Addressing the Global Cardiovascular Risk of Hypertension, Dyslipidemia, Diabetes Mellitus, and the Metabolic Syndrome in the Southeastern United States, Part II: Treatment Recommendations for Management of the Global Cardiovascular Risk of Hypertension, Dyslipidemia, Diabetes Mellitus, and the Metabolic Syndrome

WILLIAM BESTERMANN, MD; MARK C. HOUSTON, MD; JAN BASILE, MD; BRENT EGAN, MD; CARLOS M. FERRARIO, MD; DAN LACKLAND, DRPH; RALPH G. HAWKINS, MD; JAMES REED, MD; PHILIP ROGERS, MD; DANIEL WISE, MD; MICHAEL A. MOORE, MD

ABSTRACT: An aggressive global approach to screening and to the management of the metabolic syndrome is recommended to slow the growth of the syndrome throughout the United States. Prevention should begin in childhood with healthy nutrition, daily physical activity, and annual measurement of weight, height, and blood pressure beginning at 3 years of age. Such screenings will identify cardiovascular risk factors early, allow the health care provider to define global cardiovascular risk with the COSEHC Cardiovascular Risk Assessment Tool, and allow treatment of each risk factor. Lifelong lifestyle modifications and pharmacologic therapy will be required in most patients. Antihypertensive therapy for these patients should begin with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker unless a compelling indication for another drug is present. Metformin should be considered the first drug for glucose control in the patient with type 2 diabetes. A statin should be used initially for hyperlipidemia unless contraindicated. Combinations of antihypertensive, antiglycemic, and lipid-lowering agents will often be required. **KEY INDEXING TERMS:** Metabolic syndrome X; Hypertension; Diabetes mellitus type 2; Hyperlipidemia; Cardiovascular disease. **[Am J Med Sci 2005; 329(6):292–305.]**

The combination of abdominal obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance or type 2 diabetes mellitus defines the metabolic syndrome.[1] The current increasing annual prevalence of the metabolic syndrome is driven by the epidemic of obesity occurring throughout the Western world and especially in the Southeastern United States.[1] Beginning with childhood obesity, insulin resistance develops to maintain normal blood glucose level. Over time, type 2 diabetes mellitus, hypertension, and dyslipidemia develop in the majority of obese individuals. Increasing risk for cardiovascular disease and death parallels the lifelong increase in body weight and development of associated cardiovascular risk factors. Unfortunately, cardiovascular risk factor screening has traditionally focused on only one or another risk factor rather than on a comprehensive or global approach.

As recommended in Part I of this paper,[1] cardiovascular risk factor screening should begin at birth with weight and height measurement followed by annual blood pressure measurement beginning at 3 years of age. Any child or adolescent with weight or blood pressure greater than the 90th percentile for his or her age should also have blood lipids and fasting blood glucose level measured. Adults, beginning at age 18, should have an annual comprehensive assessment for cardiovascular risk factors, with a calculation of their global cardiovascular risk using the COSEHC Cardiovascular Risk Assessment Tool.[1] Most individuals will have more than one cardiovascular risk factor, including excessive body weight in association with one or more conditions that define the metabolic syndrome.[1] This paper presents a comprehensive, or global, approach to the management of the metabolic syndrome based on available evidence. These recommendations were developed by the authors based on the available

From the Consortium for Southeastern Hypertension Control, and from the Low Country Medical Group, Beaufort, South Carolina (WB), Vanderbilt University School of Medicine and St. Thomas Hospital, Nashville, Tennessee (MCH, RGH), the Ralph H. Johnson VA Medical and the Center Medical University of South Carolina, Charleston, South Carolina (JB, BE, DL), the Wake Forest University Baptist Medical Center, Winston Salem, North Carolina (CMF, MAM), Morehouse School of Medicine, Atlanta, Georgia (JR), the Hattiesburg Clinic, Hattiesburg, Mississippi (PR), and the Presbyterian Center for Preventative Cardiology, Charlotte, North Carolina (DW).

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Correspondence: Michael A. Moore, MD, COSEHC, 144 Winston Court, Danville, VA 24541, 336716-5819 (E-mail: mamls@earthlink.net).

clinical research and their clinical experience. It is acknowledged that there have been few randomized clinical trials based on patients using the current definitions of the metabolic syndrome to determine the best treatments. These recommended approaches represent expert opinion formulated from observational studies and randomized clinical trials on the various components of the metabolic syndrome. For an individual patient, his or her health care provider should determine the best treatment based on the available information from randomized clinical trials, observational studies, and expert opinion with consideration of the individual patient's clinical needs and treatment capabilities.

The treatment plan should be based on a strategy directed to (1) address all reversible cardiovascular risk factors, (2) encourage long-term treatment adherence, (3) utilize medicines based on well-designed randomized clinical trial outcomes, and (4) when possible, utilize treatments that provide concomitant benefits to more than one risk factor. As an example, weight loss and increased physical activity will assist in controlling hypertension and dyslipidemia while reducing insulin resistance. Each identified component of the metabolic syndrome should be vigorously treated. Recommended treatment goals for reversible cardiovascular risk factors based on clinical trial outcomes are summarized in Table 1.

Table 1. Recommended Treatment Goals for Cardiovascular Risk Factors in Patients with the Metabolic Syndrome

Factor	Goal
Weight reduction	BMI 18.5–24.9
Hypertension	<140/90 mm Hg
Hypertension in diabetes	<130/80 mm Hg
LDL-cholesterol[3]	60–70 mg/dL
Triglycerides[4]	<150 mg/dL
Smoking	Cessation
Physical activity[5]	60 minutes daily
Alcohol	Reduce to <20 g per day
Homocysteine[6]	<9 μmol/L

BMI, body mass index; LDL, low-density lipoprotein.

Hypertension Treatment Goals

Since cardiovascular risk increases proportionally to increases in blood pressure above 115/75 mm Hg, it could be assumed that hypertension treatment should be aimed at reducing blood pressure to less than 120/80 mm Hg.[2] However, there are no hypertension treatment clinical trial data that show that reducing the blood pressure to below 139/82 mm Hg will reduce the risk of future cardiovascular morbidity or mortality except in patients with hypertension and diabetes mellitus and/or renal insufficiency.[3,4] Thus, the goal for hypertension treatment of a blood pressure of less than 140/90 mm Hg, and less than 130/80 mm Hg for patients with diabetes mellitus or renal insufficiency, are appropriate, and they reflect a large body of clinical trial data.[5,6]

Lipid Treatment Goals

The definition of the metabolic syndrome uses an elevation of triglycerides and reduced high-density lipoprotein (HDL) cholesterol level. In the Framingham Study, the triglyceride/ HDL ratio was demonstrated to be the strongest predictor of coronary artery disease risk among the various lipid indicators.[7] In practice, the therapeutic strategy should be to reduce low-density lipoprotein (LDL) cholesterol to 60 to 70 mg/dL beginning with statin therapy when a subject with the metabolic syndrome also has underlying coronary heart disease.[8–11] The Helsinki Heart Study showed a 65% reduction in coronary heart disease among metabolic syndrome–type patients treated with gemfibrozil.[12] Treatment of patients with lipid abnormalities for LDL-cholesterol, HDL-cholesterol, or triglycerides should be aimed at the lower levels within the range recommended in the ATP-1II Report.[8–11,13] Ideally, HDL-cholesterol should be greater than 40 mg/dL in men and greater than 50 mg/dL in women. Triglyceride levels should be less than 150 mg/dL and optimally less than 75 mg/dL.[8] Patients with the metabolic syndrome typically have elevated triglyceride levels, low HDL-cholesterol levels, an increased number of LDL particles, and a propensity to smaller dense LDL particles.[14] These abnormalities are partially addressed by calculating the non-HDL-cholesterol level (Total cholesterol − HDL-cholesterol) when the triglyceride level is greater than 200 mg/dL. Accordingly, combinations of lipid-lowering drugs may be needed in some patients to reach the recommended treatment goals.

Diabetes Mellitus Treatment Goals

Glycemic control reduces the risk for all complications from diabetes mellitus. Glycemic related risks, including those for cardiovascular disease, have been reported to begin when either the fasting blood glucose level is greater than 75 mg/dL or the 2-hour postprandial blood glucose level is greater than 110 mg/dL.[15] In a meta-analysis of published studies including more than 95,000 patients with type 2 diabetes followed for more than 12 years, there was a 1% increase in annual cardiovascular mortality for each 1 mg/dL increase in fasting blood glucose over 75 mg/dL and a 2% increase in annual cardiovascular mortality for each 1 mg/dL increase of the postprandial blood glucose over 110 mg/dL.[15] Thus, optimal glycemic goals in patients with type 2 diabetes mellitus may be lower than those currently recommended.[16] However, there have been no randomized clinical trials of the benefit of reducing the risk of diabetic microvascular, macrovascular events, or

Table 2. Current versus Probable Optimal Glycemic Goals for Type 2 Diabetes Mellitus

	Current Recommendations[16]	Probable Optimal Goals[15]
Preprandial plasma glucose	90–130 mg/dL	80–99 mg/dL
Postprandial plasma glucose	<180 mg/dL	
2-hour Postprandial glucose		110 mg/dL
Hemoglobin A1 C	<7.0%	<6.5%

mortality through treatment to the lower optimal glycemic treatment goals listed in Table 2.

Lifestyle Changes

It cannot be emphasized enough that the cornerstone for clinical management of adults with the metabolic syndrome is appropriate lifestyle change (Table 3). Although drug therapy may be required, weight loss, exercise, and appropriate nutritional supplements are important for patients with the metabolic syndrome. Moderate levels of weight loss (5–10%) with optimal nutrition and exercise (walking at least 60 minutes each day) have proven effective in reducing the risk for developing diabetes mellitus, improving the other components of the metabolic syndrome, and decreasing the risk for cardiovascular events.[17] Consequently, all metabolic syndrome patients are encouraged to seek the proven health benefits of prudent lifestyle change. Approximately 50% of patients with stage I hypertension can reach the blood pressure goal with lifestyle modifications.[17] Some metabolic syndrome patients can achieve normalization of insulin resistance, fasting blood glucose level, lipid levels, and C-reactive protein level with lifestyle changes.[17] Treatment of metabolic syndrome, beginning with lifestyle changes, should always be initiated when the blood glucose level is greater than 110 mg/dL.[15]

Weight Loss

Loss of excessive body weight reduces the risk for developing hypertension, dyslipidemia, type 2 diabetes mellitus, congestive heart failure, coronary artery disease, transient ischemic attacks, stroke, renal disease, several cancers, and arthritis. There is a great deal of ongoing research into possible genetic and hormonal factors that contribute to excessive body weight, but currently the only effective approach is a reduction in daily caloric intake of a balanced diet with a simultaneous increase in physical activity.

The DASH Eating Plan

The Dietary Approach to Stop Hypertension Eating Plan is very appropriate for hypertensive patients. It causes significant lowering of blood pressure in hypertensive individuals, particularly African Americans and other minority population groups. DASH is rich in fruits, vegetables, and low-fat dairy foods and reduced in total and saturated fat. Compared with the usual American diet, it also is reduced in red meat, sweets, and sugar-containing drinks. It is rich in potassium, calcium, magnesium, fiber, and protein. A DASH Eating Plan with lower sodium content (DASH-II) reduces blood pressure levels beyond what the DASH-I diet can produce. Studies have shown that the DASH Eating Plan lowers blood pressure, LDL-cholesterol, and plasma homocysteine levels[18–20] and reduces insulin resistance among diabetic patients. Information concerning the DASH Eating Plan is available at www.nih.gov.

The Mediterranean Diet also reduces markers of vascular inflammation in metabolic syndrome patients.[21] This diet has been associated with a significant reduction in cardiovascular disease and is a worthy alternative to the DASH Eating Plan.[21]

Exercise

Daily, low-impact aerobic activity should be encouraged. Reduced physical activity promotes obesity. Low levels of daily activity are particularly common among African American women, a group with higher rate of cardiovascular mortality.[22] Daily physical activity of 60 minutes will assist in weight loss, hypertension, and dyslipidemia control and reduction of insulin resistance to help prevent the onset of, and to assist in glycemic control of, type 2 diabetes mellitus.[17,23] A formal exercise program is not necessary, but it can be very beneficial. Daily walking, or any daily activity that maintains the pulse rate at 70% of 220 minus one's age for 30 to 60 minutes, should be undertaken to increase aerobic capacity and to assist with weight loss. Less intense exercise for a shorter time can also reduce cardiovascular risk among patients with type 2 diabetes. Cardiovascular mortality correlates inversely with the distance of walking.[23] Supervised low-intensity resistance exercise for 30 minutes, three to four times a week, can improve lean muscle mass, reduce insulin resistance, and improve glycemic control in patients with type 2 diabetes.[24]

Smoking

Cigarette smoking continues to be very prevalent in the Southeast, with West Virginia being the state with the highest annual use within the United States.[25] Cigarette smoking as well as exposure to passive smoke increases cardiovascular disease risk

Table 3. Recommended Lifestyle Changes[94a]

Nutrition	Daily Intake/Potential Result
DASH 1 and DASH II-Na+ diets	Lowers BP about 11–12/6–7 mm Hg
Dietary sodium restriction	50–100 mmol, lowers SBP 2–8 mm Hg
Dietary potassium	60–100 mEq, lowers SBP 2–4 mm Hg, CVA risk, reduce FBG
Potassium/sodium ratio >5:1	
Magnesium	1000 mg, lowers SBP 2 mm Hg, reduce FBG
Calcium	1000–1500 mg may benefit hypertension control
Zinc	25 mg
Protein:	30% total calories, approximately 1.0–1.5 g/kg
Nonanimal sources preferred but lean animal protein in moderation is acceptable	1 serving per week of animal protein
Hydrolyzed whey protein	30 g (has ACEI action)
Soy protein (fermented is best)	30 g (lowers BP, lipids)
Coldwater fish, fowl, poultry	3 servings/week of fish, 3 servings/week fowl or poultry
Fats:	30% total calories
Omega-3 fatty acids (30%) PUFA; limit intake GLA	3–4 g, lowers BP, IR, FBG, TG, and CVD risk
Omega-6 fatty acids (10%) PUFA	May benefit hypertension control
Omega-9 fatty acids (30%) MUFA	4 tablespoons; lowers BP, lipids, FBG
Saturated fatty acids (lean, wild animal meat)	30% total daily dietary fat intake
Ratio of (polyunsaturated/saturated fats)	>2.0
Omega-3/omega-6 PUFA	Ratio 2:1–4:1 recommended
No *trans*-fatty acids (hydrogenated margarines, hydrogenated vegetable oils)	Elimination potentially reduces CV disease risk
Nuts: almonds, walnuts, hazelnuts, etc.	½ cup daily recommended if no allergy to nuts
Carbohydrates:	40% total daily calories
Reduce or eliminate refined sugars and simple carbohydrates; reduce glycemic load and glycemic index; use Stevia, alcohol sugars (xylitol), and cinnamon sweetners; avoid sodas, diet drinks (aspartame, saccharin)	Reduces FBG, IR; may benefit hypertension and dyslipidemia
Increase complex carbohydrates and fiber whole grains (oat, barley, wheat), fruits, vegetables, beans, legumes	Reduces FBG, insulin resistance, may benefit hypertension and dyslipidemia
Fresh, relatively uncooked vegetables and legumes (>4 servings a week)	Contributes to reducing risk for CV disease
Oatmeal	60 g; lowers BP, lipids, FBG[a]
Oatbran (dry)	40 g; lowers BP, lipids, FBG[a]
β-Glucan	3 g; lowers BP, lipids, FBG[a]
Psyllium	7 g; lowers BP, lipids, FBG[a]
Garlic	4 cloves/4 g; lowers BP, lipids
Celery	
Celery, 4 pieces	May benefit hypertension control
Celery juice, 8 teaspoonfuls tid	May benefit hypertension control
Celery seed extract	1000 mg bid
Celery oil	½–1 teaspoon tid
Lycopene: Tomatoes and tomato products, guava, apricots, pink grapefruit,[b] papaya	10 mg
Green tea, 12 oz	Reduces FBG; may improve hypertension or dyslipidemia
Exercise, aerobic	7 days/week
60 minutes daily (brisk walk, jog, etc.)	Reduces BP ~10–15/5–10 mm Hg[a]
4200 kJoules/week	Reduces CV risk >30%, reduces BS and lipids, increases EPCs
Resistance training	Supervised light intensity 3×/week for 30 minutes
Weight loss (10 lbs or 4.5 kg will have a beneficial effect)	Weight reduction reduces SBP 5–20 mm Hg/10 kg, lowers blood sugar, lipids, improves insulin resistance, reduces CRP[a]
To ideal body weight	
Lose 1–2 pounds/week	
BMI <25	
Waist circumference	<35 inches in female, <40 inches in male
Total body fat	<22% in females, <16% in males
Increase lean muscle mass	
Alcohol restriction	<20 g/day, limit alcohol to 1 oz (30 ml) or 2 drinks a day for men and 0.5 oz for women
Wine (red wine preferred)	1 drink = 5 oz (lowers SBP 2–4 mm Hg)
Beer	1 drink = 12 oz
Liquor	1 drink = 1.5 oz of 80 proof liquor

Table 3.—*Continued*

Nutrition	Daily Intake/Potential Result
Caffeine restriction	100 mg/day or discontinue
Tobacco and smoking	STOP
Vitamins, antioxidants and supplements	
Vitamin C	250–500 mg bid, may improve blood pressure and endothelial dysfunction
Vitamin B-6	100 mg qd to bid, may improve hypertension and dyslipidemia and fasting blood glucose
Co-enzyme Q-10	60 mg qd to bid, may improve hypertension and dyslipidemia and fasting blood glucose
Lipoic acid with biotin	100–200 mg bid
N-acetyl cysteine	1000 mg bid, may improve hypertension
L-Arginine (lentils, hazelnuts, walnuts, peanuts) and supplement	5 g bid, may improve hypertension
Folate	800 μg, lowers homocysteine
Vitamin B-12	1000 μg, lowers homocysteine
Selenium	200 μg

ACEI, angiotensin-converting enzyme inhibitor; bid, twice daily; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CRP, C-reactive protein; CV, cardiovascular; CVA, cardiovascular accident; CVD, cardiovascular disease; EPC, endothelial progenitor cell; FBG, fasting blood glucose; GLA, gamma linoleic acid; IR, insulin resistance; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; qd, daily; SBP, systolic blood pressure; TG, triglycerides; tid, three times daily.

[a] *Reduce* total caloric intake *consistent with patient's nutritional requirements, exercise level, gender, age, ethnicity and required weekly weight loss. Recommendations are for patients with normal renal and hepatic function and who are not allergic or intolerant to any recommended substance.*

[b] *Grapefruit juice is contraindicated with certain CCBs and statins.*

and mortality. Smoking cessation reverses this risk. Smoking is an addiction that often begins in childhood and adolescence. Professional help is needed by most adults to stop smoking. Vigorous antismoking programs should be promoted for children and adolescents.

Dietary Supplements

There have been many observational and clinical trials on the use of dietary supplements, including vitamins, in the prevention of cardiovascular risk factors or disease. To date, none have been shown to predictably reduce cardiovascular risk to the degree that can be obtained with hypertension, dyslipidemia, or hyperglycemic treatment. Clinical trials have shown mixed results as to the benefit of dietary supplements in reducing cardiovascular risk due to methodologic problems. Some studies have shown positive effects in reducing the incidence of coronary artery disease, but others have been neutral or negative.[26]

Initial Drug Selection for Patients with the Metabolic Syndrome

Metabolic syndrome patients are the victims of a lifelong process. Clinical trials are relatively brief in duration, usually less than 5 or 6 years. Interventions that are beneficial over the short term may not be beneficial over time, and interventions that appear to be neutral or equal may, over time, prove to be more beneficial than accepted drug treatments. Specifically, any therapy for a component of the metabolic syndrome that causes weight gain (increased central obesity), increases plasma homocysteine and glucose levels, augments glomerular hyperfiltration and microalbumin, worsens endothelial dysfunction, promotes vascular inflammation, increases insulin resistance, or aggravates dyslipidemia or other parameters of the metabolic syndrome should be avoided in the absence of compelling indications. Metabolic syndrome patients require pharmacologic therapy that is carefully designed, keeping several important requirements in mind. Drugs selected for initial treatment should meet several critical criteria. One ideal drug to correct all of the abnormalities of the metabolic syndrome does not exist. Only drugs that have been demonstrated to reduce cardiovascular morbidity and mortality in properly designed randomized clinical trials should be used to treat each component. Drugs chosen to treat the individual abnormalities of the metabolic syndrome should have many of the characteristics listed in Table 4. Initial preferred drugs for the management of the various components of the metabolic syndrome are listed in Table 5.

Lipid Management

Elevated triglyceride levels with a reduced HDL-cholesterol level is the typical lipid abnormality seen in the metabolic syndrome. All patients with hypertriglyceridemia have small dense LDL particles, and all diabetic patients are considered to be at equivalent risk of coronary artery events as patients with established coronary artery disease. Metabolic syndrome patients should be treated according to the

Table 4. Optimal Drug Effects in the Metabolic Syndrome

Improve endothelial function and arterial compliance
Improve insulin resistance
Cause no adverse effect on weight
Provide favorable effects on other cardiovascular risk factors
Improve dyslipidemia
Control hypertension
Improve or maintain renal function
Reduce vascular inflammation and the surrogate markers such as CRP or microalbuminuria
Reduce prothrombotic activity
Reduce adverse vascular remodeling such as left ventricular hypertrophy
Prevent or reverse atherosclerosis
Have minimal side effects
Provide best efficacy at the lowest price
Demonstrate no tachyphylaxis
Have enhanced efficacy with lifestyle modifications
Are effective as once-a-day therapy

lipid goals listed in Table 1.[8,13] Because an elevation in LDL-cholesterol is often present in the metabolic syndrome, it remains an important target for clinical management.

Reduction of LDL-cholesterol to 60 mg/dL may reduce cardiovascular risk even in the presence of a low HDL-cholesterol level.[8] In addition, the level of pretreatment LDL-cholesterol may not be such an important factor, since statin therapy reduces cardiovascular risk even in patients with an initial LDL-cholesterol level of 100 mg/dL.[8–11] In the Heart Protection Study, patients with diabetes mellitus treated with simvastatin had a reduction in the risk of a cardiovascular event regardless of their baseline LDL-cholesterol levels.[9]

Accordingly, a 30% to 40% reduction in LDL-cholesterol, regardless of the individual's baseline value, is recommended in those with the metabolic syndrome when the LDL-cholesterol level is above the recommended treatment goal.[8,9]

Statins are the drug of first choice for the treatment of type 2 diabetic patients unless contraindicated. All patients with type 2 diabetes mellitus should receive a statin regardless of cholesterol level.[13] Patients on a statin with glycemic control improve their dyslipidemia with reductions of cardiovascular events.[27–34] Statins may also provide favorable effects on the many clinical abnormalities seen in the metabolic syndrome, including hypertension control, reduction of uric acid, improvement of insulin resistance, and reduction in the frequency of new-onset type 2 diabetes mellitus.[35–39] When a statin has been used with an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or calcium channel blocker (CCB), and metformin, there was improvement in dyslipidemia, hypertension, and glycemic control.[40] In addition, there was a reduction or reversal of anatomical coronary artery disease and a reduced frequency of cardiovascular events.[41] The efficacy, potential side effects, long-term safety experience, and results of clinical trials should be used in the selection of a specific statin. Before considering the addition of a second antilipid drug, the statin should be increased to the full recommended dose if tolerated, and every effort should be made to achieve good glycemic control.

Table 5. Preferred Drugs in the Metabolic Syndrome

	Hypertension	Hyperlipidemia	Hyperglycemia
First Step	ACEI/ARB	Statins	Metformin
Second Step	CCB	Fibrates	Thiazolidinedione

To reach the recommended LDL-cholesterol treatment goal, two lipid-lowering drugs in addition to lifestyle changes will often be necessary. Niacin, fibrate, or ezetimibe may be added to a statin. It should be noted that gemfibrozil can increase plasma 1evels of atorvastatin, lovastatin, and simvastatin, creating an increased risk for myopathy and rhabdomyolosis.[42] Alternatively, combining these statins with fenofibrate, regardless of the dose used, does not appear to increase the risk for myopathy and may be a safer strategy in those with the metabolic syndrome.

Initial Hypertension Management

For patients with hypertension and either the metabolic syndrome or type 2 diabetes mellitus without any concomitant disease or compelling indication for a specific antihypertensive drug, the recommended initial antihypertensive drug is an ACEI or an ARB, with a CCB being a reasonable alternative.[40,41] These medications meet all of the criteria listed in Table 4 and merit selection because of a demonstrated effect on cardiovascular event reduction and multiple positive metabolic effects. The CAPPP, LIFE, HOPE, and ALLHAT clinical trials demonstrated significant reductions of cardiovascular events associated with inhibition of the renin-angiotensin-aldosterone system.[43–46] ACEI and ARB therapy have been associated with reducing the frequency of new onset type 2 diabetes mellitus among hypertensive patients compared with beta blockers, and in some studies, compared with thiazide diuretics.[43–49]

The incidence of cardiovascular disease is time dependent, usually occurring after many years of risk factors being present. Currently available clinical trials are limited by their relatively short durations. For example, diabetic retinopathy in patients with type 2 diabetes mellitus for more than 10 years has been reported to have a 3-year cumulative incidence of sight-threatening diabetic retinopathy almost 20 times higher than in patients with type 2 diabetes mellitus for less than 10 years.[50] There

should be concern when any pharmacologic treatment increases another cardiovascular risk factor, since drugs are used for life by the diabetic patient. Certain antihypertensive medications, such as thiazide diuretics, can induce adverse metabolic effects, increasing the risk of cardiovascular complications over several decades.[51]

Even though thiazides and beta-blockers have been repeatedly shown in clinical trials to reduce all cardiovascular complications from hypertension, adverse effects can occur with their use.[46] In 60-year-old men who were receiving thiazide and beta-blockers, a rise in blood glucose level was associated with an increase of myocardial infarction over a 17-year period.[52] The combination of a beta-blocker and a thiazide diuretic in hypertensive patients has been reported to worsen glycemic control more than an ARB and CCB.[53] Beta-blocker therapy for hypertension has been associated with weight gain, which potentially would aggravate the metabolic syndrome.[54,55] Beta-blockers and thiazide diuretics are also associated with insulin resistance, hyperglycemia, dyslipidemia, homocystinemia, and hyperuricemia.[52,53,56] In addition, thiazide diuretics can cause electrolyte disorders and hypercalcemia. Thus, they should be used with concern in patients with metabolic syndrome unless a compelling indication for their use exists.

Several clinical trials have reported an increased incidence of type 2 diabetes mellitus in hypertensive patients treated with thiazides and/or beta-blockers. Thiazides and beta-blockers are not the best first choice antihypertensive agents in metabolic syndrome patients unless there are compelling clinical indications for them. Patients in ALLHAT receiving chlorthalidone experienced a relative greater risk for developing new diabetes—-43% to 65% higher than the risk in those receiving lisinopril and 18% to 30% higher than the risk in those receiving amlodipine.[46] The absolute risk of developing diabetes was 11.6%, 9.8%, and 8.1% for chlorthalidone, amlodipine, and lisinopril, respectively.[46] These and other adverse metabolic risks were also noted in the Alpine Study, in which diuretics and beta-blockers were compared with a CCB with an ARB. The risk of developing metabolic syndrome was significantly greater among patients treated with beta-blockers and thiazide compared with those treated with ACE-CCB.[49]

The results of the ALLHAT trial have been used to argue that thiazide diuretics should be used as first-step antihypertensive therapy for most hypertensive patients, including those with type 2 diabetes mellitus. This recommendation was based on the ALLHAT outcome that neither an ACEI- nor a CCB-based antihypertensive therapy reduced cardiovascular mortality to a greater extent than chlorthalidone-based therapy. The trial did not demonstrate chlorthalidone to provide more risk reduction for coronary artery disease than the other two classes of drugs. The primary endpoint in ALLHAT demonstrated that there was no statistically significant difference in the frequency of the combination end points of fatal and nonfatal coronary artery disease among the three drug treatment groups.[46]

Second-Step Antihypertensive Therapy

The ALLHAT trial and several other hypertensive clinical trials (AASK, HOPE, HOT) showed that more than one class of antihypertensive agents will be needed to reach goal blood pressure.[3,43,46,57] This is particularly true among patients with type 2 diabetes mellitus and those with renal insufficiency.[58,59] In ALLHAT, 70% of patients with stage 1 hypertension required two or more antihypertensive drugs.[46] There are no randomized prospective clinical trials comparing one combination of antihypertensive agents to another with cardiovascular mortality as an outcome measure. Numerous clinical trials have demonstrated the efficacy of several antihypertensive drug combinations used either concomitantly or in fixed-dose combinations to reduce blood pressure (Table 5). These include ACEI-thiazide, ARB-thiazide, beta-blocker–thiazide, and ACEI-CCB.

A CCB is an attractive second antihypertensive agent to add to an ACEI or ARB if goal blood pressure has not been reached. Amlodipine has beneficial effects on insulin resistance and endothelial function that are additive to or synergistic with an ACEI.[60–64] Verapamil in combination with an ACEI reduced the frequency of coronary artery disease events 15% more than did a thiazide diuretic in combination with a beta-blocker, although the difference was not significantly different.[46] On the other hand, the verapamil-based strategy employed in the INVEST trial showed a 15% reduction in new-onset diabetes.[65] The use of verapamil in combination with an ACEI may be quite appropriate in patients with proteinuria, since this combination has been shown to reduce proteinuria to a greater extent than that observed with either drug alone. ACEI and CCB in combination were significantly better than a combination of thiazide and beta-blocker in preventing stroke in older patients with isolated systolic hypertension.[66]

Since metabolic syndrome patients are frequently obese with increased sympathetic tone and salt-sensitive hypertension, a thiazide diuretic is also a reasonable secondary antihypertensive after optimal inhibition of the renin-angiotensin-aldosterone system has been obtained.[67–69] The negative metabolic effects of thiazide diuretics, such as hyperkalemia, dyslipidemia, and insulin resistance can be minimized with lower doses (up to 25 mg a day) or in combination with medications that have more favorable metabolic effects.[70–73] The thiazide-type di-

uretic, indapamide, merits consideration because of minimal or absent adverse effects on glucose, insulin resistance, potassium excretion, plasma lipids, and renal function but with a significant improvement in left ventricular hypertrophy.[70,71,74,75] Finally, it should be recognized that since multiple agents are usually required for hypertension control, the initial agent, such as an ACEI or an ARB as recommended, often assumes less importance toward achieving hypertension control.

Glycemic Management

Glycemic control reduces the risk for all complications from diabetes mellitus. Good glycemic control requires a continual combination of proper diet, daily physical activity, and usually antiglycemic drug therapy.

Initial Antiglycemic Drug Recommendations

Although there are several classes of oral antiglycemic drugs approved and effective for glycemic control in patients with type 2 diabetes mellitus, metformin is recommended as the preferred initial drug when diet and exercise have not been adequate. Contraindications to metformin include an allergy to the drug, significant hepatic or renal insufficiency, or congestive heart failure.[76] In choosing antiglycemic therapy for type 2 diabetes mellitus, it is important to look beyond glycemic control to therapies that will more effectively protect the cardiovascular system. The magnitude of metformin's benefit on the prevention of macrovascular complications has been reported to be similar to that achieved by lipid-lowering drugs and antihypertensive agents in high-risk cardiovascular populations.[76] Metformin is the only antiglycemic medication that has been shown to reduce the incidence of macrovascular events in type 2 diabetes mellitus regardless of glycemic control.[77] The reported vascular benefits of metformin are shown in Table 6.

In the United Kingdom Prospective Diabetes Study (UKPDS) more than 5000 (5102) type 2 diabetic patients were randomized to glycemic treatment with metformin, chlorpropamide, glyburide, insulin therapy, or conventional therapy of diabetic diet and exercise for an average of 10 years. Comparison was also made between the intensity of glycemic control and the frequency of diabetic complications among patients in the various treatment regimens. The frequency of diabetic complications, but not macrovascular disease, was reduced by the three drug treatments, which all produced lower blood glucose levels than diet and exercise. With each drug treatment group, regardless of blood glucose treatment goals, there was almost identical glycemic control, and the quality of blood glucose control was essentially identical in patients randomly assigned to any of the treatment groups.[77]

Table 6. Potential Beneficial Cardiovascular Effects of Metformin Therapy in Type 2 Diabetes Mellitus

Decreases hyperglycemia[76]
Reduces hepatic gluconeogenesis[76]
Decreases total cholesterol levels[76]
Decreases very-low-density lipoprotein cholesterol levels (triglycerides)[76]
Decreases LDL cholesterol levels[76]
Increases HDL cholesterol levels[76]
Decreases oxidative stress[76]
Improves vascular relaxation[76]
Reduces hypercoagulation state[76]
Decreases plasminogen activator inhibitor-1 levels (PAI-1)[76]
Increases tissue plasminogen activator activity (TPA)[76]
Decreases von Willebrand factor levels[76]
Decreases platelet aggregation and adhesion[76]
Reduction of C-reactive protein[94]
Improves experimental animal model diastolic dysfunction[76]
Inhibition of protein glycation[95]
Improvement of vascular wall structure[96]
Improves vascular redox balance[97,98]
Increases functional capillary density[99,100]
Reduces plasma free fatty acid concentration and oxidation[76, 100–102]
Reduces cross-linkage of fibrin[103]
Reduces neo-vascularization[103]
Improves post-ischemic arterial flow[104,105]
Improves endothelial function[106]
Reduces insulin resistance/Increases insulin sensitivity[76,107–109]

In a subgroup of obese patients treated with metformin, there was a 36% reduction in myocardial infarction and a 42% reduction in diabetes-related deaths compared with the group on conventional treatment with only diet and exercise.[77] In addition, the metformin-treated patients had less weight gain and fewer episodes of hypoglycemia compared with the patients receiving other treatments with equivalent reductions in HbAlc. The UKPDS results support the idea that metformin provides superior cardiovascular protection compared with sulfonylurea and insulin therapies while achieving similar glycemic control.[77]

In a placebo-controlled study, 324 nondiabetic subjects with upper body obesity were randomized to either metformin or placebo (conventional therapy with diabetic diet and exercise) for a year. The metformin-treated group demonstrated a greater reduction in body weight, plasma insulin, total and LDL cholesterol, and fasting blood glucose concentration.[78] Studies have been conducted on the possible mechanism by which metformin improves cardiovascular outcomes. The microvascular circulation is fundamental to organ health, and it is the site of early vascular injury in the metabolic syndrome patient. The insulin resistance seen in metabolic syndrome patients, obese patients, and those who smoke is accompanied by changes in the microcirculation prior to the development of hyperglycemia. Animal models of type 2 diabetes show changes in coronary arteriolar structure and function prior to the development of hyperglycemia.[79] Metformin has also been demonstrated to pro-

vide numerous benefits at the vascular level (Table 6). These microcirculatory effects of metformin make it an attractive treatment in the type 2 diabetic patient. The beneficial effects of metformin on the microcirculation occur independently of the glycemic actions of the drug and are found at doses lower than or equal to those required for its glycemic effects.[80,81]

Second-Step Antiglycemic Drug Recommendations

Adequate control of blood sugar can be very difficult to achieve and to maintain. In the UKPDS, quarterly glycosylated hemoglobin values rose from 7% to approximately 8% over the 10 years of the study in spite of aggressive drug therapy.[77] Poor control of blood glucose level impairs endogenous insulin production, resulting in a vicious cycle. On the other hand, good glycemic control will enhance endogenous insulin production. Aggressive glycemic therapy with an appropriate combination of pharmacologic agents will be required to reduce blood glucose to target levels and to maintain it over time. A second oral antiglycemic drug or insulin can be added to metformin to achieve glycemic control. Since patients who fail maximal monotherapy with metformin may be insulin deficient, the addition of insulin is usually recommended if appropriate for the patient. Insulin resistance results in an increased requirement for insulin production for the maintenance of normal blood glucose level. Patients with metabolic syndrome who have declining beta cell function and reduced insulin production develop insulin resistance that progresses to type 2 diabetes mellitus. The inability to maintain an adequate insulin supply in the face of increasing insulin resistance occurs in most, if not all, type 2 diabetic patients. In addition, the rate of insulin production decreases over time in the majority of patients with type 2 diabetes mellitus.

Patients who have not achieved goal glycemic control on maximal monotherapy with metformin should have bedtime intermediate or long-acting insulin added.[82,83] When metformin alone fails to control hyperglycemia, it is on the basis of a relatively inadequate insulin production. The improved glycemic control seen with the combination of insulin with metformin is a result of metformin upregulating insulin receptors through activation of the intracellular phosphatidyl inositol triphosphate pathway. Insulin added to metformin can also improve endothelial function.[83]

Unfortunately, the pattern of diabetic care in the United States has been a rather relaxed, stepped-care approach progressing from diet and exercise, through oral medications, and finally on to insulin when the disease is advanced. This approach ignores knowledge that insulin is the most powerful and uniformly effective medication available for the treatment of diabetes and that glucose levels close to the normal range appear necessary to reduce all diabetic complications. Insulin use among patients with type 2 diabetes mellitus in the United States could best be described as "too little, too late." Humulin insulin is a natural human product. The only potential side effect is hypoglycemia from overdosing.

Since poor dietary efforts and a lack of regular physical activity can cause increasing hyperglycemia in patients on metformin, insulin is often needed.[84] The benefits of metformin combined with long-acting insulin have been demonstrated in a randomized controlled clinical trial of 96 obese type 2 diabetic patients. The study compared the combination of bedtime intermediate acting insulin with twice-daily insulin therapy, a sulfonylurea, metformin, or the two oral medications together with bedtime insulin. Over a 1-year period, the combination of bedtime insulin plus metformin produced the best HbAlc with the fewest episodes of hypoglycemia compared with the other treatment regimens. Unlike the other treatment groups, patients receiving bedtime insulin and metformin showed a progressive decrease in glycosylated hemoglobin values over time. The group with the metformin bedtime insulin combination had the least amount of weight gain. The regimens containing sulfonylurea produced more episodes of hypoglycemia than other treatments.[82]

If adequate glycemic control is not obtained with 1000 mg of metformin twice a day, then 10 units of long-acting human insulin, either NPH or glargine, is added at bedtime. The bedtime insulin dose is increased by 2 units every 3 days (up to 20 units daily dose) until goal fasting blood sugar is obtained. Conversely, if the 3-day average for the fasting blood glucose is less than 80 mg/dL, the patient drops the dose by 2 units. This technique allows patients to taper their insulin up or down as required. Occasionally, some patients are able to discontinue insulin after a time. This regimen has been shown to produce sustained reductions in HbAlc to an average of 6.8% in 230 type 2 diabetic patients in a rural Southeastern internal medicine practice.[40]

Alternatively, other drugs, including thiazolidinediones or sulfonylureas can be added to metformin to achieve glycemic control.[85] The thiazolidinediones are attractive as a second drug class because they lower insulin resistance, may provide antiatherosclerotic effects, and may provide some blood pressure lowering in hypertensive patients.[85–88] One thiazolidinedione, pioglitazone, has been demonstrated to reduce pulse wave velocity, vascular intima-media thickness, and urinary albumin excretion compared with either glibenclamide (a sulfonylurea) or voglibose, in normotensive type 2 diabetic patients over 1 year.[89] However, there have not yet been any randomized clinical trials with this combination demonstrating a reduction in cardiovascular events.

Concern has been expressed about the cardiovascular safety of sulfonylureas in type 2 diabetes mellitus. Blood glucose can be viewed as a secondary target in diabetic treatment, since the ultimate

death in patients with type 2 diabetes mellitus is due to cardiovascular disease. Thus, the ultimate goal of diabetic therapy can be seen as protecting the patients from cardiovascular events. In one of the first large clinical trials evaluating type 2 diabetic glycemic control, a double-blind placebo-controlled study comparing two different insulin regimens versus tolbutamide, the sulfonylurea (tolbutamide) was stopped early because of relative excess cardiovascular mortality.[90]

The addition of metformin to sulfonylurea treatment in the UKPDS produced a 96% increase of diabetes-related deaths.[78] In diabetic patients undergoing coronary artery angioplasty for acute myocardial infarction, patients on sulfonylurea have been reported to have a mortality odds ratio of 2.77 greater than similar patients not taking sulfonylureas.[91] In another study, type 2 diabetic patients undergoing percutaneous coronary artery intervention had a mortality rate three times higher over the 250 days following the procedure if they were on a sulfonylurea or insulin as compared with metformin alone or in combination.[92]

In summary, every effort should be made to achieve recommended glycemic control in patients with type 2 diabetes mellitus. Unless contraindicated, the use of metformin initially with bedtime intermediate- or long-acting Humulin insulin is preferred, although the addition of a thiazolidinedione may be an alternative.

Antiplatelet Therapy

Unless contraindicated, low-dose enteric aspirin (81–325 mg) daily is recommended for patients over the age of 30 years with type 2 diabetes mellitus and one or more cardiovascular risk factors.[93]

Implementation of Comprehensive Treatment for Cardiovascular Management

Comprehensive cardiovascular treatment must be learned and optimally delivered to produce successful patient outcomes. Health care providers have responsibilities to stay informed of optimal treatments, to provide a clinic setting conducive to achieving optimal outcomes, and to have the necessary communication skills to guide patients in the recommended treatment. Regular continuing medical educational updates are very important. Use of an algorithm such as those used in clinical trials will improve the chance of patients achieving any cardiovascular treatment goal. Certain principles should be used in the development of any treatment algorithm to optimize outcomes:

- The provider establishes one or more treatment algorithms for certain groups of patients.
- The treatment plan and algorithm are explained in detail to the patient at the beginning, including alternative treatments, the frequency of follow-up visits and laboratory work, the goal or goals of treatment, any potential treatment side effects, and methods for communication with the provider if problems arise.
- Clinic allied health professionals are utilized in a treatment team with the provider.
- A mechanism is developed within the clinic to measure periodically the number of patients achieving treatment goals, and these are reviewed and clinic strategies are revised as needed.

Furthermore, effective communication between the provider and patient is critical to patient adherence. As included in the JNC 7, the following guidelines can be helpful:

- Establish provider-patient partnerships based on trust and respect.
- Educate the patient as to the importance of his/her lifestyle and adherence with medications in treatment.
- Consider behavioral interventions as a part of therapy.
- Assess the patient's knowledge of blood pressure and lipid and glucose control.
- Include the patient in all decision making about his/her therapy.
- Recognize when it becomes necessary to refer the patient to a specialist.
- Determine the patient's literacy level for any written educational materials.

Summary and Conclusions

The mission of the Consortium for Southeastern Hypertension Control (COSEHC) is to reduce the mortality rate associated with cardiovascular disease in the Southeastern United States. The metabolic syndrome with the simultaneous expression of excess body weight, insulin resistance, glucose intolerance or type 2 diabetes mellitus, hypertension, dyslipidemia, homocystinemia, vascular inflammation, and prothrombosis has reached an epidemic level, not only in the Southeast but throughout the country. A more aggressive and comprehensive approach to the detection and management of all aspects of the metabolic syndrome is needed. Healthy nutrition and daily physical activity should begin in childhood. Annual cardiovascular screening with measurement of weight, height, and blood pressure should begin at 3 years of age. For adults, weight, blood pressure, blood lipids, and fasting cardiovascular disease and one or more cardiovascular risk factors, a comprehensive cardiovascular risk assessment, including all of the recognized risk factors, should be performed and their cardiovascular risk calculated with the COSEHC Cardiovascular Risk Assessment Tool. Such annual screenings will identify cardiovascular risk factors early and allow

health care providers to prescribe prevention and/or appropriate treatment measures.

Lifelong lifestyle modifications and often pharmacologic therapy will be necessary in patients with the metabolic syndrome to achieve the recommended cardiovascular risk factor treatment goals. Initial antihypertensive therapy in the metabolic syndrome should be an ACEI or an ARB, unless there are contraindications or concomitant diseases with compelling indications for other drugs. Appropriate second-step antihypertensive drugs include a CCB or a thiazide diuretic. Most patients will need more than one antihypertensive drug to achieve goal blood pressure. Metformin combined with either intermediate- or long-acting bedtime insulin or a thiazolidinedione is recommended for glycemic control in patients with type 2 diabetes mellitus. A statin, unless there is a contraindication, is recommended as the first preferred drug for type 2 diabetic patients with dyslipidemia.

Combination therapy for multiple cardiovascular risk factors is critical for the successful management of the metabolic syndrome. For long-term sustained treatment success, there must be a combined effort among the patient, the family, the health care provider, and the community. An increased public awareness concerning the metabolic syndrome and the importance of its treatment is also needed. Education of health care providers, patients, and the community concerning the importance of recognizing and treating the metabolic syndrome will be crucial for the future reduction of cardiovascular disease not only in the Southeast but throughout the United States.

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