The Endocrine Society's
CLINICAL GUIDELINES

Primary Prevention of Cardiovascular Disease and Type 2 Diabetes in Patients at Metabolic Risk:

An Endocrine Society Clinical Practice Guideline

The Endocrine Society®

The Journal of Clinical Endocrinology & Metabolism

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Abstract

Objective: The objective was to develop clinical practice guidelines for the primary prevention of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) in patients at metabolic risk.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee (CGS) of The Endocrine Society, six additional experts, one methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

Evidence: Systematic reviews of available evidence were used to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group criteria to describe both the quality of evidence and the strength of recommendations. We used 'recommend' for strong recommendations and 'suggest' for weak recommendations.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during one group meeting, several conference calls, and e-mail communications. The drafts prepared by the task force with the help of a medical writer were reviewed successively by The Endocrine Society's CGS, Clinical Affairs Committee (CAC), and Council. The version approved by the CGS and CAC was placed on The Endocrine Society's Web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Conclusions: Healthcare providers should incorporate into their practice concrete measures to reduce the risk of developing CVD and T2DM. These include the regular screening and identification of patients at metabolic risk (at higher risk for both CVD and T2DM) with measurement of blood pressure, waist circumference, fasting lipid profile, and fasting glucose. All patients identified as having metabolic risk should undergo 10-yr global risk assessment for either CVD or coronary heart disease. This scoring will determine the targets of therapy for reduction of apolipoprotein B-containing lipoproteins. Careful attention should be given to the treatment of elevated blood pressure to the targets outlined in this guideline. The prothrombotic state associated with metabolic risk should be treated with lifestyle modification measures and in appropriate individuals with low-dose aspirin prophylaxis. Patients with prediabetes (impaired glucose tolerance or impaired fasting glucose) should be screened at 1- to 2-yr intervals for the development of diabetes with either measurement of fasting plasma glucose or a 2-h oral glucose tolerance test. For the prevention of CVD and T2DM, we recommend that priority be given to lifestyle management. This includes antiatherogenic dietary modification, a program of increased physical activity, and weight reduction. Efforts to promote lifestyle modification should be considered an important component of the medical management of patients to reduce the risk of both CVD and T2DM.

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AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; ALT, alanine transferase; apo B, apolipoprotein B; ATP, Adult Treatment Panel; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Foundation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; JNC7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL, low-density lipoprotein; MR, magnetic resonance; NCEP, National Cholesterol Education Program; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; PROCAM, Prospective Cardiovascular Munster; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; UKPDS, United Kingdom Prospective Diabetes Study; VFA, visceral fat area; VLDL, very-low-density lipoprotein.

SUMMARY OF RECOMMENDATIONS

The dramatic increase in the incidence of patients at risk for the development of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) throughout the developed and developing world requires that physicians and other care providers be aware of the risk factors for these conditions and be able to identify patients at risk in order to initiate treatment to prevent these diseases. This guideline focuses on the population of individuals with the components of the metabolic syndrome who do not yet have diagnosed CVD or T2DM and on the steps that can be taken to prevent these two diseases. Several risk factors for CVD and T2DM—hypertension, lipid abnormalities, hyperglycemia, and abdominal adiposity—tend to cluster together. We recommend that physicians screen for these key risk factors for CVD and T2DM at routine clinical visits when they obtain a patient's history and perform physical examinations.

1. DEFINITIONS AND DIAGNOSIS

There is growing evidence that many patients who develop CVD or T2DM have common antecedents of metabolic origin. Although the pathophysiology underlying these antecedents is not fully understood, there is a strong overlap between cardiovascular risk factors and prediabetes [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)]. For this reason, it is reasonable to identify a general condition called metabolic risk. The Endocrine Society has recognized the importance of identifying patients who are at metabolic risk so that efforts can be instituted to prevent both CVD and T2DM. This guideline follows the recommendations of the GRADE working group for grading of evidence and recommendations (see Appendix 1 for presentation of symbols and language).

The Task Force decided to define metabolic risk as reflecting an individual's risk for CVD and T2DM (see Appendix 2 for a full discussion of this choice of terminology). Individuals at high metabolic risk often have 1) elevations of apolipoprotein B (apo B)-containing lipoproteins [low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL)] with elevated triglycerides, 2) reduced levels of high-density lipoprotein cholesterol (HDL-C), 3) increased plasma glucose levels, 4) hypertension, 5) enlarged waist circumference, 6) a prothrombotic state, and 7) a proinflammatory state.

1.1. The Task Force did not attempt to reach consensus on endorsement of a specific definition of the metabolic syndrome. The two currently used definitions describe closely overlapping but not identical populations (Table 1). Of the most commonly used definitions of the metabolic syndrome, we suggest that physicians screen for the components of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition at the clinical visit, because of its ease of use and convenience of implementation in the office setting. The finding of at least three components especially should alert the clinician to a patient at metabolic risk (at higher risk for CVD and T2DM) (2 | ⊕◯◯◯).

1.2. We recommend that providers screen for the main components of the metabolic syndrome at regular intervals (1 | ⊕⊕⊕◯). We suggest that this should be done at least every 3 yr (2 | ⊕◯◯◯) in those individuals who have one or more risk factors but do not meet the established definitions of the syndrome. These components include measurement of blood pressure, waist circumference, fasting lipid profile, and fasting glucose.

1.3. We recommend that waist circumference be measured by clinicians as a routine part of the clinical examination. This measurement does not replace the routine measurement of weight or calculation of body mass index (BMI) but can provide more focused information regarding risk for CVD and T2DM (1 | ⊕◯◯◯).

We recommend that the cutoffs for elevated waist circumference be at least 102 cm for men and at least 88 cm for women in Caucasian, African-American, Hispanic, and Native American populations (3). We recommend that the cutoffs for waist circumference in Asian populations (both East Asian and South Asian) be at least 90 cm for men and at least 80 cm for women (1| ⊕◯◯◯).

1.4. We suggest that individuals previously diagnosed with prediabetes (IGT or IFG) be screened for the presence of overt T2DMat 1- to 2-yr intervals (2| ⊕◯◯◯). This can be done with fasting plasma glucose (FPG) and, wherever possible, with an oral glucose tolerance test (OGTT). For individuals at metabolic risk without IFG, there is less consensus on the recommended interval of screening.

1.5. A number of additional biological markers have been associated with metabolic risk: apo B, adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, alanine transferase (ALT) as a marker of liver fat, C-reactive protein (CRP), inflammatory cytokines (*e.g.* IL-6), liver or myocellular fat content by magnetic resonance (MR) spectroscopy, and microalbuminuria (in patients without diabetes). Evidence that these markers provide an indication of metabolic risk beyond routine measurements is limited. Their measurement is not recommended for routine evaluation of metabolic risk in clinical practice. (2| ⊕◯◯◯).

Some of the above measurements may have utility for determining the pattern or severity of metabolic risk, but must be considered as optional based on clinical judgment. Although these measures are not recommended for routine measurement, one or more of them may be measured according to physician discretion to confirm or clarify estimates of metabolic risk.

2. ABSOLUTE RISK ASSESSMENT

2.1. We recommend that all patients identified as having metabolic risk undergo global risk assessment for 10-yr risk for either coronary heart disease (CHD) or CVD. Framingham and Prospective Cardiovascular Munster (PROCAM) scoring assesses 10-yr risk for CHD. The European SCORE algorithm predicts 10-yr risk for total cardiovascular mortality. Risk factor scoring with these algorithms can be easily carried out. Global risk assessment for cardiovascular outcomes is recommended before starting preventative treatment (1| ⊕◯◯◯).

3. TREATMENT TO PREVENT ATHEROSCLEROTIC CVD (ESPECIALLY CHD AND STROKE)

3.1.1. We recommend that apo B-containing lipoproteins (LDL and VLDL) be lowered in patients at metabolic risk to reduce risk for CVD (1| ⊕⊕⊕⊕).

3.1.2. We recommend that LDL cholesterol (LDL-C) be the primary target of lipoprotein-lowering therapy (1| ⊕⊕⊕⊕) and that non-HDL-C (an indicator for all apo B-containing lipoproteins) be the secondary target (1| ⊕⊕⊕◯). Furthermore, if HDL-C remains reduced after treatment of non-HDL-C, consideration can be given to therapies designed to raise HDL-C (2| ⊕⊕◯◯).

3.1.3. We recommend that intensity of lipoprotein-lowering therapy be adjusted to the absolute 10-yr risk for CVD. (1| ⊕⊕◯◯) We suggest that intensity of lipoprotein-lowering therapy further be adjusted to the absolute lifetime risk for CVD (2| ⊕◯◯◯).

3.2.1. We recommend that when blood pressure is elevated, it be lowered to reduce the risk for CVD (1| ⊕⊕⊕⊕).

3.2.2. We recommend that type and intensities of blood pressure-lowering therapies be selected to optimize risk reduction, safety, and cost-effectiveness. We recommend that blood pressure be treated to a target of less than 140/90 mm Hg (or <130/80 in individuals with diabetes or chronic kidney disease). If weight loss or lifestyle modifications are not successful, then antihypertensive medications should be instituted and dose adjusted to treat to target (1| ⊕⊕⊕◯).

3.3. We recommend that lifestyle management be considered first-line therapy for patients at increased metabolic risk (1 | ⊕◯◯◯).

3.4.1. We recommend that the prothrombotic state be treated with lifestyle therapies to reduce risk for CVD (1 | ⊕◯◯◯).

3.4.2. In individuals at metabolic risk who are over age 40 and whose 10-yr risk is more than 10%, we recommend that lowdose aspirin prophylaxis for primary prevention of CVD (75–162 mg/d) be considered if there are no contraindications (1 | ⊕⊕⊕◯).

There is no consensus on the specific recommended dose within this range.

4. TREATMENT TO PREVENT T2DM

4.1.1. For primary prevention of T2DM, we recommend that patients found to be at higher metabolic risk on the basis of multiple metabolic syndrome components be started on a clinical program of weight reduction (or weight maintenance if not overweight or obese) through an appropriate balance of physical activity, caloric intake, and formal behavior modification programs to achieve a lowering of body weight/waist circumference below the targets indicated (see 1.3. for waist circumference and 4.1.2. for weight) (1 | ⊕⊕◯◯).

Although it is important to aim for these targets, any lowering of body weight/waist circumference is beneficial, and we recommend use of lifestyle modification programs for this purpose (1 | ⊕⊕◯◯).

4.1.2. In individuals at metabolic risk who have abdominal obesity, we suggest that body weight be reduced by 5–10% during the first year of therapy (2 | ⊕◯◯◯). Efforts to continue weight loss or maintain the weight loss over the long term should be encouraged.

4.1.3. We recommend that patients at metabolic risk undergo a program of regular moderate-intensity physical activity (1 | ⊕⊕◯◯). This activity would be for at least 30 min, but preferably 45–60 min, at least 5 d/wk. It could include brisk walking or more strenuous activity. It can be supplemented by an increase in physical exercise as part of daily lifestyle activities.

4.1.4. We recommend that all individuals at metabolic risk follow a diet that is low in total and saturated fat, is low in *trans* fatty acids, and includes adequate fiber (1 | ⊕⊕◯◯). We suggest that saturated fat be less than 7% of total calories and dietary cholesterol less than 200 mg/d (2 | ⊕◯◯◯). We recommend that *trans* fat in the diet should be avoided as much as possible (1 | ⊕◯◯◯). There is much controversy regarding the proportion of carbohydrates in the diet. We were unable to reach consensus on the optimal ratio of carbohydrates to fats in the diet. We recommend that individuals at metabolic risk increase the proportion of fiber, unprocessed grains, and unsaturated fat in their diet. Avoiding foods with high glycemic index may help lower metabolic risk.

4.2. We recommend that priority be given to reducing risk for diabetes with lifestyle therapies rather than drug therapies (1 | ⊕⊕⊕◯).

The dramatic increase in the incidence of patients at risk for the development of CVD and T2DM throughout the developed and developing world requires that physicians and other care providers be aware of the risk factors for these conditions and be able to identify patients at risk to initiate treatment to prevent these diseases. This guideline focuses on the population of individuals with the components of the metabolic syndrome who do not yet have diagnosed CVD or T2DM, and on the steps that can be taken to prevent these two diseases. Several risk factors for CVD and T2DM, hypertension, lipid abnormalities, hyperglycemia, and abdominal adiposity, tend to cluster together. We recommend that physicians screen for these key risk factors for CVD and T2DM at routine clinical visits when they obtain a patient's history and perform physical examinations.

METHOD OF DEVELOPMENT OF EVIDENCE-BASED GUIDELINES

The Clinical Guidelines Subcommittee of the Endocrine Society deemed therapy of metabolic risk a priority area in need of practice guidelines and appointed a seven-member Task Force to formulate evidence-based recommendations. The Task Force elected to use the approach recommended by the GRADE group, an international group with expertise in development and implementation of evidence-based guidelines (122). The Task Force reviewed the available literature to inform its key recommendations and used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence. The strength of a recommendation is indicated by the number 1 (strong recommendation, associated with the phrase "we recommend") or 2 (weak recommendation, associated with the phrase "we suggest"). The quality of the evidence is indicated by cross-filled circles, such that ⊕◯◯◯ denotes very low quality evidence, ⊕⊕◯◯ low quality, ⊕⊕⊕◯ moderate quality, and ⊕⊕⊕⊕ high quality. Recommendations are followed by a description of the evidence, and in some instances the values, that the Expert Panel considered in making the recommendation. A detailed description of this grading scheme has been published elsewhere (123).

1. DEFINITIONS AND DIAGNOSIS

There is growing evidence that many patients who develop CVD or T2DM have common antecedents of metabolic origin (4, 5). Although the pathophysiology underlying these antecedents is not fully understood, there is a strong overlap between cardiovascular risk factors and prediabetes (IFG and IGT). Accordingly, it is reasonable to identify a general condition called metabolic risk. The Endocrine Society has recognized the importance of identifying patients who are at metabolic risk so that efforts can be instituted to prevent both CVD and T2DM. This guideline follows the recommendations of the GRADE working group for grading of evidence and recommendations.

The Task Force decided to define metabolic risk as reflecting an individual's risk for CVD and T2DM (see Appendix 2 for a full discussion of the choice of terminology). Individuals at high metabolic risk often have 1) elevations of apo B-containing lipoproteins (LDL and VLDL) with elevated triglycerides, 2) reduced levels of HDL-C, 3) increased plasma glucose levels, 4) hypertension, 5) enlarged waist circumference, 6) a prothromboticstate, and 7) a proinflammatory state.

1.1. The Task Force did not attempt to reach consensus on endorsement of a specific definition of the metabolic syndrome. The two currently used definitions describe closely overlapping but not identical populations (Table 1, see page 8). Of the most commonly used definitions of the metabolic syndrome, we suggest that physicians screen for the components of the AHA/NHLBI definition at the clinical visit because of its ease of use and convenience of implementation in the office setting. The finding of at least three components especially should alert the clinician to a patient at metabolic risk (at higher risk for CVD and T2DM) (2 | ⊕◯◯◯).

Evidence

Of the various proposed definitions of the metabolic syndrome, only two are currently of practical use in the clinical setting (1, 2) (see Table 1). Although there are numerous analyses of the various components of these definitions to independently predict risk for CVD and T2DM, there are very few that investigate the definitions as a whole or compare them with each other with regard to effectiveness. The major difference between the AHA/NHLBI and the International Diabetes

TABLE 1. Criteria proposed for clinical diagnosis of the metabolic syndrome

Clinical measure	AHA/NHLBI (1): any 3 of the following 5 features	IDF (2)
Waist circumference	≥102 cm in men or ≥88 cm in women (non-Asian origin); ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians)	≥94 cm in men or ≥80 cm in women (Europids, Sub-Saharan Africans, and Middle Eastern); ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians; South and Central Americans); ≥85 cm in men or ≥90 cm in women (Japanese), plus any 2 of the following:
Triglycerides (fasting)	≥150 mg/dl or on drug therapy for high triglycerides	≥150 mg/dl or on drug therapy for high triglycerides
HDL-C	<40 mg/dl in men or <50 mg/dl in women or on drug therapy for low HDL-C	<40 mg/dl in men or <50 mg/dl in women or on drug therapy for low HDL-C
Blood pressure	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on drug therapy for hypertension	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on drug therapy for hypertension
Glucose (fasting)	≥100 mg/dl or drug therapy for elevated glucose	≥100 mg/dl (includes diabetes)

Foundation (IDF) definitions is that the former posits the presence of three of five possible components, whereas the latter requires that central obesity, as defined by waist circumference, be present first before examining for the other components. Because some individuals at risk for CVD and T2DM do not have obesity, and a substantial number of obese individuals may not be at higher risk, we believe that the AHA/NHLBI definition might identify a better population for further targeted screening for CVD and T2DM. Using the AHA/NHLBI definition, metabolic syndrome is common and is associated with increased risk for T2DM and CVD in both sexes, accounting for up to half of new cases of T2DM and up to one third of new CVD cases, over 8 yr of follow-up (6).

The concept of the metabolic syndrome has been, and continues to be, very useful to the medical community to enhance awareness of risk clustering and to promote thorough screening in individuals presenting with risk factors for CVD and T2DM. Although such a benefit appears likely, no study has formally addressed this issue. Focusing on the metabolic syndrome should not divert attention from other major, established CVD risk factors such as LDL-C and family history. Therefore, the concept of metabolic risk has value only when these additional clinical factors are considered by the physician.

It remains possible that some combination of subclinical abnormalities, more or less closely related to insulin resistance/hyperinsulinemia/visceral obesity, may signal a significant surplus of CVD risk that is not predicted by the classical risk engines [Framingham, United Kingdom Prospective Diabetes Study (UKPDS), PROCAM, *etc.*]. This hypothesis must be rigorously tested. In general, the concept of identifying predictors from the physical/lifestyle domain (*e.g.* waist circumference as a proxy of visceral adiposity, resting heart rate as a proxy of cardiorespiratory fitness, *etc.*) and/or from the large pool of biochemical markers (*e.g.* CRP, adiponectin, HDL-C, triglycerides, apo A/apo B ratio, fibrinogen, *etc.*) does not require assumptions about etiology or pathogenesis. As long as the aim is to configure a risk syndrome (7), all that matters is the ability of its components to consistently and substantially contribute to the identification of those who may be at risk for CVD and T2DM. Data from the Framingham Study indicate that the AHA/NHLBI definition of the metabolic syndrome may be associated with

increased risk for CVD independent of insulin resistance (8). Although the currently available definitions of the metabolic syndrome are not yet validated as quantifiable predictors of risk, and more study is necessary to test their ability to predict CVD and T2DM, they can be used to identify more susceptible populations for more intensive screening.

1.2. We recommend that providers screen for the main components of the metabolic syndrome at regular intervals (1| ⊕⊕⊕◯). We suggest that this should be done at least every 3 yr (2| ⊕◯◯◯) in those individuals who have one or more risk factors but do not meet the established definitions of the syndrome. These components include measurement of blood pressure, waist circumference, fasting lipid profile, and fasting glucose.

Evidence

The suggested time frames for screening are based on clinical consensus, without established evidence from controlled clinical studies. Epidemiological evidence suggests that approximately 30% of the people with T2DM in the United States have not had their disease diagnosed (9) and that regular screening with fasting blood glucose could identify those individuals for appropriate treatment, which could delay or decrease the development of related complications. In addition, the identification of individuals with prediabetes (IFG or IGT) could allow for those individuals to be treated with lifestyle modification and exercise to prevent the development of diabetes in the future.

1.3. We recommend that waist circumference be measured by clinicians as a routine part of the clinical examination. This measurement does not replace the routine measurement of weight or calculation of BMI but can provide more focused information regarding risk for CVD and T2DM (1| ⊕◯◯◯).

We recommend that the cutoffs for elevated waist circumference be at least 102 cm for men and at least 88 cm for women in Caucasian, African-American, Hispanic, and Native American populations (3). We recommend that the cutoffs for waist circumference in Asian populations (both East Asian and South Asian) be at least 90 cm for men and at least 80 cm for women (1| ⊕◯◯◯).

Evidence

Numerous studies have indicated that waist circumference and waist-to-hip ratio are better predictors of risk for CVD and diabetes than weight or BMI (10). We advocate waist measurement because of its ease of use in the clinical setting, when performed properly. Currently, waist circumference is rarely used by clinicians in the primary care setting. Greater use would help identify those individuals at higher risk who should receive further screening. It should not replace weight measurement or BMI, because longitudinal measurement of weight is important for follow-up of any major clinical interventions to treat obesity.

Both AHA/NHLBI and IDF recognize that the definition of elevated waist circumference is variable among different populations. The IDF suggests that for Europids the threshold for increased waist circumference be at least 94 cm in men and at least 80 cm in women. For the U.S. population, the AHA/NHLBI defines elevated waist circumference as at least 102 cm for men and at least 88 cm for women (Table 2, see page 10).

To assess the implication of metabolic syndrome in different ethnic populations, there is some concern that the recommended cutoff for waist circumference is inappropriate for different ethnic groups, especially for Asian individuals. There are two important studies showing the rationale for using different cutoff points of waist circumferences in people of Asian extraction. Tan *et al.* (11) used receiver operating characteristic analysis to identify the level of waist circumference in people living in Singapore (mainly composed of Chinese, Malay, and Asian Indian populations) that best predicted the clustering of impaired glucose metabolism and low HDL-C. They found that a waist circumference cutoff of at least

TABLE 2. Recommended waist circumference thresholds to define abdominal obesity

Region/ethnicity	Recommending body	Waist circumference threshold for abdominal obesity
United States	AHA/NHLBI	≥102 cm in men; ≥88 cm in women[a]
Europe/Europids	IDF	≥94 cm in men; ≥80 cm in women
Asia	AHA/NHLBI IDF	≥90 cm in men; ≥80 cm in women[b]

Data are not available for Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations, and Ethnic South and Central Americans. IDF suggests using waist thresholds for Europe/Europids for populations in these regions.

a AHA/NHLBI guidelines indicate that waist circumference thresholds of at least 94 cm in men and at least 80 cm in women are optional in persons who show clinical evidence of insulin resistance.

b In Japan, national recommendations for waist circumference thresholds for abdominal obesity are at least 85 cm in men and at least 90 cm in women.

90 cm in men and at least 80 cm in women seems to be comparable to that in U.S. people. On the other hand, according to the reports from the examination committee of Criteria for Obesity Disease in Japan, Japanese people with visceral fat area (VFA) of more than 100 cm^2 have more than one of the obesity-related disorders such as hyperglycemia, dyslipidemia, and hypertension. Correlation between VFA and waist circumference in men and women showed 85 cm of waist circumference in men and 90 cm of waist circumference in women correspond to a VFA of 100 cm^2 (12). There are several studies showing the rationale for using different cutoff points of waist circumferences in different ethnic groups in Asian populations (13, 14). The Task Force recognizes that East Asian and South Asian populations may have significant differences in lipid indices, fat mass as a proportion of BMI, and cardiovascular morbidity. More studies are necessary to clarify these differences before consensus on separate cutoffs for waist circumference might be established for these ethnic groups. It can be argued whether cutoff points should vary according to race or ethnicity. However, because of the huge variation of standard waist circumference depending on race, it is practical to use the ethnicity specific values for waist circumferences in the AHA-NHLBI definitions of the metabolic syndrome until more specific data are available.

Values

Our recommendation that physicians routinely measure waist circumference for determination of metabolic risk places a higher value on use of this measure in risk scoring to identify appropriate patients for further screening and more intensive goals of therapy to treat blood pressure and hyperlipidemia and a lower value on the fact that this measurement is not routinely performed in most practices at the present time. We also recognize that practicality in the clinical setting is an important determinant in the use of a measurement like waist circumference. We also place high value on the need to identify risk for diabetes and CVD in ethnic populations where the incidence is increasing especially rapidly.

Remarks

Waist circumference can be easily measured in the clinical setting according to the NHANES III Protocol (15).To define the level at which waist circumference is measured, a bony landmark is first located and marked. The subject stands, and the examiner, positioned at the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor, and the tape is snug but does not compress the skin. The measurement is made at a normal minimal respiration (see Fig. 1).

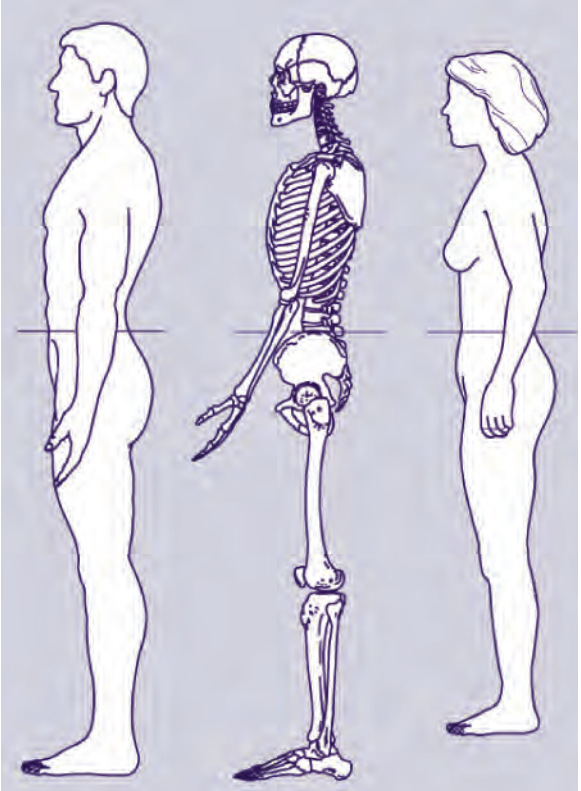

Figure 1. Measuring waist circumference according to NHANES III protocol. http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid obesity.figgrp.237.

1.4. We suggest that individuals previously diagnosed with prediabetes (IGT or IFG) be screened for the presence of overt T2DM at 1- to 2-yr intervals (2| ⊕◯◯◯). This can be done with FPG and, wherever possible, with an OGTT. For individuals with metabolic syndrome without IFG, there is less consensus on the recommended interval of screening.

Evidence

The natural history of both IFG and IGT can be defined in terms of progression to T2DM. The majority of people with IFG/IGT will eventually meet the criteria for T2DM. Early diagnosis of T2DM should result in a decrease in duration-dependent diabetes-related microvascular complications; however, direct data are not available to determine whether this decrease occurs. Published trials have not been sufficiently powered to show a reduction in these hard outcomes. One of the other major reasons to recommend early therapeutic interventions for individuals with diabetes is the potential to reduce the increased risk of CVD.

The OGTT is more sensitive but also more time-consuming and costly than the FPG test. Some evidence suggests that the OGTT is more sensitive for identifying those individuals with a higher degree of cardiovascular risk, but as a screening test for cardiovascular risk in the clinical, nonresearch setting, it is not always practical. Recently, the suggestion has been made to use OGTTs in populations at high risk for diabetes, as for example persons with hypertension (16, 17). The main reason for this suggestion is the high prevalence of glucose abnormalities in hypertensive patients attending hospital clinics and the low sensitivity of the FPG test. The relatively low sensitivity of the FPG to diagnose diabetes is well known, but that in itself does not warrant universal implementation of the OGTT in clinical practice.

There is less information on progression to metabolic syndrome than on progression to diabetes in various populations. In the Framingham Offspring Study of 2,848 adult men and women who did not have diabetes or CVD at their baseline examination, it was found that 12.5% of women and 21.4% of men had metabolic syndrome (or metabolic risk as defined in this document) according to the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria (8, 18). When these patients were reexamined 8 yr later, the percentages had increased to 23.6 and 33.9% (after direct adjustment to the baseline age) or by 47 and 56%, respectively (6). When Framingham Offspring Study patients satisfying ATP III criteria for metabolic syndrome were followed for up to 11 yr, it was found that metabolic syndrome criteria increased the risk for developing diabetes 6-fold, regardless of the degree of insulin resistance (19).

In the Diabetes Prevention Program (DPP) study, 53% of subjects met the ATP III criteria for metabolic syndrome at baseline, and approximately 60% of those who initially did not meet the criteria did meet them after 4 yr (20).

On the basis of these data, it is suggested that people with IFG or IGT be screened for metabolic risk factors at 1- to 2-yr intervals so that the presence of new risk factors can be identified and treated appropriately.

1.5. A number of additional biological markers have been associated with metabolic risk: apo B, adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, PAI-1, fibrinogen, ALT as a marker of liver fat, CRP, inflammatory cytokines (*e.g.* IL-6), liver or myocellular fat content by MR spectroscopy, and microalbuminuria (in patients without diabetes). Evidence that they provide an indication of metabolic risk beyond routine measurements is limited. Measurement of these markers is not recommended for routine evaluation of metabolic risk in clinical practice (2 | ⊕◯◯◯).

Some of the above measurements may have utility for determining the pattern or severity of metabolic risk but must be considered as optional based on clinical judgment. Although these measures are not recommended for routine measurement, one or more of them may be measured according to physician discretion to confirm or clarify estimates of metabolic risk.

Evidence

A large number of different markers of CVD risk have been identified. Some of these have also been identified as markers of high diabetes risk. Still, we cannot recommend the measurement of these markers for routine clinical practice for several reasons.

The so-called classic risk factors are used in clinical practice to estimate the absolute risk of CVD. The most widely applied prediction equation is the Framingham risk score (21). This score is less well validated for persons with T2DM. More recently, the UKPDS risk engine has been developed with validated CVD risk estimates for people with T2DM (22, 23). Both methods apply easy-to-collect clinical parameters, for example, age, use of cigarettes, blood pressure, and serum lipid levels. The UKPDS risk engine also includes duration of diabetes and glycemia, additions based on the earlier observations of that study (24).

The main question is whether the addition of one or more of the new markers will enhance the predictive power of these simple equations. Another relevant question is whether these markers will affect the therapeutic intervention. The ability to estimate the risk of a CVD event will determine whether the patient requires intervention to lower that risk. If the marker is causally related to the disease process, then it will also determine which therapeutic intervention is indicated.

An example of a widely debated marker is CRP (25). A high CRP level is indicative of a high CVD risk. The therapeutic consequence may be that general therapy to lower CVD risk should be initiated earlier than would be done without an elevated CRP level for a given Framingham risk score. In that case, measures might need to be taken to decrease LDL-C and blood pressure to lower targets, but the specific evidence for lower targets has not yet been identified.

Are these new markers, and CRP in particular, able to enhance the risk estimates of the well-known risk scores/engines? Recent studies have addressed this clinically important question (26). The main and consistent conclusion of these studies is that adding CRP, or in fact other novel risk markers, to more basic risk models does not improve prediction of CVD risk. This is not very surprising. Most of the risk factors are interrelated and by themselves not able to provide a good prediction. This means that in a clinical setting we can rely on simple, less expensive measures, as for example asking about family history, cigarette smoking, and measuring blood pressure and serum lipids. These simple measures will enable us to identify those patients at highest CVD risk, thus the persons who will benefit the most from any medical intervention to lower that risk (27).

Traditionally recognized risk factors (such as those included in CVD risk calculators) explain a large

proportion of the variation in CVD risk across individuals. Researchers have shown an association between abnormalities in other biological markers and elevated metabolic risk. These include apo B, LDL fractionation, adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, PAI-1, fibrinogen, ALT as a marker of liver fat, CRP, inflammatory cytokines (*e.g.* IL-6), liver or myocellular fat content by MR spectroscopy, and microalbuminuria (in patients without diabetes). Ease of measurement, convenience, cost, and extent to which changes in these markers enhance our ability to identify individuals at different CVD risk above and beyond the information traditional risk factors provide will determine their future role in practice.

In conclusion, none of the mentioned markers can be recommended for routine clinical use. The readily available simple and much less expensive parameters are able to provide a risk assessment that enables the physician to target treatment to those who will experience the most benefit.

2. ABSOLUTE RISK ASSESSMENT

2.1. We recommend that all patients identified as having metabolic risk undergo global risk assessment for 10-yr risk for either CHD or CVD. Framingham and PROCAM scoring assess 10-yr risk for CHD. The European SCORE algorithm predicts 10-yr risk for total cardiovascular mortality. Risk factor scoring with these algorithms can be easily carried out. Global risk assessment for cardiovascular outcomes is recommended before starting preventative treatment (1| ⊕◯◯◯).

Evidence

Several risk assessment algorithms have been published for estimating 10-yr risk for CHD. These include Framingham scoring for the United States (21) and PROCAM (28) and SCORE for Europe (29). These methods use easy-to-collect clinical parameters, for example, age, use of cigarettes, blood pressure, and serum lipid levels. Others that are less widely used also have been published. The UKPDS risk engine has been developed with validated CVD risk estimates for people with T2DM (22, 23), but the population with previously diagnosed diabetes is outside the framework of the primary prevention population considered in this guideline. We recommend that 10-yr risk for CHD be assessed for individuals using published algorithms that best pertain to the individuals from a particular population group. Clinical judgment or national or regional recommendations can be used for making these assessments. The Task Force made no attempt to compare the different algorithms among different population groups. Data are not available for making these comparisons.

Currently accepted categories of risk for primary prevention in patients with metabolic syndrome are high risk, moderately high risk, and moderate risk. The absolute cutoff points of 10-yr risk to define these three categories vary somewhat from one country to another. Currently accepted categories of Framingham risk for patients with metabolic syndrome are high risk (10-yr risk for major coronary events, >20%), moderately high risk (10–20%), and moderate risk (<10%).

Values

Our recommendations place high value on the need for early preventative care in vulnerable populations and the need for simple, easy-to-measure tools in the clinical setting. We place relatively low value on the burden of early therapy with medications to lower blood pressure and cholesterol and the lack of data to compare the relative efficacy of the different scoring systems.

3. TREATMENT TO PREVENT ATHEROSCLEROTIC CVD (ESPECIALLY CHD AND STROKE)

3.1.1. We recommend that apo B-containing lipoproteins (LDL and VLDL) be lowered in patients at metabolic risk to reduce risk for CVD (1| ⊕⊕⊕⊕).

3.1.2. We recommend that LDL-C be the primary target of lipoprotein-lowering therapy (1| ⊕⊕⊕⊕) and that non-HDL-C (an indicator for all apo B-containing lipoproteins) be the secondary target (1| ⊕⊕⊕◯). Furthermore, if HDL-C remains reduced after treatment of non-HDL-C, consideration can be given to therapies designed to raise HDL-C (2| ⊕⊕◯◯).

3.1.3. We recommend that intensity of lipoprotein-lowering therapy be adjusted to the absolute 10-yr risk for CVD (1| ⊕⊕◯◯). We suggest that intensity of lipoprotein-lowering therapy further be adjusted to the absolute lifetime risk for CVD (2| ⊕◯◯◯).

Evidence

3.1.1. Elevations of apo B-containing lipoproteins (LDL and VLDL), which are characteristic of most patients at metabolic risk, are associated with increased CVD risk. A large number of randomized controlled clinical trials document that the lowering of apo B-containing lipoproteins will reduce risk for CVD (30). For this reason, we recommend that in patients at metabolic risk, an effort be made to reduce apo B-containing lipoproteins.

3.1.2. Non-HDL-C is highly correlated with apolipoprotein B levels. Recent evidence shows that non-HDL-C is a better predictor of future CHD events than is LDL-C (31–40). The NCEP recommends that in patients with elevated triglycerides non-HDL-C be a secondary target of cholesterol-lowering therapy, after LDL-lowering treatment. In patients at metabolic risk, most of whom have some elevation of triglycerides, treatment to lower both non-HDL-C and LDL-C to appropriate targets is prudent.

A low level of HDL-C is a well-accepted risk factor for CVD (41). In a *post hoc* analysis of the Treating to New Targets study, low HDL-C was shown to be a risk factor for future CHD, even among CHD subjects who have an LDL-C less than 70 mg/dl who were treated on statins. However, no clinical trials have definitively shown that raising HDL-C has reduced CHD in statin treated subjects, although such trials are currently underway (42).

Evidence that raising HDL-C with specific therapies will reduce risk for CVD has not been documented adequately in controlled clinical trials. Smaller clinical trials are supportive of benefit, but they do not provide the strength of evidence necessary to make a strong recommendation. Nonetheless, on the basis of epidemiological evidence and smaller trials, we suggest that therapy be instituted to raise serum levels of HDL-C to reduce the risk for CVD in patients at metabolic risk.

HDL-C levels can be raised with both lifestyle therapies and drugs. Lifestyle therapies include weight reduction, increased physical activity, and avoidance of very low fat diets. Drugs that will raise HDL-C levels include nicotinic acid and, to a lesser extent, fibrates and statins (43–46). All of these agents will reduce apo B-containing lipoproteins, and thus the possibility cannot be ruled out that their actions to lower risk for CVD is due to this mechanism and not to raising HDL-C. Furthermore, according to practice norms, drug therapies to raise HDL-C levels generally are limited to patients at higher risk for CVD.

The recent Fenofibrate Intervention and Event Lowering in Diabetes trial (47) tested the efficacy of fenofibrate for reducing CVD risk in patients with established T2DM. In that trial, fenofibrate therapy failed to reduce CHD events as the primary endpoint. It did, however, significantly lower total CVD and

microvascular complications as secondary endpoints. In contrast, subgroup analysis of the Veterans Affairs High-Density Lipoprotein Intervention Trial indicated that gemfibrozil reduced risk for CHD/CVD events in patients with diabetes (48). In a *post hoc* analysis of the Coronary Drug Project, nicotinic acid was found to reduce risk for CHD events in patients with diabetes (45). Although nicotinic acid produces a favorable effect on the lipoprotein pattern, its use in patients with diabetes must be carefully monitored because some patients show a worsening of glucose control.

Fibrates may be considered as an option as an add-on drug to statins (or LDL-lowering drugs) in patients who persist with high triglycerides and low HDL after LDL-lowering therapy. This choice depends on physician judgment. It is supported by a metaanalysis of fibrate trials (30) that show fibrates in general reduce risk by 15–20%. If a fibrate is used with the statin, fenofibrate is the drug of choice. It is recommended because of evidence of minimal interaction with statins and decreased risk of myopathy with this drug (49).

3.1.3. If it is accepted (3.1.1.) that patients with metabolic risk deserve therapies to reduce CVD risk, we recommend that intensity of lipoprotein-lowering therapy be adjusted to the absolute 10-yr risk for CVD. The purpose is to optimize risk reduction, safety, and cost-effectiveness. The NCEP has identified LDL-C as the primary target of therapy and has made non-HDL-C a secondary target in patients with elevated triglycerides (50). The NCEP has made recommendations for balancing these three factors for achieving these objectives based on 10-yr risk projections for CHD. The Task Force accepted these recommendations as reasonable treatment goals for elevations of apo B-containing lipoproteins.

One of the major aims of this guideline is to reduce lifetime risk for CVD in patients with increased metabolic risk. Prospective studies suggest that evidence of metabolic risk is associated with an increase in lifetime risk for CVD. We suggest that intensity of lipoprotein-lowering therapy further be adjusted to the absolute lifetime risk for CVD. Evidence to support this suggestion comes from prospective epidemiological and genetic studies but not from long-term controlled clinical trials. If absolute risk scoring reveals a person at metabolic risk to be at moderately high or high risk (*i.e.* 10-yr risk for CHD ≥10%), the treatment goals outlined in Table 3 pertain. Here the LDL-C goal is less than 130 mg/dl, but an optional goal is LDL-C less than 100 mg/dl. Corresponding goals for non-HDL-C are 30 mg/dl higher than the LDL-C goal. If 10-yr CHD risk is less than 10%, which can be called moderate risk for patients found to be at metabolic risk, the ranges for LDL-C and non-HDL-C defined by NCEP guidelines can be taken as a guide to evaluate therapy. Here the LDL-C and non-HDL-C goals are less than 130 mg/dl and less than 160 mg/dl, respectively.

TABLE 3. Treatment goals for apo B-containing lipoproteins

Therapeutic target and goals of therapy for apo B-containing lipoproteins
LDL-C goals
• High-risk patients[a]: <100 mg/dl (2.6 mmol/liter) (for very-high-risk patients[b] in this category, optional goal is <70 mg/dl)
• Moderately high-risk patients[c]: <130 mg/dl (3.4 mmol/liter) (for higher-risk patients in this category, optional goal is <100 mg/dl [2.6 mmol/liter])
• Moderate-risk patients[d]: <130 mg/dl (3.4 mmol/liter)
Non-HDL-C goals
• High-risk patients[a]: <130 mg/dL (3.4 mmol/L) (optional: <100 mg/dL for very high risk patients[b])
• Moderately high-risk patients[c]: <160 mg/dL (4.1 mmol/L); therapeutic option: <130 mg/dL (3.4 mmol/L)
• Moderate-risk patients[d]: <160 mg/dL (4.1 mmol/L)

a High-risk patients are those with established atherosclerotic CVD, diabetes, or 10-yr risk for CHD higher than 20%. For cerebrovascular disease, high-risk condition includes transient ischemic attack or stroke of carotid origin or more than 50% carotid stenosis.

b Very-high-risk patients are those who are likely to have major CVD events in the next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes and established CHD along with any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and metabolic syndrome.

c Moderately high-risk patients are those with 10-yr risk for CHD 10–20%. Factors that favor the therapeutic option of non-HDL-C less than 100 mg/dl are those that can raise persons to the upper range of moderately high risk: multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (e.g. coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex).

d Moderate-risk patients are those with at least two major risk factors and 10-yr risk <10%.

To achieve the goals of therapy outlined in 3.1.3., we recommend that for adjustment of intensity of lipoprotein-lowering therapy the therapies be selected that optimize risk reduction, safety, and cost-effectiveness. Depending on the level of risk, several therapeutic options are available. For patients at moderate risk for CVD (10-yr risk for CHD <10%), lifestyle therapies (antiatherogenic diet and weight reduction) may be sufficient to lower LDL-C and non-HDL-C adequately to reduce long-term risk. Table 4 (see page 16) outlines strategies for use of lifestyle therapies for reduction in apo B-containing lipoproteins in clinical practice. This table also shows the degree of reduction of LDL-C accompanying each dietary change; it also shows the estimated reduction in risk for CHD accompanying the dietary change projected from the change in LDL-C levels. Increase physical activity can also be recommended simultaneously with other lifestyle therapies because of prospective studies that suggest it will reduce cardiovascular risk. Furthermore, in all patients, cessation of cigarette smoking is mandatory to reduce CVD risk. In patients at moderate metabolic risk, ATP III guidelines recommend reserving cholesterol-lowering drugs to those with higher cholesterol levels, e.g. LDL-C at least 160 mg/dl (non-HDL-C ≥190 mg/dl). On the basis of recent clinical trials, many authorities favor employing cholesterol-lowering drugs if the LDL-C remains more than 130 mg/dl on maximal lifestyle therapy. For patients at higher risk (10-yr risk for CHD 10%), lifestyle therapy still should be employed to maximize lowering of lipoproteins. However, consideration can be given to using cholesterol-lowering drugs if LDL-C is at least 130 mg/dl on lifestyle therapies, with an optional goal of less than 100 mg/dl (51–65). It must be recognized that cholesterol-lowering drugs have not been studied in all subgroups of the population or in many different populations, but that they have the ability to reduce risk for CVD under a broad range of circumstances is beyond doubt (66–68). For this reason, the Task Force does not exclude patients on the basis of ethnicity, gender, or age. Nonetheless, different subgroups of the population may require special considerations, as discussed below.

Women. In women, onset of CHD is delayed by 10–15 yr as compared with men in general (69). However, management for risks is as important for women as for men. To prevent premature CHD (*i.e.* before age 65 yr), metabolic syndrome in women should be treated the same as in men.

Ethnic groups. Despite relatively higher rates of CHD in African-Americans as compared with Caucasians (69), typically the triglyceride levels in African-Americans are lower and the HDL-C levels are higher than those in Caucasians (70). These lipid profiles are

TABLE 4. Recommended dietary changes to reduce apo B-containing lipoproteins and estimated reduction in CHD[a]

Dietary factor	Suggested change	LDL-C reduction (%)	Estimated CHD reductionb (%)
Saturated fat reduction	Reduce saturated fat to <7% of total energy	8–10	>8–10
Trans fat reduction	Reduce *trans* fat to <1% of total energy	2	≅2
Dietary cholesterol reduction	Reduce dietary cholesterol to <200 mg/d	3–5	>3
Plant stanols/sterols	Add plant stanols/sterols 2 g/d	6–10	>6
Dietary fiber	Add viscous fiber 5–10 g/d	3–5	>3
Weight reduction	Reduce body weight by 7–10%	5–8	>5
Total		~25–35	~25

a LDL-C is used as a surrogate marker for apo B-containing lipoproteins because the available data are more robust for this marker than for other lipoprotein fractions.

b Estimate based on results of controlled clinical trials that a 1% reduction in LDL-C reduces risk for CHD by approximately 1%.

not explained by differences in BMI or other factors (71). It is not clear whether this lipid pattern works protectively. On the other hand, African-Americans have long been known to have the highest prevalence of hypertension of all ethnic groups. This higher incidence might cancel the favorable lipid profile.

Younger adults. In the younger population, CHD is rare. However, years of life lost, defined as the difference between the number of years a person would be expected to live if he/she were not obese, showed that the younger population lost more years than the older population (72). Thus, the younger population with metabolic syndrome should be treated more strictly than the older population.

Table 5 summarizes the available cholesterol-lowering drugs. It also provides estimated reductions in LDL-C accompanying each therapeutic regimen as well as projected reductions in CHD.

3.2.1. We recommend that when blood pressure is elevated, it be lowered to reduce the risk for CVD (1 | ⊕⊕⊕⊕).

3.2.2. We recommend that type and intensities of blood pressure-lowering therapies be selected to optimize risk reduction, safety, and cost-effectiveness. We recommend that blood pressure be treated to a target of less than 140/90 mm Hg (or 130/80 in individuals with diabetes or chronic kidney disease). If weight loss or lifestyle modifications are not successful, then antihypertensive medications should be instituted and dose adjusted to treat to target (1 | ⊕⊕⊕◯).

Evidence

3.2.1. An elevated blood pressure is a major risk factor for CVD. Its effect on CVD risk has been documented in many prospective studies. The higher the blood pressure is, the greater will be the risk for both CHD and stroke. This fact has led treatment guidelines to classify severity of hypertension according to increasing levels of blood pressure. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) (73) provides an

TABLE 5. Summary of efficacy of drugs that reduce apo B-containing lipoproteins

Drug category	Standard dose: LDL-C reduction (%)	Standard dose: estimated CHD reduction[a] (%)	High dose: LDL-C reduction (%)	High dose: estimated CHD reduction[a] (%)
Statins	30–40[b]	30–40	45–55[h]	45–55 (for more potent statins)
Cholesterol-absorption blocker (ezetimibe)	18–25[c]	18–25		
Bile acid sequestrants	15–20[d]	15–20	20–25[i]	20–25
Niacin	10–15[e]	10–15[g]	15–20[i]	15–20
Fibrates	5–15[f]	10–20[g]		

a The estimated reduction in CHD is based on clinical trial evidence that a 1% reduction in LDL-C is associated with a 1% reduction in CHD risk. However, because LDLlowering drugs also reduce VLDL-C, some of the risk reduction attributed to LDL-C lowering may be the result of a simultaneous reduction in VLDL-C.

b Lovastatin 40 mg, pravastatin 40 mg, simvastatin 20–40 mg, fluvastatin 40–80 mg, atorvastatin 10 mg, rosuvastatin 5–10 mg.

c Ezetimibe 10 mg.

d Cholestyramine 4–16 g, colestipol 5–20 g, colesevelam 2.6–3.8 g.

e Extended release niacin (Niaspan) 2 g.

f Gemfibrozil 1200 mg, fenofibrate 145–200 mg.

g A portion of the reduction in CHD risk may be related to a rise in HDL.

h Simvastatin 80 mg, atorvastatin 80 mg, rosuvastatin 40 mg.

i Cholestyramine 24 g, colestipol 30 g, colesevelam 4.4 g.

j Crystalline nicotinic acid 4.5 g.

TABLE 6. Categories of blood pressure

Blood pressure category	Systolic and/or diastolic blood pressures (mm Hg)
Normal	<120 and <80
Prehypertension	120–139 or 80–89
Hypertension, stage 1	140–159 or 90–99
Hypertension, stage 2	≥160 or ≥100

Blood pressure categories based on the JNC7 (73).

acceptable classification of progressively elevated blood pressure (Table 6). Furthermore, a large number of controlled clinical trials demonstrate that lowering of blood pressure will reduce risk for CVD, both CHD and stroke. For these reasons, we recommend that when the blood pressure is elevated, it be lowered to reduce the risk for CVD in patients at metabolic risk. The primary goal for blood pressure lowering according to JNC7 is a level of less than 140/90 mm Hg. However, because even milder forms of elevated blood pressure are accompanied by increased risk for CVD, reducing blood pressure to the normal range (<120/<80 mm Hg) is considered optimal for long-term prevention of CVD. Still, the incremental benefit of achieving normal blood pressure levels, compared with the prehypertensive range, has not been documented in controlled clinical trials. This potential benefit can be extrapolated from prospective studies in which people with normal blood pressure have the lowest rates of CVD.

3.2.2. Blood pressure can be lowered by both lifestyle and drug therapies (74–78). For this reason, we recommend that the type and intensities of blood pressure-lowering therapies be selected to optimize risk reduction, safety, and cost-effectiveness. For example, for patients at metabolic risk whose blood pressures are in the prehypertensive range, lifestyle therapies are preferable to drug treatment for both safety and cost reasons. The extent to which various lifestyle therapies can lower blood pressure was estimated by JNC7 (73) and is shown in Table 7. When blood pressure reaches the hypertensive range, lifestyle therapies should be continued, but consideration can be given to adding drug therapy. Dietary sodium restriction is an important component of lifestyle therapies to control blood pressure, and we support the recommendations of JNC7 with respect to this. Tailoring drug therapy to treat hypertension is beyond the scope of this document and has been outlined in detail in the JNC7 report. There is controversy as to whether certain antihypertensive drugs are to be preferred in patients at metabolic risk. Some investigators favor use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers over diuretics and β-blockers (77, 79–81). However, in practice, treatment of hypertension often requires multiple drugs to achieve the goal of therapy, and preferences must give way to the priority of attaining the desired blood pressure (82–85).

TABLE 7. Projected reductions in blood pressure accompanying lifestyle therapies

Lifestyle therapy	Specific recommendation	Projected reduction in systolic blood pressure (mm Hg)
Weight reduction	Weight reduction of 7–10% of body weight	5–20
Moderate exercise	Moderate exercise (30 min/d)	4–9
Reduce dietary sodium	<2 g/d (100 mmol/d)	2–8
Other nutrient change	Increased fruits and vegetables (*e.g.* DASH Diet) 5 servings per day	8–14
Moderation of alcohol intake		2–4
Total		Total BP lowering >10 mm Hg

Estimations of efficacy of lifestyle modification taken from the JNC7 (73). BP, Blood Pressure

3.3. We recommend that lifestyle management be considered first-line therapy for patients at increased metabolic risk (1 | ⊕◯◯◯).

Evidence

Lifestyle therapies (weight reduction, increased physical activity, and antiatherogenic diet) have been shown to reduce all of the components of the metabolic syndrome simultaneously (86–91). The only drugs that have the same effects are weight reduction drugs. However, currently available drugs of this type are associated with side effects that limit their use in many patients. In addition, drugs that treat individual risk components do not modify all of them simultaneously. For these reasons, lifestyle therapies clearly have priority over drug treatment. Nonetheless, in patients at increased risk for CVD or those with clinically significant risk factors (*e.g.* elevated cholesterol or blood pressure), drug therapy targeted to treat those specific risk factors may be required to achieve current goals of therapy.

Although one study has suggested, in a secondary analysis, a beneficial effect of a thiazolidinedione (TZD) in reduction of cardiovascular risk (92), we cannot recommend such use for primary prevention at this time. Concerns related to the increased risk of fractures with these agents, the possibility of exacerbation of previously undetected congestive heart failure with thiazolidinedione, and the possible increased risk of cardiovascular events with rosiglitazone (93) make inadvisable the use, at present, of this class of medications in large populations for prevention.

Complete cessation of smoking and elimination of exposure to tobacco smoke in the environment are important goals of lifestyle intervention to reduce the risk of cardiovascular disease and stroke. We support the recommendations of the American Heart Association with respect to smoking cessation (94).

Values

Our recommendations for lifestyle management as first-line therapy place high value on avoiding the potential risks and side effects of the use of TZDs and metformin in very large populations, in which the relationship of risk to potential benefit is not yet established. We also place high value on the relative safety and public health benefit of lifestyle modification measures in the clinical setting and low value on the current difficulties of instituting these measures in the clinical office setting.

3.4.1. We recommend that the prothrombotic state be treated with lifestyle therapies to reduce risk for CVD (1 | ⊕◯◯◯).

3.4.2. In individuals at metabolic risk who are over age 40 and whose 10-yr risk is more than 10%, we recommend that low-dose aspirin prophylaxis for primary prevention of CVD (75–162 mg/d) be considered if there are no contraindications (1 | ⊕⊕⊕◯).

There is no consensus on the specific recommended dose within this range.

Evidence

3.4.1. A prothrombotic state is recognized as a significant risk factor for CVD. Patients with metabolic syndrome exhibit an increase in coagulation factors and antifibrinolytic factors. These factors can be reduced by weight loss (95–99). In addition, aspirin therapy will reduce the likelihood of cardiovascular thrombosis (coronary thrombosis and stroke) (100, 101). We therefore recommend that the prothrombotic state be treated to reduce risk for CVD. Lifestyle therapies should be introduced in all patients at metabolic risk to reduce coagulation factors and antifibrinolytic factors.

3.4.2. Several analyses suggest that if the 10-yr risk for CHD is 10% or more, the risk-to-benefit ratio is favorable for prevention of CVD. Therefore, we suggest that aspirin therapy be instituted (if not

contraindicated) when 10-yr risk for CHD exceeds 10%. The existing evidence indicates that aspirin therapy will reduce risk for CVD in primary prevention. On the other hand, a small fraction of treated subjects will experience major bleeding episodes including stroke. Even so, the aspirin prophylaxis option is favored by the American Heart Association. It must be noted nonetheless that some authorities express caution about the use of aspirin for primary prevention; they contend that the benefit-to-risk ratio is not high enough to justify aspirin therapy in this risk category. One report also suggests that aspirin therapy may be only marginally efficacious for CVD reduction in women. Despite these caveats, the Task Force favors institution of aspirin treatment for patients at metabolic risk when their 10-yr risk for CHD is more than 10%.

Values

Our recommendation for the use of lifestyle therapies to reduce the prothrombotic state places a higher value on the use of exercise, fitness, and behavior modification for CVD and T2DM prevention because of its multiple health benefits as part of a coordinated plan of care. We place a lower value on the evidence for specific benefits with regard to reduction of the prothrombotic state and the difficulties in instituting such therapies in the medical office setting.

4. TREATMENT TO PREVENT T2DM

4.1.1. For primary prevention of T2DM, we recommend that patients found to be at higher metabolic risk on the basis of multiple metabolic syndrome components be started on a clinical program of weight reduction (or weight maintenance if not overweight or obese) through an appropriate balance of physical activity, caloric intake, and formal behavior modification programs to achieve a lowering of body weight/waist circumference below the targets indicated (see 1.3. for waist circumference and 4.1.2. for weight) (1| ⊕⊕◯◯).

Although it is important to aim for these targets, any lowering of body weight/waist circumference is beneficial, and we recommend use of lifestyle modification programs for this purpose (1| ⊕⊕◯◯).

4.1.2. In individuals at metabolic risk who have abdominal obesity, we suggest that body weight be reduced by 5–10% during the first year of therapy (2| ⊕◯◯◯). Efforts to continue weight loss or maintain the weight loss over the long term should be encouraged.

4.1.3. We recommend that patients at metabolic risk undergo a program of regular moderate-intensity physical activity (1| ⊕⊕◯◯). This activity would be for at least 30 min, but preferably 45–60 min, at least 5 d/wk. It could include brisk walking or more strenuous activity. It can be supplemented by an increase in physical exercise as part of daily lifestyle activities.

4.1.4. We recommend that all individuals at metabolic risk follow a diet that is low in total and saturated fat, is low in *trans* fatty acids, and includes adequate fiber (1| ⊕⊕◯◯). We suggest that saturated fat be less than 7% of total calories and dietary cholesterol less than 200 mg/d (2| ⊕◯◯◯). We recommend that *trans fat* in the diet should be avoided as much as possible (1| ⊕◯◯◯). There is much controversy regarding the proportion of carbohydrates in the diet. We were unable to reach consensus on the optimal ratio of carbohydrates to fats in the diet. We recommend that individuals at metabolic risk increase the proportion of fiber, unprocessed grains, and unsaturated fat in their diet. Avoiding foods with high glycemic index may help lower metabolic risk.

Evidence

During the past 20 yr there have been numerous studies of the effects of weight reduction and

increased physical activity on the development of T2DM in high-risk populations (102–107). These have been reviewed by Norris and colleagues (108) and by Yamaoka and Tango (109). At least three of these trials, the Da Qing Study (105), The Finnish Diabetes Prevention Study (107), and the DPP in the United States (103), have demonstrated that weight reduction and increased physical activity significantly decrease the risk of progression from IGT to diabetes by 40–58%. In the Da Qing Study, subjects with IGT were assigned by clinic, rather than individually, to one of four treatment groups: a calorie-restricted diet, an exercise program, a combined program of diet and exercise, or a control group. During this 6-yr study, the progression to diabetes was significantly lower in all three intervention groups than in the control group: 44% in the diet-only group, 41% in the exercise-only group, and 46% in the combined diet and exercise group, as compared with 68% in the control group.

The Finnish Diabetes Prevention Study (107) was a randomized clinical trial conducted in overweight men and women with IGT who were identified by screening high-risk populations. Subjects were randomized to usual care or to an individualized lifestyle modification program that emphasized weight reduction of at least 5% by reduced caloric intake, decreased intake of dietary fat and saturated fats, increased fiber intake, and the addition of 4 h/wk moderate-intensity exercise. After a mean 3.2 yr follow-up, the risk of developing diabetes was decreased by 58% in the intensive lifestyle modification group. Moreover, in those subjects who exceeded the weight loss goal of 5%, the risk reduction was 74%, and in those who exceeded the exercise goal of 4 h/wk, the relative risk reduction was 80%. In follow-up studies done 3 yr after completion of active counseling, the beneficial effects of the lifestyle program persisted with 36% risk reduction (110).

The DPP (103), conducted in 27 centers in the United States, randomized 3,234 adults with IGT to groups receiving an intensive lifestyle modification intervention, treatment with metformin, or placebo. Initially, there was also a group treated with troglitazone, but this was discontinued early in the study before recruitment was completed, and follow-up of this group was less than 1 yr compared with a mean of 2.8 yr for the three completed groups, which included over 1,000 subjects per group. The goals for the group receiving the intensive lifestyle modification intervention were to lose at least 7% of body weight through a 24-wk program of diet and exercise and to maintain this weight loss throughout the duration of the study (111). Lifestyle modification emphasized reducing caloric intake, principally by reduction of fat to less than 25% of energy, decreasing saturated fats, increasing dietary fiber, and increasing physical activity by at least 150 min/wk moderate-intensity exercise equivalent to brisk walking (20). The intensive lifestyle modification intervention decreased the risk of developing diabetes by 58% as compared with the placebo-treated control group. The intensive lifestyle modification intervention was significantly more effective than treatment with metformin, up to 850 mg, which reduced the risk of diabetes by 31% (103, 112).

In the DPP, 53% of subjects met the NCEP ATP III criteria for the metabolic syndrome at baseline, whereas 47% did not. This provided an opportunity to evaluate the effects of the treatment strategies to prevent or reverse the features of the metabolic syndrome and other metabolic risk factors in this high-risk population. *Post hoc* analyses found that in subjects without metabolic syndrome at baseline, approximately 60% of the control group developed it over 4 yr. Metformin treatment reduced the risk by 17% and the intensive lifestyle modification intervention decreased it by 41%. Furthermore, in subjects who had metabolic syndrome at baseline, the intensive lifestyle modification intervention resulted in a reversal of the syndrome in 38%, whereas reversal occurred in 18% of the control group (20).

In other analyses of the DPP data (113), it was found that hypertension was present in 30% of subjects at baseline. Over 3 yr, it increased in the placebo- and metformin-treated groups but significantly decreased in the group receiving the intensive lifestyle modification intervention.

Serum triglycerides decreased in all groups but significantly more in the intensive lifestyle modification intervention group. This group also had significantly increased HDL-C levels and decreased small dense LDL-C. After 3 yr, the quantity of medications used to control blood pressure and dyslipidemia was reduced by 25–28% in the group receiving intensive lifestyle modification intervention. At baseline, high-sensitivity CRP was increased in all groups and was correlated with BMI, waist circumference, FPG, and insulin resistance (114). After 1 yr, use of metformin resulted in a modest 7–14% reduction in high-sensitivity CRP, but the intensive lifestyle modification intervention resulted in a 29–33% reduction.

Thus, there is convincing evidence from well-conducted randomized controlled trials that weight reduction of 5–10% of initial body weight in overweight subjects with metabolic risk is effective in decreasing the development of T2DM and reducing multiple CVD risk factors. In general, weight loss programs are designed to achieve a negative energy balance of 500–1000 kcal/d, which results in a weight loss of 1–2 lb/wk (0.5–1.1 kg/wk). Both the DPP and the Finnish Diabetes Prevention Study used a diet with 25% of energy from fat (7% from saturated fats) and increased amounts of fiber. Consumption of high-fructose corn syrup-containing beverages has been associated with obesity and T2DM (115, 116), and restriction of their use is recommended in most weight-loss programs. Considerable controversy exists on the amounts and types of carbohydrates that should be incorporated into weight-loss diets. This controversy includes the use of low glycemic index foods, glycemic load, and percentage of energy from carbohydrate sources.

Values

Our recommendations for dietary modification and exercise to reduce the risk of diabetes place high value on the use of these programs in a coordinated manner to improve health and reduce multiple risk factors simultaneously and low value on the socioeconomic factors that currently tend to prevent these interventions from being implemented. We believe that proper implementation of these recommendations extends beyond the realm of the medical office practice and enters the areas of public health and public policy.

4.2. We recommend that priority be given to reducing risk for diabetes with lifestyle therapies rather than drug therapies (1 | ⊕◯◯◯).

Evidence

There is growing clinical trial evidence, particularly the DPP, that risk for diabetes can be reduced by lowering plasma glucose levels in patients with prediabetes. Glucose concentrations can be reduced by either lifestyle therapies or by drug therapy. Lifestyle therapy consists of weight reduction and increased physical activity (Table 8). In addition, glucose concentrations can be reduced by either metformin or a TZD. In the DPP, both metformin and a TZD (troglitazone) were shown to delay the conversion of prediabetes to diabetes (103, 117). This delay was confirmed in two other clinical TZD trials, the TRIPOD study using troglitazone (118) and the DREAM trial using rosiglitazone (119). One clinical trial with a TZD provided suggestive evidence that treatment of diabetes with pioglitazone may also reduce the risk for CVD (92, 120), but such a result

TABLE 8. Recommendations for lifestyle reduction of plasma glucose to lower risk for T2DM[a]

Dietary recommendation	Goals of therapy
Weight reduction	Achieve and maintain a weight loss of 7% with healthy eating[b]
Physical activity	Maintain physical activity at least 150 min/wk with moderate exercise, such as walking or biking

a Recommendations correspond to the intervention arm of the DPP (111).

b For healthy eating, follow dietary guidelines for lowering cholesterol and blood pressure (see Tables 3 and 6).

has not been confirmed in patients at metabolic risk without diabetes. Moreover, recent studies with rosiglitazone have raised questions about the long-term safety of this drug for diabetes prevention or treatment (93, 121). We suggest that priority be given to reducing risk for diabetes with lifestyle therapies rather than drug therapies. There are three reasons for this suggestion. First, lifestyle therapies appear to be as effective as drug treatment for reducing conversion to diabetes (20). Second, there are limited data on the long-term safety of drug therapy for the treatment of prediabetes. Third, the cost-effectiveness and long-term risks of drug therapy in these populations have not been adequately assessed.

Appendix

CHOICE OF TERMINOLOGY

In this guideline, we focus on a specific set of risk factors for CVD and T2DM. The term metabolic syndrome has been used to describe a set of clinical features clustered in individuals, most of whom have abdominal adiposity, conferring an increased risk for CVD and T2DM. There are various definitions of the metabolic syndrome; they all include a subset of the relevant risk factors for CVD and T2DM. Although these risk factors (high triglycerides/low HDL, increased small dense LDL, elevated blood pressure, elevated plasma glucose, abdominal obesity, insulin resistance, and inflammatory and thrombotic markers) tend to occur together in the same individuals, the etiology is not fully understood. Furthermore, because these definitions do not contain all CVD risk factors and dichotomize the population into those with and without the metabolic syndrome, it should not be used as an indicator of absolute, short-term risk for CVD. The occurrence of multiple metabolic risk factors in one individual, nonetheless, does indicate the presence of a higher long-term risk for both CVD and T2DM.

The concept that insulin resistance clusters with glucose intolerance, dyslipidemia, and hypertension to enhance CVD risk was proposed by Reaven in 1988 (124). At that time, it was presumed that the various clinical characteristics were linked by an overriding pathophysiological mechanism tied to insulin resistance, hence the term insulin resistance syndrome (IRS). In IRS, the primacy of insulin resistance is posited on the grounds that insulin resistance is an effective transducer of environmental influences, obesity (especially visceral) (10), cardiorespiratory fitness (125), and stress (126) being the most important ones. On the effector side, insulin exerts potent actions not only in pathways of glucose homeostasis but also on lipid turnover, blood pressure control, and vascular reactivity. Moreover, chronic hyperinsulinemia, the in vivo adaptive response to insulin resistance, has been shown to have pathogenic potential in its own right [for example, by down-regulating insulin action (127), strengthening antinatriuresis (128), or stimulating the adrenergic nervous system (129)], thereby creating reinforcement circuits in the network (130). These facts are supported by a wealth of experimental and clinical investigation (131). However, it is crucial to emphasize that just as insulin resistance alone is insufficient to alter glucose tolerance, for which some degree of β-cell dysfunction is required, insulin resistance/hyperinsulinemia is neither strictly necessary nor sufficient to alter lipid metabolism, blood pressure, or vascular function. Each of these homeostatic systems is under the control of multiple factors. Also, each of these systems is redundant, with plenty of interactions.

More recently, the pathophysiological IRS has been replaced by combinations of clinical criteria, defined by various organizations, which attempt to describe a clinical entity, the metabolic syndrome. The major purpose initially was to use clinical signs and symptoms to identify people with a clustering of risk factors, with a higher risk for CVD and T2DM than the general population.

In fact, hyperinsulinemia predicts diabetes, dyslipidemia (132), and to a lesser extent hypertension (133), and it is an independent, if weak, CVD predictor (134). Measuring insulin resistance directly (by the glucose clamp technique or by glucose tolerance testing) is too difficult for practical clinical use. Using fasting plasma insulin levels as a proxy for insulin resistance introduces confounding, due to the partly different physiology of hyperinsulinemia and insulin resistance (135) as well as lack of measurement standardization across studies.

These practical hurdles have prompted the search for practical, easily measured surrogates of insulin resistance, among which the waist girth or the waist-to-hip ratio seemed best in certain epidemiological studies (136). Thus, anthropometric measures have tended to replace insulin resistance in various definitions of the syndrome, such as those from

AHA/NHLBI (1), WHO (137), NCEP ATP III (50), IDF (2), European Group for the Study of Insulin Resistance (138), and American College of Endocrinology (139). These varying definitions have adopted mixtures of anthropometric, patho-physiological, and clinical criteria. Predictors (waist girth, insulin, and triglycerides) and outcomes (diabetes and hypertension) have been dichotomized (thresholds rather than continuous variables), assembled (any two of three or three of five criteria), and even prioritized (e.g. waist girth first, then any two of three) as a result of clinical consensus, without hard evidence for their usefulness.

The stability of the metabolic syndrome over time is ill defined; it may display a relatively high rate of spontaneous regression (as is the case with IGT). In the only relevant study (140), the prevalence of the metabolic syndrome did not increase in Mexico City between 1990–1992 and 1997–1999 despite increasing central obesity. The metabolic syndrome by itself offers little substantial advantage in CVD risk prediction over available algorithms (*e.g.* the Framingham score). However, a careful metaanalysis has shown that depending on the definition (and modifications thereof), sample size, subject selection, duration of follow-up, outcome event, and type of statistical analysis, using the metabolic syndrome as a predictor may provide some improvement in risk assessment (141). To predict diabetes, on the other hand, the current definitions of metabolic syndrome do not offer any significant advantage over other algorithms (142, 143), although they efficiently detect impaired glucose tolerance (19), which is an important antecedent of diabetes. Which component of the syndrome carries what weight has not been established.

For the metabolic syndrome to be a better predictor of risk for CVD and T2DM, its criteria must be unambiguously defined (144). Physiological parameters should not be dichotomized unless independent evidence proves the existence of a threshold in their relation to risk. Modeling should explore nonlinearities and weighting, and established predictors (*e.g.* age, familial diabetes, premature CVD, *etc.*) should be included in the model.

In this document, the term metabolic risk is employed so as not to favor one term over another. One reason for avoiding use of metabolic syndrome, the most popular term, is that major organizations that have produced guidelines for the metabolic syndrome allow its diagnosis to be extended to patients with T2DM. The Endocrine Society recognizes T2DM as a separate disease entity, for which other guidelines specific to diabetes are applicable. Therefore, to avoid any confusion, metabolic risk is restricted to patients who do not manifest clinical diabetes. It does not, however, exclude prediabetes from the category of metabolic risk.

References

1. **Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA, Costa F** 2005 Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735–2752

2. **Alberti KG, Zimmet P, Shaw J 2005 The metabolic syndrome: a new worldwide definition. Lancet 366:1059–1062 3.** 1998 Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. National Institutes of Health. Obes Res [Erratum (1998) 6:464] 6 (Suppl 2):51S–209S

4. **GamiAS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM** 2007 Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 49:403–414

5. **Meigs JB, Rutter MK, Sullivan LM, Fox CS, D'Agostino Sr RB, Wilson PW** 2007 Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. Diabetes Care 30:1219–1225

6. **Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB** 2005 Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 112:3066–3072

7. **Ferrannini E, Stern MP** 1995 Primary insulin resistance: a risk syndrome. In: Leslie RDG, Robbins DC, eds. Diabetes: clinical science in practice. Cambridge, UK: Cambridge University Press; 200–220

8. **Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PW** 2005 Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes 54:3252–3257

9. **Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW** 2006 Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999–2002. Diabetes Care 29:1263–1268

10. **Lebovitz HE, Banerji MA** 2005 Point: visceral adiposity is causally related to insulin resistance. Diabetes Care 28:2322–2325

11. **Tan CE, Ma S, Wai D, Chew SK, Tai ES** 2004 Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care 27:1182–1186

12. **Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity** 2002 New criteria for 'obesity disease' in Japan. Circ J 66:987–992

13. **Ko GT, Cockram CS, Chow CC, Yeung V, Chan WB, So WY, Chan NN, Chan JC** 2005 High prevalence of metabolic syndrome in Hong Kong Chinese: comparison of three diagnostic criteria. Diabetes Res Clin Pract 69: 160–168

14. **Ramachandran A, Snehalatha C, Vijay V** 2004 Low risk threshold for acquired diabetogenic factors in Asian Indians. Diabetes Res Clin Pract 65:189–195

15. **U.S. Department of Health and Human Services, Public Health Service** 1996 NHANES III anthropometric procedures video. Washington, DC: U.S. Government Printing Office

16. **Salmasi AM, Alimo A, Dancy M** 2004 Prevalence of unrecognized abnormal glucose tolerance in patients attending a hospital hypertension clinic. Am J Hypertens 17:483–488

17. **Salmasi AM, Dancy M** 2005 The glucose tolerance test, but not HbA1c, remains the gold standard in identifying unrecognized diabetes mellitus and impaired glucose tolerance in hypertensive subjects. Angiology 56:571–579

18. **Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, D'Agostino RB** 2006 Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab 91:2906–2912 19. Meigs JB, Williams K, Sullivan LM, Hunt KJ, Haffner SM, Stern MP, Gonzalez Villalpando C, Perhanidis JS, Nathan DM, D'Agostino Jr RB, D'Agostino Sr RB, Wilson PW 2004 Using metabolic syndrome traits for efficient detection of impaired glucose tolerance. Diabetes Care 27:1417–1426

20. **Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S** 2005 The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 142:611–619

21. **Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB** 1998 Prediction of coronary heart disease using risk factor categories. Circulation 97:1837–1847

22. **Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, Holman RR** 2002 UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke 33:1776–1781

23. **Stevens RJ, Kothari V, Adler AI, Stratton IM** 2001 The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond) 101:671–679

24. **Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR** 1998 Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 316:823–828

25. **Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V** 2004 C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 350:1387–1397

26. **Folsom AR, Chambless LE, Ballantyne CM, Coresh J, Heiss G, Wu KK, Boerwinkle E, Mosley Jr TH, Sorlie P, Diao G, Sharrett AR** 2006 An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med 166:1368–1373

27. **Davey Smith G, Timpson N, Lawlor DA** 2006 C-Reactive protein and cardiovascular disease risk: still an unknown quantity? Ann Intern Med 145:70–72

28. **Assmann G, Cullen P, Schulte H** 2002 Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 105:310–315

29. **Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM** 2003 Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 24:987–1003

30. **Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, Pasternak RC, Smith Jr SC, Stone NJ** 2004 Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol 44:720–732

31. **Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL** 2001 Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med 161:1413–1419

32. **Frost PH, Havel RJ** 1998 Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for libalt1 poprotein cholesterol screening and assessment of risk and therapy. Am J Cardiol 81:26B–31B

33. **Jiang R, Schulze MB, Li T, Rifai N, Stampfer MJ, Rimm EB, Hu FB** 2004 Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. Diabetes Care 27:1991–1997

34. **Liu J, Sempos C, Donahue RP, Dorn J, Trevisan M, Grundy SM** 2005 Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diabetes Care 28:1916–1921

35. **Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM** 2006 Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol 98:1363–1368

36. **Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, Robbins DC, Howard BV** 2003 Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the Strong Heart Study. Diabetes Care 26:16–23

37. **Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB** 2005 Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 112:3375–3383

38. **Schulze MB, Shai I, Manson JE, Li T, Rifai N, Jiang R, Hu FB** 2004 Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. Diabetologia 47:2129–2136

39. **Simon A, Chironi G, Gariepy J, Del Pino M, Levenson J** 2005 Differences between markers of atherogenic lipoproteins in predicting high cardiovascular risk and subclinical atherosclerosis in asymptomatic men. Atherosclerosis 179:339–344

40. **Xydakis AM, Ballantyne CM** 2003 Role of non-high-density lipoprotein cholesterol in prevention of cardiovascular disease: updated evidence from clinical trials. Curr Opin Cardiol 18:503–509

41. **Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs Jr DR, Bangdiwala S, Tyroler HA** 1989 High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 79:8–15

42. **Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC** 2007 HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med 357:1301–1310

43. 1975 Clofibrate and niacin in coronary heart disease. JAMA 231:360–381

44. **Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W** 1986 Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 8:1245–1255

45. **Canner PL, Furberg CD, McGovern ME** 2006 Benefits of niacin in patients with versus without the metabolic syndrome and healed myocardial infarction (from the Coronary Drug Project). Am J Cardiol 97:477–479

46. **Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J** 1999 Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 341:410–418

47. **Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M** 2005 Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 366: 1849–1861

48. **Barter PJ, Rye KA** 2008 Is there a role for fibrates in the management of dyslipidemia in the metabolic syndrome? Arterioscler Thromb Vasc Biol 28:39–46

49. **Zambon A, Cusi K** 2007 The role of fenofibrate in clinical practice. Diab Vasc Dis Res 4 (Suppl 3): S15–S20

50. **National Cholesterol Education Program** 2002 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106:3143–3421

51. **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group** 2002 Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 288:2998–3007

52. **Amarenco P, Bogousslavsky J, Callahan 3rd A, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA** 2006 High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 355:549–559

53. **Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM** 2004 Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 350:1495–1504

54. **Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, Kastelein JJ, LaRosa JC, Schachner H, Shepherd J, Waters DD** 2006 Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet 368:919–928

55. **Heart Protection Study Collaborative Group** 2002 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360:7–22

56. **Law MR, Wald NJ, Rudnicka AR** 2003 Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 326:1423

57 **Law MR, Wald NJ, Thompson SG** 1994 By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 308:367–372

58. **LIPID Study Group** 1998 Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 339:1349–1357

59. **Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E** 1996 The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335:1001–1009

60. **Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, Keech A, Packard C, Simes J, Byington R, Furberg CD** 2000 Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. Circulation 102:1893–1900

61. **Scandinavian Simvastatin Survival Study Group** 1994 Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389

62. **Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J** 2003 Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 361:1149–1158

63. **Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D** 2006 Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 29:1220–1226

64. **Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG** 2002 Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360:1623–1630

65. **Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ** 1995 Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 333:1301–1307

66. **Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto Jr AM** 1998 Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279:1615–1622

67. **Frost PH, Davis BR, Burlando AJ, Curb JD, Guthrie Jr GP, Isaacsohn JL, Wassertheil-Smoller S, Wilson AC, Stamler J** 1996 Serum lipids and incidence of coronary heart disease. Findings from the Systolic Hypertension in the Elderly Program (SHEP). Circulation 94:2381–2388

68. **Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J** 2005 High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 294:2437–2445

69. **Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, Hogelin G, Marler J, McGovern P, Morosco G, Mosca L, Pearson T, Stamler J, Stryer D, Thom T** 2000 Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation 102:3137–3147

70. **Hutchinson RG, Watson RL, Davis CE, Barnes R, Brown S, Romm F, Spencer JM, Tyroler HA, Wu K** 1997 Racial differences in risk factors for atherosclerosis. The ARIC Study. Atherosclerosis Risk in Communities. Angiology 48:279–290

71. **Sprafka JM, Norsted SW, Folsom AR, Burke GL, Luepker RV** 1992 Life-style factors do not explain racial differences in high-density lipoprotein cholesterol: the Minnesota Heart Survey. Epidemiology 3:156–163

72. **Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB** 2003 Years of life lost due to obesity. JAMA 289:187–193

73. **Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ** 2003 Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206–1252

74. **Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, Stevens VJ, Vollmer WM, Lin PH, Svetkey LP, Stedman SW, Young DR** 2003 Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA 289:2083–2093

75. **Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A** 2004 Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. Lancet 363:2022–2031

76. **Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N, Black HR, Grimm Jr RH, Messerli FH, Oparil S, Schork MA** 2006 Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 354:1685–1697

77. **Julius S, Weber MA, Kjeldsen SE, McInnes GT, Zanchetti A, Brunner HR, Laragh J, Schork MA, Hua TA, Amerena J, Balazovjech I, Cassel G, Herczeg B, Koylan N, Magometschnigg D, Majahalme S, Martinez F, Oigman W, Seabra Gomes R, Zhu JR** 2006 The Valsartan Antihypertensive Long-TermUse Evaluation (VALUE) trial: outcomes in patients receiving monotherapy. Hypertension 48:385–391

78. **Law MR, Wald NJ, Morris JK, Jordan RE** 2003 Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 326:1427

79. **Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S** 2001 Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861–869

80. **Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, OmvikP, Oparil S,Wedel H** 2002 Cardiovascular morbidityandmortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359:995–1003

81. **Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J** 2005 Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 366:895–906

82. **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group** 2002 Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA [Errata (2003) 289:178; (2004) 291:2196] 288:2981–2997

83. **Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm Jr RH, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ** 2003 Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 289:2073–2082

84. **Verdecchia P, Reboldi G, Angeli F, Gattobigio R, Bentivoglio M, Thijs L, Staessen JA, Porcellati C** 2005 Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension 46:386–392

85. **Wright Jr JT, Agodoa L, Contreras G, Greene T, Douglas JG, Lash J, Randall O, Rogers N, Smith MC, Massry S** 2002 Successful blood pressure control in the African American Study of Kidney Disease and Hypertension. Arch Intern Med 162:1636–1643

86. **Balagopal P, George D, Patton N, Yarandi H, Roberts WL, Bayne E, Gidding S** 2005 Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. J Pediatr 146:342–348

87. **De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D** 2003 European guidelines on cardiovasculardisease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 24:1601–1610

88. **Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D** 2003 Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 289:1799–1804

89. **Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, Moussa A, Caselli A, Caballero AE, Economides PA, Veves A, Horton ES** 2003 Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care 26:2119–2125

90. **Selvin E, Paynter NP, Erlinger TP** 2007 The effect of weight loss on C-reactive protein: a systematic review. Arch Intern Med 167:31–39

91. **Wadden TA, Butryn ML, Byrne KJ** 2004 Efficacy of lifestyle modification for long-term weight control. Obes Res 12(Suppl):151S–62S

92. **Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM** 2007 The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol 49:1772–1780

93. **Nissen SE, Wolski K** 2007 Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 356:2457–2471

94. **Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis Jr JF, Smith Jr SC, Stone NJ, Taubert KA** 2002 AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke. 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 106:388–391

95. **Folsom AR, Qamhieh HT, Wing RR, Jeffery RW, Stinson VL, Kuller LH, Wu KK** 1993 Impact of weight loss on plasminogen activator inhibitor (PAI-1), factor VII, and other hemostatic factors in moderately overweight adults. Arterioscler Thromb 13:162–169

96. **Hamalainen H, Ronnemaa T, Virtanen A, Lindstrom J, Eriksson JG, Valle TT, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Rastas M, Aunola S, Uusitupa M, Tuomilehto J** 2005 Improved fibrinolysis by an intensive lifestyle intervention in subjects with impaired glucose tolerance. The Finnish Diabetes Prevention Study. Diabetologia 48:2248–2253

97 **Lindahl B, Nilsson TK, Jansson JH, Asplund K, Hallmans G** 1999 Improved fibrinolysis by intense lifestyle intervention. A randomized trial in subjects with impaired glucose tolerance. J Intern Med 246:105–112

98. **Marckmann P, Toubro S, Astrup A** 1998 Sustained improvement in blood lipids, coagulation, and fibrinolysis after major weight loss in obese subjects. Eur J Clin Nutr 52:329–333

99. **Rissanen P, Vahtera E, Krusius T, Uusitupa M, Rissanen A** 2001 Weight change and blood coagulability and fibrinolysis in healthy obese women. Int J Obes Relat Metab Disord 25:212–218

100. **Antithrombotic Trialists' Collaboration** 2002 Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324:71–86

101. **Hayden M, Pignone M, Phillips C, Mulrow C** 2002 Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 136:161–172

102. **Eriksson KF, Lindgarde F** 1991 Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. Diabetologia 34:891–898

103. **Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group** 2002 Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403

104. **Kosaka K, Noda M, Kuzuya T** 2005 Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract 67:152–162

105. **Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV** 1997 Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT andDiabetes Study. Diabetes Care 20:537–544

106. **Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V** 2006 The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 49:289–297

107. **Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M** 2001 Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344:1343–1350

108. **Norris SL, Zhang X, Avenell A, Gregg E, Bowman B, Schmid CH, Lau J** 2005 Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. Am J Prev Med 28:126–139

109. **Yamaoka K, Tango T** 2005 Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Care 28:2780–2786

110. **Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, Hamalainen H, Harkonen P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J** 2006 Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 368:1673–1679

111. **Diabetes Prevention Program Research Group** 2002 The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 25:2165–2171

112. **Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE** 2005 The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med 142:323–332

113. **Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, Temprosa M** 2005 Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. Diabetes Care 28:888–894

114 **Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton E, Marcovina S, Mather K, Orchard T, Ratner R, Barrett-Connor E** 2005 Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. Diabetes 54:1566–1572

115. **Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ** 2002 Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr 76:911–922

116. **Gross LS, Li L, Ford ES, Liu S** 2004 Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr 79:774–779

117. **Knowler WC, Hamman RF, Edelstein SL, Barrett-Connor E, Ehrmann DA, Walker EA, Fowler SE, Nathan DM, Kahn SE** 2005 Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes 54:1150–1156

118. **Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP** 2002 Preservation of pancreatic-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 51:2796–2803

119. **DREAM Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR** 2006 Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet 368:1096–1105

120. **Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J** 2005 Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglit Azone Clinical Trial In macro Vascular Events): a randomised controlled trial. Lancet 366:1279–1289

121. **Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G** 2006 Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 355:2427–2443

122. **Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams Jr JW, Zaza S** 2004 Grading quality of evidence and strength of recommendations. BMJ 328:1490

123. **Swiglo BA, Murad MH, Schunemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM** 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the GRADE system. J Clin Endocrinol Metab 93:666–673

124. **Reaven GM** 1988 Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595–1607

125. **LaMonte MJ, Barlow CE, Jurca R, Kampert JB, Church TS, Blair SN** 2005 Cardiorespiratory fitness is inversely associated with the incidence of metabolicsyndrome: a prospective study of men and women. Circulation 112:505–512

126. **Bjorntorp P** 1995 Insulin resistance: the consequence of a neuroendocrine disturbance? Int J Obes Relat Metab Disord 19 Suppl 1:S6–S10

127. **Del Prato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA** 1994 Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. Diabetologia 37:1025–1035

128. **Ferrannini E** 1995 The phenomenon of insulin resistance: its possible relevance to hypertensive disease. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 2281–2300

129. **Muscelli E, Emdin M, Natali A, Pratali L, Camastra S, Gastaldelli A, Baldi S, Carpeggiani C, Ferrannini E** 1998 Autonomic and hemodynamic responses to insulin in lean and obese humans. J Clin Endocrinol Metab 83:2084–2090

130. **Ferrannini E** 2006 Is insulin resistance the cause of the metabolic syndrome? Ann Med 38:42–51

131. **Reaven GM, Laws A, eds.** 1999 Insulin resistance: the metabolic syndrome X. Totowa, NJ: Humana Press

132. **Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP** 1992 Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 41:715–722

133. **Haffner SM, Ferrannini E, Hazuda HP, Stern MP** 1992 Clustering of cardiovascular risk factors in confirmed prehypertensive individuals. Hypertension 20:38–45

134. **HuG, Qiao Q, Tuomilehto J, Eliasson M, Feskens EJ, Pyorala K** 2004 Plasma insulin and cardiovascular mortality in non-diabetic European men and women: a meta-analysis of data from eleven prospective studies. Diabetologia 47:1245–1256

135. **Ferrannini E, Balkau B** 2002 Insulin: in search of a syndrome. Diabet Med 19:724–729

136. **Despres JP** 2006 Is visceral obesity the cause of the metabolic syndrome? Ann Med 38:52–63

137. **Alberti KG, Zimmet PZ** 1998 Definition, diagnosis and classification of diabete mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus

provisional report of a WHO consultation. Diabet Med 15:539–553

138. **Balkau B, Charles MA** 1999 Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 16:442–443

139. **Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW** 2003 American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 9:237–252

140. **Lorenzo C, Williams K, Gonzalez-Villalpando C, Haffner SM** 2005 The prevalence of the metabolic syndrome did not increase in Mexico City between 1990–1992 and 1997–1999 despite more central obesity. Diabetes Care 28:2480–2485

141. **Ford ES** 2005 Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 28:1769–1778

142. **Saaristo T, Peltonen M, Lindstrom J, Saarikoski L, Sundvall J, Eriksson JG, Tuomilehto J** 2005 Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. Diab Vasc Dis Res 2:67–72

143. **Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM** 2004 Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 27:2676–2681

144. **Kahn R, Buse J, Ferrannini E, Stern M** 2005 The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 48:1684–1699

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**As of January 1, 2008, Robert J. Heine joined Eli Lilly in Indianapolis as the Executive Medical Director of the Diabetes and Endocrine Division, but retained his affiliation with the Vrije Universiteit Medical Center in Amsterdam, The Netherlands.*

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