

Comparing the New European Cardiovascular Disease Prevention Guideline With Prior American Heart Association Guidelines: An Editorial Review

Van-Khue Ton, MD, PhD; Seth S. Martin, MD; Roger S. Blumenthal, MD; Michael J. Blaha, MD, MPH

The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland

ABSTRACT

Atherosclerotic heart disease and stroke remain the leading causes of death and disability worldwide. Cardiovascular disease (CVD) prevention can improve the well-being of a population and possibly cut downstream healthcare spending, and must be the centerpiece of any sustainable health economy model. As lifestyle and CVD risk factors differ among ethnicities, cultures, genders, and age groups, an accurate risk assessment model is the critical first step for guiding appropriate use of testing, lifestyle counseling resources, and preventive medications. Examples of such models include the US Framingham Risk Score and the European SCORE system. The European Society of Cardiology recently published an updated set of guidelines on CVD prevention. This review highlights the similarities and differences between European and US risk assessment models, as well as their respective recommendations on the use of advanced testing for further risk reclassification and the appropriate use of medications. In particular, we focus on head-to-head comparison of the new European guideline with prior American Heart Association statements (2002, 2010, and 2011) covering risk assessment and treatment of asymptomatic adults. Despite minor disagreements on the weight of recommendations in certain areas, such as the use of coronary calcium score and non-high-density lipoprotein cholesterol in risk assessment, CVD prevention experts across the 2 continents agree on 1 thing: prevention works in halting the progression of atherosclerosis and decreasing disease burden over a lifetime.

*Superior doctors prevent the disease
 Mediocre doctors treat the disease before evident
 Inferior doctors treat the full-blown disease*
 Huang Dee: Nai-Ching
 First Chinese Medical Text, 2600 BC

Introduction

Despite progressive advances in our understanding of the determinants of atherosclerosis, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality across the globe. In the large, international INTERHEART study, dyslipidemia and smoking were shown to be the 2 most important risk factors for myocardial infarction around the globe, with abdominal obesity, diabetes, and hypertension following closely behind.¹ According to the World Health Organization, the vast majority of CVD can be prevented with lifestyle and risk factor modifications.² For example, up to 80% of CVD cases and 90% of diabetes type 2 cases may be avoided with lifestyle changes.² This year, the European Society of Cardiology published an updated guideline on CVD prevention in the *European Heart Journal*.³ The new guideline incorporates results of recent observational studies and clinical trials on risk assessment

and treatment modalities (for example, studies derived from the Multi-Ethnic Study of Atherosclerosis [MESA] cohort,⁴ The Heinz Nixdorf Recall study,⁵ Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study,⁶ and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes study⁷) since the last guideline statement in 2007.⁸

The key message conveyed by this year's guideline is: prevention works.³ "[Greater than] 50% of the reductions seen in CVD mortality relate to changes in risk factors, and 40% to improved treatments."³ Importantly, the guideline statement stresses that prevention should remain a lifelong effort, because atherosclerosis is a systemic process that begins early and accrues over the lifetimes of both men and women.

Disease manifestations of atherosclerosis are numerous. They include coronary artery disease, peripheral artery disease, and ischemic stroke. The latter is notably absent in traditional risk assessment models such as the version of the Framingham Risk Score adapted by the National Cholesterol Education Program.⁹ In fact, women are more likely to present with a stroke as the first manifestation of CVD than they are with a myocardial infarction (MI). Therefore, an accurate risk assessment model that includes end points other than MI is crucial to identify patients who would most benefit from more aggressive preventive measures.

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Risk Assessment Models

Clinicians in North America are familiar with the Adult Treatment Panel III Framingham Risk Score (ATP III FRS),⁹ as it is 1 of the risk assessment models recommended in the 2010 American Heart Association (AHA) guidelines for assessment of cardiovascular risk in asymptomatic adults.¹⁰ ATP III FRS is limited in only predicting the 10-year risk of MI and coronary heart disease-related death, while underestimating the total atherosclerotic vascular disease risk by excluding stroke and angina requiring revascularization.

European physicians employ the Systematic Coronary Risk Evaluation (SCORE).³ SCORE estimates the 10-year risk of a first fatal atherosclerotic event (eg, MI, stroke, aortic aneurysm). Calibrated versions of SCORE exist to adjust for different death rates in European countries. Why fatal outcomes? The guideline argues that fatality is a hard outcome, whereas nonfatal events vary with definitions, diagnostic criteria, and tests. Instead of discriminating primary from secondary prevention, the new European guideline emphasizes the lifelong progressive nature of atherosclerosis. Included in the guideline are examples of studies linking increased lifetime risk of CVD to in utero exposure to risk factors,³ as illustrated in a Dutch study of early coronary artery disease after prenatal exposure to famine.¹¹ The guideline stresses that preventive measures should take top priority in patients with established CVD. This is followed by asymptomatic individuals with a high risk of CVD mortality, first-degree relatives of patients with premature CVD, and last, other asymptomatic patients in routine practice.

A high-risk patient is one who has a SCORE of $\geq 5\%$ plus any of the following: single risk factors (familial dyslipidemia, hypertension), diabetes, renal insufficiency (glomerular filtration rate 30–59 mL/min/1.73m²), known coronary heart disease, peripheral artery disease, or ischemic stroke. A 5% SCORE risk roughly correlates with a 10% to 25% 10-year CVD FRS risk, depending on which of the Framingham functions is selected (Table 1).

Judging the Evidence – the GRADE System

In contrast to the classes of evidence and levels of recommendation traditionally used in guidelines from the AHA and American College of Cardiology, the European experts employ a system called Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The GRADE quality indicators are: study limitations, inconsistency of findings, indirectness of evidence, imprecision, and publication bias. Using GRADE, reviewers may demote a biased, randomized, controlled trial to a lower level of evidence, while elevating a precise observational study to a higher level. “Strong” and “weak” are the only 2 qualifiers for strength of recommendation in GRADE. A “strong” recommendation means a readily practiced approach, whereas “weak” implies careful weighing of risks and benefits before implementing the intervention.

Inclusion of Stroke in Risk Prediction

Stroke secondary to atherosclerotic carotid disease is already a coronary heart disease equivalent according to the National Cholesterol Education Program Adult Treatment Panel III.¹² However, 90% of ischemic strokes occur not

Table 1. Risk Assessment Tools, United States vs European 5% SCORE = 10–25% 10-year CVD FRS

	ATP III FRS ⁸	SCORE ³
Risks	Age, gender, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, diabetes	Age, gender, total cholesterol, smoking status, systolic blood pressure
Outcomes	10-year risk of MI and coronary heart disease-related death	10-year risk of a first fatal atherosclerotic event.
Points	<10%: low risk, 10%–20%: moderate risk, $\geq 20\%$: high risk	<1%: low risk, 1%–5%: moderate risk

Abbreviations: ATP III FRS, Adult Treatment Panel III Framingham Risk Score; FRS, Framingham Risk Score; HDL, high-density lipoprotein; MI, myocardial infarction; SCORE, European System for Cardiac Operative Risk Evaluation.

as a result of symptomatic carotid disease, but as a result of intracranial cerebral or vertebral arterial atherosclerosis, cardiac emboli, or lacunar infarcts due to small vessel occlusion.¹³ Growing evidence suggests the coexistence of cerebrovascular disease and coronary heart disease, because they share the same pathophysiology and risk factors.

Patients with strokes from intracranial large vessel atherosclerosis and cardiac emboli seem to have an increased risk of heart disease compared to those with lacunar strokes. Data from observational studies and clinical trials suggest a similarly elevated risk of heart disease in patients with ischemic stroke and those with other coronary heart disease equivalents such as diabetes and peripheral artery disease.¹⁴

The 2011 AHA guideline for CVD prevention in women recommends that cerebrovascular disease should be considered a very strong risk factor for CVD.¹⁵ More recently, the AHA and the American Stroke Association in their joint statement propose a class I recommendation to consider large vessel atherosclerotic ischemic stroke a coronary heart disease risk equivalent (level of evidence B).¹⁴ As similarly stated in the European guideline, ischemic stroke can be considered a relevant outcome in the assessment of risk for prevention. The AHA cautions that ischemic stroke is a heterogeneous group of disorders, and more studies are needed to delineate the true cardiovascular outcomes in patients suffering from ischemic stroke of large or small vessels.

Additional Considerations for Risk Prediction in the European Guideline

Other than ischemic stroke, the European guideline lists the following as diseases associated with an increased CVD risk: influenza, chronic kidney disease (CKD), obstructive sleep apnea (OSA), erectile dysfunction, autoimmune diseases, periodontitis, and vascular disease after radiation exposure or transplantation. The guideline gives a “strong” GRADE recommendation to classify CKD patients in the high-risk category, and those with OSA and erectile dysfunction should undergo risk stratification and treatment.

In the 2010 AHA risk assessment guideline, it is a class I recommendation to obtain a family history of

atherothrombotic CVD as part of the risk assessment process.¹⁰ Even if the family history is not premature (CVD in men <55 years and women <65 years), it still confers an increased CVD risk.¹⁰ The new European guideline also strongly emphasizes the importance of family history, although it cautions that family history can be a crude risk-modifying factor that is likely underestimated due to complex genetic and environmental influences.

The Concept of Biological vs Chronological Age

Besides coronary heart disease equivalents, the European guideline suggests that there are other simple ways to view risk and communicate it to our patients, such as “heart” or “biological” age. Age features prominently in the FRS as an important predictor of CVD, because it correlates with the duration of CVD risk factor exposure. However, a young patient with a low absolute risk score may have a significantly increased risk relative to others of the same age but without any risk factor. In other words, this young patient’s heart age, or biological age, might be older than his or her chronological age. The European guideline applies the heart age concept in the form of relative risk SCORE charts. We find that the heart age is an effective concept to use in communicating with patients and motivating them. Further studies are needed to elucidate the best way of employing this framework for management decisions in younger patients with multiple risk factors.

New Risk Predictors: Biomarkers and Imaging Modalities

There is a growing body of literature on the utility of newer biomarkers such as highly sensitive C-reactive protein (hsCRP). Both the 2010 AHA and European guidelines agree that hsCRP may be useful in refining a moderate risk profile and help guide the initiation of a statin.^{3,10} However, this is a class IIa recommendation for adults meeting JUPITER entry criteria in the 2010 AHA guideline, whereas it is a class IIb, “weak” GRADE recommendation in the European guideline. Both guidelines discourage hsCRP testing in low- or high-risk individuals (Table 2). Overall, the totality of the literature suggests that the independent risk carried by hsCRP is modest, and hsCRP itself may not be causally related to CVD. Moreover, it is not known whether using hsCRP routinely identifies selective statin benefit or is a cost-effective strategy. Many experts still view hsCRP more as a research tool than a clinically useful biomarker.

In addition to novel biomarkers such as hsCRP, genetic markers borne out of genome-wide linkage sibs-pair analyses for single nucleotide polymorphisms (SNPs) are emerging as candidates for CVD risk prediction.¹⁶ To date, there is a rich knowledge base of SNPs found to be associated with increased risks of myocardial infarction and coronary heart disease. What to do with such knowledge remains elusive. Currently, the AHA and European Society of Cardiology guidelines do not support routine genetic testing as part of the CVD risk-prediction process.

In the arena of atherosclerosis imaging modalities, coronary artery calcium (CAC) score and carotid intima-media thickness measurement (CIMT) feature prominently in the guidelines. These modalities integrate risk exposure over a lifetime, and have been described as a means

Table 2. Utility of Biomarkers and Imaging Tests

European	AHA
hsCRP	
May be measured in patients with moderate CVD risk profile (class IIb, LOE B, weak GRADE)	Class IIa, LOE B
Should not be measured in low-risk or asymptomatic high-risk patients (class III, LOE B, strong GRADE)	Class III, LOE B
Coronary calcium score	
Measurement is reasonable for risk assessment in asymptomatic adults at intermediate risk (class IIa, LOE B, weak GRADE)	Class IIa, LOE B

Abbreviations: AHA, American Heart Association; CVD, cardiovascular disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; hsCRP, highly sensitive C-reactive protein; LOE, level of evidence.

to directly measure the disease (atherosclerosis) that clinicians seek to treat in preventive cardiology.

The CAC score has been shown to correlate with total coronary atherosclerotic burden, although not necessarily with the degree of coronary luminal stenosis. Emerging evidence suggests that total atherosclerotic burden is a much more useful predictor than degree of stenosis in primary prevention.¹⁷ A meta-analysis in 2009 examined 49 studies aimed at evaluating the diagnostic value of the CAC score.¹⁸ In 18 of these 49 studies, the presence of any CAC has a sensitivity of 98% for detecting significant coronary artery disease on angiography. However, the European guideline raises some doubt regarding this negative predictive value in selected patients, as significant coronary stenosis and plaque rupture in younger patients can occur without calcium deposits. Nevertheless, the presence and extent of CAC can strongly risk stratify the vast majority of adult patients.

In many observational studies, CIMT is a moderately strong predictor of cardiovascular death. Carotid artery thickening correlates with plaques in other arterial territories, including plaques in the carotid artery itself. According to the Mannheim CIMT Consensus Report, plaque is defined “as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT or demonstrates a thickness of ≥ 1.5 mm.”¹⁹ It is important to remember that the CVD risk predicted by CIMT is graded and not linear.

As indicated in the MESA study, CIMT is a less-potent predictor of coronary outcomes compared to CAC.⁴ The 2010 AHA guideline points to a lack of sufficient data supporting the superiority of 1 test vs the other.¹⁰ Both tests receive a class IIa recommendation in the European guideline, but it surprised many that the CAC score was assigned a “weak” GRADE, whereas CIMT garners a “strong” GRADE, perhaps due to the lack of ionizing radiation (Table 2). One important drawback of CIMT is that its accuracy depends on the sonographer’s skills, whereas coronary calcium scoring results do not vary significantly from 1 scanner to the next.

In fact, CAC scoring is standardized by the method of Agatston. The amount of radiation for a cardiac CT scan is small, ~1 mSv, which is the equivalent of 2 mammograms.¹⁸ CAC scoring, therefore, might be the better method to reclassify most intermediate-risk patients to higher- and lower-risk categories in a standardized fashion. It can be used with accuracy across healthcare delivery systems in the United States, Europe, and worldwide.

Key Messages in Preventive Measures

First and foremost, successful implementation of CVD prevention depends on physicians' awareness and agreement with guidelines. According to a survey of 500 randomly selected physicians (300 primary care physicians, 100 obstetricians/gynecologists [OBGyns], and 100 cardiologists), fewer than two-thirds recommended physical activity to low-risk patients.²⁰ Only one-third of OBGyns prescribed statins to high-risk women, but serve as primary care doctors to 67% of patients in this study. A more recent survey of 925 US physicians reported that only 41% used a risk assessment model in their daily practices.²¹ Therefore, educational and practice improvements are needed to increase physicians' awareness and effective use of global CVD risk scores and preventive implementation, as well as to elucidate whether physicians' strict adherence to preventive guidelines actually improve clinical outcomes.

As mentioned previously, the new European guideline made no distinction between primary and secondary prevention. We feel that it is more appropriate to compare this new guideline with the prior 2011 updated AHA secondary prevention guideline, as both documents have parallel recommendations regarding the following categories^{3,22} (Table 3).

Behavioral Changes

A healthy lifestyle is essential in combating the lifelong progression of atherosclerosis. It is a class I, level of evidence A, "strong" GRADE recommendation in the European guideline to implement a multifaceted approach in treating high CVD-risk patients. The 2011 AHA guideline gives lifestyle modification a class I, level of evidence B. Despite this minor difference in levels of recommendations, healthy lifestyle education, exercise training, stress management, and psychological counseling should be the cornerstones of modern preventive cardiology practice.

Both European and AHA guidelines strongly recommend smoking cessation, as well as avoidance of secondhand smoke. A "5 As" approach should be utilized in routine practice: (1) ask about smoking status, (2) advise quitting, (3) assess willingness to quit, (4) assist with counseling and medications, and (5) arrange for follow-up.

Physical activity is also paramount in CVD prevention. Both guidelines agree that moderate exercise of at least 2.5 to 3 hours a week is beneficial, and patients with previous MI with or without revascularization, heart failure, or stable angina should be encouraged to enroll in a cardiac rehabilitation program.

There is a linear relationship between increasing body mass index (BMI) and all-cause mortality, especially CVD-related death. Besides BMI, both guidelines use waist circumference (≥ 102 cm or 40 inches in men and ≥ 88 cm or

35 inches in women) to guide weight loss advice. A healthy diet low in salt, saturated and trans-unsaturated fat, rich in fiber, fruits, and vegetables is a cornerstone of CVD prevention. Energy intake should be limited to what is needed to maintain a BMI <25 kg/m². The new European guideline highlights that more evidence has accumulated on dietary patterns, and the Mediterranean diet is associated with reduced cardiovascular and all-cause mortality.

A healthy lifestyle may be impossible to maintain in the case of moderate depression. It is thus reasonable to screen for depression and anxiety, particularly in those with recent CVD events (no specific level of recommendation in European guideline and AHA guideline gives a class IIa recommendation).

Blood Pressure Control

Both guidelines suggest a target blood pressure of $<140/90$ mm Hg in all hypertensive individuals (class I recommendation in AHA, class IIa in European guideline). Evidence supporting benefits of lower blood pressure goals is inconsistent. The European guideline discourages β -blockers and thiazide diuretics in patients at risk of diabetes (class III recommendation), although it is not proven that these medications directly cause diabetes or contribute to any increase in cardiovascular risk. Carvedilol and nebivolol are exceptions owing to their lack of diabetogenic properties. The AHA, on the other hand, considers all antihypertensives relatively equal.

Renin-angiotensin-aldosterone system blockers receive special attention in both guidelines. angiotensin-converting enzyme (ACE) inhibitors are strongly recommended in diabetics (to delay progression of nephropathy) and in those with left ventricular ejection fraction $\leq 40\%$. The European guideline emphasizes a combination of ACE inhibitor (or angiotensin-receptor blocker if ACE inhibitor intolerant), a calcium channel blocker, and/or a diuretic in the treatment of patients with long-standing hypertension.

Lipid-Lowering Therapy

The European guideline considers low high-density lipoprotein (HDL) cholesterol, elevated low-density lipoprotein (LDL) cholesterol and hypertriglyceridemia as independent CVD risk factors. Nevertheless, only total cholesterol is included in the SCORE. In our view, risk may be more completely and consistently captured by non-HDL cholesterol, the total cholesterol to HDL cholesterol ratio, or atherogenic particle number.²³ The new guideline correctly realizes that high-risk patients should be selectively treated with statin therapy, further strengthening the argument for the merits of a statin in primary prevention.²⁴

Focused on LDL cholesterol, as routinely estimated by the Friedewald formula, both guidelines support low LDL cholesterol goals for at-risk individuals: those with the highest risks would benefit from LDL cholesterol <70 mg/dL or $\geq 50\%$ LDL cholesterol reduction (European class I recommendation, level of evidence (LOE) A vs American class IIa, LOE C recommendation). The highly anticipated ATP IV guideline (now nearly 4 years in the making) may provide a stronger recommendation for LDL cholesterol <70 mg/dL, given growing evidence supporting the benefit

Table 3. Preventive Implementations

	European	AHA
Preventive implementations		
Behavioral changes	Smoking cessation (class I, LOE A, strong GRADE)	Same LOE
	Regular exercise (at least 2.5–3 hours a week) (class I, LOE A, strong GRADE)	Similar recommendation (class I LOE B)
	Weight reduction (goals: BMI <25, waist circumference <40 inches for men and <35 inches for women) (class I, LOE A, strong GRADE)	Similar recommendation (class I LOE B)
Antihypertensive agents		
Blood pressure control	Goal is <140/90 mm Hg (class IIa, LOE A, strong GRADE); all antihypertensives are equal (class I, LOE A, strong GRADE)	Treat with β blockers \pm ACE-inhibitors and other agents if BP \geq 140/90 mm Hg (class I, LOE A)
	β -Blockers and thiazides not recommended in those with increased risk of diabetes (class III, LOE A, strong GRADE)	No such specific caution
	Lifestyle modifications are key (class I, LOE B, strong GRADE)	Same recommendation (class I, LOE B)
Cholesterol-lowering therapy		
Goal	LDL cholesterol <100 mg/dL for moderate-risk patients (class I, LOE A, strong GRADE)	Similar recommendation (class I, LOE C)
	LDL cholesterol <70 mg/dL for high-risk patients (class I, LOE A, strong GRADE)	(class IIa, LOE C)
	No specific recommendation regarding non-HDL cholesterol	If triglycerides \geq 200 mg/dL, goal non-HDL cholesterol <130 mg/dL (class I, LOE B)
Special candidates	All patients with non-embolic ischemic stroke and peripheral artery disease or carotid disease should be treated with cholesterol-lowering medications (class I, LOE A, strong GRADE)	No specific recommendations
Drugs	Statin should be the first-line drug (strong recommendation, no evidence qualifier)	Similar recommendation (class I, LOE A)
Diabetes management, antiplatelet therapy, influenza vaccine		
Type 2 diabetes	Goal HbA _{1c} \leq 7% (class I, LOE A, strong GRADE)	(class IIb, LOE C)
Antiplatelet therapy	Individuals without overt CVD, including those with diabetes, should not take low-dose aspirin daily (class III, LOE B, weak GRADE)	No such recommendation
	Individuals with high risk of CVD may take low dose aspirin daily (81 mg) (no evidence qualifier)	Recommended in those with FRS \geq 10%
Influenza vaccine	Yearly for all patients with cardiovascular disease (strong recommendation, but no evidence qualifier)	Similar recommendation (class I, LOE B)
Abbreviations: ACE, angiotensin-converting enzyme; AHA, American Heart Association; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; FRS, Framingham Risk Score; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LOE, level of evidence.		

of this LDL cholesterol level, or as some have suggested may eliminate LDL targets altogether.²⁵ The European guideline also emphasizes initiation of lipid-lowering therapy in peripheral artery disease patients, irrespective of their plasma lipid concentrations. Consistent with the inclusion of stroke in risk assessment, a statin is generally indicated in patients with noncardioembolic ischemic stroke.

Type 2 Diabetes Management

The European guideline places a stronger emphasis on achieving HbA_{1c} \leq 7% (class I, “strong” GRADE vs class IIb in AHA guideline). The American guideline suggests

a less stringent HbA_{1c} goal for those with limited life expectancy, advanced vascular complications, and extensive comorbidities. Both guidelines recognize the importance of lifestyle modifications, blood pressure control, and lipid management in patients with diabetes.

Antiplatelet Therapy

We compare recommendations regarding antiplatelet therapy in the European guideline with those published in the 2002 AHA primary prevention guidelines.²⁶ In asymptomatic individuals with a moderate 10-year FRS risk \geq 10%, the AHA recommended the initiation of low-dose aspirin,

with caution regarding gastrointestinal bleeding and hemorrhagic stroke. The European guideline dissuades against routine use of low-dose aspirin for primary CVD prevention, even in diabetic patients who do not have overt evidence of coronary or cerebrovascular disease. Interestingly, both the European and the 2002 AHA guidelines cite the same study from the Antithrombotic Trialists' Collaboration in 2002²⁷ as the basis of their respective recommendations.

Influenza Vaccination

It is a strong recommendation in both guidelines to vaccinate CVD patients every year, as influenza epidemics correlate with increased adverse CVD events. It is also imperative that healthcare workers receive vaccination, so as not to expose patients to undue risk.

Conclusion

Despite the differences (Tables 1–3), the European and AHA prevention guidelines share many similarities. Listed below are the key messages from these documents:

- Preventive measures are effective in reducing CVD mortality and morbidities.
- Prevention must be a lifelong effort to combat the progressive nature of atherosclerosis.
- Prevention means a multifaceted approach encompassing lifestyle modifications and treatment modalities aimed at reducing estimated CVD risks.
- Further research is needed in developing more accurate CVD risk assessment models for different ethnic and cultural groups.

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