

Cases in
Vascular Protection:
Reducing Risk Factors

COMPLIMENTARY
CME
JULY 2007

Target Audience

This program is designed to educate primary care physicians, endocrinologists, nephrologists, and cardiologists on the management of cardiovascular disease progression and the long-term benefits associated with optimal treatment plans.

Medicine Accreditation Statement

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Equal Opportunity Statement

The University of Kentucky and CTI Clinical Trial and Consulting Services provide equal educational and employment opportunities.

Learning Objectives

After reading this article, the reader should be able to:

- Describe the conditions associated with the development of the metabolic syndrome.
- Identify basic diagnosing criteria for the metabolic syndrome and identify patients at risk for developing metabolic syndrome.
- Describe the various complications associated with a diagnosis of metabolic syndrome.
- Discuss various treatment strategies, including both nonpharmacologic and pharmacologic, for patients affected by metabolic syndrome.
- Review the best available treatment options to provide vascular protection and reduce the development of complications associated with the development and diagnosis of metabolic syndrome.

RATIONALE

Metabolic syndrome is a cluster of conditions including abnormal glucose metabolism, abdominal obesity, increased lipid levels, and hypertension. Patients affected by this syndrome often have a variety of associated complications including, but not limited to, development of type 2 diabetes, increased cardiovascular complications, and renal complications. As such, control of the risk factors leading to this syndrome and identification of at-risk patients has led to increased research of both the syndrome and potential treatment options.

The aim of managing metabolic syndrome is to decrease the development of cardiovascular disease, a major

cause of morbidity and mortality. Therapeutic lifestyle changes remain key in reducing metabolic risk factors. However, pharmacological approaches may include the use of antihypertensive medications such as angiotensin-converting enzyme inhibitors and other treatments including lipid-lowering drugs, antiplatelet therapies, hypoglycemic agents, and weight-loss agents. The objective of this educational program is to provide the audience with an overview of the conditions associated with metabolic syndrome and treatment approaches that provide vascular protection to limit the development of associated cardiovascular complications.

Case 2

Metabolic Syndrome and Vascular Protection

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Metabolic syndrome, also termed *insulin resistance* and *syndrome X*, is a prevalent condition in which certain physiologic and metabolic abnormalities cluster together, mainly insulin resistance and abdominal obesity. Although insulin resistance is the most widely accepted pathological condition associated with metabolic syndrome, other conditions such as abdominal obesity and chronic low-grade inflammation have been suggested as part of the definition of metabolic syndrome.^{1,2} Although the syndrome has been around since 1940, it was initially defined by the World Health Organization (WHO) in 1998, and since that time, 2 additional conceptually different descriptions of the metabolic syndrome have been published. Each delineates criteria for diagnosis, although one common definition of the metabolic syndrome is not accepted. These definitions, summarized in Table 1,³⁻⁵ share a common rationale for diagnosing metabolic syndrome, namely, to identify persons at excessive risk for cardiovascular disease (CVD).⁶

The WHO's definition of the metabolic syndrome is complex and offers specific parameters to the various diagnosing criteria. These criteria include impaired glucose tolerance, impaired fasting glucose, diabetes, or insulin resistance, together with 2 or more of the following

factors: increased arterial pressure $\geq 140/90$ mm Hg (revised from $>160/90$ mm Hg), increased plasma triglycerides (≥ 150 mg/dL/ ≥ 1.7 mmol/L) and/or low high-density lipoprotein (HDL) cholesterol (HDL-C) (<35 mg/dL, 0.9 mmol/L in men and <39 mg/dL, 1.0 mmol/L in women), central obesity (waist-to-hip ratio >0.90 in men and >0.85 in women) and/or body mass index >30 kg/m², and microalbuminuria (≥ 20 μ g/min urinary albumin excretion rate or albumin-to-creatinine ratio ≥ 30 mg/g). Of note, a concurrent diagnosis of type 2 diabetes is not required to meet the definition of metabolic syndrome. However, many patients with diabetes also meet the criteria for metabolic syndrome.

The metabolic syndrome is associated with prothrombotic, proatherogenic, and inflammatory risk factors that predispose to cardiac disease.

The second definition, provided by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), requires 3 or more of the following to make the diagnosis of metabolic syndrome: abdominal obesity

(waist circumference >102 cm for men and >88 cm for women), triglycerides ≥ 150 mg/dL, HDL-C decreased (<40 mg/dL for men and <50 mg/dL for women), blood pressure $\geq 130/85$ mm Hg, and fasting glucose ≥ 110 mg/dL.

The most recent definition of the metabolic syndrome was proposed by the International Diabetes Federation (IDF) in 2005. The IDF criteria are based on expert opinion and are similar to the NCEP ATP III definition; however, abdominal obesity is required for making the diagnosis, and the waist circumference threshold differs according to ethnicity. Abdominal obesity, usually measured by waist circumference, is a metabolic risk factor. The concept of abdominal obesity as a risk factor is consistent with emerging data regarding the relationship between waist circumference and metabolic risk factors in different populations.^{1,2}

Visceral fat tissue, in particular, is resistant to insulin's activities, whereas it is more sensitive to effects from catecholamines and glucocorticoids.⁶ One of the resulting sequelae of the latter include higher concentrations of hepatic free fatty acids, promoting production of triglycerides, and impairing first pass metabolism of insulin. This results in dyslipidemia and hyperinsulinemia. Additionally, visceral obesity is associated

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with increased concentrations of inflammatory substances such as plasminogen activator inhibitor, C-reactive protein (CRP), and tumor necrosis factor-alpha, further contributing to endothelial dysfunction.^{7,8} All in all, this combination of effects predisposes patients to atherosclerosis and premature CVD.

Using the NCEP ATP III definition, the prevalence of metabolic syndrome in the United States has been estimated based on 8814 subjects aged >20 years from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), a nationally representative sample of the noninstitutionalized civilian US population, and was found to be highly prevalent, with similar age-adjusted preva-

lence in men (24%) and women (23%).^{2,9}

Despite the varying definitions of the metabolic syndrome, the importance of the syndrome lies with the cardiovascular risk that it portends. The metabolic syndrome is associated with prothrombotic, proatherogenic, and inflammatory risk factors that predispose to cardiac disease.^{10,11} A prothrombotic state includes the presence of procoagulant factors (ie, increases in fibrinogen and factor VII), antifibrinolytic factors, platelet aberrations, and endothelial dysfunction.¹¹

Metabolic syndrome is associated with procoagulant and proinflammatory states, which have been correlated with CVD for some time. A proinflammatory state can be characterized by increases in

the level of circulating cytokines and acute phase reactants (such as CRP).¹¹ CRP, an acute phase vascular inflammatory reactant, currently receives considerable attention in terms of association with both type 2 diabetes and CVD. Evidence of interrelationships between inflammation and metabolic syndrome are derived from prospective studies observing that higher levels of high-sensitivity CRP (hs-CRP) predict onset of type 2 diabetes, even after controlling for other risk factors such as obesity.¹² Therefore, it is suggested that measuring hs-CRP concentrations affords prognostic information in addition to the diagnosis of metabolic syndrome itself in relation to future vascular events. Although there are no spe-

TABLE 1

Defining Levels of Metabolic Syndrome Diagnostic Criteria

Criteria	NCEP ATP III* ³	WHO† ⁴	IDF‡ ⁵	
			Europeans	South Asians/Chinese/Japanese
Abdominal obesity	Waist circumference: Men >102 cm (40 in) Women >88 cm (35 in)	Waist-to-hip ratio: Men >0.90, Women >0.85 <i>Or</i> BMI >30 kg/m ²	Waist circumference: Men ≥94 cm Women ≥80 cm	Waist circumference: Men ≥90 cm Women ≥80 cm
Triglycerides	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (≥1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L)	
HDL-C	Men <40 mg/dL (1.03 mmol/L) Women <50 mg/dL (1.29 mmol/L)	Men <35 mg/dL (0.9 mmol/L) Women <39 mg/dL (1.0 mmol/L)	Men <40 mg/dL (1.03 mmol/L) Women <50 mg/dL (1.29 mmol/L)	
Blood pressure	≥130/85 mm Hg	≥140/90 mm Hg	≥130/85 mm Hg	
Abnormal glucose metabolism	Fasting glucose ≥110 mg/dL (6.1 mmol/L)	Diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, and/or insulin resistance	Fasting glucose ≥100 mg/dL (5.6 mmol/L)	
Microalbuminuria	N/A	Urinary albumin excretion rate ≥20 µg/min or albumin-to-creatinine ratio ≥30 mg/g	N/A	

*The NCEP ATP III criteria require ≥3 of these risk factors.
 †The WHO requires diabetes, impaired glucose tolerance, impaired fasting glucose, or evidence of insulin resistance together with ≥2 of the other risk factors.
 ‡The IDF requires abdominal obesity plus ≥2 of the other risk factors.
 NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; WHO = World Health Organization; IDF = International Diabetes Federation; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol.

cific drug therapies that target lowering the proinflammatory state paramount to metabolic syndrome, therapies like lipid-lowering agents that target other metabolic risk factors are also known to reduce CRP.⁷

Patients with metabolic syndrome are at considerable risk for developing atherosclerotic CVD, including an increased risk of cardiovascular and coronary heart disease mortality, when compared with those without metabolic syndrome.^{13,14} Overall, patients with metabolic syndrome are at increased risk of cardiovascular complications that may increase morbidity and mortality.^{2,15,16}

ASSOCIATED COMPLICATIONS OF METABOLIC SYNDROME

Patients with metabolic syndrome are affected by several associated complications (Figure). The metabolic syndrome is associated with a 5- to 9-fold increased risk for developing type 2 diabetes.¹⁷ Patients with metabolic syn-

drome manifest insulin resistance or glucose intolerance, hypertension, obesity, and dyslipidemia. Each of these factors viewed separately may lead to further complications, including heart disease, increased risk of stroke, type 2 diabetes, renal disease, and further cardiovascular damage. Therefore, patients with a combination of these factors are at an even higher risk of developing cardiovascular and renal disease, increasing patient mortality and morbidity.¹⁸

Abnormal glucose metabolism is a key factor in the diagnosis of metabolic syndrome. A common complication occurring in increasing percentages is the number of people developing kidney disease as a result of type 2 diabetes mellitus.¹⁹ Studies have shown that up to 20% of patients with type 2 diabetes have kidney disease at the time of diabetes diagnosis,²⁰ and an additional 30% to 40% will develop kidney disease, most within 10 years of the diabetes diagnosis.²¹ Linked to both metabolic syndrome and kidney disease is hypertension. Hypertension is closely related to insulin

resistance as part of the metabolic syndrome, and diabetic kidney disease may lead to hypertension.¹⁹ In patients with diabetes, the progression of kidney disease is often measured by the onset of microalbuminuria, or an increase in the albumin excretion rate.¹⁹ Data have indicated that blood pressure reduction reduces the risk of microalbuminuria in patients with type 2 diabetes, demonstrating the interest in blood pressure control in the metabolic syndrome.^{19,22,23}

The risk for CVD mortality over an 11-year follow-up period was higher in patients with metabolic syndrome versus those without.

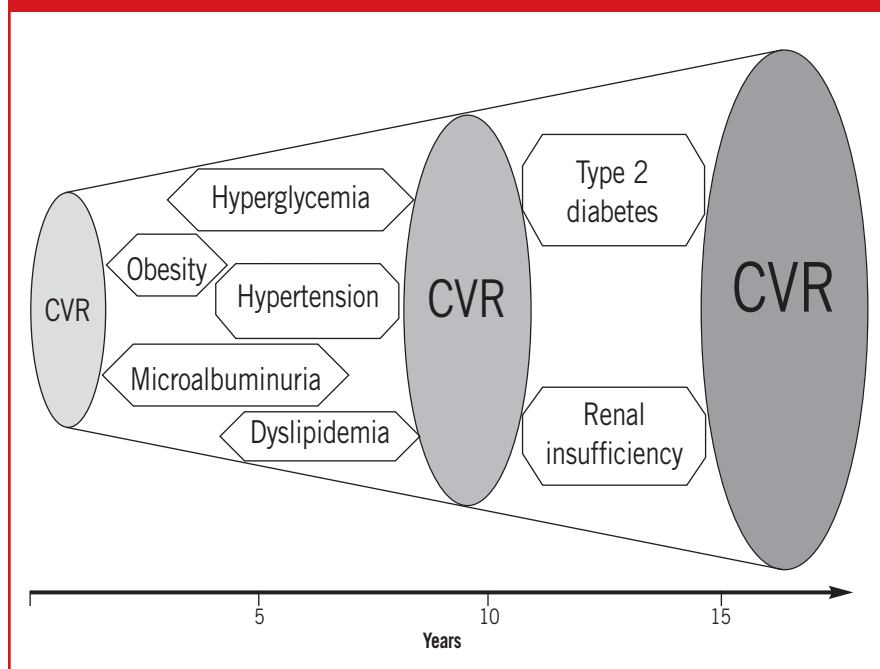
Cardiovascular Risk of Metabolic Syndrome

It is well documented that the metabolic syndrome is associated with CVD and atherosclerotic CVD-related mortality. A 2.5- to 2.8-fold increased risk of cardiovascular mortality has been reported in patients with metabolic syndrome.¹⁴ In a Finnish prospective cohort study, the risk for CVD mortality was evaluated in 1209 men aged 42 to 60 years with or without metabolic syndrome, as defined by WHO and NCEP, and no history of CVD or diabetes at baseline. The risk for CVD mortality over an 11-year follow-up period was higher in patients with metabolic syndrome versus those without.¹⁴ Data from this study suggested that patients with metabolic syndrome may have an increased risk for CVD mortality. Another population-based study of 4483 men and women aged 35 to 70 years in Finland and Sweden found a 1.81-fold increased risk for cardiovascular mortality due to the metabolic syndrome.²⁴

The development of type 2 diabetes is part of the constellation of complications associated with the metabolic syndrome, as well as criteria for its diagnosis. Although diabetes in itself increases the

FIGURE

Metabolic Syndrome: Cardiovascular Risk (CVR)



risk for CVD, evidence suggests that this risk starts to increase long before the diagnosis of diabetes.² Such evidence was provided by the San Antonio Heart Study, a population-based, epidemiologic study of diabetes and coronary heart disease. Six hundred fourteen subjects who were nondiabetic at baseline were followed for 8 years, by which time 43 subjects developed overt type 2 diabetes. Subjects who later developed diabetes had a significantly more atherogenic pattern of cardiovascular risk factors at baseline, compared with subjects who remained nondiabetic. The difference persisted even when subjects with impaired glucose tolerance at baseline (n = 106) were excluded from the analysis.²⁵ This suggests that diabetes is preceded by an atherogenic pattern of risk factors that may be present for years before overt diabetes develops.²⁵ Another study also demonstrated an elevated risk of CVD before the development of type 2 diabetes in a group of 117 629 female nurses fol-

lowed for 20 years.²⁶ Among the women who developed type 2 diabetes during follow-up (n = 5894), the age-adjusted relative risk of myocardial infarction (MI) was 3.75 before diabetes diagnosis and 4.57 after diagnosis compared with women who remained free of diabetes throughout follow-up. The relative risk of stroke was also increased, indicating a need for cardiovascular risk factor management before the diagnosis of type 2 diabetes in at-risk persons.²⁶

Additional evidence supporting increased cardiovascular risk with the presence of metabolic syndrome was noted in the NHANES III population. The incidence of coronary heart disease increased with the presence of NCEP ATP III-defined metabolic syndrome. The incidence of coronary heart disease was 8.7% in subjects without the metabolic syndrome or diabetes, 7.5% in the small population of patients with diabetes only, 13.9% in patients with the metabolic syndrome only, and 19.2% in patients with

both diabetes and metabolic syndrome.²⁷ However, it should be noted that metabolic syndrome was a significant predictor of coronary heart disease only in the univariate analysis; in the multivariate analysis factors associated with metabolic syndrome (such as abnormal blood pressure, increased HDL-C, and diabetes) were significant predictors, but metabolic syndrome itself was not.²⁷

Atherogenic dyslipidemia occurs frequently in patients with the metabolic syndrome, and is characterized by increased triglycerides; low concentrations of HDL; small, dense low-density lipoprotein (LDL) particles; and abnormal apolipoprotein metabolism. Dyslipidemia is a well-known risk factor for CVD, and several studies have demonstrated that cholesterol-lowering therapy was beneficial for people with diabetes even if they did not already have a history of coronary heart disease or elevated cholesterol concentrations.¹⁵ The aim of managing metabolic syndrome is to

TABLE 2

Risk of New-onset Diabetes in Selected Randomized Controlled Trials of RAAS Inhibition

Trial	Nondiabetic Patients at Baseline	New-onset Diabetes	Risk Ratio
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) ³¹	15 569*	Lisinopril: 119/4096 (8.1%) Chlorthalidone: 302/6766 (11.6%)	0.70
Captopril Prevention Project (CAPPP) ³²	10 440	Captopril: 337/5183 (6.5%) Diuretic/Beta blocker: 380/5230 (7.3%)	0.86 (P = .039)
Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality Trial (CHARM) ³³	5436	Candesartan: 163/2715 (6%) Placebo: 202/2721 (7%)	0.78 (P = .020)
Heart Outcomes Prevention Evaluation (HOPE) ³⁴	5720	Ramipril: 102/2837 (3.6%) Placebo: 155/2883 (5.4%)	0.66 (P < .001)
Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) ³⁵	8256	Trandolapril: 335/3432 (9.8%) Placebo: 399/3472 (11.5%)	0.83 (P = .01)
Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) ³⁶	15 245	Valsartan: 690/5267 (13.1%) Amlodipine: 845/5152 (16.4%)	0.77 (P < .0001)

*Number of patients is for lisinopril and chlorthalidone arms only, not overall. RAAS = renin-angiotensin-aldosterone system.

decrease the development of CVD, a major cause of morbidity and mortality. Challenges of managing metabolic syndrome include improved implementation of guidelines using existing therapies and revised therapeutic targets based on new clinical data.¹⁰

PATIENT CASE

- 51-year-old man
- Presented to his family physician for a routine check-up
- No history of CVD in his family
- His mother had a history of type 2 diabetes for many years and died from cancer
- Patient does not smoke and drinks 1 to 2 glasses of wine per week with dinner
- Patient known to have moderate hypertriglyceridemia and was put on diet and exercise 6 months earlier
- On physical examination, the patient is an obese white man; height, 5 ft 6 in; weight, 225 lb; waist circumference, 106 cm

- Blood pressure on 2 measurements was 145/90 mm Hg and 140/90 mm Hg
- Remainder of physical examination was unremarkable

This patient has a number of components of the metabolic syndrome, including moderate hypertriglyceridemia, abdominal obesity, and elevated blood pressure. In addition to a physical examination, the following laboratory tests would be reasonable to obtain: total cholesterol, triglycerides, HDL-C, measured LDL, fasting glucose, glycated hemoglobin, urine for protein and microalbuminuria, thyroid-stimulating hormone, and electrocardiogram (ECG).

The following laboratory values returned:

- Total cholesterol, 231 mg/dL
- Triglycerides, 320 mg/dL
- HDL-C, 32 mg/dL
- LDL, 135 mg/dL
- Fasting glucose, 112 mg/dL
- ECG, nonspecific T wave changes

How would you approach the treatment of the metabolic syndrome in this patient?

In this patient, we would target blood pressure and lipid (LDL) goals per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and ATP III guidelines, respectively. The first line of therapy would be to encourage continuation of the diet and exercise program. Because his blood pressure was elevated on 2 measurements, lowering blood pressure to a target of <140/90 mm Hg is in order. Although a number of agents could be used to lower his blood pressure, he would not be an ideal candidate for starting with a diuretic and/or beta blocker, because these might worsen his already marginal glycemic profile. We would recommend an inhibitor of the renin-angiotensin-aldosterone system (RAAS) in the form of an angiotensin-converting enzyme

TABLE 3

ACE Inhibitor Clinical Trials—Outcomes and Conclusions

	MICRO-HOPE ⁴⁰	PERSUADE ⁴¹	DREAM ³⁹
Drug	Ramipril 10 mg/day or placebo	Perindopril 8 mg/day (n = 721) or placebo (n = 781)	Ramipril up to 15 mg/day or placebo
Trial overview	Substudy of diabetic patients (n = 3577) from HOPE trial	Substudy of diabetic patients (n = 1502) and CV events from EUROPA trial	Study evaluating effects of ramipril on diabetes mellitus (n = 5269)
Results for ACE inhibitor versus placebo	Relative risk reduction Primary outcome: composite of MI, stroke, and CV death, 25% (P = .0004) Secondary outcome: all-cause mortality, 24% (P = .004)	Relative risk reduction Primary outcome: composite of CV death, nonfatal MI, and resuscitated cardiac arrest, 19% (P = .13)—similar to the 20% risk reduction (P = .0003) in the main EUROPA population	Hazard ratio Primary outcome: diabetes or death, 0.91 (P = .15) Secondary outcome: regression to normoglycemia, 1.16 (P = .001)
Study conclusion	Ramipril use significantly decreases CV risk in diabetic patient population	Although not statistically significant, the study results show a trend consistent with previous studies linking positive CV effects of ACE inhibitors in diabetic subjects	Use of ramipril for 3 years does not significantly reduce incidence of diabetes or death, but significantly increases regression to normoglycemia

MICRO-HOPE = Microalbuminuria, Cardiovascular, and Renal Outcomes HOPE study; PERSUADE = Perindopril Substudy in Coronary Artery Disease and Diabetes; DREAM = Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; HOPE = Heart Outcomes Prevention Evaluation; EUROPA = European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; ACE = angiotensin-converting enzyme; MI = myocardial infarction; CV = cardiovascular.

Expert Commentary

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The definition—indeed the very existence—of what has been commonly referred to as metabolic syndrome continues to be debated. However, most agree that the presence of visceral adiposity and associated metabolic abnormalities such as insulin resistance are significant risk factors for the subsequent development of type 2 diabetes and cardiovascular disease (CVD). The presence of hypertension, impaired glucose tolerance (IGT), and dyslipidemia with an increase in waist circumference (or an increase in the waist-to-hip ratio) are easily detectable in a busy clinician's practice. This clustering of physical and laboratory findings may signal the presence of insulin resistance and an increase in metabolically active visceral adipocytes. Thus, whether we label this cluster or constellation of risk factors as a syndrome becomes a discussion of semantics. The critical issue relates to the recognition and aggressive treatment of the patient demonstrating these findings. However, metabolic syndrome has become commonly accepted terminology and a useful signal to the busy practitioner identifying a patient at increased risk for developing CVD and possible type 2 diabetes.

The adipocytes associated with visceral (peritoneal) fat are more metabolically active than the adipocytes of subcutaneous fat. Therefore, individuals with the same body mass index may have different degrees of cardiovascular risk depending on the ratio of visceral to subcutaneous fat: the more visceral fat, the higher the likelihood of an increased cardiovascular risk. Insulin resistance and IGT have been correlated with the degree of visceral adiposity.

Visceral adipocytes secrete a number of metabolically active substances that are proinflammatory, proatherogenic, procoagulant, and prodiabetic. Paradoxically, plasma adiponectin, a cardioprotective cytokine, is suppressed by excess visceral adiposity. An increase in angiotensinogen secretion links visceral adiposity with activation of the renin-angiotensin-aldosterone system (RAAS).

The prescribing of therapeutic lifestyle changes, includ-

ing exercise, weight loss, and an antiatherogenic diet, are pivotal in the management of the metabolic syndrome. Indeed, these lifestyle improvements alone can improve all aspects of the metabolic syndrome. However, pharmacotherapy for individual risk factors may also be required. The treatment of hypertension, in the absence of contraindications, should include an angiotensin-converting enzyme (ACE) inhibitor. ACE inhibitors, because of their favorable pleiotropic effects, are preferred as either monotherapy or in combination with other antihypertensive drugs. Low-dose niacin and fenofibrate with or without statins are beneficial in decreasing triglycerides, raising high-density lipoproteins, and decreasing small, dense low-density lipoproteins. Recently, a meta-analysis of studies utilizing the thiazolidinedione (TZD) rosiglitazone suggested a possible increase in cardiovascular events. It is premature to suggest that the findings from this analysis may extend to other TZDs. Large-scale trials are ongoing and will aid in assessing the potential cardiovascular risks (if any) of the TZDs. Rimonabant, an endocannabinoid receptor blocker, which appears to be an effective antiobesity aid with potentially favorable effects on the dyslipidemia associated with the metabolic syndrome, is currently being evaluated by the US Food and Drug Administration and is not yet approved for use in the United States.

Obesity, type 2 diabetes, and the metabolic syndrome are increasing in the Western world and in developing countries worldwide. However defined, the clustering of risk factors associated with abdominal adiposity and insulin resistance defines a patient at increased risk for CVD and type 2 diabetes, and this is the important clinical issue. Therapeutic lifestyle changes are the cornerstone of treatment for these patients and should be aggressively prescribed. Additional pharmacotherapy, primarily with drugs that block the RAAS like ACE inhibitors, is important to achieve therapeutic goals, mainly lowering the overall risk of CVD.

(ACE) inhibitor, such as ramipril or perindopril, based on available data. Use of other ACE inhibitors may be appropriate if one accepts the concept of class effect with these agents. The patient's LDL level would be measured, with a target LDL cholesterol goal of <130 mg/dL, and his Framingham 10-year coronary heart disease score would be calculated. Depending on his LDL concentration, we would initiate therapy with a statin and/or fibrate. Finally, he is a good candidate for lipid-lowering therapy.

CURRENT THERAPEUTIC APPROACHES

Treatment of Risk Factors

To lower risk for clinical atherosclerotic disease, therapeutic lifestyle changes are first-line interventions to reduce metabolic risk factors. These include weight loss in overweight or obese individuals, increased physical activity, and elimination of an atherogenic diet. Currently no specific drug therapy is recommended for those with metabolic syndrome. However, there are several approved agents for treatment of well-recognized risk factors such as impaired glucose tolerance, dyslipidemia, and hypertension.^{28,29} These agents include antihypertensive agents, lipid-lowering drugs, antiplatelet therapies, hypoglycemic agents, and weight-loss agents.

Potential Benefits of Inhibiting the RAAS in Metabolic Syndrome

The RAAS plays a pivotal role in the pathogenesis of atherosclerotic CVD. Angiotensin II, which is responsible for the majority of the adverse effects attributed to the RAAS, has multiple effects on inflammation, oxidation, atherosclerotic plaque initiation, and progression.^{13,16} It is now recognized that hypertension is a multidimensional syndrome that overlaps with many of the risk factors of the metabolic syndrome.¹⁶ Antihypertensive drugs in use today that block the RAAS were designed primarily to affect physiological

mechanisms contributing to increased blood pressure, but also appear to address a number of the manifold metabolic abnormalities comprising the metabolic syndrome and attendant risks of CVD.¹⁶

It can be presumed that control of RAAS with ACE inhibitors or otherwise is an important step in managing patient outcomes.

ACE inhibitors are a class of drugs frequently used as antihypertensive treatment, either alone or in combination with other agents. ACE inhibitors competitively attenuate the conversion of angiotensin I to angiotensin II in the RAAS, thereby inhibiting peripheral vasoconstriction and reducing blood pressure.³⁰ Antihypertensive properties of ACE inhibitors are well documented; however, any beneficial metabolic effects, especially with regard to glucose and lipid metabolism regulation, are unknown.¹⁹ The progression of CVD begins with risk factors such as diabetes and dyslipidemia, which are associated with levels of angiotensin II that trigger further cardiovascular complications.¹⁶ Progression from these risk factors to atherosclerotic disease can lead to acute coronary syndrome and MI.¹⁶ Based on this information, it can be presumed that control of RAAS with ACE inhibitors or otherwise is an important step in managing patient outcomes.

A number of studies³¹⁻³⁶ have suggested a potential metabolic benefit of inhibiting the RAAS (Table 2). Unexpected findings from the Captopril Prevention Project (CAPPP) and Heart Outcomes Prevention Evaluation (HOPE) trials demonstrated a reduction in new-onset diabetes associated with ACE inhibitor use. Comparing a blood pressure-lowering strategy utilizing an ACE inhibitor (captopril) versus diuretics and beta blockers, the CAPPP study found a 14% reduction in the risk of developing diabetes in patients randomized to captopril (patients

had blood pressure ≥ 100 mm Hg on 2 occasions for inclusion in the study).³² Whether these results could be ascribed to the beneficial effects of the ACE inhibitor or to the potential adverse effects on glycemic control of the diuretic/beta-blocker combination could not be determined.³⁷ The HOPE trial—a trial of the ACE inhibitor ramipril versus placebo (and vitamin E versus placebo, in a 2 X 2 factorial design) in patients at high risk for cardiovascular events—demonstrated a 34% risk reduction in the development of diabetes in patients randomized to ramipril.³⁴ Similarly in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), despite no difference in the primary outcome of prevention of coronary heart disease, patients randomized to an ACE inhibitor had a 30% reduced risk of developing diabetes compared with those in the diuretic arm.³¹ These non-placebo-controlled studies were more difficult to interpret because of the potential confounding metabolic effects of alternative strategies of diuretics and beta blockers.³⁷ In the subsequent Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial, a study of patients with chronic stable coronary disease in which the population was much healthier and the overall cardiovascular event rate was lower, a 17% reduction in new-onset diabetes was observed with trandolapril versus placebo.³⁵ However, it should be noted that new-onset diabetes was not a prespecified end point in this trial, but was rather evident on post hoc analysis.³⁵

The HOPE trial demonstrated a 34% risk reduction in the development of diabetes in patients randomized to ramipril.

Similar reductions in new-onset diabetes have been observed with angiotensin receptor blockers (ARBs). The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial, comparing

losartan with atenolol in patients with hypertension and left ventricular hypertrophy, showed a 25% reduced risk of new-onset diabetes in the ARB arm.³⁸ Similarly, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, a comparison of valsartan and amlodipine in hypertensive patients, demonstrated a 23% reduction in new-onset diabetes in the valsartan arm, despite the fact that blood pressure-lowering and cardiovascular events—particularly MI—were reduced to a greater extent in the amlodipine arm.³⁶ The Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality (CHARM) study of candesartan versus placebo in heart failure patients across the spectrum of ejection fraction demonstrated a 22% overall reduced risk of diabetes.³³

There are a number of potential mechanisms by which inhibiting the RAAS might improve glucose handling and the metabolic syndrome in general. These include a protective effect on pancreatic beta-cell function by inhibiting the potential fibrotic effects of angiotensin II in the pancreas, improved insulin sensitivity by improving blood flow to skeletal muscle, activation of the bradykinin and nitric oxide pathways, and improved peripheral glucose utilization.¹⁶

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial prospectively tested the hypothesis that inhibiting the RAAS with an ACE inhibitor could prevent new-onset diabetes or improve glucose control in patients without CVD but with impaired fasting glucose or impaired glucose tolerance. These patients at high risk for diabetes were randomized to ramipril or placebo, and to rosiglitazone or placebo, in a 2 × 2 factorial design. The ramipril arm demonstrated a trend toward reduction in new-onset diabetes that did not reach statistical significance, although significantly more patients in the ramipril arm demonstrated improvement in glucose control with regression to normoglycemia (defined as

fasting glucose <100 mg/dL and 2-hour glucose levels <140 mg/dL).³⁹ Despite the fact that the DREAM trial failed to prove the primary hypothesis with respect to ACE inhibitor benefit on new-onset diabetes, the trends observed were encouraging. There are a number of potential explanations for the apparent discrepancy between the findings of prior trials such as CAPPP, HOPE, and PEACE, and the findings of DREAM, the first prospective trial to assess new-onset diabetes as a primary end point. Prior trials may have been subject to ascertainment bias; for example, because these trials included patients with or at high risk for CVD, the patients randomized to placebo may have been more likely to be diagnosed with diabetes, due to more hospitalizations for cardiovascular events.²⁸ It is also possible that demonstrating a benefit with respect to diabetes might have required more patients or longer follow-up.²⁸ Nevertheless, DREAM and other trials demonstrate both metabolic and cardiovascular benefits of an ACE inhibitor in patients diagnosed with, or at high risk for the development of, diabetes (Table 3).³⁹⁻⁴¹

DREAM and other trials demonstrate both metabolic and cardiovascular benefits of an ACE inhibitor in patients diagnosed with, or at high risk for the development of, diabetes.

Potential Role of Other Therapies to Improve Insulin Sensitivity in Metabolic Syndrome

Pharmacologic therapies that target insulin resistance hold promise for delaying progression of metabolic syndrome and decreasing risk for atherosclerotic CVD. These include peroxisome proliferator-activated receptor (PPAR)-alpha

agonists (fibrates), PPAR-gamma agonists (thiazolidinediones [TZDs]), and dual PPAR agonists.¹⁰ In the DREAM trial, the TZD rosiglitazone (together with lifestyle modifications) decreased the risk for diabetes or death (the composite primary outcome) by 60% ($P < .0001$) in participants at risk for diabetes.³⁹ Additionally, individuals taking rosiglitazone had a >70% higher likelihood of regressing to normoglycemia in comparison with those taking placebo.³⁹ It is anticipated that dual PPAR agonists will substantially affect metabolic risk factors, and these are currently under development.¹⁰

CONCLUSION

The metabolic syndrome consists of a constellation of physiologic and metabolic abnormalities such as insulin resistance and abdominal obesity that predispose patients to development of diabetes and atherosclerotic CVD. There are numerous clinical criteria available for diagnosis of this condition. The goal of identifying patients with metabolic syndrome is to prevent or delay progression to overt diabetes and CVD and their ensuing adverse outcomes. In addition to treating the component risk factors, and encouraging beneficial lifestyle modification, there is a growing confluence of evidence that inhibiting the RAAS might provide greater benefits in this group of patients than other pharmacologic approaches to lowering blood pressure. Novel agents under development (such as dual PPAR agonists and endocannabinoid antagonists) offer the potential to directly affect pathways of the metabolic syndrome that lead to CVD.

REFERENCES

1. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-2752.
2. Haffner SM. Risk constellations in patients with the metabolic syndrome: epidemiology, diagnosis, and treatment patterns. *Am J Med*. 2006;119(5 suppl 1):S3-S9.

3. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
4. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539-553.
5. Alberti KG, Zimmet P, Shaw J, Grundy SM. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006;23:469-480.
6. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr*. 2006;83:1237-1247.
7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Cardiol Rev*. 2005;13:322-327.
8. Govindarajan G, Whaley-Connell A, Mugo M, et al. The cardiometabolic syndrome as a cardiovascular risk factor. *Am J Med Sci*. 2005;330:311-318.
9. 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;287:356-359.
10. Pershad Singh HA. Treating the metabolic syndrome using angiotensin receptor antagonists that selectively modulate peroxisome proliferator-activated receptor-gamma. *Int J Biochem Cell Biol*. 2006;38:766-781.
11. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol*. 2006;47:1093-1100.
12. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004;109:2818-2825.
13. Khan BV, Sola S, Lauten WB, et al. Quinapril, an ACE inhibitor, reduces markers of oxidative stress in the metabolic syndrome. *Diabetes Care*. 2004;27:1712-1715.
14. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709-2716.
15. Berry C, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes: part I: recent advances in prevention and noninvasive management. *J Am Coll Cardiol*. 2007;49:631-642.
16. Vijayaraghavan K, Deedwania PC. The renin angiotensin system as a therapeutic target to prevent diabetes and its complications. *Cardiol Clin*. 2005;23:165-183.
17. Laaksonen DE, Lakka HM, Niskanen LK, et al. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol*. 2002;156:1070-1077.
18. Kannel WB, D'Agostino RB, Sullivan L, et al. Concept and usefulness of cardiovascular risk profiles. *Am Heart J*. 2004;148:16-26.
19. Thomas MC, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. *Drugs*. 2006;66:2213-2234.
20. Standl E, Stiegler H. Microalbuminuria in a random cohort of recently diagnosed type 2 (non-insulin-dependent) diabetic patients living in the greater Munich area. *Diabetologia*. 1993;36:1017-1020.
21. Schmitz A, Vaeth M, Mogensen CE. Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM. *Diabetologia*. 1994;37:1251-1258.
22. Strippoli GF, Craig M, Schena FP, et al. Antihypertensive agents for primary prevention of diabetic nephropathy. *J Am Soc Nephrol*. 2005;16:3081-3091.
23. Kasiske BL, Kalil RS, Ma JZ, et al. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med*. 1993;118:129-138.
24. Ronnback M, Isomaa B, Fagerudd J, et al. Complex relationship between blood pressure and mortality in type 2 diabetic patients: a follow-up of the Botnia Study. *Hypertension*. 2006;47:168-173.
25. Haffner SM, Stern MP, Hazuda HP, et al. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA*. 1990;263:2893-2898.
26. Hu FB, Stampfer MJ, Haffner SM, et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care*. 2002;25:1129-1134.
27. Alexander CM, Landsman PB, Teutsch SM, et al. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210-1214.
28. Ingelfinger JR, Solomon CG. Angiotensin-converting-enzyme inhibitors for impaired glucose tolerance—is there still hope? *N Engl J Med*. 2006;355:1608-1610.
29. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
30. Oron-Herman M, Rosenthal T, Mirelman D, et al. The effects of S-allylmercaptocaptopril, the synthetic product of allicin and captopril, on cardiovascular risk factors associated with the metabolic syndrome. *Atherosclerosis*. 2005;183:238-243.
31. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997.
32. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPP) randomised trial. *Lancet*. 1999;353:611-616.
33. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759-766.
34. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-153.
35. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-2068.
36. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031.
37. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs*. 2006;66:1169-1177.
38. Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:1004-1010.
39. Bosch J, Yusuf S, Gerstein HC, et al. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006;355:1551-1562.
40. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet*. 2000;355:253-259.
41. Daly CA, Fox KM, Remme WJ, et al. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy. *Eur Heart J*. 2005;26:1369-1378.

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Educational value:

1. Did the newsletter meet each of the following objectives?
 - a. Describe and define the metabolic syndrome and its diagnosing criteria. Yes No
 - b. Describe the various complications associated with a diagnosis of metabolic syndrome. Yes No
 - c. Discuss various available treatment strategies for patients diagnosed with metabolic syndrome. Yes No
 - d. Describe available data on current treatment options used to provide vascular protection and reduce complications associated with the metabolic syndrome. Yes No
2. The content level was:
 Too easy About right Too difficult
3. After reading this newsletter, do you feel more confident about
 - a. Evaluating and identifying patients at risk for developing the metabolic syndrome? Yes No
 - b. Making decisions regarding treatment options for the metabolic syndrome? Yes No
4. What is the most important thing you learned from this newsletter?

Follow-up:

1. Do you plan to read future issues of this newsletter? Yes No
2. Would you recommend these newsletters to a colleague? Yes No
3. Would you be willing to participate in follow-up research to evaluate the long-term impact of the newsletter on your practice? (CME credit will be provided for participating in the follow-up survey.) Yes No
4. If yes, what is your preferred mode of follow-up?
 E-mail Phone Web site Fax
5. What information not included in this newsletter should be included in future issues? _____

6. What is your preferred mode of continuing medical education? (Please rank top 3; 1 = most preferred.)
____ Print newsletter or journal article ____ Internet
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____ Symposium ____ Internet ____ CD-ROM

Commercial bias:

I found the material objective and free of commercial bias. Yes No

Commitment to change:

What change(s) (if any) do you plan to make in your practice as a result of reading this newsletter? _____

Questions

- Which of the following is the most widely accepted pathological condition associated with the metabolic syndrome?
 - Insulin resistance
 - Abdominal obesity
 - Increased cholesterol
 - Increased blood pressure
- Which of the following organizations have *not* developed diagnosing criteria for metabolic syndrome?
 - National Cholesterol Education Program Adult Treatment Panel III
 - World Health Organization
 - American Heart Association
 - International Diabetes Federation
- Patients with the metabolic syndrome are at risk of developing all of the following complications *except* _____.
 - coronary heart disease
 - type 2 diabetes
 - renal disease
 - chronic pancreatitis
- Which of the following is a common complication shown to occur in increasing percentages as a result of type 2 diabetes?
 - Myocardial infarction
 - Kidney disease
 - Stroke
 - Cardiovascular atherosclerosis
- The onset of microalbuminuria in patients with diabetes can indicate the progression of what condition?
 - Hypertension
 - Hyperlipidemia
 - Kidney disease
 - Obesity
- The main goal of managing metabolic syndrome is to decrease the development of _____.
 - cardiovascular complications
 - type 2 diabetes
 - chronic renal disease
 - All of the above
- Which of the following may be considered a first-line intervention to reduce metabolic risk factors?
 - Antihypertensive medications
 - Weight loss
 - Lipid-lowering therapy
 - Hypoglycemic agents

- The progression of cardiovascular disease begins with risk factors such as diabetes and dyslipidemia, which are associated with levels of angiotensin II that trigger further cardiovascular complications.
 - True
 - False
- Antihypertensive properties of angiotensin-converting enzyme (ACE) inhibitors are well documented; however, which of the following clinical trials indicated a more broad vascular protection effect of ACE inhibitors?
 - Heart Outcomes Prevention Evaluation (HOPE)
 - Captopril Prevention Project (CAPPP)
 - Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM)
 - Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
- Which of the following trials was the first to prospectively assess new-onset diabetes as a primary end point with ACE inhibitors?
 - Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)
 - CAPPP
 - DREAM
 - ALLHAT

Answer Form

 Circle the correct answer.

1	a b c d	6	a b c d
2	a b c d	7	a b c d
3	a b c d	8	a b
4	a b c d	9	a b c d
5	a b c d	10	a b c d

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