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Title: Primary Prevention of Cardiovascular Disease and Type 2 Diabetes in Patients at Metabolic Risk: An Endocrine Society Clinical Practice Guideline

Short Title: Guidelines for Patients at Metabolic Risk

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Abstract

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

Conclusions: Health care 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-year global risk assessment for either CVD or coronary heart disease. This scoring will determine the targets of therapy for reduction of apo 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 pre-diabetes (IGT or IFG) should be screened at 1- to 2-year intervals for the development of diabetes with either measurement of fasting plasma glucose or a 2-hour oral glucose tolerance test.

For the prevention of CVD and T2DM, we recommend that priority be given to lifestyle management. This includes anti-atherogenic 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.

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 (a) elevations of apolipoprotein B (apo B)-containing lipoproteins (low-density lipoprotein [LDL] and very-low-density lipoprotein [VLDL]) with elevated triglycerides, (b) reduced levels of high-density lipoprotein cholesterol (HDL-C), (c) increased plasma glucose levels, (d) hypertension, (e) enlarged waist circumference, (f) a prothrombotic state, and (g) 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 AHA/NHLBI definition at the clinical visit, because of its ease of use and convenience of implementation in the office setting. The finding of ≥3 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 years (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 BMI, but can provide more focused information regarding risk for CVD and T2DM. (1|⊕○○○)

We recommend that the cut-offs for elevated waist circumference be ≥102 cm for men and ≥88 cm for women in Caucasian, African, Hispanic and Native American populations (3). We recommend that the cut-offs for waist circumference in Asian populations (both East Asian and South Asian) be ≥90 cm for men and ≥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 T2DM at 1- to 2-year intervals. (2|⊕○○○) This can be done with fasting plasma glucose and, wherever possible, with an oral glucose tolerance test. 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: apolipoprotein B, adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, PAI-1, fibrinogen, ALT as a marker of liver fat, C-reactive protein, inflammatory cytokines (e.g., interleukin 6), liver or myocellular fat content by 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-year risk for either coronary heart disease (CHD) or CVD. Framingham and PROCAM scoring assess 10-year risk for CHD. The European SCORE algorithm predicts 10-year risk for total cardiovascular mortality. Risk factor scoring with these algorithms can be easily carried out. Global risk assessment for cardiovascular outcomes is recommended prior to 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|⊕⊕⊕○). Further, 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-year 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 <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-year risk is >10%, we recommend that low-dose aspirin prophylaxis for primary prevention of CVD (75-162 mg/day) 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% to 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 minutes, but preferably 45-60 minutes, at least 5 days a week. 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 <7% of total calories and dietary cholesterol <200 mg/day. (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|⊕⊕⊕○)

Introduction

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 (4, 5). Although the pathophysiology underlying these antecedents is not fully understood, there is a strong overlap between cardiovascular risk factors and pre-diabetes (impaired fasting glucose [IFG] and impaired glucose tolerance [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 (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 the choice of terminology). Individuals at high metabolic risk often have (a) elevations of apolipoprotein B (apo B)-containing lipoproteins (low-density lipoprotein [LDL] and very-low-density lipoproteins [VLDL]) with elevated triglycerides, (b) reduced levels of high-density lipoprotein-cholesterol (HDL-C), (c) increased plasma glucose levels, (d) hypertension, (e) enlarged waist circumference, (f) a prothrombotic state, and (g) a proinflammatory state.

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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). While 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 to each other with regard to effectiveness. The major difference between the AHA/NHLBI and the IDF definitions is that the former posits the presence of three out 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. Since 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 pf T2DM and up to one third of new CVD cases, over 8 years 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 cholesterol 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, 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 cardio-respiratory fitness, etc.) and/or from the large pool of biochemical markers (e.g., C-reactive protein, adiponectin, HDL-cholesterol, 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 years (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 in order 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 cut-offs for elevated waist circumference be ≥102 cm for men and ≥88 cm for women in Caucasian, African, Hispanic, and Native American populations (3). We recommend that the cut-offs for waist circumference in Asian populations (both East Asian and South Asian) be ≥90 cm for men and ≥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 ≥94 cm in men and ≥80 cm in women. For the USA population, the AHA/NHLBI defines elevated waist circumference as ≥102 cm for men and ≥88 cm for women (Table 2).

To assess the implication of metabolic syndrome in different ethnic populations, there is some concern that the recommended cut-off for waist circumference is inappropriate for different ethnic groups, especially for Asian individuals. There are two important studies showing the rationale for using different cut-off points of waist circumferences in people of Asian extraction. Tan et al. (11) used receiver operating characteristic analysis (ROC) 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 ≥90 cm in men and ≥80 cm in women seems to be comparable to that in USA 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 >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 corresponds to a VFA of 100 cm^2 (12). There are several studies showing the rationale for using different cut-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 cut-offs for waist circumference might be established for these ethnic groups. It can be argued whether cut-off 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 in order 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, 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 Figure 1).

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-year intervals. (2|⊕○○○) This can be done with fasting plasma glucose and, wherever possible, with an oral glucose tolerance test. 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 oral glucose tolerance test (OGTT) is more sensitive, but also more time-consuming and costly than the fasting plasma glucose (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, non-research 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 2848 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 NCEP ATP III criteria (8, 18). When these patients were reexamined 8 years 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 years, it was found that metabolic syndrome criteria increased the risk for developing diabetes sixfold, regardless of the degree of insulin resistance (19).

In the Diabetes Prevention Program 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 years (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-year 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: apolipoprotein B, adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, PAI-1, fibrinogen, ALT as a marker of liver fat, C-reactive protein, inflammatory cytokines (e.g., interleukin 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 United Kingdom Prospective Diabetes Study (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 C-reactive protein (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-cholesterol 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 apolipoprotein B, LDL fractionation, adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, PAI-1, fibrinogen, ALT as a marker of liver fat, C-reactive protein, inflammatory cytokines (e.g., interleukin 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-year risk for either coronary heart disease (CHD) or CVD. Framingham and PROCAM scoring assess 10-year risk for CHD. The European SCORE algorithm predicts 10-year risk for total cardiovascular mortality. Risk factor scoring with these algorithms can be easily carried out. Global risk assessment for cardiovascular outcomes is recommended prior to starting preventative treatment. (1|⊕○○○)

Evidence

Several risk assessment algorithms have been published for estimating 10-year 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 United Kingdom Prospective Diabetes Study (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-year 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 cut-points of 10-year risk to define these three categories varies somewhat from one country to another. Currently accepted categories of Framingham risk for patients with metabolic syndrome are high risk (10-year 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 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|⊕⊕⊕○). Further, 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-year 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 National Cholesterol Education Program 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 cholesterol was shown to be a risk factor for future coronary heart disease, even among CHD subjects who have an LDL cholesterol below 70 mg/dL who were treated on statins. However, no clinical trials have definitively shown that raising HDL cholesterol has reduced CHD in statin-treated subjects although such trials are currently underway (42).

Evidence that raising HDL-C with specific therapies will reduced 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. Further, according to practice norms, drug therapies to raise HDL-C levels generally are limited to patients at higher risk for CVD.

The recent FIELD 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 end-point. It did, however, significantly lower total CVD and microvascular complications as secondary end-points. In contrast, subgroup analysis of the VA-HIT 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 meta-analysis 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-year 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 as 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-year 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-year risk for CHD ≥10%), the treatment goals outlined in Table 3 pertain. Here the LDL-C goal is <130 mg/dL, but an optional goal is LDL-C <100 mg/dL. Corresponding goals for non-HDL-C are 30 mg/dL higher than the LDL-C goal. If 10-year CHD risk is <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 <130 mg/dL and <160 mg/dL, respectively.

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-year risk for CHD <10%), lifestyle therapies (anti-atherogenic diet and weight reduction) may be sufficient to lower LDL-C and non-HDL-C adequately to reduce long-term risk. Table 4 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. Increased physical activity can also be recommended simultaneously with other lifestyle therapies because of prospective studies that suggest it will reduce cardiovascular risk. Further, 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 ≥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 >130 mg/dL on maximal lifestyle therapy. For patients at higher risk (10-year 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 ≥130 mg/dL on lifestyle therapies, with an optional goal of <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 to 15 years 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 years), 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-cholesterol levels are higher than those in Caucasians (70). These lipid profiles are 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 <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 acceptable classification of progressively elevated blood pressure (Table 6). Further, 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 <140/<90 mm Hg. However, since 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 anti-hypertensive drugs are to be preferred in patients at metabolic risk. Some investigators favor use of ACE inhibitors and angiotensin receptor blockers (ARBs) over diuretics and beta-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).

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 anti-atherogenic 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 usage 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-year risk is >10%, we recommend that low-dose aspirin prophylaxis for primary prevention of CVD (75-162 mg/day) 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 anti-fibrinolytic 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 anti-fibrinolytic factors.

3.4.2 Several analyses suggest that if the 10-year risk for CHD is ≥10%, the risk-to-benefit ratio is favorable for prevention of CVD. Therefore, we suggest that aspirin therapy be instituted (if not contraindicated) when 10-year 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. In spite of these caveats, the Task Force favors institution of aspirin treatment for patients at metabolic risk when their 10-year risk for CHD is >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% to 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 minutes, but preferably 45-60 minutes, at least 5 days a week. 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 <7% of total calories and dietary cholesterol <200 mg/day. (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 years 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 Diabetes Prevention Program 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-year 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 ≥5% by reduced caloric intake, decreased intake of dietary fat and saturated fats, increased fiber intake, and the addition of 4 hours per week of moderate-intensity exercise. After a mean of 3.2 years of 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 hours per week the relative risk reduction was 80%. In follow-up studies done 3 years after completion of active counseling, the beneficial effects of the lifestyle program persisted with 36% risk reduction (110).

The Diabetes Prevention Program (103), conducted in 27 centers in the United States, randomized 3234 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 year as compared to a mean of 2.8 years for the three completed groups, which included over 1000 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-week 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 <25% of energy, decreasing saturated fats, increasing dietary fiber, and increasing physical activity by at least 150 minutes per week of 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 years. 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 years 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 years, 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, hsCRP was increased in all groups and was correlated with body mass index, waist circumference, fasting plasma glucose, and insulin resistance (114). After 1 year, use of metformin resulted in a modest 7%-14% reduction in hsCRP, 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% to 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/day, which results in a weight loss of 1-2 pounds/week (0.5-1.1 kg/week). Both the DPP and the Finnish Diabetes Prevention Study utilized 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|⊕⊕⊕O)

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 pre-diabetes to diabetes (103, 117). This delay was confirmed in two other clinical thiazolidinedione 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 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.

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Figure Legend:

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

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

Clinical measure	**American Heart Association/ National Heart Lung and Blood Institute (1)**	**International Diabetes Federation (2)**
	Any 3 of the following 5 features	
Waist circumference	WC ≥102 cm in men or ≥88 cm in women (non-Asian origin) WC ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians)	WC ≥94 cm in men or ≥80 cm in women (Europids, Sub-Saharan Africans, and Middle Eastern) WC ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians; South and Central Americans) WC ≥85 cm in men or ≥90 cm in women (Japanese) **plus any 2 of the following**
Triglycerides (fasting)	TG ≥150 mg/dL or on drug therapy for high TG	TG ≥150 mg/dL or on drug therapy for high TG
HDL cholesterol	HDL-C <40 mg/dL in men or <50 mg/dL in women or on drug therapy for low HDL-C	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 diastolic or on drug therapy for hypertension	≥130 mm Hg systolic or ≥85 diastolic or on drug therapy for hypertension
Glucose (fasting)	≥100 mg/dL or drug therapy for elevated glucose	≥100 mg/dL (includes diabetes)

WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol

TABLE 2. Recommended waist circumference thresholds to define abdominal obesity

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

Abbreviations: AHA/NHLBI: American Heart Association/National Heart Lung and Blood Institute; IDF: International Diabetes Federation

[a] 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.

[b] AHA/NHLBI guidelines indicate that waist circumference thresholds of ≥94 cm in men and ≥80 cm in women are optional in persons who show clinical evidence of insulin resistance.

[c] In Japan, national recommendations for waist circumference thresholds for abdominal obesity are ≥85 cm in men and ≥90 cm in women.

TABLE 3. Treatment goals for apolipoprotein 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/L)
(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/L)
(for higher risk patients[d] in this category, optional goal is <100 mg/dL [2.6 mmol/L])
• Moderate-risk patients[e]: <130 mg/dL (3.4 mmol/L)
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)

Abbreviations: LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol

[a] High risk patients: those with established atherosclerotic cardiovascular disease, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes transient ischemic attack (TIA) or stroke of carotid origin or >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: those with 10-year risk for coronary heart disease 10%-20%. Factors that favor the therapeutic option of non-HDL-C <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: those with ≥2 major risk factors and 10-year risk <10%.

TABLE 4. Recommended dietary changes to reduce apolipoprotein B-containing lipoproteins and estimated reduction in coronary heart disease[a]

Dietary factor	**Suggested change**	**LDL-C reduction**	**Estimated CHD reduction[b]**
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/day	3%-5%	>3%
Plant stanols/sterols	Add plant stanols/sterols 2 gm per day	6%-10%	>6%
Dietary fiber	Add viscous fiber 5-10 g/day	3%-5%	>3%
Weight reduction	Reduce body weight by 7%-10%	5%-8%	>5%
Total		~25%-35%	~25%

Abbreviations: LDL-C: LDL cholesterol; CHD: coronary heart disease

[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%.

TABLE 5. Summary of efficacy of drugs that reduce apolipoprotein 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%[j]	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 LDL-lowering 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[a]

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

[a] Blood pressure categories based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (73).

TABLE 7. Projected reductions in blood pressure accompanying lifestyle therapies[a]

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

[a] Estimations of efficacy of lifestyle modification taken from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (73).

TABLE 8. Recommendations for lifestyle reduction of plasma glucose to lower risk for type 2 diabetes [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 minutes a week with moderate exercise, such as walking or biking

[a] Recommendations correspond to the intervention arm of the Diabetes Prevention Program (111).
[b] For healthy eating, follow dietary guidelines for cholesterol- and blood pressure-lowering (see Tables 3 and 6).

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