The U.S. Prevention of Cardiovascular Disease Guidelines and Implications for Implementation in LMIC

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ABSTRACT

The 2013 guidelines for the Prevention of Cardiovascular Disease released by the American College of Cardiology and the American Heart Association included guidelines of assessment of cardiovascular disease (CVD) risk, lifestyle management, management of overweight and obesity, and treatment of blood cholesterol. In addition, there were also 2014 guidelines on hypertension management released by members appointed to the Eighth Joint National Committee. Taken together, these guidelines, though extensively discussed and disseminated in the United States, have not been widely recognized beyond the United States, nor have their implications been considered for lower- and middle-income developing countries. With an estimated 80% of the global burden in CVD occurring in developing countries, it is important to develop strategies to adequately detect those at increased CVD risk and to manage their risk through lifestyle and where appropriate, pharmacologic means. Though certain aspects of each guideline may be suitable for implementation globally, including in developing countries, other recommendations would be unrealistic for many countries based on local epidemiology and resources. CVD prevention priorities can be set using guidance from recently published CVD prevention guidelines if appropriately modified to the context of lower- and middle-income developing countries. Establishment of global CVD prevention standards and rapid adaptation and dissemination of clinical guidelines are of paramount importance if we are to make significant progress into achieving World Health Organization 2025 goals to reduce the burden from CVD and other noncommunicable diseases.

In November 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) jointly released a set of 4 cardiovascular disease (CVD) prevention guidelines involving: 1) assessment of cardiovascular risk [1]; 2) lifestyle management to reduce cardiovascular risk [2]; 3) management of overweight and obesity in adults [3]; and 4) treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [4]. In addition, members appointed to the Eighth Joint National Committee panel subsequently published guidelines relating to blood pressure management in 2014 [5] as did the International Society of Hypertension/American Society for Hypertension [6]. Though most high-income regions look to guidelines issued by their local governments or professional societies, an estimated 80% of the global burden in CVD occur in low- and middle-income countries [7], where local guidelines are frequently not available [8]. The relevance and applicability of high-income regions' guidelines in low- and middle-income countries, and optimal mechanism for adapting and disseminating new guidelines to practitioners in low- and middle-income countries have not been often been discussed. The World Health Organization (WHO) published CVD prevention guidelines in 2007 [9], which can serve as a base from which further/revised recommendations based on those of the ACC/AHA may be considered. A key recommendation of the 2007 WHO guidelines was to use global cardiovascular risk to set thresholds for the scale of CVD prevention efforts.

With aggressive control of major risk factors, the WHO goal of a 25% reduction in noncommunicable disease mortality by the year 2025 may be achievable [10]. This report is intended to summarize key features of each of the latest U.S. prevention guidelines and to discuss their applicability to low- and middle-income countries, including what features of each of the guidelines may be suitable or if there are alternative mechanisms that may be more appropriate for low- and middle-income countries.

CARDIOVASCULAR RISK ASSESSMENT GUIDELINES

The National Heart Lung and Blood Institute initially charged the working group developing the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [10] to examine the scientific evidence for assessing risk for initial atherosclerotic cardiovascular disease (ASCVD) events and to develop an approach for quantitative risk assessment that could be used in practice and used or adapted by the other guideline groups. The Risk Assessment Work Group endorsed the paradigm of 10-year risk estimation and judged that a new tool was needed that would be inclusive of whites and African Americans (the 2 race/ethnic groups with adequate observational cohort data) and also with an expanded endpoint that

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included stroke. Cohorts included were sought to be representative of the U.S. population as a whole, community- or population-based, and had to at least include whites and African Americans with recent follow-up data for ASCVD events of at least 10 years. For this, 4 cohort studies qualified: 1) the ARIC (Atherosclerosis Risk in Communities) study; 2) the CHS (Cardiovascular Health Study); 3) the CARDIA (Coronary Artery Risk Development in Young Adults) study; and 4) the Framingham original and offspring studies. A composite endpoint of 10-year risk of hard ASCVD consisting of coronary heart disease death, nonfatal myocardial infarction, and fatal/nonfatal stroke common to all 4 cohorts was chosen. Models were tested using traditional risk factors and newer markers when possible and were internally and externally validated. The resulting 10-year pooled cohort equations risk estimator is available on the ACC website [11] (and is shown in Figure 1 and can be downloadable by several applications (iTunes, Google Play, and web version). The ASCVD calculator predicts both 10-year and lifetime ASCVD risk. The guideline gives a Class I level of recommendation B for its use to predict 10-year risk in non-Hispanic African Americans and non-Hispanic whites ages 40 to 79 years and a weaker IIb level of evidence C recommendation in other populations (using the equations for whites). The guideline committee also noted that such assessment should occur every 4 to 6 years in those ages 20 to 79 years of age, and that in those with a low 10-year risk (<7.5%) to assess 30-year or lifetime risk in those ages 20 to 59 years of age. This guideline recommended that risk scores should provide an opportunity for a "risk discussion" with the patient, emphasizing the role of lifestyle guidelines for prevention of CVD [2] and discussing risk and benefits of initiating or intensifying pharmacologic therapy before making a treatment decision.

If a treatment decision remains uncertain after quantitative risk assessment, the guideline recommended that 1 or more of the following could be assessed in order to better inform treatment decisions (Class IIb level of evidence B recommendation): 1) family history; 2) high-sensitivity

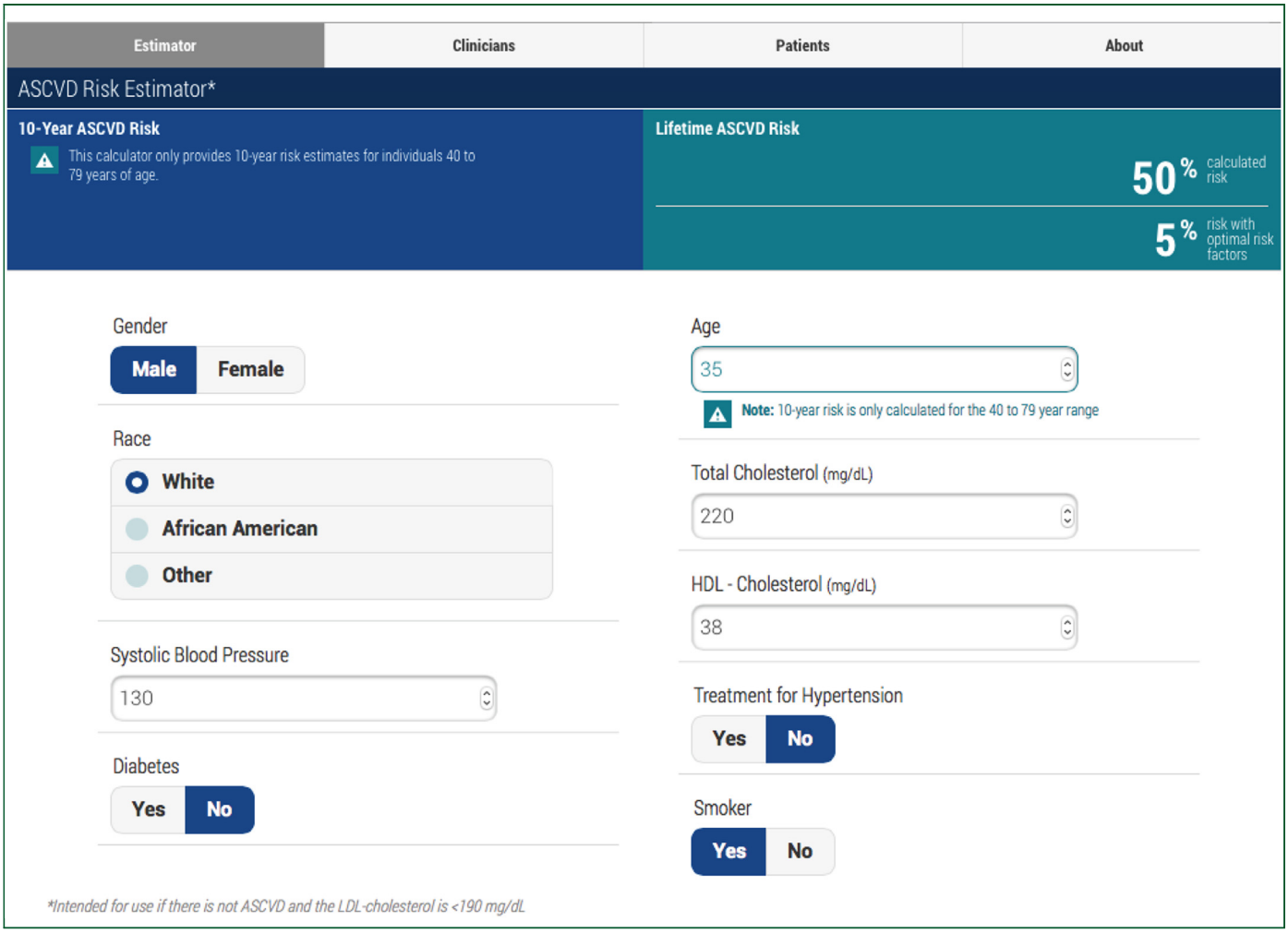

FIGURE 1. ACC/AHA pooled cohort equations risk estimator for 10-year risk of atherosclerotic cardiovascular disease (ASCVD). ACC, American College of Cardiology; AHA, American Heart Association; HDL, high-density lipoprotein. Reproduced, with permission, from Goff et al. [1].

C-reactive protein; 3) coronary calcium scoring; or 4) ankle brachial index. Routine measurement of carotid intima-media thickness, however, was not recommended for risk assessment of an initial ASCVD event (Class III-B). If there was evidence of a positive family history of premature ASCVD (<55 years of age in a male first-degree relative or <65 years of age in a female first-degree relative), high-sensitivity C-reactive protein of ≥2 mg/l, coronary calcium score of ≥300 or ≥75th percentile for age and sex, or ankle brachial index <0.9 diagnostic of peripheral arterial disease, the guideline recommended these could further risk stratify persons with borderline calculated ASCVD risk.

Applicability to low- and middle-income countries

Is it realistic to consider global risk assessment using the U.S. ASCVD calculator in most if not all developing countries? The proposed pooled cohort equations require information on age, sex, ethnicity, total cholesterol and high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, whether the patient is on treatment for high blood pressure, and whether they have diabetes and are a current cigarette smoker. While many laboratories worldwide now have these tests available, for settings where laboratory services are unavailable or unaffordable, the WHO/International Society of Hypertension (ISH) risk prediction charts [9] (Figure 2), an updated Framingham risk calculator that predicts 10-year risk of total CVD [12], and the INTERHEART (A Study of Risk Factors for First Myocardial Infarction in 52 Countries and Over 27,000 Subjects) risk score [13] all assess risk without serum cholesterol concentration testing (the latter 2 essentially using body mass index (Framingham) or waist-to-hip ratio (INTERHEART) and other factors as cholesterol and undiagnosed diabetes proxies). A study in South Africa suggested that non-laboratory-based risk assessment is reasonably accurate [14].

The traditional Framingham equations are based on the primarily white middle-class population of Framingham, Massachusetts. It is uncertain how they would perform in all other regions of the world, and in certain particularly low CVD risk countries, they may overpredict. The pooled cohort equations were based on more geographically and socioeconomically representative cohorts, but were estimated for U.S. whites and blacks only. Whereas some evidence exists that the Framingham prediction equations, and by extension, the pooled cohorts equations, could be recalibrated to accurately predict risk in different populations [15], not every recalibration analysis has produced results supporting the use of this method [16]. There has been criticism that the pooled cohorts equations overpredict risk because they are based on "old" data, specifically, higher background CVD risk in an era 1 or 2 decades ago when risk factors were on average less well controlled. Given the PURE (Prospective Urban Rural Epidemiology) evidence that risk factor control is currently substantially less in many low- and middle-income countries [17], it is possible that the pooled risk equations may underpredict in some countries, and future risk equations from high-income regions estimated in even more contemporary cohorts could underpredict more.

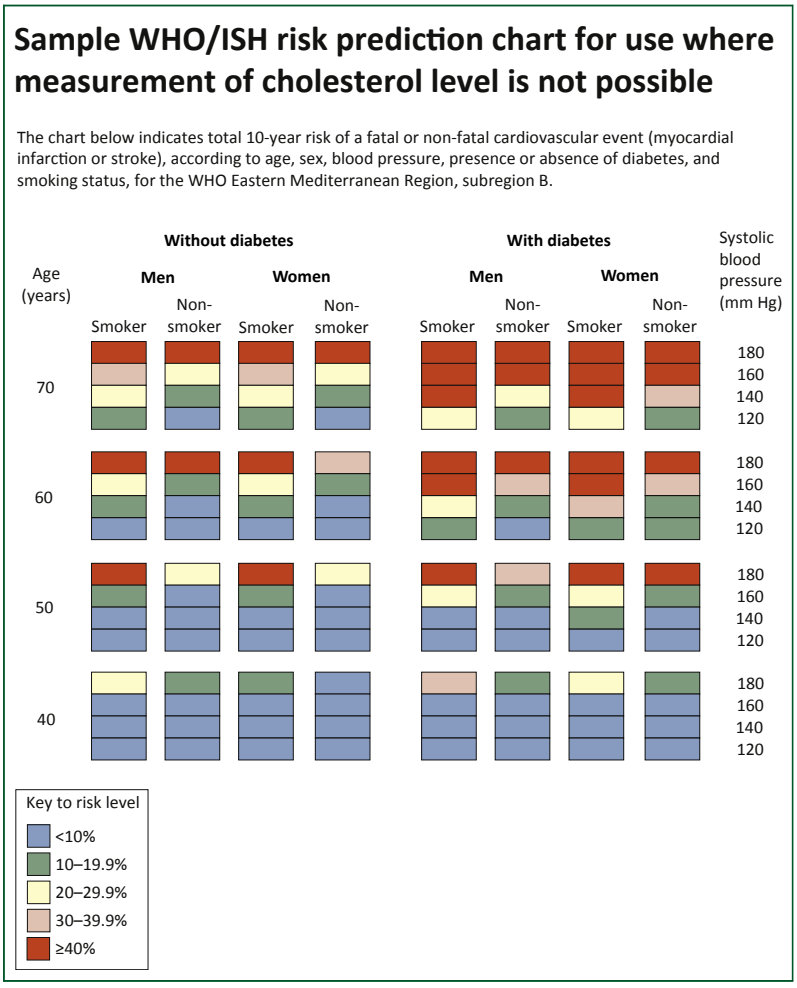

FIGURE 2. Sample WHO/ISH risk prediction chart for use when measurement of cholesterol is not available. ISH, International Society of Hypertension; WHO, World Health Organization. Reproduced, with permission, from World Health Organization [9].

In addition, age is the most powerful predictor of 10-year risk in most risk scores, so they tend to underestimate longer term risk attributable to other CVD risk factors in younger persons. In developing countries, where CVD events often occur at younger ages, use of 30-year or lifetime risk estimates may be more applicable.

Another issue for consideration, however, is whether the threshold of estimated CVD risk used to guide treatment decisions should depend on the availability of resources in the public sector. The Prevention of Cardiovascular Disease guideline [9] from WHO defines individual total CVD risk based on 10-year risk of a fatal or nonfatal cardiovascular event as very high if >30%, high if 20% to 30%, moderate if 10% to 20%, and low if <10% according to their own published risk score charts. The WHO guideline

recommended that the 10-year total CVD risk threshold for intensive intervention might be set at 20% (a previously defined high risk threshold) for high-resource developed countries, but might be set at perhaps 30% for a medium-resource developing country or even 40% for a low-resource underdeveloped country. The lower the threshold for intervention, the more individuals who are eligible to benefit increases along with costs and number of adverse events caused by drug treatments [9]. But a contrary view is that whereas adoption of a high threshold for intervention might seem attractive in terms of short-term health gains, this approach would deny access to prevention interventions to much of the population who will otherwise suffer an event. Setting a high risk threshold may also appear attractive in terms of "up-front" prevention costs, but it fails to consider long-term cost-savings from future prevented hospitalizations, prevented chronic care costs for CVD patients, and prevented lost wages due to illness. Even if the necessary data are available, in settings where primary care practitioners bear a heavy daily caseload, the prospect of taking the time to calculate 10-year CVD risk patient-by-patient is intimidating. In all of high-income countries, the critical innovation required for universal uptake of the global CVD risk assessment will be automated risk calculation embedded in an electronic medical record that includes all necessary variables. For settings without electronic records, color-coded WHO/ISH charts and potentially mobile phone calculator applications may succeed in making it easy for practitioners to "look up" a patient's 10-year CVD risk, but it is unclear how much the charts have been taken up for use by local health care providers.

LIFESTYLE GUIDELINES

The ACC and AHA lifestyle management guidelines [2] recognize the importance of lifestyle factors in CVD risk management and prevention. The lifestyle workgroup focused on examining 3 critical questions:

1. Among adults, what is the effect of dietary patterns and/or macronutrient composition on CVD risk factors, when compared with no treatment or to other types of interventions?
2. Among adults, what is the effect of dietary intake of sodium and potassium on CVD risk factors and outcomes, when compared with no treatment or with other types of interventions?
3. Among adults, what is the effect of physical activity on blood pressure and lipids when compared with no treatment, or with other types of interventions?

Systematic reviews and meta-analyses formed the basis of the guidelines and both risk factor and CVD outcomes were considered. The new guideline provides more emphasis on dietary patterns and was based on the availability of more data supporting saturated and trans-fat restriction and dietary salt restriction.

For both low-density lipoprotein cholesterol (LDL-C) and blood pressure lowering, a Class I level of evidence A recommendation was given to consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts, and limits intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adapted to appropriate caloric requirements, personal and cultural food preferences, and nutrition therapy used for certain medical conditions, including diabetes. The DASH (Dietary Approaches to Stop Hypertension) dietary pattern, U.S. Department of Agriculture food pattern, or the AHA diet were specifically recommended. Specifically for LDL-C lowering, a dietary pattern that achieves 5% to 6% calories from saturated fat and reduces the percentage of calories both from saturated and trans-fat (all Class I level of evidence A recommendations) was advised. Specifically for blood pressure lowering, lower sodium intake (Class I, level of evidence A) consuming no more than 2,400 mg of sodium a day with a further reduction being reasonable to provide even greater blood pressure reduction, or at least a reduction by 1,000 mg/day even if these goals were not met, was recommended with a Class IIa, level of evidence B. For physical activity, for the purposes of reducing LDL-C, non-HDL-C, and blood pressure, 3 to 4 sessions of moderate to vigorous intensity physical activity lasting an average of 40 min per session were recommended.

Applicability to low- and middle-income countries

Clearly, appropriate practices in lifestyle management if implemented in populations globally are going to have the greatest impact on prevention of subsequent morbidity and mortality from CVD and other noncommunicable diseases. In an increasingly urbanized world with changing dietary habits, dietary patterns associated with increased CVD risk and more sedentary lifestyle have become prevalent in high-income and developing countries alike [18]. It has been estimated that up to 80% of heart disease, stroke, and type 2 diabetes could be prevented by eliminating obesity, unhealthy diets, and physical inactivity, which has called for commitments at the global and national level to address these issues by controlling food supply, food information, and marketing and promotion of energy-dense, nutrient-poor foods that are high in saturated, trans-fat, salt, or refined sugars [19].

Simple messages are needed to effectively promote the recommended dietary patterns on a widespread population basis. Regarding sodium intake, in countries where sodium intake is much higher than the recommended 2,400 mg/day or even 3,000 mg/day levels, the recommendation to lower sodium intake by 1,000 mg/day from current intake is a practical one that should be stressed in most populations and if implemented on a widespread basis, could have a dramatic impact on reducing hypertension in particular, and especially global morbidity and mortality from CVD. The English government has demonstrated that population-wide dietary salt lowering is feasible and acceptable to the public [20]. However, the approach of lowering salt in

industrially processed and prepared foods emphasized in England would have less impact where dietary salt comes from unprocessed foods. Culturally tailored salt reduction interventions have already been implemented: in Argentina, the government partnered with bakers to lower salt content in bread [21], and in China, in a randomized trial, a cooking salt formulation that substituted potassium and magnesium for sodium was investigated [22].

The World Health Organization Prevention of Cardiovascular Disease guideline notes total fat intake reduction to 30% of calories, saturated fat to <10% of calories with most dietary fat from polyunsaturated or monounsaturated fat sources, and reduction of salt intake by at least one-third and if possible to <5 g (2 g sodium) a day [9]. Moreover, 30 min of moderate intensity physical activity is recommended.

OVERWEIGHT AND OBESITY GUIDELINES

The release of the ACC/AHA guideline for the management of overweight and obesity [3] represents the first such joint guideline addressing these conditions for the purposes of CVD risk reduction and highlights the attention both societies have to addressing these important causes of CVD. The guideline focused on several key recommendations:

1. To identify patients who might be at risk for obesity-related health problems, a Class I level of evidence B recommendation was given to using body mass index (BMI) as an easily performed first screening step. Waist circumference was recommended for use as an indicator of risk for CVD, type 2 diabetes, and all-cause mortality (Class IIa, level of evidence B) with the recommendation to continue to use current BMI and waist circumference cut points.
2. Patients should be counselled about the benefits of weight loss (Class I, level of evidence A) including lifestyle changes that produce modest (3% to 5%) sustained weight loss that results in clinical meaningful health benefits including improvements in triglycerides, glucose, hemoglobin A_{1c}, and diabetes risk, and that greater amounts of weight loss improve blood pressure, LDL-C, HDL-C, and reduce the need for medications to control blood glucose, blood pressure, and lipids, as well as further reducing triglycerides and glucose.
3. In recommending a diet for weight loss, there is no ideal diet for weight loss and no superiority for any of the many diets reviewed, but that a prescribed diet should achieve reduced caloric intake and be part of a comprehensive lifestyle intervention. Diet composition should consider the patient's preferences and health status with referral to a nutrition professional recommended (Class I, level of evidence A).
4. Patients who need to lose weight should receive a comprehensive program (diet, physical activity, and behavior modification) of 6 months or longer, with the gold standard being an on-site, high-intensity (≥14 sessions over 6 months) comprehensive intervention delivered in group or individual sessions by a trained interventionalist and persisting for a year or more (Class I, level of evidence A), with other approaches (web--based) being secondary because the amount of weight loss is less (Class IIa, level of evidence A).
5. Patients with a BMI >35 kg/m^2 with a comorbidity or >40 kg/m^2 should be advised that bariatric surgery may be an appropriate option to improve health, and they should be referred to an experienced bariatric surgeon for consultation and evaluation (Class IIa, level of evidence A).

Applicability to low- and middle-income countries

The increasing prevalence of obesity globally has made this a key target of efforts by WHO, the World Heart Federation, and other groups. Several of the key recommendations from the ACC/AHA are appropriate and paramount to helping to address this issue globally. The recommendation to evaluate BMI and waist circumference is particularly useful and should be implemented globally with ethnicity-specific waist circumference measures considered in the diagnosis of abdominal obesity. Health care providers should disseminate to their patients the simple message that even modest weight loss can have highly meaningful health benefits. Outside of the clinic, the message can be spread by traditional media as well as by novel media such as smartphones. Although it is realized that many developing countries do not have expert lifestyle specialists working in the clinical setting available to deliver multiple individual sessions, nor would such resources likely exist anyway (even in developed countries, such practice is unfortunately rare due to a lack of emphasis of current health care systems on providing for lifestyle management specialists), novel cost-effective means to deliver such programs, including those that may be Internet- or smartphone based should be developed. Whereas most of these lifestyle modification-based guidelines are appropriate for lower- and middle-income countries, further management, particularly referral to a bariatric surgeon for those with more severe obesity, is unlikely to be practical in most such settings.

BLOOD CHOLESTEROL MANAGEMENT GUIDELINES

The new ACC/AHA guideline for the management of blood cholesterol [4] is a novel approach that is a significant departure from all previous U.S. and European guidelines for cholesterol management. The National Heart Lung and Blood Institute charge to the expert panel was to evaluate higher quality randomized controlled trial evidence for cholesterol-lowering drug therapy to reduce ASCVD risk. They were limited to addressing 3 critical questions: 1) What is the evidence for LDL-C and non-HDL-C goals for secondary prevention of ASCVD? 2) What is the evidence for LDL-C and non-HDL-C goals for primary prevention of ASCVD? 3) For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

The new guideline was novel in abandoning the use of specific LDL-C (or non-HDL-C) initiation and treatment goals for therapy, as well as the use of measurement of lipids for the specific purpose of checking for goal attainment. It did, however, still specify the measurement of lipids 3 to 12 weeks following initiation of therapy to check for whether the patient has achieved a therapeutic response based on the intensity of statin therapy prescribed. Moreover, in primary prevention, it stipulated the use of the pooled cohort risk equations (see the Risk Assessment section) for identification of those who may benefit from moderate or high intensity therapy. Further, the guideline does address the importance of recognizing adverse effects and potential statin intolerance and the consideration of use of nonstatin therapies for those higher risk patients who despite maximum tolerated intensity of statin therapy still have less than a therapeutic response (defined as 30% to <50% on a moderate intensity or ≥50% on a high intensity statin) (Class IIb, level of evidence C).

The guideline specifically identified 4 groups of patients who were identified, on the basis of the available evidence, to benefit from statin therapy, and recommended such therapy according to the algorithm shown in Figure 3. These 4 statin benefit groups are as follows:

1. Persons with clinical ASCVD (with the recommendation for use for use of a high-intensity statin in those aged ≤75 years (Class I, level of evidence A), or a moderate intensity statin in those aged >75 years or if not a candidate for a high intensity statin (Class IIa, level of evidence B).
2. Those with an LDL-C of 190 mg/dl or higher, with the recommendation to use a high-intensity statin (Class I, level of evidence B).
3. Those with diabetes and LDL-C 70 to 189 mg/dl and age 40 to 75 years on the basis of available clinical trial evidence, where a moderate intensity statin is recommended (Class I, level of evidence A), or if the estimated 10-year ASCVD risk is ≥7.5% (based on the pooled cohort risk equations), a high-intensity statin (Class IIa, level of evidence B).
4. In primary prevention without diabetes, LDL-C 70 to 189 mg/dl, and not currently on statin therapy, estimating the 10-year ASCVD risk (Class I, level of evidence) and considering a moderate- or high-intensity statin for those at ≥7.5% risk (Class I, level of evidence A), or moderate-intensity statin for those at 5% to <7.5% risk (Class IIa, level of evidence B). In those outside these groups, consideration of additional factors (e.g, family history, high-sensitivity C-reactive protein, coronary calcium score, or ankle brachial index) in the risk assessment may be used to inform the treatment decision (Class IIb, level of evidence C).

In all cases, however, and especially in primary prevention, a clinician-patient discussion focusing on the potential for ASCVD risk-reduction benefits, potential for adverse effects and drug-drug interaction, heart healthy lifestyle, management of other risk factors, patient preferences, and if the treatment decision is not clear, consideration of other testing should be done. The pooled cohort risk calculator should not be an automatic prescription for therapy.

Applicability to low- and middle-income countries

Recently published data from the PURE study shows a dramatic range in the use of cardioprotective medications that is particularly low in low-income countries. For instance, statin use in those with coronary heart disease in China is unacceptably low at 2% [23]. The simplification of the guideline to focus on 4 statin-eligible groups and no longer requiring treatment titration goals represents an advance that potentially has great applicability to developing countries. Availability of generic statins at reasonable cost should make these a priority to provide at least for those at highest risk such as those with known coronary heart disease, diabetes, and with the highest known lipid levels (e.g., LDL-C of 190 mg/dl or highest based on the guideline).

The potential limitation of the 2013 U.S. lipid guidelines is reliance on 10-year CVD risk calculation as the basis for treatment of most eligible patients. If a global risk score such as the pooled cohort risk equations for SCORE (Systematic Coronary Risk Evaluation) algorithms can be accurately calibrated to a given region or country, it could identify those at highest risk (e.g., ≥7.5% from the pooled cohort risk calculator) who may benefit from a further "risk discussion" and consideration of statin therapy. However, as stated in the Risk Assessment section, even recalibrated risk functions may not be accurate in a new population of interest. Though risk functions derived from cohort studies may always be flawed by differences between the sample and the general population, country-specific risk prediction functions are desperately needed if global CVD risk is to be the global standard for risk assessment and treatment decision-making.

Ten-year CVD risk scores are highly influenced by age, which is also potentially a limitation because CVD events in developing countries often occur at younger ages. Consideration for a lower threshold (e.g., 5%) could be considered as being eligible for statin therapy, as the ACC/AHA guideline does suggest would be reasonable for a moderate-intensity statin. In certain ethnic groups such as East Asians, especially Japanese and Chinese who have been shown to have greater sensitivity to statins, both from a standpoint of efficacy as well as side effects, lower dosages that would provide the same efficacy in terms of LDL-C reduction recommended for a moderate-intensity (e.g., 30% to 50%) or high-intensity (e.g., >50%) statin might be considered as well.

In patients with a measured cholesterol, the WHO 2007 guideline [9] actually used a total cholesterol threshold of 8 mmol/l (320 mg/dl) for universal recommendation of statin therapy (this would likely be higher in most cases than the LDL-C 190 mg/dl threshold recommended for by the ACC/AHA) regardless of risk level but

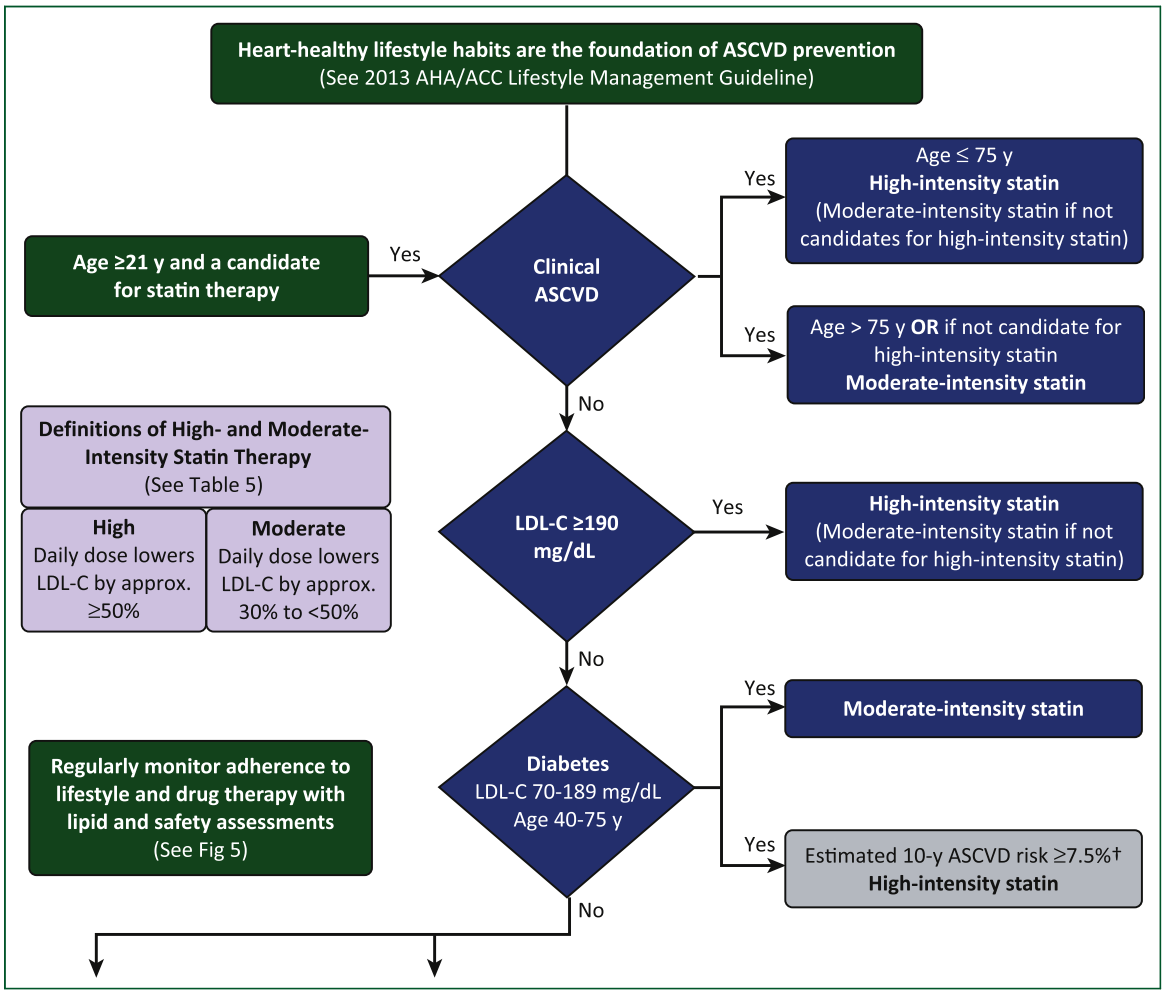

FIGURE 3. ACC/AHA guideline for cholesterol management flowchart. ABI, ankle brachial index; CAC, coronary artery calcification; DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; other abbreviations as in Figure 1. Reproduced, with permission, from Stone et al. [4].

with very high-risk persons (e.g., those with known CVD) given a statin and high-risk persons if the LDL-C is 3.0 mmol/l (100 mg/dl) or higher, with lower-risk persons advised just to follow a lipid-lowering diet. The WHO/ISH risk prediction charts, 1 Framingham risk calculator, and the INTERHEART risk score all assess risk without serum cholesterol concentration testing (the latter 2 essentially use BMI [Framingham] [12] or waist-to-hip ratio [INTERHEART] [13] and other factors as cholesterol and undiagnosed diabetes proxies). Unlike the U.S. guidelines, the WHO 2007 clinical guidelines recommended initiation of lipid-lowering therapy in high-risk patients without any information about directly measured cholesterol.

BLOOD PRESSURE MANAGEMENT GUIDELINES

The 2014 evidence-based guideline for the management of high blood pressure in adults [5], a report from panel members appointed to the Eighth Joint National Committee was also charged with the task of evaluating evidence based primarily on randomized controlled trials. Figure 4 gives a flowchart overview of the guideline.

Most important and controversial was the first recommendation of raising the initiation systolic blood pressure level for pharmacologic treatment in those aged 60 years and over to 150 mm Hg or higher. The previous threshold was 140 mm Hg or higher, which still remains the initiation level in all other guidelines including those released nearly simultaneously by the American Society for Hypertension and International Society for Hypertension [6]. The committee did not feel that there was additional benefit from setting a systolic blood pressure goal <140 mm Hg in this age group based on the clinical trial evidence reviewed; however, a corollary recommendation noted that in those already on pharmacologic treatment where the treatment is well tolerated and a lower blood pressure goal has been

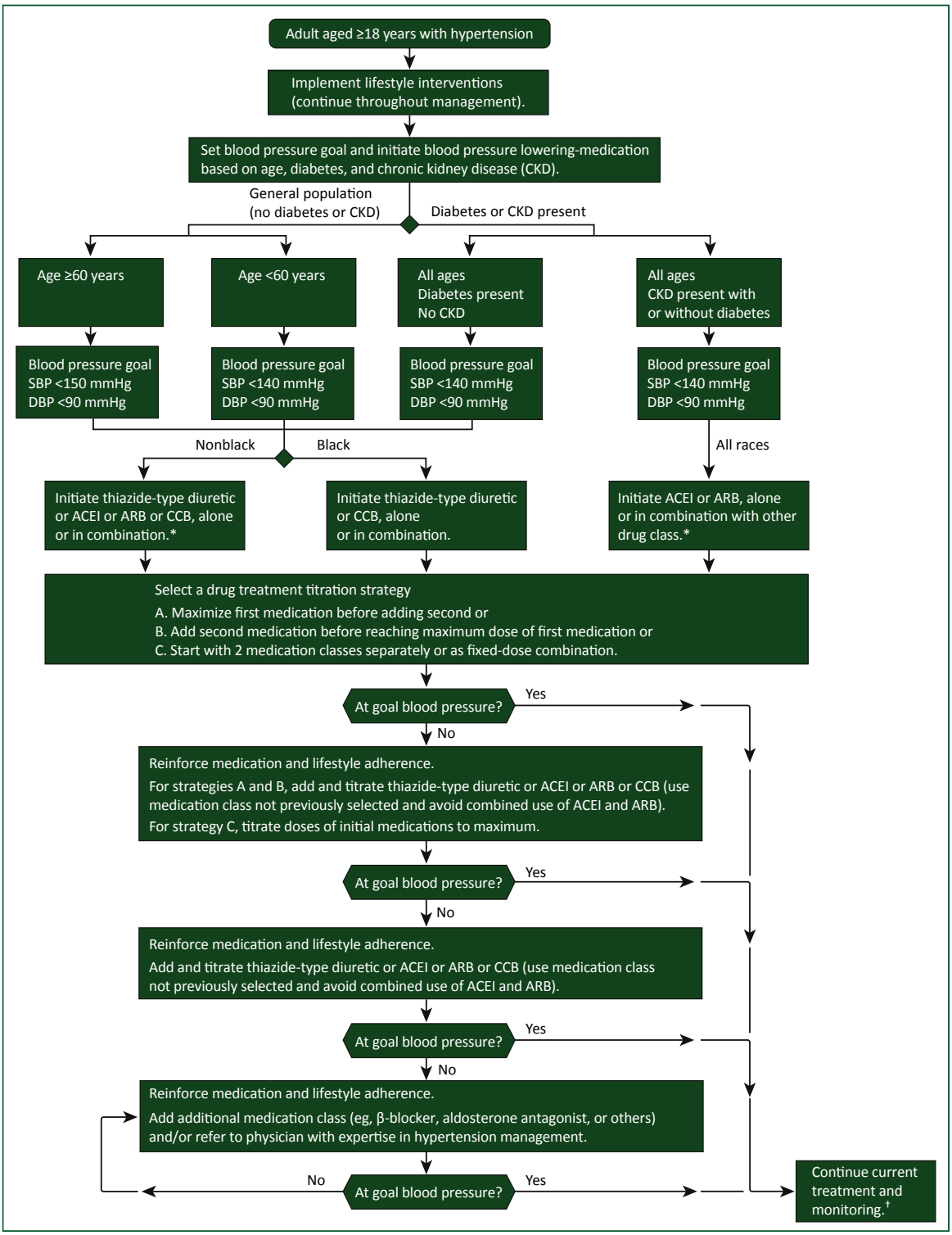

FIGURE 4. The 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *ACEIs and ARBs should not be used in combination. †If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure. Reproduced, with permission, from James et al. [5].

reached, the treatment does not need to be adjusted. Whereas most guidelines have already used this higher goal of treatment for those aged 80 years and over, the debate remains on whether those between ages 60 and 79 years should still be treated, when possible, to a lower treatment initiation and goal level of 140 mm Hg systolic, especially when the patient is robust and does not experience symptoms, as there is still the potential benefit of fewer strokes, in particular, from a lower goal [22]. A minority view published by some members of the Eighth Joint National Committee panel expressed concern that this revised guideline would result in less intensive therapy in many at significant risk for CVD and possibly reverse the decades-long decline in CVD and especially stroke mortality [24]. Although much research has focused on CVD risk prediction, providers making hypertension treatment decisions have few tools available for objectively assessing the probability of side effects and adverse events in patients before starting pharmacologic therapy, especially in older adults.

Other important modifications in the 2014 hypertension guidelines include raising the initiation and goal level for treatment in those with diabetes to 140/90 mm Hg from previous recommendations of 130/80 mm Hg, as well as broadening of the choices of initial antihypertensive treatment, including among those with diabetes to include thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers (except in blacks where it was recommended that initial therapy be either a thiazide-type diuretic or calcium channel blocker).

The 2014 guidelines focus specifically on management and do not discuss hypertension staging or the need for more intensive therapy in those with more severe blood pressure; those with stage 2 hypertension (160/100 mm Hg or higher) are at clearly higher risk and an important target in the WHO guidelines for immediate antihypertensive therapy [9]. Unlike the 2013 U.S. lipid guidelines, the 2014 hypertension guidelines did not incorporate 10-year CVD risk in treatment decisions. A body of research is building the case for risk-based hypertension treatment decisions [25–27]. The WHO 2007 guidelines illustrated how blood pressure and global CVD risk can be used to prioritize the highest risk patients for hypertension treatment. Those guidelines promote a risk-based approach, where treatment at a lower threshold of 130/80 mm Hg is recommended for those at highest (>30% in 10 years) risk and 140/90 mm Hg in those at 20% to 30% 10-year risk, but lifestyle management is the key focus in those at lower risk who are below the 160/100 mm Hg threshold.

Applicability to developing countries

The new recommendation for a higher initiation and goal systolic blood pressure could be argued by some as being a more conservative and therefore more achievable target for developing countries where hypertension rates are generally poorer. However, in practice, a blood pressure treatment target often operates only as well as a highway speed limit sign—treatment inertia often blurs the goal, leading practitioners to accept clinic blood pressures well above the goals achieved in clinical trials. Given that hypertension is the leading cause of mortality globally [28] and the greatest burden of hypertension lies in developing countries, one could argue that an advertised higher blood pressure goal could be counterproductive to our efforts to better control blood pressure as a key priority to make headway toward achieving our 2025 goals for reduction of noncommunicable disease mortality by the year 2025. In developing countries with under-resourced health care delivery infrastructure and a shortage of health care practitioners, population-wide dietary salt reduction should be considered, especially if resources for screening and treating hypertension are limited. At the same time, where infrastructure was developed for the fight against the human immunodeficiency virus, it can potentially be expanded to include hypertension diagnosis and treatment, even in people without the human immunodeficiency virus [29]. This example suggests that the goal of achieving individual-level primary prevention of CVD may be closer than we now know.

SUMMARY

This review of the state-of-the-art U.S. CVD prevention guidelines suggests that certain aspects of each guideline appear to be highly suitable for implementation in developing countries; however, other recommendations would be unrealistic to consider for many populations and have to be adapted accordingly. Risk factor prevalence and availability and costs of therapies vary substantially by country. Ideally, countries will decide prevention priorities for themselves, and cost-effectiveness comparisons using local data should identify the highest value strategies for controlling CVD risk factors in low- and middle-income countries. Proper education of health care providers globally on key simple messages about how to implement CVD prevention using guidance from the most up-to-date CVD prevention guidelines is a priority, but this review suggests that high-income world guidelines must be adapted to local epidemiology and resources if we are to make significant progress toward achieving 2025 goals to reduce by 25% premature mortality from CVD and other noncommunicable diseases. WHO has adopted key global targets to address noncommunicable diseases in an effort to reach these goals. These include the following: 1) a 10% relative reduction in prevalence of insufficient physical activity; 2) 25% relative reduction in prevalence of raised blood pressure; 3) 30% relative reduction in mean population intake of salt, with the aim of achieving the recommended level of <5 g/day (2,000 mg of sodium), and a 30% relative reduction in prevalence of current tobacco smoking [30]. In secondary prevention high-risk individuals, some have also supported widespread use of a polypill to cost-effectively address risk in these populations in developing countries [31].

Principles for the development of evidence-based national and regional guidelines on CVD prevention have

been proposed [32]. Key strategic principles recommended include the following:

1. collaboration between governments, national societies and foundations;
2. incorporation of professional judgment on relation of evidence into effective and efficient care;
3. assessment of CVD risk should be based on epidemiological risk factor data appropriate to the population where it is being applied;
4. a total risk approach for CVD should be emphasized in policy recommendations and guidelines;
5. intensity of interventions should be a function of total risk of CVD;
6. national cardiovascular societies/foundations should promote prospective collection of validated national vital statistics on causes and outcomes of CVD;
7. national professional societies should inform policymakers as to risk factor targets and drug therapies that are culturally and financially appropriate for their nation;
8. CVD prevention should be facilitated through education and training programs for health professionals;
9. lifestyle, risk factor, and therapeutic targets in guidelines should be assessed by national societies; and
10. health professionals should include prevention of CVD as part of their daily practice.

The recommendation to emphasize the use of total CVD risk in all guidelines is a potential problem for low- and middle-income countries with limited resources. Hopefully the use of non-laboratory-based risk assessment charts and mobile phone risk calculator applications can help health care providers to overcome this obstacle.

Recently published guidelines presented in this report, including the ACC/AHA guidelines on CVD prevention [1—4], recent hypertension management guidelines [5,6], and WHO guidelines on CVD prevention [9] are meant to provide guidance and not to replace clinical judgment. There are great variations between ethnic, racial, and socioeconomic groups within a country, and even greater interindividual variability in personal characteristics and preferences that always emphasizes the need for individualized approaches in applying or translating these guidelines to developing countries.

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