Addressing the Global Cardiovascular Risk of Hypertension, Dyslipidemia, and Insulin Resistance in the Southeastern United States

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ABSTRACT: An expanded occurrence of the metabolic syndrome in the U.S. population, especially in the Southeastern United States, has raised awareness of a need to revise our approach to the management of global cardiovascular risk factors while underscoring a need for more aggressive interventions and prevention measures. In defining the components of the metabolic syndrome and the interrelationship among obesity, hypertension, dyslipidemia, and insulin resistance, a basic framework for the medical management of this syndrome has been defined. In Part I of the consensus report prepared by the Workgroup on Medical Guidelines of the Consortium for Southeastern Hypertension Control (COSEHC), we analyze the components of the metabolic syndrome, discuss its pathophysiology, and recommend an approach to the quantitative analysis of the risk factors contributing to excess cardiovascular death in the region.
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The metabolic syndrome may be a common phenotype increasing risk for hypertension, type 2 diabetes, and cardiovascular disease (CVD).[1] The increased prevalence of this syndrome in the U.S. population demands reconsideration of the approach to the management of hypertension, hyperglycemia, and dyslipidemia, with a focus on understanding the potential intertwining relationships by which these risk factors contribute to cardiovascular mortality. The metabolic syndrome denotes a constellation of cardiovascular risk factors related to insulin resistance. Individuals with the metabolic syndrome are often obese with a centripetal pattern of fat distribution. The metabolic syndrome has been defined differently by several organizations, but its components are well validated. The National Cholesterol Education Program-ATP-III,[2-6] the World Health Organization guidelines,[7,8] and the American Association of Clinical Endocrinologists guidelines (2003) all include hypertension, dyslipidemia (high triglyceride level, low high-density lipoprotein [HDL] cholesterol level, dense low-density lipoproteins [LDL]), obesity (elevated waist circumference, increased body mass index [BMI], waist/hip ratio), and hyperglycemia, whereas microalbuminuria is an additional component of the metabolic syndrome in the World Health Organization guidelines (Table 1). This definition takes into consideration that the metabolic syndrome originates from both insulin resistance and activation of vascular inflammatory mechanisms related to increased oxidative stress,

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Table 1. Published Criteria for the Diagnosis of the Metabolic Syndrome

Risk Factor Component	World Health Organization	NCEP-ATP-III	AACE Clinical Criteria
Hypertension	Current antihypertensive therapy and/or BP > 140/90 mm Hg	Current antihypertensive therapy or BP > 130/85 mm Hg	BP > 130/85 mm Hg
Dyslipidemia	Plasma triglyceride level > 1.7 mmol/L (150 mg/dL) and/or HDL-C level < 0.9 mmol/L (35 mg/dL) in men, < 1.0 mmol/L (40 mg/dL) in women	Plasma triglyceride level > 150 mg/dL mg/dL, HDL-C level < 40 mg/dL in men, HDL-C level < 50 mg/dL in women	HDL < 40 mg/dL (1.04 mmol/L) in men, < 50 mg/dL (1.29 mmol/L) in women
Obesity	BMI > 30 kg/m^2 and/or waist/hip ratio > 0.90 in men, > 0.85 in women	Waist circumference > 40 inches in men and > 35 inches in women	BMI > 25 kg/m^2
Glucose	Type 2 diabetes or IGT	Fasting blood glucose level > 110 mg/dL	Fasting glucose level 110 & 126 mg/dL
Other	Microalbuminuria (overnight urinary albumin excretion rate > 20 μg/min [30 mg/g Cr])		
Requirements for diagnosis	Confirmed type 2 diabetes or IGT and any two of the above criteria. If normal glucose tolerance, must demonstrate three of the above criteria	Any three of the above disorders	Family history of type 2 diabetes, hypertension, or CVD; polycystic ovary syndrome; sedentary lifestyle; advancing age; ethnic groups w/high risk for type 2 diabetes or CVD

NCEP-ATP-III, National Cholesterol Education Program, Adult Treatment Panel; AACE, American Association of Clinical Endocrinology.

vascular endothelial dysfunction, thrombosis, and atheroembolic disease.

This article examines the relationships among hypertension and cardiovascular risk factors, focusing on the metabolic syndrome as a paradigm for understanding the pathophysiology of CVD and defining medical guidelines for the management of global cardiovascular risk factors. In this context, the purpose of this article is to raise awareness of this problem in the management of hypertension-related morbidity and mortality in the Southeastern United States, since this region has been recognized as having an excess burden of CVD and stroke for more than five decades.[9-12] Whereas the original "stroke belt" was restricted to the coastal areas of North Carolina, South Carolina, and Georgia,[11] the last five decades have witnessed an expansion of high stroke mortality rates throughout the entire Southeast.[13] The excess risk of stroke and CVD is even greater for African Americans, who often have their stroke at an earlier age than those residing outside the southeastern United States.[11,14-16]

The disease burden for residents of the Southeast and specifically for African Americans is also seen for end-stage renal disease (ESRD).[17-21] The link between stroke and ESRD include the common risk factors of hypertension, diabetes, and dyslipidemia. As the rates of ESRD continue to increase in the Southeast, the rates of hypertensive ESRD and diabetic ESRD are also increasing.[22,23] Considering an average cost of $80,000/yr for dialysis, the increasing rates of renal disease constitute a considerable public health burden and a drain on increasingly limited public health resources. The geographic and racial patterns for stroke and ESRD implicate uncontrolled hypertension, diabetes, and dyslipidemia as major targets for population intervention. These associations were confirmed by the Charleston Heart Study, which followed a large cohort of black and white adults from 1960 through 1990.[24] In this large study, hypertension was identified as a major risk factor for mortality for all four race-gender groups.[24] In fact, after adjusting for socioeconomic status, smoking, cholesterol level, and body mass index, the population risk estimates of death due to hypertension were substantial for each race-sex group: white males, 23.8%; white females, 18.3%; black males, 45.2%; and black females, 39.6%. In other words, 23.8% of the deaths for white males and 45.2% of the deaths for black males were attributable to high blood pressure alone. These results suggest that racial disparity in mortality would be significantly reduced or perhaps eliminated with aggressive hypertension control of the entire population.

The Metabolic Syndrome

The expanding epidemic of obesity has fueled an increase in the prevalence of hypertension in particular and CVD in general. Escalating rates of obesity predict further substantial increases in the metabolic syndrome, type 2 diabetes mellitus, coronary heart disease (CHD), myocardial infarction (MI), and total CVD during the next decade, at rates that are likely to eclipse the rates observed throughout the past.[25-29] Although the pathophysiology of the metabolic syndrome remains to be fully understood, data suggest that environmental and lifestyle factors, as

well as genetic considerations, are major contributors to the syndrome. These factors include inappropriate nutrition with consumption of high-calorie foods, refined carbohydrates with high glycemic index and load, and reduced physical activity. Definitive associations of CVD and the metabolic syndrome include a markedly increased risk in CHD, MI, stroke, and total mortality that is directly proportional to the number of components of the metabolic syndrome.[25-29] The incident risk of CVD is more than 5-fold in subjects with four or more components compared with those with only one component, although there is clearly a continuum of risk, both within the severity of the risk factor itself and with combinations of risk factors. The metabolic syndrome and obesity are major public health and economic problems that require urgent and aggressive identification, prevention, and treatment with lifestyle modifications (nutrition, weight reduction, exercise) and, when indicated, pharmacologic therapy.

The overall prevalence of the metabolic syndrome in the United States is 24% in adults (47 million adults), with the highest incidence in Mexican Americans.[30] The risk of metabolic syndrome progressively increases with age, rising from approximately 7% for adults in the third decade of life to nearly 45% for those older than 60 years of age.[2] Prevention and treatment of the metabolic syndrome and its components include early detection, aggressive nutritional intervention, antiplatelet therapy (aspirin), functional foods, weight management, aerobic and resistance exercise, moderation of alcohol ingestion, discontinuation of all tobacco products, limited caffeine intake, and pharmacologic therapy.

There is evidence that vascular endothelial dysfunction is one of the initial abnormalities that occurs in individuals with the metabolic syndrome. An excess angiotensin II synthesis and a deficiency of nitric oxide (NO) bioavailability cause vasoconstriction, growth promotion, and a prothrombotic, proinflammatory, and prooxidant state. This constellation of events is directly related to insulin resistance and to the frequent clinical association of hypertension, dyslipidemia, and diabetes mellitus.[31,32] Insulin mediates metabolic, mitogenic, and vasodilatory-vascular functions in skeletal muscle and adipose tissue, as well as in the liver, brain, heart, blood vessels, pancreas, and other tissues.[31,32] Insulin binds and acts mainly through the insulin receptor and also via the insulin-like growth factor-1 receptor.[33] The beta subunit of the insulin receptor is a tyrosine kinase, which is activated when insulin binds to the alpha subunit. Insulin resistance results in an imbalance of the mitogen-activated protein kinase and the phosphoinositide 3-hydroxykinase (PI3K) pathways. Since the PI3K pathway regulates insulin-mediated glucose uptake into heart muscle and insulin-dependent endothelial NO production, a defect in this pathway may be responsible for both insulin resistance and reduced NO production. This leads to cellular proliferation and migration, thrombosis, and inflammation, with increased cytokines and cell adhesion molecules, causing a reduction in both glucose transport and eNOS/NO bioactivity.[34-36] Because the enhanced mitogen-activated protein kinase pathway is proatherogenic, it overrides the antiatherogenic actions of the PI3K pathway. The role of the insulin receptor, mitochondrial function, pancreatic beta cell, inflammatory cytokines, radical oxygen species, and free fatty acids are important in the clinical expression of insulin resistance and type 2 diabetes. The combination of chronic insulin resistance followed by beta cell dysfunction and failure eventually produces type 2 diabetes.

Adipose tissue is an endocrine organ that produces a variety of "adipokines," including inflammatory mediators and hormones that result in chronic inflammation and endocrine and metabolic dysfunction, manifesting as insulin resistance and the clinical diseases of hypertension, dyslipidemia, hyperglycemia, diabetes, and CVD.[37-40] Adipocytes are both a source and a target of proinflammatory signals, such as interleukin-6 and tumor necrosis factor alpha (TNF-α). An increase in high-sensitivity C-reactive protein may correlate with future cardiac events. [41-45] The role of the peroxisome proliferator-activated receptor alpha and gamma receptors are important in insulin resistance, glucose and lipid metabolism, and overall vascular function, inflammation, atherosclerosis, and hypertension.[46]

Hypertension as a Component of the Metabolic Syndrome

Hypertension, defined as a systolic blood pressure greater than or equal to 140 mm Hg and a diastolic blood pressure greater than or equal to 90 mm Hg, or 130/80 mm Hg in subjects with the metabolic syndrome, is a powerful, independent, and modifiable cardiovascular risk factor. Its presence increases the risk of atherosclerosis, peripheral arterial disease, cerebrovascular accidents, CHD, congestive heart failure, chronic renal insufficiency and chronic renal failure, dementia, and death. The risk for hypertensive end organ disease doubles with every 20/10 mm Hg increase of blood pressure beginning at 115/75 mm Hg.[47] The finding that more than 90% of people who have normal blood pressure at age 55 years will develop hypertension within their lifetimes emphasizes the huge public health problem that hypertension poses, especially in the Southeast.[48]

The recently completed NHANES IV survey showed that hypertension prevalence is increasing in the United States.[49] Current analysis showed that 28.7% (approximately 58.4 million individuals) had hypertension in 1999–2000, an increase of 3.7% compared with 1988–1991. Non-Hispanic blacks had the highest prevalence of hypertension in 1991–1994 and

1999–2000. Mexican Americans had the lowest prevalence of hypertension during the same period of time. Non-Hispanic black women had the greatest increase in hypertension prevalence (7.2%), and non-Hispanic white men had the smallest increase (1.0%). Furthermore, hypertension prevalence in individuals aged 40 to 59 years and those aged 60 years and older was higher in the non-Hispanic blacks than in non-Hispanic whites and Mexican Americans.[49]

The observed increase in known hypertension prevalence during the last 10 years is in accordance with results from the Behavioral Risk Factor Surveillance System (BRFSS).[50,51] In the BRFSS report, 38% of women 65 to 74 years old reported hypertension, compared with 31% of men in the same age group. Furthermore, the increased prevalence may be related to an increase in BMI as well as the aging of the U.S. population.[50,51] The BRFSS data suggest that persons who were never told they had high blood pressure ranged from 20% in New Mexico to 32.5% in West Virginia. The southeastern United States has a continued increase in the prevalence of hypertension as well as obesity (15.5% in Colorado and 27.1% in Mississippi) and elevated levels of cholesterol (24.8% in New Mexico to 37.7% in West Virginia). According to the National Hospital Statistics 2000, essential hypertension accounted for the largest percentage of discharges: 28,000 or 43.8% in the southeastern United States. It is clear from these data that control rates of hypertension in the southeastern United States are suboptimal. More aggressive detection, treatment, and follow-up are required to reduce cardiovascular morbidity and mortality in the southeastern United States.

The definition of normal blood pressure as less than 120 and less than 80 mm Hg in recent hypertension treatment recommendations (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC-7) or optimal (European Society of Hypertension) is appropriate, as is the definition of clinical hypertension being greater than or equal to 140/90 mm Hg.[7,52-54] Defining hypertension as greater than or equal to 140/90 mm Hg is valid, since nearly all clinical trials evaluating hypertension treatment have demonstrated a reduction in cardiovascular mortality by achieving a goal blood pressure of less than 140/90 mm Hg. As stated in JNC-7, defining higher levels of blood pressure beyond stage 2 hypertension is not clinically helpful. The same vigor in treatment should be applied to any degree of hypertension. Because the relationship between blood pressure and risk of CVD events is continuous, consistent, independent, and compounded by the presence of other risk factors, the term prehypertension was introduced in JNC-7 to replace the older definitions of normal or high-normal blood pressure.[52] It should be emphasized that prehypertension is not a disease category. Its designation was chosen from epidemiologic data suggesting that these individuals remain at higher risk for future hypertension development and CVD compared with those with optimal blood pressure. The presence of prehypertension by itself is not necessarily an indication for antihypertensive drug therapy, since JNC-7 states that antihypertensive drug therapy is recommended only in those prehypertensive individuals who have a compelling indication for therapy, such as diabetes or renal disease.[52]

We agree with JNC-7 recommendations that the presence of prehypertension should be a powerful stimulus to the clinician to look for other cardiovascular risk factors and for individuals to engage in appropriate lifestyle changes, as many of these patients may be presenting themselves with clinical evidence of the metabolic syndrome.[55] It is vitally important, however, to bear in mind the potentially negative medical insurance ramifications for patients classified as prehypertensive. There is the very real possibility that the use of the word prehypertension in a patient's medical record could raise red flags in the underwriting community, with a variety of potentially adverse consequences. Preliminary research indicates that individuals can be charged up to seven times the "normal" premiums for red-flagged conditions, otherwise known as "max-rated." Preexisting condition clauses might also be problematic, as it could be argued that a patient with prehypertension who later develops hypertension would not be covered for hypertensive treatment should he or she attempt to purchase insurance with this type of stipulation in the interim. There is a real need to be cognizant of each individual patient's insurance situation so as not to burden him or her with undue medical costs. One solution may be a verbal acknowledgment of this "prehypertensive" condition and documentation of the blood pressure readings without including the prehypertension "label" if the patient's insurance coverage is less than optimal.

The rise in blood pressure leading to adult hypertension begins at an early age. This has been recently demonstrated by the National Heart, Lung, and Blood Institute (NHLBI) Education and Dissemination Centers in the Southeast using serial blood pressure measurement and blood pressure cuffs appropriate to arm size. In these communities, the incidence of hypertension among children was highest among those with increased body weight. Therefore, we recommend that blood pressure be measured annually at least by age 3, adjusted for age, height, and gender.[56,57] Annual blood pressures should be charted in the same way as height and weight. Comprehensive efforts should be undertaken that includes the child, family, school, and community to prevent excessive weight gain in children and to screen the children regularly for cardio-

Table 2. Clinical Abnormalities Associated With the Metabolic Syndrome

Major criteria
Hyperglycemia
Fasting glucose over 110 mg/dL,
Hemoglobin A1C over 6.5% or 2 hour PPG > 140 mg/dL
(Fasting C-peptide elevation may be helpful).
Abdominal obesity (visceral)
Men over 40 inches, (102 cm) in waist circumference (WC)
Women over 35 inches (88 cm) in waist circumference (WC)
Waist Hip Ratio (WHR) over 0.85 in women
Waist Hip Ratio (WHR) over 0.90 in men
BMI over 30 kg/m^2
Body Fat over 29% in men (normal is < 16%)
Body Fat over 37% in women (normal is < 22%)
Dyslipidemia (atherogenic type)
TG over 150 mg/dL (usually large VLDL)
HDL less than 40 mg/dL in men and 50 mg/dL in women (usually small HDL)
TG/HDL ratio > 3.0
Small dense type B LDL with increased LDL particle number exceeding 1100 (NMR analysis)
Elevated Lp(a)
Hypertension
Blood pressure over 135/85 mm Hg (In some circumstances a 24 hour ABM with BP load, mean, circadian cycle and nocturnal dipping will be helpful)
Microalbuminuria
Over 30 mg in 24 hours or over 20 μg/minute or ACR (albumin:creatinine ratio) over 30 mg/g
Prothrombotic state:
Elevation of PAI-I,
Increased platelet activation and aggregation,
Elevated fibrinogen, von Willebrand factor, Factor VII, and thrombin
Insulin resistance and hyperinsulinemia
Fasting insulin (FI) proinsulin, C-peptide, OGTT, and the TG/HDL ratio
Pro-inflammatory state
(Hs-CRP, plasma fibrinogen, IL-6, IL-1B, TNF-alpha, leukocytosis)
Minor criteria
Endothelial dysfunction (Indirect assessment by computerized arterial pulse wave analysis, CAPWA).
Abnormal arterial compliance: especially small resistance arteries, low C2 compliance, and increased PWV (pulse wave velocity) (assessed by CAPWA).
LVH and diastolic dysfunction (2-D echo)
Hyperuricemia
Increased vascular oxidative stress (urinary isoprostanes, MDA)
Homocysteine over 9 μg/L
Objective evidence of accelerated atherogenesis for aged matched gender, ethnicity and age (EBT, carotid IMT or ultrasound, CHD, PAD, ABI, etc.)
Abnormalities in autonomic nervous system regulation and activation of the cardiovascular system (PRA, aldosterone, catecholamines)

vascular risk factors, particularly body weight/height, blood pressure, and cholesterol level.

Global and Absolute Cardiovascular Risk Assessment

The usefulness of guidelines for the treatment of any single cardiovascular risk factor should necessarily hinge on the concept of overall risk reduction. Table 2 documents the clinical abnormalities associated with the metabolic syndrome. In the context of the existence of multiple risk factors, clinical guidelines that purport to address the risk of any single cardiovascular risk factor without considering global risk are in peril of being so limited in their applicability as to be considered fatally flawed. Obviously there would be no utility in reducing a risk factor in someone who has no likelihood of developing the disease in question; on the other hand, someone with very high risk of morbidity from a disease like CHD would be expected to benefit significantly from reductions of coexisting risk factors. The benefit of reducing one risk factor may be attenuated by undesired elevations of other risk factors. The challenge left in creating guidelines rests in identifying evidence-based risk factors and recommending approaches to testing and intervention that are easily applied in the office of the primary physician while at the same time predicting risk in a robust fashion.

The traditional approach has been to identify risk estimates in two ways: absolute risk and relative risk. Absolute risk estimates the probability of an adverse event occurring in an individual within a defined period of time, for example the likelihood of cardiovascular death within 5 or 10 years. Relative risk identifies the probability of an adverse event happening for an individual compared with average or normal individuals sharing similar demographic characteristics other than the risk factor. A number

of statistical tools have been developed to help clinicians stratify their patients according to risk factors. Hundreds of cardiovascular risk factors have been described, but the risk factors most commonly recognized by members of the public are tobacco use, high cholesterol level, high blood pressure, physical inactivity, overweight and obesity, and diabetes mellitus.

Organizations such as the American Heart Association (AHA) and the American College of Cardiology have generally recommended use of the Framingham Heart Study global risk assessment scoring system for estimating patient risk of CVD. [48,58-60] Although the Framingham scoring uses "standard" risk factors (smoking, blood pressure, serum cholesterol, HDL cholesterol, blood glucose, and age), other recognized predisposing risk factors for cardiovascular mortality are not included in that scoring system. The generalizability of the Framingham results have also been questioned, particularly for use in the Southeastern United States, since the study was done on 5208 predominantly homogenously white, healthy individuals residing in Framingham, Massachusetts. Other investigators have used newer, more encompassing biostatistical techniques to estimate the risk of CVD.[61] One such analysis has determined that identification of high-risk individuals is more discriminating using a synthesis of multiple risk factors, some of which are beyond those included in the Framingham formula. This analysis, for example, identifies that 10% to 20% of the American population between the ages of 35 and 70 with borderline-high to high total cholesterol levels (200-240 mg/dL) are actually at relatively low risk for CHD.[61]

Rather than relying on the Framingham Heart Study scoring system, with its limited generalizability and discriminatory sensitivity, we looked to the risk score model published by the INDANA project (individual data analysis of antihypertensive intervention trials) (Tables 3 through 5).[62-64] As indicated in Tables 3 to 8,[61,65-67] this project analyzed results from eight randomized controlled trials of antihypertensive treatment to generate a robust risk score system to predict short-term cardiovascular risk (absolute risk) and to qualitatively place individuals into one of four risk categories on the basis of their risk scores compared with population averages for their own ages (relative risk). The analysis includes 23,000 North American individuals taken from three well-known studies based in the United States (HDFP, MRFIT, SHEP), and overall includes 47,008 patients for analysis. The risk factors identified by the project include those used by Framingham (age, gender, smoking, blood pressure, cholesterol level, diabetes, LVH) but also additional risk factors not used in the Framingham scoring but demonstrably independently associated with increased risk for cardiovascular mortality (stature, creatinine level,

Table 3. Original Validated INDANA Risk Score for Women Showing Risk Factors and Additions to Risk Score

Age			Systolic BP		Total Cholesterol		Height		Creatinine Concentration		Prior MI		Prior Stroke		LVH		Diabetes	
Years	Add	Extra for Smoking	mm Hg	Add	mg/dL	Add	Inches	Add	mg/dL	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add
35–39	0	+13	110–119	0		0	<57	+6	<0.6	0	No	0	No	0	No	0	No	0
40–44	+5	+12	120–129	+1	194–231	0	57–<61	+4	0.6	+1	Yes	+8	Yes	+8	Yes	+3	Yes	+9
45–49	+9	+11	130–139	+2	232–269	+1	61–<65	+3	0.7	+1								
50–54	+14	+10	140–149	+3	270–308	+1	65–<69	+2	0.8	+2								
55–59	+18	+10	150–159	+4	309–347	+2	≥69	0	0.9	+2								
60–64	+23	+9	160–169	+5	≥348	+2			1.0	+2								
65–69	+27	+9	170–179	+6					1.1	+3								
70–74	+32	+8	180–189	+8					1.2	+3								
			190–199	+9					>1.2	+4								
			200–209	+10														
			≥210	+11														

Table 4. Modified Risk Score for Women Showing Risk Factors and Additions to Risk Score

Age			Systolic BP		Total Cholesterol		Height		Creatinine Concentration		Homocysteine		Prior MI		Prior Stroke		LVH		Diabetes		Nondiabetic	
Years	Add	Extra for Smoking	mm Hg	Add	mg/dL	Add	Inches	Add	mg/dL	Add	μmol/L	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	FBS (mg/dL)	Add
35–39	0	+13	110–119	0		0	<57	+6	<0.6	0		−4	No	0	No	0	No	0	No	0	≤71	−1.5
40–44	+5	+12	120–129	+1	194–231	0	57–<61	+4	0.6	+1	5–5.0	−3	Yes	+8	Yes	+8	Yes	+3	Yes	+9	72–77	−1
45–49	+9	+11	130–139	+2	232–269	+1	61–<65	+3	0.7	+1	6–6.9	−2									78–84	−0.5
50–54	+14	+10	140–149	+3	270–308	+1	65–<69	+2	0.8	+2	7–7.9	−1									85–95	0
55–59	+18	+10	150–159	+4	309–347	+2	≥69	0	0.9	+2	8–8.9	0									96–101	+0.5
60–64	+23	+9	160–169	+5	≥348	+2			1.0	+2	10–10.9	+1									102–107	+1
65–69	+27	+9	170–179	+6					1.1	+3	11–11.9	+2									108–113	+1.5
70–74	+32	+8	180–189	+8					1.2	+3	12–12.9	+3									114–119	+2
			190–199	+9					>1.2	+4	13–13.9	+4									120–125	+2.5
			200–209	+10							14–14.9	+5									≥126	D
			≥210	+11							15–15.9	+6										
											≥16	+7										

D, diabetic.

60th percentile relative risk scores by age-range are 18 for age 35–39 yr, 21 for age 40–44 yr, 27 for age 45–49 yr, 31 for age 50–54 yr, 36 for age 55–59 yr, 41 for age 60–64 yr.

Table 5. Original Validated INDANA Risk Score for Men Showing Risk Factors and Additions to Risk Score

Age			Systolic BP		Total Cholesterol		Height		Creatinine Concentration		Prior MI		Prior Stroke		LVH		Diabetes	
Years	Add	Extra for Smoking	mm Hg	Add	mg/dL	Add	Inches	Add	mg/dL	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add
35–39	0	+0	110–119	0		0	<63	+6	<0.8	0	No	0	No	0	No	0	No	0
40–44	+4	+7	120–129	+1	194–231	+2	63–<67	+4	0.9	+1	Yes	+8	Yes	+8	Yes	+3	Yes	+2
45–49	+7	+7	130–139	+2	232–269	+4	67–<71	+3	1.0	+1								
50–54	+11	+6	140–149	+3	270–308	+5	71–<75	+2	1.1	+2								
55–59	+14	+6	150–159	+4	309–347	+7	≥75	0	1.2	+2								
60–64	+18	+5	160–169	+5	≥348	+9			1.3	+3								
65–69	+22	+4	170–179	+6					1.4	+3								
70–74	+25	+4	180–189	+8					>1.4	+4								
			190–199	+9														
			200–209	+10														
			≥210	+11														

Being male—add 12 points.

Relative risk score cutoffs by age-range are: 29 for age 35–39; 32 for age 40–44; 36 for age 45–49; and 40 for age 50–54.

Table 6. Modified Risk Score for Men Showing Risk Factors and Additions to Risk Score

Age			Systolic BP		Total Cholesterol		Height		Creatinine Concentration		Homocysteine		Prior MI		Prior Stroke		LVH		Diabetes		Nondiabetic	
Years	Add	Extra for Smoking	mm Hg	Add	mg/dL	Add	Inches	Add	mg/dL	Add	μmol/L	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	FBS (mg/dL)	Add
35–39	0	+9	110–119	0		0	<63	+6	<0.8	0		−6	No	0	No	0	No	0	No	0	≤75	−1.5
40–44	+4	+7	120–129	+1	194–231	+2	63–<67	+4	0.9	+1	5–5.9	−5	Yes	+8	Yes	+8	Yes	+3	Yes	+2	76–81	−1
45–49	+7	+7	130–139	+2	232–269	+4	67–<71	+3	1.0	+1	6–6.9	−4									82–88	−0.5
50–54	+11	+6	140–149	+3	270–308	+5	71–<75	+2	1.1	+2	7–7.9	−3									89–99	0
55–59	+14	+6	150–159	+4	309–347	+7	≥75	0	1.2	+2	8–8.9	−2									100–105	+0.5
60–64	+18	+5	160–169	+5	≥348	+9			1.3	+3	9–9.9	−1									106–111	+1
65–69	+22	+4	170–179	+6					1.4	+3	10–11.8	0									112–117	+1.5
70–74	+25	+4	180–189	+8					>1.4	+4	11.9–12.9	+1									118–125	+2
			190–199	+9							13–13.9	+2									≥126	D
			200–209	+10							14–14.9	+4										
			≥210	+11							15–15.9	+5										
											≥16	+6										

D, diabetic.

Table 7. COSEHC Risk Assessment Tool (Merged and Modified, Extrapolated Risk Score for Men)

Age			Systolic BP		Total Cholesterol		LDL Cholesterol		HDL Cholesterol		Triglyceride		Height		Creatinine Concentration		Homocysteine		Prior MI		Family History of pre-60 MI		Prior Stroke		LVH		Diabetes		Nondiabetic FBS	
Years	Add	Extra for Smoking	mm Hg	Add	mg/dL	Add	mg/dL[a]	Add	mg/dL[a]	Add	mg/dL[a]	Add	Inches	Add	mg/dL	Add	μmol/L	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	No/Yes	Add	mg/dL	Add
35–39	0	+9	110–119	0		0	<100	0	<35	+4	<100	0	<63	+6	<0.8	0		−6	No	0	No	0	No	0	No	0	No	0	≤75	−1.5
40–44	+4	+7	120–129	+1	194–231	+2	100–129	+1	35–44	+2	100–149	0	63–<67	+4	0.9	+1	5–5.9	−5	Yes	+8	Yes	+1	Yes	+8	Yes	+3	Yes	+2	76–81	−1
45–49	+7	+7	130–139	+2	232–269	+4	130–159	+3	45–54	+1	150–199	+1	67–<71	+3	1.0	+1	6–6.9	−4											82–88	−0.5
50–54	+11	+6	140–149	+3	270–308	+5	160–189	+4	≥55	0	≥200	+1	71–<75	+2	1.1	+2	7–7.9	−3											89–99	0
55–59	+14	+6	150–159	+4	309–347	+7							≥75	0	1.2	+2	8–8.9	−2											100–105	+0.5
60–64	+18	+5	160–169	+5	≥348	+9									1.3	+3	9–9.9	−1											106–111	+1
65–69	+22	+4	170–179	+6											1.4	+3	10–11.8	0											112–117	+1.5
70–74	+25	+4	180–189	+8											>1.4	+4	11.9–12.9	+1											118–125	+2
			190–199	+9													13–13.9	+2											≥126	D
			200–209	+10													14–14.9	+4												
			≥210	+11													15–15.9	+5												
																	≥16	+6												

D, diabetic.

[a] *If total cholesterol is 193 or less.*

Table 8. Cutoffs for "High" Relative Risk By Age (Approximate 60th Percentile Relative Risk Scores[a])

Men	Age Range	Women
29	35–39	18
32	40–44	21
36	45–49	27
40	50–54	31
44	55–59	36
48	60–64	41
53	65–69	45
57	70–74	49

[a] *60% risk scores adapted from our Reference 61.*

Men at age 50 yr or women at age 60 yr = relative risk of ≥60th percentile.

history of stroke, history of MI). Notably, the risk score does not include diastolic blood pressure, HDL cholesterol, triglycerides, C-reactive protein, physical activity, weight or BMI.[62-64] Certain risk factors, such as more detailed assessment of blood lipids (for example, HDL-cholesterol and triglycerides) or presence of angina or intermittent claudication, could in principle be included but were not available in all the targeted trials, and it was felt that there was a danger of making risk scores too detailed and complicated. Race was not included in the score as a variable, since the data has been based, in part, on large North American trials that included reasonable populations of Americans of African descent and the risk score would therefore be inclusive for risk in African Americans. Diastolic blood pressure does not help to predict the risk score once systolic pressure is taken into account, and hence the diastolic pressure is not included. Increased weight is associated with raised blood pressure, raised cholesterol, and an increased risk of diabetes; however, since these factors are included in the risk score already, weight (or BMI) per se does not contribute any extra information in predicting the risk of cardiovascular death. Being physically active is good for cardiovascular health, but it would be difficult to define a simple objective criterion of what constitutes being physically active across a wide age range. The resulting risk score is an objective aid to identifying a patient's risk for CVD and can be directive for intervention based on other risk factors besides blood pressure control (Tables 3 and 6).

Other investigations have identified homocysteine[66] and blood glucose level[68] as being independent risk factors for CVD in an incremental, concentration-dependent fashion. Blood glucose contributes risk of CVD even at levels not high enough to be designated as "diabetic." In collaboration with the INDANA investigators, COSEHC has modified their risk score to add the variables of nondiabetic fasting blood glucose levels and homocysteine levels to modify the risk score, reflecting the continuum of risk associated with varying glucose and homocysteine blood levels (Table 7). Population averages for homocysteine levels and blood glucose levels by gender[67] were identified from published reports of the NHANES III survey, and the resulting adjustments to the risk score could be estimated for each variable to represent the risk for American adults for cardiovascular mortality if the risk parameters are known. The resulting modified risk score tables are appended as Tables 4 and 7. Rather than relying on only seven variables to estimate risk, as used by the Framingham risk score, the reported risk calculator makes use of 13 variables. Rather than relying on the single Framingham database (n = 5208) to estimate event occurrence, this method uses eight databases with more than 47,000 individuals with mixed ethnicity, gender, age, and socioeconomic status, half of whom come from American studied populations.

The 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) study group has resulted in the creation of another risk tool that includes parameters common to the Framingham risk calculator but absent from the INDANA risk calculator. The PROCAM score is valid only for men, but by merging the two risk score calculators (PROCAM and INDANA) using the common risk factors employed in both scoring systems (age and systolic blood pressure) to estimate a conversion factor to equate the risk scores, it is possible to extrapolate values for risk factors to include in a merged risk score model. Such an extrapolated risk score model is included (for men only) as Table 7. Although this model has not been validated by long-term outcome studies, it is mathematically consistent with the methodology described herein and includes 17 different scoring parameters for consideration of a global cardiovascular risk in men. The absence of PROCAM data for women precludes application of this model for this gender, but comparison of the INDANA risk score tables by gender (Tables 4 and 6) implies that cholesterol parameters for women are not as significant a relative risk factor as they are for men, which would then leave the modified risk table (Table 4) for women as a reasonable tool for cardiovascular global risk prediction.

In terms of absolute risk, both the European Society of Hypertension and the National Cholesterol Education Program (NCEP) have identified patients with a 10-year absolute risk of event greater than or equal to 20% as being "high risk," and those with absolute risk of event greater than 10% at 10 years as "intermediate risk." These levels would equate to 10.6% and 5.1% 5-year event rate risk, respectively. However, this risk score calculates mortality risk and not event risk. The European Society has adopted a 10-year mortality risk of 5% as designating "high risk," which would equate to a 5-year mortality risk of 2.5%. Tables 3 through 8 identify that such absolute predicted mortality results when

Table 9. Risk Score Grading for Tables 3–8

Risk Score	% Dying From Cardiovascular Disease in 5 Years
0	0.04
5	0.07
10	0.11
15	0.19
20	0.31
25	0.51
30	0.84
35	1.4
40	2.3
45	3.7
50	6.1
55	9.8
60	15.6
65	24.5
70	37.0

Scores exceeding 40 are High Absolute Risk category.

the calculated risk score exceeds 40. In terms of relative risk, there are several ways in which this risk has been defined (Table 9). The INDANA group has used a comparison reference population from the Medical Research Council trials to identify expected rates of cardiovascular death. Their methods and assumptions are published.[61] Based on their reference population, an individual's score can be identified as "low," "average," "high," or "very high" risk, reflecting, respectively, 0 to thirtieth percentile, thirtieth to sixtieth percentile, sixtieth to ninetieth percentile, or over ninetieth percentile. The project group has a downloadable PC format risk calculator available online at www.riskscore.org.uk and also has an online calculator available at the same web site. The scores identified by this computer model would be the same as use of Tables 3 and 5, with added precision for both absolute risk calculation and relative risk estimation comparing the subject to the Medical Research Council database.

The Framingham scoring system identifies people as "below average risk," "average risk," "moderately above average risk," and "high risk" based on how their Framingham score increases their risk compared with the risk generated by their ages alone. The group "moderately above average risk" has risk that is threefold increased above the lowest risk level, and the "high risk" group has risk that is fourfold increased above the lowest risk level. The population-based analysis of the INDANA risk score makes its method more objectively attractive than the arbitrary relative risk level designation of the Framingham score.

It is reported that dramatic reductions in risk (approximately 33-50% in 5 years) can be seen with aggressive use of risk reduction therapies. The implication of this finding would be that patients at high risk could conceivably be reduced to intermediate or even average risk categories within 5 years. The AHA guidelines (2002) for primary prevention of CVD and stroke recommend that risk-factor screening in adults should begin at age 20 and should be repeated at least every 5 years in the absence of risk factors or every 2 years if risk factors are present. We would encourage risk-factor screening in children starting at the age of 10 years. The rationale for frequent risk factor assessment would only be sensible if aggressive treatment measures were being applied with the intention of reducing global risk. Thus, a high-risk individual may warrant treatment of blood pressure, glucose, cholesterol, and homocysteine at levels that would not warrant treatment for a lower-risk individual, and once treatment lowers the risk factors to lower levels, it would legitimize continued therapy to maintain the lower level of risk.

The risk score profile we advocate herein would identify an individual as warranting closer follow-up and therapy for predisposing treatable risk factors in the presence of excessive absolute risk (defined as a 5-year mortality risk exceeding 2.5%; risk score 41 or higher) or if the relative risk places that person into a "high-risk" or "very high risk" stratum (relative risk exceeding the sixtieth percentile for age) (Table 8). These individuals would warrant therapy of any treatable predisposing risk factor (blood pressure, cholesterol, glycemia, smoking cessation, homocysteine) and evaluation of risk score every second year at least. This approach would obviously identify more than 40% of the adult population as targets for monitoring and potential intervention, but this is not unreasonable in the context of the published prevalence of the metabolic syndrome of 45% among adults aged 60 years and older in National Health and Nutrition Examination Survey (NHANES) III.

Assessing for premature mortality risk from CVD can also involve strategies to evaluate for the presence of early, asymptomatic or preclinical disease. This approach, while still considered to be "screening," would not be considered global risk assessment, since it measures disease activity or pathologic vascular responses, and therefore serves a diagnostic rather than a predictive or prognostic function. An example of such an early detection approach to CVD diagnosis in asymptomatic diseased individuals was recently reported and shows considerable promise. It is interesting to note that in the asymptomatic population they studied, 49% of patients exhibited scores suggestive of early disease warranting change in medical therapy. The implication is that traditional screening approaches have been insufficiently sensitive to identifying patients whose disease condition requires more aggressive therapy. An expanded global risk assessment approach could certainly improve early identification of those not just at high or intermediate absolute

risk, but also those at sufficiently increased relative risk to warrant intervention at an earlier age without necessarily having high short-term absolute risk. Furthermore, since blood pressure, cholesterol, glycemia, creatinine level, and homocysteine all contribute to global risk as a continuum of risk across a wide range, there may actually be rationale for interventions in high-relative risk individuals to reduce levels that would not ordinarily be associated with increased risk in lower-risk or average individuals. We see guidelines today using exactly this rationale to recommend treatment of hypertension in diabetic patients, for example, to target levels lower than those recommended for the nondiabetic general public and initiated at levels lower than those employed for nondiabetic individuals.

COSEHC's endorsement of a novel global risk assessment tool that would be expected to be more comprehensive than the Framingham score, more sensitively discriminating for individuals at increased risk than Framingham, and which employs more variables generated from more numerous patient observations than Framingham, may be used to identify patients who would benefit from more intensified medical interventions as well as serve to monitor the beneficial effects that intervention delivers. This is the first risk analysis tool to use both nondiabetic glycemic and homocysteine levels as variables to modify the global assessment of cardiovascular risk.

Role and Importance of Early Detection, Aggressive Prevention, and Treatment

To approach this topic systematically, it is necessary to understand the factors that define the cardiovascular risk associated with the metabolic syndrome, such as obesity, insulin resistance, and dyslipidemia.

1. Obesity. More than 64% of the U.S. population is now considered overweight (BMI $\geq$25), with 30% considered obese (BMI $\geq$30).[30] Central or truncal obesity is associated with a greater cardiovascular risk. Although both waist circumference as suggested by ATP III and BMI have been used to define the metabolic syndrome, these factors are not shown consistently to be independent markers for CVD risk in patients with the metabolic syndrome.[69] BMI, often used as a surrogate marker, has limitations, since Asians, for instance, have an increased likelihood of insulin resistance beginning with BMIs above 21 kg/mg^2. In the U.S. population, there is a continuous rise with increasing BMI in the risk of unstable angina and myocardial infarction. Beginning at a BMI of 22, which had an odds ratio of 1.2, the risk increases progressively to an odds ratio of 4.6 at a BMI of 40.[70] In their analysis, BMI was independent of, age, gender, blood pressure, insulin resistance, leptin, fibrinogen, high-sensitivity C-reactive protein, CHD severity on angiography, smoking status, and a history of myocardial infarction or hypertension.[70]

2. Insulin Resistance. This component of the metabolic syndrome does not occur in all obese patients, but the metabolic abnormalities associated with increased cardiovascular risk in overweight patients are seen primarily in insulin-resistant individuals. Accurate assessment of insulin resistance is not easily performed in clinical practice. The authors of the ATP III guidelines have suggested a fasting blood glucose level of greater than or equal to 110 mg/dL as evidence of insulin resistance, but a triglyceride-to-HDL ratio may be the most sensitive and specific predictor.[69] Other determinations of insulin resistance may be more sensitive but would add more tests and generate extra cost. The American Diabetes Association has redefined impaired fasting glucose as greater than or equal to 100 mg/dL. In the recent analysis of the West of Scotland data by Sattar et al,[71] the use of a fasting glucose level of greater than 99 mg/dL significantly improved the sensitivity of identifying those individuals who had the metabolic syndrome. With four or more components of the metabolic syndrome, the hazard ratio of developing CHD was 3.65 and that of developing diabetes was 24.4. In previous studies by Haffner et al,[72] the prediction of which individuals develop CHD and/or diabetes was significantly greater with elevated fasting plasma insulin levels or elevated level on the 2-hour oral glucose tolerance test. In a recent study, McLaughlin and colleagues,[73] reported that while the diagnosis of insulin resistance is easily defined, the measurement of insulin resistance is cumbersome, especially when done by the insulin suppression test, which is the criterion standard. To make the diagnosis of insulin resistance more practical, they demonstrated that fasting plasma insulin levels of greater than or equal to 108 pmol/L, triglyceride levels of greater than or equal to 130 mg/dL, or a ratio of triglyceride to HDL of 1.8 SI units or greater than 3.0 using mg/dL correlated with insulin resistance. Of the three surrogate markers, fasting plasma insulin levels and the triglyceride-to-HDL ratio correlated the best.

3. Dyslipidemia. Defined cutpoints include a triglyceride level greater than 150 mg/dL and HDL cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women. Elevated serum triglycerides (large very low density lipoprotein particle size), decreased HDL cholesterol (small HDL particle size), normal to minimally increased LDL cholesterol, and small LDL particles define atherogenic dyslipidemia, a characteristic feature associated with the metabolic syndrome. This lipid phenotype occurs because of simultaneous overproduction of lipoprotein particles, impaired lipoprotein particle clearance, and dynamic changes in core lipoprotein particle composition (eg, variation in the amount of

cholesterol carried per particle).[74] Conventional lipid testing, however, often fails to capture the broad heterogeneity of lipoprotein particle number and size present in patients with insulin resistance, the metabolic syndrome, and type 2 diabetes.

Recent trials with nuclear magnetic resonance (NMR) spectroscopy have provided additional insight into the lipoprotein characteristics of insulin resistance and metabolic syndrome patients. Given the variability of cholesterol carried per particle, NMR lipoprotein measurement affords the opportunity to study the prevalence and characteristics of patients manifesting a "disconnect" between conventional lipid measurements and directly measured number of lipoprotein particles. In a post hoc analysis of the Framingham Offspring Study, Otvos et al[75,76] reported the prevalence and characteristics of discrepancies between LDL cholesterol and NMR-measured LDL particle number. Subjects identified with LDL cholesterol below the twentieth percentile (100 mg/dL) and above the eightieth percentile (160 mg/dL) were compared with subjects with LDL particle concentrations below the twentieth percentile (<1100 nmol/L) and above the eightieth percentile (>1800 nmol/L). Among those with LDL cholesterol values deemed "optimal" by current guidelines (<100 mg/dL), 34% of subjects manifested increased numbers of LDL particles (>1100 nmol/L). Further analysis indicated that increased triglycerides and decreased HDL cholesterol were significantly associated with the "disconnect" between normal LDL cholesterol and increased numbers of LDL particles.

Data regarding NMR LDL particle number associations with ATP III defined metabolic syndrome in the Framingham Offspring Study provides further insight into the magnitude of LDL particle excess in the metabolic syndrome.[77] Consistent with previous observations, mean LDL cholesterol levels were marginally higher in patients with the metabolic syndrome (139 mg/dL versus 129 mg/dL in patients without the metabolic syndrome), with values showing little or no change as a function of the number of components of the metabolic syndrome present. Conversely, patients with the metabolic syndrome showed disproportionately higher numbers of LDL particles (1722 nmol/L versus 1375 nmol/L in patients without the metabolic syndrome) overall. In contrast to LDL cholesterol level, LDL particle concentration is a function of the number of components of the metabolic syndrome present. The disparity between LDL cholesterol and number of LDL particles was explained by abnormal LDL composition. Among metabolic syndrome patients, a threefold increase in small LDL particle number and corresponding decrease in large LDL particle number occurred with components of the metabolic syndrome ranging from zero to five. One consequence of abnormal LDL composition in metabolic syndrome subjects was that only 23% of subjects with "optimal" LDL-cholesterol levels of <100 mg/dL (<twentieth percentile) had correspondingly low LDL particle numbers (less than the twentieth percentile). In terms of the magnitude of this disparity, 34% of individuals with an LDL-cholesterol level below the twentieth percentile had LDL particle number over the fiftieth percentile. With these emerging data, it is becoming clear that advanced lipid testing using NMR spectroscopy not only makes it easier to evaluate CVD risk at the initiation of therapy but also is predictive of subsequent risk while the patient is on therapy and may be cost effective. Prediction of on-trial risk is not accurate by conventional lipid measurements.

4. Hypertension. High blood pressure is defined as systolic blood pressure greater than or equal to 130 mm Hg and/or diastolic blood pressure greater than or equal to 85 mm Hg or on antihypertensive therapy. The goal for blood pressure in persons with diabetes is less than 130/80 mm Hg. However, blood pressure may not be the best hemodynamic determinant of cardiovascular risk. Pulse pressure has been recognized as having better predictive power for the presence of CVD.[78,79]

5. Vascular Endothelial Dysfunction and Inflammation. Research has demonstrated a number of inflammatory markers with predictive power for subsequent cardiovascular events. These include TNF-α, interleukin-6, and high-sensitivity C-reactive protein.[80] Some of these have better predictive power than high-sensitivity C-reactive protein, but because of methodologic limitations high-sensitivity C-reactive protein has become the most used marker. Guidelines for its use in clinical practice were presented in the joint discussion by the Centers for Disease Control and Prevention and the AHA.[80] Ridker et al[81] clearly showed, in the Women's Health Study, that for each additional criterion for the metabolic syndrome a woman possesses, the higher the cardiovascular risk and the higher the level of high-sensitivity C-reactive protein. Furthermore, when women possessed four or five of the criteria for the metabolic syndrome, the presence of a high-sensitivity C-reactive protein level greater than 3 mg/dL further increased their cardiovascular risk over the 8-year follow-up period. Measurements of high-sensitivity C-reactive protein level in patients with the metabolic syndrome may be useful in determining which patients need the most aggressive therapy.

6. Prothrombotic State. Within the spectrum of metabolic abnormalities present in patients with the metabolic syndrome, alterations in coagulation mechanisms and fibrinolytic pathways remains one of the least frequently recognized components of the process. The underlying atherogenic processes that culminate in thrombotic events associated with the concept of a "vulnerable plaque"[82] results in platelet activation and aggregation, thrombin generation,

and activation of inflammatory cytokines. Meade et al[83] showed the importance of fibrinogen as a CVD risk factor. More recently, measurements of increased levels of plasminogen activator inhibitor-1 (PAI-1) have been used to predict the presence of clinical CVD.[84,85] An increase in PAI-1, as well as prothrombotic substances such as tissue factor, fibrinogen, and factor VII, is associated with the metabolic syndrome. Lastly, platelet-dependent thrombosis has been linked to glucose intolerance.[86] Other than fibrinogen, which is an acute-phase reactant and somewhat labile, none of the others, including PAI-1, are easily measured and therefore are not clinically useful. Despite their technical limitations, reduced fibrinolysis and a procoagulant state contribute to the constellation of factors interplaying with each other in the expression of the metabolic syndrome. In keeping with this interpretation, novel studies regarding the role of angiotensin receptor blockers in attenuating the prothrombotic state of hypertensive subjects [87-89] and decreasing the risk of atherothrombotic strokes deserves careful consideration.[90]

7. Atherosclerosis. The last consideration in the evaluation of patients with the metabolic syndrome is looking for evidence of subclinical atherosclerosis. This can be done clinically by examination of large arteries looking for decreased pulses and/or bruits. Use of an inexpensive Doppler echographer to measure ankle-brachial index (ABI) can be very helpful. Beyond the clinical examination, measures of carotid intimal medial thickness (IMT) for evaluation of subclinical coronary disease using coronary artery calcium scoring (CACS) has stimulated tremendous interest. Measuring carotid IMT is very technician dependent and is not widely available in clinical practice. CACS using either fast helical computed tomography or electron beam computed tomography (superior technique) has become much more widely available, especially since it provides a measure of total artery plaque burden. The CACS is a far more sensitive test for evaluating subclinical coronary disease than any form of stress testing. Although stress testing is relatively sensitive in detecting patients with coronary blockages greater than 70%, it is not good at detecting those who have less significant blockage. CACS will frequently detect patients with as little as 10% to 15% blockage. This is important, since two-thirds of heart attacks occur with coronary artery obstructions of less than 50%.[91] The earlier that subclinical coronary disease can be uncovered, especially in young patients, the better that aggressive prevention programs can be developed and implemented. Greenland et al[92] recently evaluated the use of CACS in addition to the Framingham Risk Score to predict cardiovascular risk in asymptomatic patients. They found that CACS can modify predicted risk determined by Framingham Risk Score alone. It is in this younger patient with intermediate risk and in cases in which the decision to treat is unclear where the CACS may have its greatest applicability.

In summary, the expanded occurrence of the metabolic syndrome in the USA population, especially in the southeastern United States, has raised awareness of a need to revise our approach to the management of global cardiovascular risks, underscoring a need for more aggressive interventions and prevention measures. In defining the components of the metabolic syndrome and their inter-relationship among hypertension, obesity, dyslipidemia, and insulin resistance, a basic framework for the medical management of this syndrome has been defined.

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