrome is ultimately determined to be a distinct biological entity, a diagnosis serves to identify patients at a two- to three-fold increased risk for ASCVD, who might benefit from more intensive lifestyle and, possibly, pharmacologic therapy.⁹ The predictive value of metabolic syndrome has generally not been shown it to be superior to the Framingham Risk Score (FRS) in delineating *short-term* (10-year) ASCVD risk.¹⁰ However, the diagnosis of metabolic syndrome remains a strong predictor of *long-term* coronary heart disease (CHD) risk and identifies potentially high-risk patients, especially in women over 55 years of age. A diagnosis of metabolic syndrome identifies those at risk for T2DM and stroke; the FRS does not. The FRS may, in fact, seriously underestimate lifetime cardiovascular risk in women.¹¹

Thus, clinicians face a dilemma with regard to accurate risk prediction and treatment, and may need to resort to additional tools, such as imaging studies, biomarkers and advanced lipoprotein analysis to augment the FRS. However, validation of cardiac imaging and biomarkers as tools to screen for long-term risk in insulin-resistant states awaits prospective trial data.¹² The diagnosis of metabolic syndrome ex-

tends the concept of CVD risk and should not be viewed as a competitor to the FRS tool, but rather as an enhancement.⁴

Metabolic Syndrome in Women: What Studies Show

Although no studies have specifically looked at menopausal women, multiple studies (the San Antonio Heart Study, the Atherosclerosis Risk in Communities study, the Hoorn study, and the Health, Aging and Body Composition study) have suggested that the metabolic syndrome may be more predictive of CHD events in women than in men.¹³⁻¹⁵ A recent, 10-year, prospective multicenter trial in China of approximately 30,000 subjects showed that metabolic syndrome significantly increased CVD risk compared with patients who do not have metabolic syndrome but who do have hyperglycemia. The risk of CVD in this population was

largely attributable to the accompanying metabolic abnormalities of metabolic syndrome rather than the hyperglycemia alone.¹⁶

Metabolic syndrome had an adverse impact on CVD health and mortality in the Botnia Study,¹⁷ a prospective 7-year trial with more than 3,000 patients (average age of women, >50 years). There was a 2- to 3-fold relative risk increase in total mortality, CHD mortality, CHD incidence, myocardial infarction and stroke (Figure 1).¹⁷

The recently completed Monitoring of Trends and Determinants in Cardiovascular Disease trial¹⁸ is a prospective Danish population-based study of 2,493 men and women, ages 41 to 72 years, without major CVD at baseline. Over a median follow-up of 9.4 years, the relative risk (RR) of cardiovascular end points (CV death, nonfatal ischemic heart disease and nonfatal stroke, adjusted for age, gender, smoking

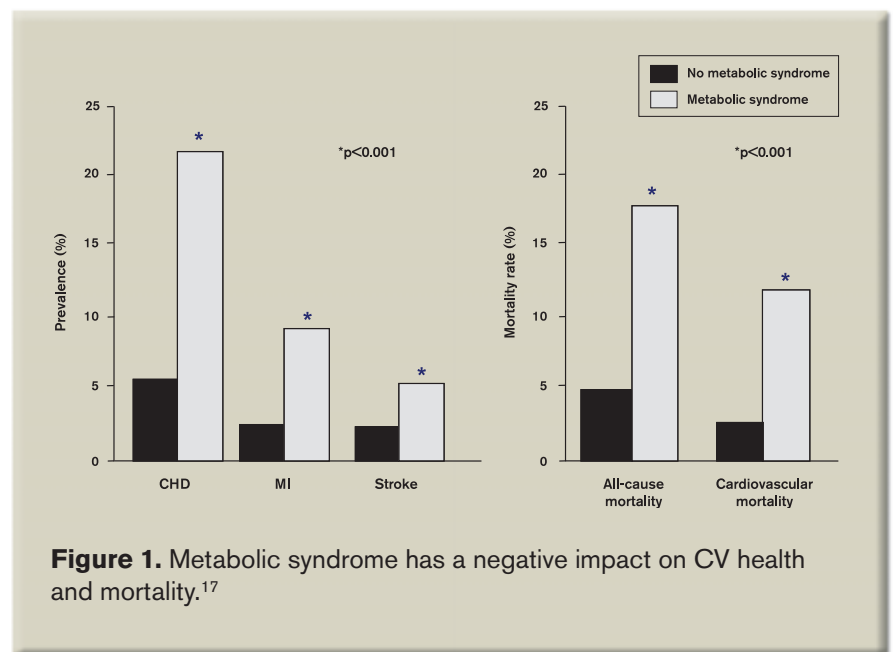


Figure 1. Metabolic syndrome has a negative impact on CV health and mortality.¹⁷

and low-density lipoprotein cholesterol [LDL-C]) was increased by 1.56 (95% confidence interval [CI], 1.12 to 2.17).¹⁸ The authors concluded that both insulin resistance and metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III), independently predict cardiovascular disease.

A new meta-analysis of 40 studies varying in length from 2 to 16 years in 172,573 individuals, using endpoints of new heart disease events or death, showed metabolic syndrome had an RR of 1.78 (95% CI, 1.58-2.00). The association was stronger in women than in men (RR, 2.63 vs. 1.98, $P = 0.09$.) Multivariate analysis adjusting for the individual components of metabolic syndrome demonstrated cardiovascular risk beyond that associated with its individual risk factors (RR, 1.54; 95% CI, 1.32-1.79).¹⁹

The Enlarged Waist/Elevated Triglycerides (EWET) trial was the first long-term prospective study of metabolic syndrome risk factors in a community-based, menopausal-specific population.²⁰ Rather than investigating all the factors of metabolic syndrome as defined by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), EWET used only the two parameters of enlarged waist size (over 35 inches) and elevated triglycerides (≥ 128 mg/dL) in estimating cardiovascular mortality in 557 menopausal women ages 48 to 76, who were followed prospectively for 8.5 years. Mortality was increased almost 5-fold by the presence of EWET, and metabolic syndrome risk factors other than

elevated triglycerides and elevated waist added little to risk prediction in this model. The authors concluded that the presence of EWET may be the best indicator of cardiovascular risk in menopausal women. New studies confirm that both fasting and nonfasting triglycerides are important independent risk factors for cardiovascular events.^{21,22}

The Role of Risk Factors

The incidence of new-onset T2DM, a CHD relative risk equivalent in the NCEP guidelines, correlates with the number of characteristics, or risk factors, of metabolic syndrome. Patients with four or five risk factors for metabolic syndrome have a 24-fold greater risk for T2DM compared with patients who have no risk factors.²³ There is also evidence that CHD risk increases with the number of components of metabolic syndrome,²⁴ as does ischemic stroke risk (two to three times increased relative risk).²⁵ Analysis of the Framingham Offspring Study (1,774 women, average age >50 years) revealed significant increases in total CVD and hard CVD outcomes (myocardial infarction or CHD death) with the diagnosis of metabolic syndrome.²⁴ The increases in these events were steeper in women than in men, which correlated with the number of metabolic syndrome risk factors present (Table 1). Increases in relative risk of T2DM were greater than increases in CVD events.

Diagnostic Criteria

The AHA/NHLBI diagnostic criteria for metabolic syndrome (Table 2) are well known and are discussed in detail elsewhere.⁹ These criteria can

be adapted for multiethnic populations; for example, by reducing the criterion for elevated waist circumference in South Asian women. The incidence of the metabolic syndrome increases with age; the prevalence of metabolic syndrome increased from approximately 7% among participants between ages 20 and 29 to approximately 43% for patients over 60 years of age.²⁶ The prevalence of metabolic syndrome differs with race, with the age-adjusted prevalence being highest among Mexican-American individuals and lowest among African-Americans and people of other racial categories. The most recent data suggest that approximately 50 million Americans have metabolic syndrome.

Pathophysiology

The pathophysiology of metabolic syndrome involves dysfunctional adipocytes (adiposopathy). Adiposopathy is defined as pathologic adipose tissue dysfunction that may be initiated and/or exacerbated by fat accumulation in genetically susceptible patients.²⁷ Increased visceral adipose tissue dysfunction often correlates with the amount of visceral adipose tissue and also with an increased number of metabolic syndrome components ("score"). The Women's Ischemia Syndrome Evaluation (WISE) study demonstrated the importance of where a menopausal woman's body fat is mainly located.²⁸ The odds ratio of significant coronary artery disease by angiography was related to the presence or absence of metabolic syndrome *at any weight*, even in the absence of obesity. The relative risk of mortality and CVD events was more

closely related to metabolic syndrome than to body mass index (BMI).

Many patients have a genetically impaired inability to make new adipose cells (adipogenesis) under conditions of positive caloric balance, resulting in adipose cell hypertrophy and resultant hypoxic-induced stress. These stressed adipocytes release pathologic adipocytokines, lipotoxic nonesterified free fatty acids (NEFAs) and other pro-inflammatory factors that promote endothelial dysfunction, increase insulin resistance and increase CVD risk. Adiposopathy reduces the beneficial cytokine adiponectin, which has a number of anti-atherosclerotic effects on the vasculature, promotes insulin sensitivity, and has been strongly linked to reduction of cardiovascular risk.²⁷

Clinical diagnosis of metabolic syndrome is an excellent way to identify the increased CVD risk of adiposopathy and the associated atherogenic triad—a cluster of “non-traditional” risk factors that confers a dramatic increase in CVD risk:

- hyperinsulinemia,
- small, dense LDL particles, and
- an elevated number of atherogenic ApoB lipoprotein particles.

The risk of ischemic heart disease is differentially increased according to the cumulative number of traditional and nontraditional risk factors. The presence of the atherogenic triad confers an almost 21-fold increased relative risk over patients in a similar quartile of traditional risk factors.²⁹

The NCEP-ATP III 2004 addendum guidelines recommend classification of risk according to

Table 1. Metabolic Syndrome Components and CV Risk

A Greater Number of Metabolic Syndrome Components Leads to Greater Risk for CV Events: Framingham Offspring Study 8-Year Follow-Up

Event	No. of Metabolic Syndrome Risk Factors	Age-Adjusted Relative Risk (95% CI)	
		Men	Women
CVD	0	Referent	Referent
	1–2	1.48 (0.69–3.16)	3.39 (1.31–8.81)
	≥3	3.99 (1.89–8.41)	5.95 (2.20–16.11)
Hard CVD	0	Referent	Referent
	1–2	0.98 (0.36–2.67)	3.77 (0.45–31.28)
	≥3	2.55 (0.96–6.79)	7.21 (0.81–64.37)
Total CHD	0	Referent	Referent
	1–2	1.24 (0.54–2.83)	3.29 (0.95–11.34)
	≥3	3.01 (1.33–6.83)	3.96 (1.02–15.38)
T2DM	0	Referent	Referent
	1–2	4.16 (0.98–17.64)	6.10 (1.85–20.10)
	≥3	23.83 (5.80–98.01)	29.69 (9.10–96.85)

CVD = cardiovascular disease; CHD = coronary heart disease; T2DM = type 2 diabetes mellitus

Wilson PWF, et al. *Circulation* 2005;112:3066-3072. Reprinted with permission of Lippincott Williams & Wilkins.

Table 2. National Cholesterol Education Program⁹

Adult Treatment Panel III (NCEP-ATP III)

Metabolic Syndrome diagnosis suggested by the presence of 3 or more of the following features:

1. **Waist >35** inches in women (>31 inches in South Asians)
2. **Triglycerides >150** mg/dL (or on drug treatment with a fibrate or niacin for elevated TG)
3. **HDL-C <50** mg/dL (or on drug treatment with a fibrate or niacin for low HDL-C)
4. **SBP ≥130** or **DBP ≥85** mm Hg (or on antihypertensive drug treatment)
5. **Fasting plasma glucose >100** mg/dL (or on drug treatment for elevated glucose)

TG = triglycerides; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure

the presence of major risk factors (family history of premature CVD, low high-density lipoprotein cholesterol [HDL-C], age, smoking history and hypertension) and the FRS. Intensity of treatment of plasma lipid concentrations is directly proportional to the risk predicted by this algorithm.³⁰ However, there are distinct advantages in shifting the

emphasis from a lipid-concentration risk management strategy to a lipoprotein-concentration risk management strategy.^{31,32} Although we have traditionally used plasma lipid (cholesterol and triglyceride) concentrations as determined by the standard lipid panel (total-cholesterol, LDL-C, HDL-C, very low-density lipoprotein cholesterol

[VLDL-C] and triglycerides), it is now well established from epidemiologic and clinical trials that, in fact, CVD risk tracks more closely with plasma lipoprotein concentrations.^{31,32} This is especially true in insulin-resistant populations.

Plasma lipoprotein concentrations are better than any of the plasma cholesterol indices at assessing residual risk patients' experience after they've begun treatment. Apolipoprotein B is a surface protein component of atherogenic lipoproteins (LDL, VLDL, intermediate density lipoproteins and remnant particles). Each of these lipoproteins contains a single molecule of ApoB. Cardiovascular risk is increased by an increased ApoB particle concentration. ApoB determination is simple, standardized and directly measured (unlike LDL-C, which is a calculated value). An easily calculated non-HDL-C value (total-cholesterol concentration minus the HDL-cholesterol concentration) serves as an alternative validated tool for assessment of risk from *all* circulating ApoB particles.³³ LDL particle concentration (LDL-P) determined by nuclear magnetic resonance imaging is an alternative method for determining plasma lipoprotein concentration-associated risk.³⁴

The lipoprotein abnormalities of metabolic syndrome are an excessive number of atherogenic ApoB lipoprotein particles, accompanied by reduced numbers, as well as dysfunction, of HDL particles (Figure 2). Under conditions of adiposopathy, visceral fat cells are unable to properly control and store NEFAs.³⁵ When the liver is confronted with an

excessive concentration of NEFAs (and/or when augmented by an excessive simple carbohydrate diet), triglyceride synthesis is initiated. The liver is not adapted to handle an excessive load of triglycerides. Hypertriglyceridemic situations like metabolic syndrome lead to an overproduction of large triglyceride-rich ApoB-containing VLDLs, which are associated with fasting and postprandial hypertriglyceridemia. Triglyceride-rich VLDLs, themselves highly atherogenic, are subject to altered lipolysis, which creates smaller VLDL particles (remnants) and small, dense LDL and HDL particles. This process results in low HDL-C and HDL particle counts (HDL-P). Patients with small LDL particles typically have high LDL-P (ApoB) concentrations.³¹ Since many metabolic syndrome patients with small LDL particles have low HDL-C, they will often have abnormalities of non-HDL-C, total

cholesterol (TC)/HDL-C and triglycerides (TG)/HDL-C (>4:1 is abnormal) ratios.³⁶ The scenario of normal LDL-C associated with elevated non-HDL-C, or abnormal TC/HDL-C or TG/HDL-C ratios can be used to identify elevated ApoB and likely contributes to the residual CV risk so common in these patients.^{34,37}

Low HDL-C is the most common abnormality associated with CVD events in the Framingham study and is often associated with insulin-resistant syndromes like metabolic syndrome. Low HDL-C is often associated with increased numbers of atherogenic VLDL remnants and small LDL particles. Also contributing to the risk is the altered functionality of HDL particles common in proinflammatory states like metabolic syndrome and T2DM. Inflammatory proteins render HDL particles less efficacious at performing macrophage reverse

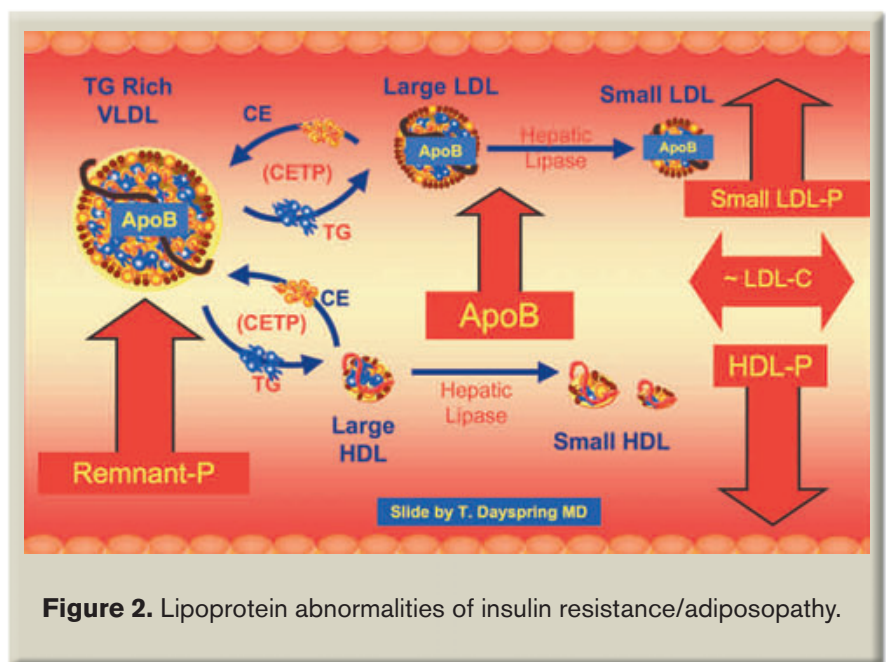


Figure 2. Lipoprotein abnormalities of insulin resistance/adiposopathy.

cholesterol transport, and delivering anti-inflammatory, anticoagulant and profibrinolytic proteins to areas of arterial plaque. It is becoming evident that the new term “HDL functionality” is likely very important in atherogenesis. Therapeutically improving HDL functionality may be more important than increasing HDL-C.^{38,39}

Treatment

The 2007 AHA guidelines for the prevention of cardiovascular disease risk in women emphasize the assessment of *lifetime* risk in women instead of the previous emphasis upon assessment of *short-term* risk.¹⁰ The Framingham risk paradigm is excellent at assessing 10-year risk in women, but we now have substantial data showing that even the presence of one major cardiovascular risk factor in a woman over 50 years of age will increase her lifetime risk for cardiovascular disease dramatically. There is also evidence that there is a broad heterogeneity of risk present in women with a given FRS. A high-risk FRS (>20%) identifies women at high risk, but a *lower score is not sufficient to ensure that an individual woman is at low risk*. The combined use of metabolic syndrome diagnosis with a lipoprotein particle-based treatment approach provides a rational approach to management of risk in menopausal women.

Therapeutic lifestyle change. The goals of treatment in metabolic syndrome are to simultaneously decrease the instance of CHD events and to prevent or delay the development of T2DM. The cornerstone of treatment is therapeutic lifestyle change directed at improving adi-

pose tissue dysfunction, not necessarily reduction in adipose tissue mass. The establishment of a metabolic syndrome clinic in the health-care provider’s office to specifically target and treat metabolic syndrome through therapeutic lifestyle change is a promising approach, as intensive lifestyle modification has been shown to improve components of metabolic syndrome.⁴⁰⁻⁴² Therapeutic lifestyle change in metabolic syndrome consists of promotion of daily moderate-intensity exercise, modest weight reduction, a healthy low glycemic index or Mediterranean-style diet and increased consumption of omega-3 fatty acids (Table 3). Modest weight reduction (5-10%) and walking 150-180 min/week improves many of the physiologic abnormalities of metabolic syndrome and slows the progression to T2DM. Self-monitoring of parameters such as food intake, body weight and exercise level is critical for success. Exercise management should consist of at least 30 minutes of moderate-to-vigorous

physical activity on most days of the week. If this activity is weight-bearing, the dual benefit of potential prevention of menopausal osteoporosis can also be accomplished. The use of inexpensive pedometers to set and track goals for the simplest form of modest-intensity exercise—walking—is practical and effective; more than 10,000 steps/day is considered an “active” lifestyle. An exercise prescription of adding >1,000 kcal/week of exercise (~20,000-25,000 steps/week) consisting of moderate-intensity walking is recommended.⁴³ Patients should be reminded that regardless of any weight loss achieved, physical activity is insulin sensitizing and is of cardiorespiratory and psychological value.⁴⁴

Goals for an individualized diet include a reasonable reduction in weight of 7% to 10% over 1 year, with the eventual goal of obtaining ideal body weight. This is achieved by the initiation of reduced caloric intake and reduced consumption of simple carbohydrates, under the supervision of a clinical nutritionist if

Table 3. Implementing Therapeutic Lifestyle Changes

- **Specific contract with patient** for goals and self-monitoring.
- **Exercise** – at least 30 minutes of moderate to vigorous physical activity on most days of the week. Using pedometer, walking >10,000 steps/day is desirable.
- **Diet** – reduction of weight by 7-10% over 1 year with reduced caloric intake and reduced consumption of simple carbohydrates (low glycemic index diet). Women should consume a diet rich in fruits and vegetables; whole-grain, high-fiber foods; limited intake of saturated fat to 10% of energy (if possible to 7%); cholesterol to 300 mg/d; no more than 1 alcoholic drink per day; consumption of trans-fatty acids (FA) should be as low as possible.
- **Increased omega-3 FA consumption** (~850-1000 mg EPA + DHA / day)
- **Women should not smoke** and should avoid environmental tobacco smoke.

EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid

possible. Attainment of ideal body weight is obviously difficult in this population, but even modest weight loss has been associated with laboratory improvement and clinical risk reduction.⁴⁰ Increased soluble fiber intake and reduction of saturated and trans fatty acid intake are to be recommended as well. Plant stanol esters significantly lower LDL-C and are available in various “functional foods.”⁴⁵ Increased omega-3 fatty acid consumption (approximately 1,000 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] per day) reduces risk in women with CVD, and it is reasonable to extend this treatment to high-risk patients such as those with metabolic syndrome.

Pharmacologic treatment. Pharmacologic treatment of cardiovascular risk in metabolic syndrome is based on the assessment and treatment of risk using an atherogenic particle-based approach.⁴⁶ Aggressive treatment is safe, effective and well within the scope of practice of all primary care providers,⁴⁷ and need not be left to internists and cardiologists once risk is identified.

An aggressive goal is to reduce the atherogenic ApoB particle count to physiologic levels associated with low CVD risk (Table 4). Statin drugs inhibit cholesterol synthesis in almost all cells, although the liver is the organ that clears ApoB particles. The largest body of evidence for pharmacologic risk reduction in insulin-resistant patients exists for statins. First-line pharmacologic strategy to reduce ApoB-containing particles would be appropriately dosed statin therapy. A complementary strategy would be to reduce the

number of circulating triglyceride-rich VLDL particles driving the lipoprotein abnormalities of metabolic syndrome, by either reducing their production in the liver or increasing their catabolism, with fibrates, niacin or high-dose omega-3 fatty acids. The fibrates regulate

multiple genes involved with glucose and fatty acid metabolism, lipoprotein synthesis and catabolism, and vascular inflammation. They decrease the hepatic production of triglycerides, increase the catabolism of triglyceride-rich lipoproteins and increase the synthesis and function-

Table 4. Metabolic Syndrome – Pharmacologic Treatment^{9,11,31,32}

- **Assessment and treatment of risk using an atherogenic particle-based approach (instead of a traditional lipid-based approach)**
- **Primary goal:** reduce atherogenic ApoB particles to physiologic levels
- **Lifestyle approaches** should be encouraged to reach the following **optimal lipid levels:**
 - > **LDL-C < 100 mg/dL**
 - > **HDL-C > 50 mg/dL**
 - > **TG < 150 mg/dL**
 - > **Non HDL-C < 130 mg/dL**
- **Framingham Risk Scoring** should be done to stratify absolute 10-year risk of ASCVD.
- Goals of treatment for those at **moderately high risk** (≥ 2 risk major risk factors, with 10-20% risk) and **high-risk patients** (known CVD or T2DM or CHD equivalent*):
 - Non-HDL-C < 130 mg/dL OR ApoB < 80 mg/dL OR NMR LDL-P < 1000 nMol/L**
- **Very high-risk women (established CVD plus any of the following: MetSyn, multiple major risk factors, severe and poorly controlled risk factors, T2DM) have lower goals:**
 - Non-HDL-C < 100 mg/dL OR ApoB < 60 mg/dL OR NMR LDL-P < 1000 nMol/L**
- **Statin** is first-line Rx to reduce ApoB particles.
- **If not at non-HDL-C, ApoB or LDL-P goal, add fenofibrate.** Ezetimibe or bile acid sequestrant or Rx extended-release niacin can be added if goal not attained.
- **Aggressive hypertension control.** Optimal BP < 120/80. Treat to < 130/80, with ACE inhibitors/ARBs preferred, with thiazide diuretics next if needed.
- **Management of hyperglycemia** (FBS > 100 mg/dL) with metformin, especially with an abnormal glucose tolerance test.
- **81- to 162-mg enteric-coated aspirin**, unless contraindicated.
- **Weight-loss medications** or bariatric surgery may be helpful in some patients.

*“CHD equivalent” = known peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, chronic renal disease (creatinine > 1.2 mg/dL)

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; ASCVD = atherosclerotic cardiovascular disease; T2DM = type 2 diabetes mellitus; CHD = coronary heart disease; Apo-B = apolipoprotein B; NMR = nuclear magnetic resonance; MetSyn = metabolic syndrome; LDL-P = LDL particle concentration; FBS = fasting blood sugar

ality of HDL particles.⁴⁸ Trial data reveal that fibrates are significantly more efficacious in insulin-resistant patients. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, fenofibrate demonstrated a trend toward CVD risk reduction (nonsignificant absolute risk reduction) in women with T2DM, as well as reduction of microvascular endpoints, such as the need for laser-photocoagulation retinal therapy, microalbuminuria and peripheral amputations.⁴⁹ Consistent with other fibrate trials, FIELD patients with dyslipidemia (triglycerides >150 mg/dL and HDL <50 mg/dL for women) experienced an absolute risk reduction (2.3%) in total CVD events, comparable to that of a statin in the Collaborative Atorvastatin Diabetes Study.⁵⁰ Extended-release niacin may also be used to decrease the production of triglyceride-rich lipoproteins, but has no outcome data in women and has the additional concerns of increasing insulin resistance as well as the incidence of flushing symptoms in a menopausal population.

There are no outcome data for women with regard to high doses of omega-3 fatty acids (approximately 3,000 mg/day EPA and DHA), but EPA and DHA can decrease the production of triglyceride-rich lipoproteins and possibly also increase their clearance.⁵¹ Many national organizations now routinely recommend treatment of the residual risk common in statin-treated patients (triglyceride/HDL-C axis abnormalities) once standard LDL-C guidelines are met. Often, the use of aggressive combination therapy, beginning with a statin, will be needed

Trial data reveal that fibrates are significantly more efficacious in insulin-resistant patients.

to accomplish these goals. Statins can be safely combined with either the triglyceride-reducing agents (fenofibrate, niacin or high-dose omega-3 fatty acids) or additional ApoB receptor upregulating agents (ezetimibe or bile acid sequestrants) or both. Clinical trials are under way to look at the potential additional risk reduction obtained by the combined use of some of these agents.

Estrogen deficiency appears to be associated with an increased risk of most features of metabolic syndrome.⁵² Prospective studies of estrogen therapy in menopausal women have consistently failed to reduce CVD events.⁵³ Obviously, there is a low incidence of CVD events during the years prior to menopause, although the role of estrogens here is also unclear, given the fact that many women have significant plaque in major vessels by the second and third decades of life. Estrogens increase the output of triglyceride-rich lipoproteins (TRLs) from the liver. Estrogens also increase ApoB receptors, helping to lower ApoB slightly. TRLs are subject to increased lipolysis and increased estrogen-produced hepatic lipase, often leading to a

drop in LDL-C with estrogens, without the expected significant drop in ApoB. All of these effects vary among estrogens and are quite dose-dependent. Low-dose oral estrogen and topical estrogens have a less dramatic negative effect on lipoprotein size.³⁶ In metabolic syndrome patients, consideration should be given to minimizing further lipoprotein abnormalities through the selective use of these dosing regimens.

Data from the Women's Health Initiative (WHI) on estrogen with⁵⁴ and without medroxyprogesterone⁵⁵ show a decrease in the self-reported incidence of new T2DM, independent of BMI, suggesting an insulin sensitizing effect of estrogen. The recently published coronary artery calcium substudy of the WHI demonstrated that conjugated equine estrogens reduced calcified plaque burden in 50- to 59-year old women who had undergone a hysterectomy, compared with placebo.⁵⁶ Ongoing clinical trials in younger menopausal women prospectively examine the cardiovascular effects of estrogen in this age group.

In addition to aggressive lipoprotein management, other features of metabolic syndrome adiposopathy need to be addressed with pharmacologic management. Pharmacologic (orlistat and sibutramine) and bariatric surgery approaches to weight reduction seem promising, although clinical correlation with event reduction awaits further research. The selective cannabinoid receptor antagonist rimonabant is being investigated for both weight reduction and improvement of adipose tissue dysfunction, although it has been plagued with safety

concerns.⁵⁷ Aggressive hypertension control (treat to <130/80 mmHg) should be pursued, and there is some evidence that aldosterone blockade with angiotensin converting enzyme inhibitors/angiotensin receptor blockers or nondihydropyridine calcium channel blockers may offer advantages in insulin-resistant situations. The first two of these may help prevent progression to T2DM.⁵⁸

All patients with a >10% 10-year risk of CVD on the FRS should receive low-dose aspirin therapy (81-162 mg enteric-coated aspirin), unless contraindicated. The management of insulin-resistant hyperglycemia (especially impaired glucose tolerance) itself can be augmented with the addition of pharmacologic therapy with metformin. Metformin additionally may provoke weight loss or stabilization, and has been shown to reduce mortality in T2DM⁵⁹ and the progression to T2DM. The use of thiazolidinediones as insulin-sensitizing agents for risk reduction and T2DM prevention has been advocated.⁶⁰ A recent meta-analysis suggested increased CVD risk with the thiazolidinedione rosiglitazone,⁶¹ although this is controversial.⁶² The role of other hypoglycemic and insulin-resistance-reducing drugs, such as acarbose, exenatide and sitagliptin, is unclear.

Summary and Conclusions

The diagnosis of metabolic syndrome helps to identify menopausal patients at increased long-term risk for ASCVD, T2DM and ischemic stroke. Despite the fact that these patients may have only modest elevations of individual risk factors, such as high blood pressure and

Pharmacologic (orlistat and sirbutramine) and bariatric surgery approaches to weight reduction seem promising, although clinical correlation with event reduction awaits further research.

elevated lipids, the presence of metabolic syndrome helps identify patients with the adverse physiologic state of adiposopathy, and its accompanying pathologic combination of abnormal lipoproteins, cytokines and pro-inflammatory factors. These patients might benefit from more intensive therapeutic lifestyle changes and pharmacologic therapy, targeted specifically at improving their underlying adiposopathy and increased atherogenic ApoB lipoproteins, and at prevention of T2DM. The patient hand-out on pages 27 and 28 will serve as a valuable tool for making patients active participants in achieving these goals. ■

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This article includes discussion of off-label use of medications.

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References

1. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1998;37:1595-1607.
2. American Heart Association. Women and cardiovascular disease facts. Available at www.americanheart.org/presenter.jhtml?identifier=3039318. Accessed 5/27/07.
3. Polotsky AJ, Santoro N. Menopause and cardiovascular disease: endogenous reproductive hormone exposure affects risk factors. *Menopause Management* 2007; 16:21-25.
4. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol* 2006;47:1093-1100.
5. Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005;28:2289-2304.
6. Blaha M, Elasy TA. Clinical use of the metabolic syndrome. Why the confusion? *Clin Diabetes* 2006;24: 125-131.
7. Schneider JG, Tompkins C, Blumenthal RS. The metabolic syndrome in women. *Cardiology Rev* 2006; 14:1-6.
8. Deedwania P, Barter P, Carmena R, et al; Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet* 2006;368:919-28.
9. Grundy SM, Cleeman JI, Daniels SR, et al. American Heart Association; National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome. *Circulation* 2005;112:2735-52.
10. Rutter M, Meigs J, Wilson P. Cardiovascular risk and the metabolic syndrome. *Metabolic Syndrome and Related Disorders* 2006;4:252-60.
11. Mosca L, Banka CL, Benjamin EJ, et al, for the Expert Panel/Writing Group. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;115:1481-1501.
12. Bax JJ, Inzucchi SE, Bonow RO, et al. Cardiac imaging for risk stratification in diabetes. *Diabetes Care* 2007;30:1295-1304.
13. Lorenzo C, Williams K, Hunt K, Haffner SM. The National Cholesterol Education Program-Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007;30:8-13.
14. Schneider JG, Tompkins C, Blumenthal RS. The metabolic syndrome in women. *Cardiology Rev* 2006; 14:1-6.

15. Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10 year cardiovascular disease risk in the Hoorn study. *Circulation* 2005;112:666-73.
16. Liu J, Grundy SM, Wang W, et al. Ten year risk of cardiovascular incidence related to diabetes, prediabetes and the metabolic syndrome. *Am Heart J* 2007;153:552-58.
17. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683-89.
18. Jeppesen J, Hansen TW, Rasmussen S, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease. *J Am Coll Cardiol* 2007;49:2112-19.
19. Gami A, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007;49:403-14.
20. Tanko LB, Bagger YZ, Qin G, et al. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. *Circulation* 2005;111:1883-90.
21. Sarwar N, Danesh J, Eiriksdottir J, et al. Triglycerides and the risk of coronary heart disease. 10,158 incident cases among 262,525 participants in 29 western prospective studies. *Circulation* 2007;115:450-58.
22. Bansal S, Buring J, Rifai N, et al. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309-16.
23. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention study. *Circulation* 2003;108:414-19.
24. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005;112:3066-72.
25. Kurl S, Laukkanen JA, Niskanen L, et al. Metabolic syndrome and the risk of stroke in middle-aged men. *Stroke* 2006 37:806-11.
26. Ford ES, Giles WH, Dietz, WH. Prevalence of the metabolic syndrome among US adults. Findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356-59.
27. Bays H, Dujovne C. Adiposopathy is a more national treatment target for metabolic disease than obesity alone. *Curr Atheroscler Rep* 2006;8:144-56.
28. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women. *Circulation* 2004;109:706-13.
29. Lamarche B, Tchernof A, Dagenais GR, et al. Small, dense LDL particles and the risk of ischemic heart disease. Prospective results from the Quebec Cardiovascular Study. *Circulation* 1997;95:69-75.
30. Grundy SM, Cleeman JI, Bairey N, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-39.
31. Barter PJ, Ballantyne CM, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten country panel. *J Intern Med* 2006;259:247-58.
32. Mudd J, Borlaug B, Johnston P, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. *JACC* 2007;50:1735-41.
33. Liu J, Sempos C, Donahue R, et al. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol* 2006;98:1363-68.
34. Cromwell W, Otvos J. Low-density lipoprotein particle number and risk for cardiovascular disease. *Curr Atheroscler Rep* 2004, 6:381-87.
35. Bays H, Abate N, Chandalia M. Adiposopathy: sick fat causes high blood sugar, high blood pressure and dyslipidemia. *Future Cardiol* 2005;1:39-59.
36. Dayspring T. Cardiovascular disease: a comprehensive primer for clinicians. *Menopause Management* 2002;11:1-9.
37. Cromwell W, Otvos J. Heterogeneity of low-density lipoprotein particle number in patients with type 2 diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dl. *Am J Cardiol* 2006;98:1599-1602.
38. Dayspring T. High density lipoproteins: emerging knowledge. *J Cardiometa Syndr* 2007;2:59-62.
39. Singh I, Shishehbor M, Ansell B. High-density lipoprotein as a therapeutic target. A systematic review. *JAMA* 2007;298:786-98.
40. Orchard TJ, Temprosa M, Goldberg R, et al, for the Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005;142:611-19.
41. Molavi B, Rasouli N, Kern PA. The prevention and treatment of metabolic syndrome and high-risk obesity. *Curr Opin Cardiology* 2006;21:479-85.
42. LaMonte MJ, Barlow CE, Jurca R, et al. Cardiorespiratory fitness is inversely related with the incidence of metabolic syndrome: a prospective study of men and women. *Circulation* 2005;112:505-12.
43. Howley E, Franks D. *Health and fitness instructors handbook*, 5th ed. Champaign IL: Human Kinetics, 2007:46-52.
44. LaForge R. *Exercise determinants of weight loss*. American Council on Exercise (ACE) Certified News 2006;12:2-6.
45. McGowan, M. The impact of supplements/nutraceuticals (functional foods) on lipid levels: what works? And how well? *The Lipid Spin (National Lipid Assn)* 2007;4:1-9.
46. Pharmacotherapeutic decisions in menopausal women with cardiovascular risk. *Future Lipidology* 2007;2:197-210.
47. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol* 2007;49:1753-62.
48. Dayspring T, Pokrywka G. Fibrate therapy in patients with metabolic syndrome and diabetes mellitus. *Curr Atheroscler Rep* 2006;8:356-64.
49. The FIELD Study Investigators. Effect of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study); randomized controlled trial. *Lancet* 2005;36:1849-61.
50. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes mellitus in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo controlled trial. *Lancet* 2004;363:685-96.
51. Davidson M. Mechanisms for hypotriglyceridemic effect of marine omega-3 fatty acids. *Am J Cardiol* 2006;98(suppl):271-331.
52. Schneider JG, Tompkins C, Blumenthal RS. The metabolic syndrome in women. *Cardiology in Review* 2006;14:1-6.
53. The ESHRE Capri Workshop Group. Hormones and cardiovascular health in women. *Human Reprod Update* 2006;12:483-97.
54. Margolis KL, Bonds DE, Rodabough RJ, et al, for the Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004;47:1175-87.
55. Bonds DE, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomized trial. *Diabetologia* 2006;49:459-68.LE
56. Manson J, Allison M, Rossouw J, et al, for the Women's Health Initiative (WHI) and WHI-Coronary Artery Calcium Study Investigators. Estrogen therapy and coronary artery calcification. *N Engl J Med* 2007;356:2591-602.
57. Van Gaal LF, Rissanen AM, Sreen AJ, et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1 year experience from the RIO-Europe study. *Lancet* 2005;365:1389-97.
58. Abuissa H, Jones PG, Marso SP, et al. Angiotensin-converting enzyme inhibitors or angiotensin receptors blockers for prevention of T2DM: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;46:821-26.
59. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with T2DM. *Lancet* 1998;352:854-65.
60. DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096-1105.
61. Nissen S, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71.
62. Krall R. Cardiovascular safety of rosiglitazone. *Lancet* 2007;16:369:1995-96.

Metabolic Syndrome and Menopause



What is metabolic syndrome? Why is it a concern?

Metabolic syndrome is a disorder that affects the way the body metabolizes fat and sugar. It can occur in those who have too much waistline fat and who inherit this tendency. With more Americans being overweight and obese, metabolic syndrome is becoming increasingly common. The metabolic syndrome has been thought of as a “prediabetic” syndrome, but doctors increasingly regard it as a “precoronary” syndrome (a condition that increases the risk of heart disease). Metabolic syndrome greatly increases your long-term risk of cardiovascular events, such as heart attacks, strokes and sudden death, and also dramatically increases your risk of type 2 diabetes.

Who is at risk for metabolic syndrome?

Metabolic syndrome affects women more severely than men, and it is more likely to occur at menopause

Resources

- <http://www.goredforwomen.org>
- <http://www.womenheart.org/index.asp>
- <http://www.hearthealthywomen.org>
- <http://www.menopause.org>
- <http://www.thewalkingsite.com>

More detailed lipid and lipoprotein information can be found at:

- <http://www.lipoprofile.com/index.cfm>
- http://cks.library.nhs.uk/lipids_management/in_depth/background_information

and beyond. Where a woman accumulates fat in her body is an important factor in determining whether she’s at higher risk for metabolic syndrome. The “apple shape” is a higher-risk situation than the “pear shape.” Excessive waistline fat causes “sick fat cells,” which produce a “toxic stew” of substances, increasing a woman’s risk of developing cardiovascular disease and diabetes.

How is metabolic syndrome diagnosed?

Metabolic syndrome is diagnosed if you have **3 of the following 5 conditions:**

- Waist (at the top of the hip) measures more than 35 inches (more than 31 inches in South Asians)
- Blood pressure is over 130/85 mmHg (or you’re already taking blood-pressure-lowering medications)
- High-density lipoprotein (“good”) cholesterol (HDL-C) is less than 50 mg/dL (or you’re already taking medication for low HDL-C)
- Triglyceride (TG) level is over 150 mg/dL (or you’re taking medication for elevated TG)
- Fasting blood sugar is greater than 100 mg/dL (or you’re taking medication to lower blood sugar)

As the number of these risk factors increases, so does your risk for cardiovascular disease.

Fortunately, metabolic syndrome is treatable and most of the events associated with it are preventable. ***The key to reversing this process is a commitment to modest weight loss and regular exercise.*** You need to make a specific contract for goals with your health-care provider, and you need to implement self-monitoring to follow your progress.

Your Treatment Goals:

Weight reduction of 10% over 1 year (with the eventual goal of attaining your ideal body weight).

YOUR WEIGHT-LOSS GOAL:

is to weigh less than _____ lbs.
(90% of your current body weight.)

Diet

Follow a reduced-calorie diet with carbohydrates that are low on the glycemic index (GI) (visit www.glycemicindex.com). The glycemic index ranks carbohydrates according to their effect on blood sugar. Foods low in GI carbohydrates create smaller changes in your levels of blood sugar and insulin, and are key to losing weight, maintaining weight loss, and lowering your risk of heart disease and diabetes. (Visit <http://www.americanheart.org/presenter.jhtml?identifier=4644>.)

Women should:

- consume a diet rich in fruits and vegetables
- choose whole-grain, high-fiber foods
- limit alcohol intake to no more than 1 drink/day
- limit cholesterol to 300 mg/day
- limit intake of saturated (animal-derived) fats to 10% of total calories (7% is even better) and keep consumption of trans-fatty acids as low as possible

YOUR Diet Plan:

Exercise

Exercise at least 30 min/day, with moderate to vigorous physical activity on most days of the week. If walking and using a pedometer, more than 10,000 steps/day is desirable (adding over 1,000 kcal/week of exercise, ~20,000-25,000 steps/week) [1 mile walked = approximately 2000 steps]. **A physician should be consulted before beginning any rigorous exercise regimen.**

YOUR Exercise Plan:

Lower your blood pressure if it's high!

A blood pressure reading of less than 120/80 mmHg is optimal. Medications are recommended if your blood pressure is consistently higher than 130/80 mmHg.

YOUR blood pressure: _____

YOUR blood pressure medication: _____

Keep your fasting blood sugar below 100 mg/dL (the optimal level).

YOUR fasting blood sugar: _____

YOUR blood-sugar reducing medication: _____

Goals for Cholesterol and Triglycerides:

- **LDL** (low-density lipoprotein, "bad") cholesterol: LESS THAN 100 mg/dL
- **HDL** (high-density lipoprotein, "good") cholesterol: GREATER THAN 50 mg/dL
- **Triglycerides:** LESS THAN 150 mg/dL
- **Non HDL-cholesterol** (total cholesterol minus HDL cholesterol): LESS THAN 130 mg/dL

Traditional cholesterol and triglyceride measurements measure fat (lipids) in the blood. In metabolic syndrome these measurements less accurately predict the number of lipoprotein particles implicated in causing cardiovascular diseases. Your doctor will use different goals, and perhaps advanced tests such as ApoB and NMR LDL-P to more accurately count the atherosclerosis-causing lipoprotein particles.

YOUR LIPID Value(s):

Future Risk of Heart Disease

Your risk of having a heart attack within 10 years is estimated in a calculation called the **Framingham Risk Score (FRS)**. The FRS is designed for adults age 20 years and older who do not have heart disease or diabetes. To calculate your FRS, visit <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp>.

YOUR Framingham Risk Score:

Women at moderately high risk (with a 10-20% 10-year risk) and high-risk patients (>20% 10-year risk OR known coronary disease, diabetes or their equivalents) should have a non-HDL cholesterol goal of LESS THAN 130 mg/dL. Very high-risk women should have an even lower non-HDL cholesterol goal (LESS THAN 100 mg/dL).

Your doctor will discuss the need for cholesterol/lipoprotein-lowering medicines to help you reach these goals.

YOUR medications are:

Additional Advice:

Stop smoking and avoid environmental smoke exposure. The following are recommended for most menopausal women with metabolic syndrome unless contraindicated by certain medical conditions. Talk to your doctor about whether you should NOT take:

- daily aspirin therapy to prevent heart attack
- Omega-3 fatty acid supplements that contain 850-1,000 mg/day of the active ingredients DHA and EPA.