World Heart Federation Cholesterol Roadmap

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ABSTRACT

Background: The World Heart Federation has undertaken an initiative to develop a series of Roadmaps.

Objectives: The aim of these is to promote development of national policies and health systems approaches and identify potential roadblocks on the road to effective prevention, detection and management of cardiovascular disease (CVD) in low-and middle-income countries (LMIC), and strategies for overcoming these. This Roadmap focuses on elevated blood cholesterol, a leading risk factor for myocardial infarction, stroke, and peripheral arterial disease.

Methods: Through a review of published guidelines and research papers, and consultation with a committee composed of experts in clinical management of cholesterol and health systems research in LMIC, this Roadmap identifies (1) key interventions for primordial, primary and secondary prevention of CVD through detection, treatment, and management of elevated cholesterol and familial hypercholesterolemia (FH); (2) gaps in implementation of these interventions (knowledge-practice gaps); (3) health system roadblocks to treatment of elevated cholesterol in LMIC; and (4) potential strategies for overcoming these.

Results: Despite strong evidence of the importance of cholesterol levels in primary or secondary prevention of CVD, and the effectiveness of statin therapy for cholesterol lowering and reduction of CVD risk, gaps exist in the detection, treatment, and management of high cholesterol globally. Some potential roadblocks include poor access to laboratory facilities or trained professionals for cholesterol management, low awareness of FH among the general population and health professionals, unaffordability of statins for patient households, and low awareness of the importance of persistent adherence to lipid-lowering medication. Potential solutions include point-of-care testing, provision of free or subsidized lipid-lowering medication, and treatment adherence support using text message reminders.

Conclusions: Known effective strategies for detection, treatment, and management of elevated cholesterol and FH exist, but there are barriers to their implementation in many low-resource settings. Priorities for health system intervention should be identified at the national level, and the feasibility and effectiveness of proposed solutions should be assessed in specific contexts. Many solutions proposed in this Roadmap may apply to other cardiovascular conditions and present opportunities for integration of CVD care in LMIC.

In 2012, all member states of the World Health Organization (WHO) endorsed a historic target to reduce premature mortality from noncommunicable diseases (NCD) by 25% by 2025. This commitment was echoed by the United Nations Sustainable Development Goals in 2015, which include a target to reduce premature mortality from NCD by 30%. These targets are especially relevant to atherosclerotic cardiovascular disease (CVD), which is the leading cause of death globally and is increasing in prevalence in low- and middle-income countries (LMIC).

In support of reaching these targets, the World Heart Federation (WHF) has undertaken an initiative to develop a series of Roadmaps to promote development of national policies and health systems approaches; identify potential roadblocks on the road to effective prevention, detection, and management of CVD in LMIC; and provide strategies for overcoming these. These Roadmaps provide guidance for countries toward developing or updating national NCD programs using the framework provided by the WHO's Global Action Plan for the prevention and control of NCD

Dr. Faria Neto has received honoraria in the form of speaker, consultancy, advisory board, or committee member fees from MSD, AstraZeneca, Pfizer, Sanofi, Amgen, Unilever, and Aegerion. Dr. Al-Rasadi has received a research grant from Sanofi; and served on the speakers bureau and as an advisory board member for Sanofi, AstraZeneca, and Pfizer. Dr. Blom has received grants for conducting clinical trials from Sanofi-Aventis, Regeneron Pharmaceuticals, Inc., Novartis, Eli Lilly & Company, Amgen, and Aegerion; honoraria for lectures from Sanofi-Aventis, Regeneron Pharmaceuticals, Inc., Aegerion, Amgen, AstraZeneca, MSD, Pfizer, Servier, and Unilever; advisory board fees from Sanofi-Aventis, Aegerion, Amgen, AstraZeneca, and MSD; travel assistance from Amgen and Aegerion; a fee for chairing a steering committee from Aegerion; a consultancy fee from Gemphire; and nonfinancial support (editorial assistance and statistical analysis) from Sanofi-Aventis and Regeneron Pharmaceuticals, Inc. Dr. Catapano has received honoraria, lecture fees, or research grants from SigmaTau, Menarini, Kowa, Eli Lilly, Recordati, Pfizer, Sanofi, Mediolanum, Merck, Aegerion, Amgen, Genzyme, Bayer, and AstraZeneca. Dr. Cuevas has received speakers' fees from Synthon, Amgen, Abbott, Saval, Novonordisk, and Sanofi; and has participated in advisory boards for Abbott, Novonordisk, and Janssen. Dr. Lopez-Jimenez has received speakers' fees from Amgen. Dr. Santos has received honoraria for consulting and/or speaker activities from Amgen, Aegerion, Akcea, AstraZeneca, Biolab, Boehringer-Ingelheim, Cerenis, Eli-Lilly, Genzyme, Kowa, Merck, Pfizer, Sanofi/Regenron, Praxis, Procaps, Torrent, and

Unilever. Dr. Sy has received honoraria for lectures from MSD and Pfizer; has been involved in the Odyssey Outcomes Study; and has received a research grant from Sanofi. Dr. Watts has received honoraria for advisory boards, lectures, or grants for research from Amgen, Sanofi, Regeneron, Kowa, and Gemphire. Dr. Yusuf has received research funding for the conduct of the HOPE 3 trial from AstraZeneca. All other authors report no relationships that could be construed as a conflict of interest.

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2013 to 2020 [1,2]. Roadmaps dedicated to secondary prevention of CVD [3]; tobacco control [4]; raised blood pressure [5], rheumatic heart disease [6], and atrial fibrillation [7] have already been published. This Roadmap focuses on blood cholesterol. While most existing global data refer to total blood cholesterol (TC), this Roadmap will reflect a growing body of evidence on the risk associated with specific subtypes of cholesterol, for example, low-density lipoprotein cholesterol (LDL-C), or the ratio of apolipoprotein B ([apo B]; the main protein in LDL-C) to apolipoprotein A1 ([apo A-I]; the main protein in high-density lipoprotein cholesterol [HDL-C]).

THE RELEVANCE OF CHOLESTEROL TO THE GLOBAL BURDEN OF CVD

Reducing cholesterol-related CVD risk, namely risk associated with myocardial infarction, stroke, and peripheral arterial disease, plays a vital role in achieving the WHO 25 × 25 target for reducing premature mortality from CVD and other NCD. Worldwide, there are about 17 million deaths due to CVD each year [8], and international studies have suggested that elevated apo B/apo A-I is among the most important risk factors for myocardial infarction (MI) [9] and for ischemic stroke [10]. Research from 2008 suggested that the global average of TC showed little change in the preceding 3 decades, because of opposing trends: decreases in Australasia, North America, and Europe and increases in east and southeast Asia and Pacific [11]. Estimated average TC by country, for men and women, is shown in Figure 1 [12].

WHO has identified control of cholesterol, as part of a Total Risk Approach to the prevention of CVD, as a public health priority [13]. Cholesterol reduction is vital to both primary and secondary prevention of CVD; lowering cholesterol in those with established CVD, and those at high risk of developing CVD, is essential to reducing CVD morbidity and premature mortality globally. Low cost methods for identifying at-risk patients in LMIC exist [14,15], and treatment with cholesterol-lowering medications in the form of statins is cost-effective in these settings [16]. Nevertheless, while the prevalence of raised cholesterol and other CVD risk factors are all lower in LMIC compared with high-income countries (HIC), mortality from CVD is higher in LMIC, suggesting that detection and management of these risk factors together with the management of CVD is poorer in LMIC [17].

This Roadmap was developed through a review of published guidelines and research papers, and in consultation with an expert committee, composed of experts in clinical management of cholesterol and health systems research in LMIC. In the following sections, we outline essential strategies for measurement and management of cholesterol in the context of primordial prevention in populations, primary prevention in asymptomatic high-risk individuals, secondary prevention in patients with established CVD, and familial hypercholesterolemia (FH). We then identify potential roadblocks to implementation of evidence-based strategies in LMIC and propose solutions for overcoming these roadblocks.

MEASUREMENT AND MANAGEMENT OF BLOOD CHOLESTEROL

Primordial prevention for the general population

LDL-C contributes to the development of CVD, either on its own or in interaction with other cardiovascular risk factors. There is clear evidence of a strong positive association between LDL-C and coronary artery disease ([CAD]; the most common CVD) [18,19]. Whereas evidence of the impact of many lifestyle-related factors on TC and LDL-C is inconclusive, there is general consensus that aerobic physical activity may increase HDL-C [19,20], and diets low in saturated and trans fats, and higher in vegetables, can reduce TC and LDL-C levels in the blood [21,22]. Among the most common sources of trans fats are hydrogenated and partially hydrogenated oils often found in processed foods [23]. As such, a primary aim of public health interventions for reducing morbidity and mortality due to elevated LDL-C should be to encourage a healthy lifestyle among the general population, irrespective of individual cholesterol levels [24]. Various dietary guidelines exist, such as those from the European Society of Cardiology, that encourage a preference for whole grains, vegetables, legumes, fresh or frozen fruit, lean and oily fish and poultry, and nonfat dairy products (Appendix 1) [19]. However, some of these have been criticized for leading to carbohydrate-heavy diets. An in-depth review of current evidence concluded that the strongest evidence supports the traditional Mediterranean-type diet as a healthy dietary pattern to reduce CVD [25]. The Mediterranean diet consists of 40% to 50% carbohydrates from mainly complex carbohydrates such as vegetables, fruits, beans, and non-refined cereals; 15% to 20% protein, emphasizing lean and plant protein sources; and a high nut and olive oil content making up 16% to 21% monounsaturated fatty acids, 7% to 11% saturated fatty acids, and 5% to 7% polyunsaturated fatty acids. Based on that review, experts developed guidance for adapting the Mediterranean diet to other regions. This guidance has been included in Appendix 2. National dietary guidelines for prevention of CVD should reflect local food availability and customs.

Primary prevention

Risk assessment. Traditionally, primary prevention of CVD has focused on a "single-risk-factor" approach, which targets patients based on their levels of individual CVD risk factors, such as raised LDL-C or high blood pressure, but this approach has been progressively replaced in all contemporary CVD prevention guidelines with the Total Risk Approach based on absolute risk of developing CVD over a defined period of time [26-28]. The level of absolute risk used to define a "high risk individual" eligible for primary prevention, including the use of drug therapies, varies

between national guidelines and depends on the ability of the health system to screen and manage that proportion of the population classified as high risk, as well as the costs of doing so. Whereas the Total Risk Approach is appropriate for most of the adult population, some people will be eligible for statin therapy without the need to calculate absolute CVD risk because they are already at high or very high risk. In addition to those with established CVD (discussed in the Secondary Prevention section), these patients include those with FH, those with very high LDL-C $\geq$190 mg/dl (4.9 mmol/l) [19,28], those with diabetes and target organ damage, and those with chronic kidney disease (see Table 1 for details) [13]. The definitions of these high-risk groups, which vary to some extent between national and regional guidelines, are shown in Table 1. More recent evidence supports the use of statin therapy in patients that have been prescribed life-long antihypertensive therapy [29,30]. Children and young people with obesity, insulin resistance, and type 2 diabetes require intensive lifestyle intervention and, if appropriate, drug therapies to reduce their lifetime risk.

The Total Risk Approach recognizes that many CVD risk factors may only be elevated to a moderate degree but because they occur in clusters and have a multiplicative effect, overall absolute CVD risk is elevated. As such, treatment of all risk factors together with healthy lifestyle changes, blood pressure, lipids, and glucose lowering [5] will produce the greatest reductions in risk of developing CVD. The Total Risk Approach relies on estimating an individual's baseline CVD risk using a risk prediction algorithm ideally developed from the population to which it is to be applied. Assessing risk based on the Total Risk Approach will assign a risk score to screened individuals. The decision of who to screen for CVD risk, and which risk threshold to use to initiate treatments with statins, is a matter of national (or local) policy and available resources but, for example, the National Health Service in the United Kingdom screens all adults without pre-existing conditions between the ages of 40 and 70, every 5 years [31]. There are limited data suggesting that systematic risk assessment (screening-like programs with a pre-determined selection process of individuals to be assessed), as opposed to opportunistic screening, may have positive effects on reducing CVD risk, and more evidence is needed [32]. Patient 10-year total risk of fatal and nonfatal CVD can be stratified according to risk score charts such as the Framingham [26] and SCORE (Systemic Coronary Risk Evaluation) [27], which have been validated primarily in HIC, and the WHO/International Society for Hypertension (ISH) [14] risk chart, which was developed for use in all regions of the world. The American College of Cardiology/American Heart Association (ACC/AHA) has recently developed a pooled cohort equation for CVD risk assessment [33]. (As examples, the WHO/ISH and SCORE risk assessment tools are included as Appendices 3 [34] and 4). These risk score charts assign absolute risk levels based on age, sex, smoking habit, blood pressure and TC levels, and other risk factors can also be incorporated.

Conventionally, cholesterol has been measured in blood samples obtained after 8 hours of fasting; however, recent evidence suggests that these fasting measurements are essentially indistinguishable from nonfasting measurements [35,36]. Therefore, more recent guidelines suggest that nonfasting blood samples are sufficient for measurement of cholesterol levels [23,37]. Ideally, the full lipid profile—total cholesterol, HDL-C, and triglycerides—will be measured and LDL-C and non-HDL-C will be calculated. Where appropriate laboratory facilities exist, apo B/apo A-I should be measured given the importance of the apo B—apo A-I ratio as a risk factor for MI [9] and ischemic stroke [10]. In fact, current evidence suggests that apo B is a more accurate marker of cardiovascular risk than LDL-C or non-HDL-C and that apo B—apo A-I ratio is at least equal to, and perhaps superior to, the cholesterol ratios (TC—HDL-C, non-HDL-C—HDL-C, LDL-C—HDL-C) as a summary index of cardiovascular risk. The measurements of apo B and apo A-I are accurate, standardized, and can be determined using automated methods in any routine clinical chemistry laboratory at a cost similar to the cost of conventional lipoprotein lipids. Except for TC, the measurements of the conventional lipoprotein lipids—LDL-C, non-HDL-C, and triglycerides—are not standardized. The accuracy of calculated LDL-C is particularly problematic at triglyceride levels >200 mg/dl (2.2 mmol/l) or LDL-C <70 mg/dl (1.8 mmol/l). There is no evidence, however, that directly measured LDL-C is a more accurate measure of cardiovascular risk than calculated LDL-C. The relative strengths of each type of cholesterol measure of cardiovascular risk are outlined in Appendix 5. Whereas apo B appears to be the most predictive measure, it is important to note that measurement of TC alone is currently more realistic for many countries, given the cost and complexity of measuring apolipoproteins in resource-limited settings. Under some rare circumstances, TC measurements should be interpreted with caution as, for example, high TC levels may be driven by high levels of HDL-C; furthermore, normal TC levels may disguise inadequate nutrition.

Although existing risk calculators (WHO/ISH, SCORE, Framingham, etc.) provide a good assessment of total CVD risk, for these charts to predict risk as accurately as possible they must be based on epidemiological data derived from the populations to which they are to be applied. Alternatively, in the absence of such epidemiological data, it is possible to adapt existing risk algorithms with adjustments for CVD mortality and prevalence of risk factors for a given country [38]. There may also be specific populations within countries who are at higher risk of CVD, such as those on antiretroviral treatment for HIV [39], for whom risk assessment tools may need to be specifically tailored. Risk scores produced by existing charts may underestimate actual risk in many LMIC, where CVD mortality is increasing [23]. There is therefore an urgent need to support data collection efforts in countries where these data are currently not available. WHO is currently in the process of revising its risk score charts to be more widely

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GLOBAL HEART

VOL. ■, NO. ■, 2017
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2017.03.002

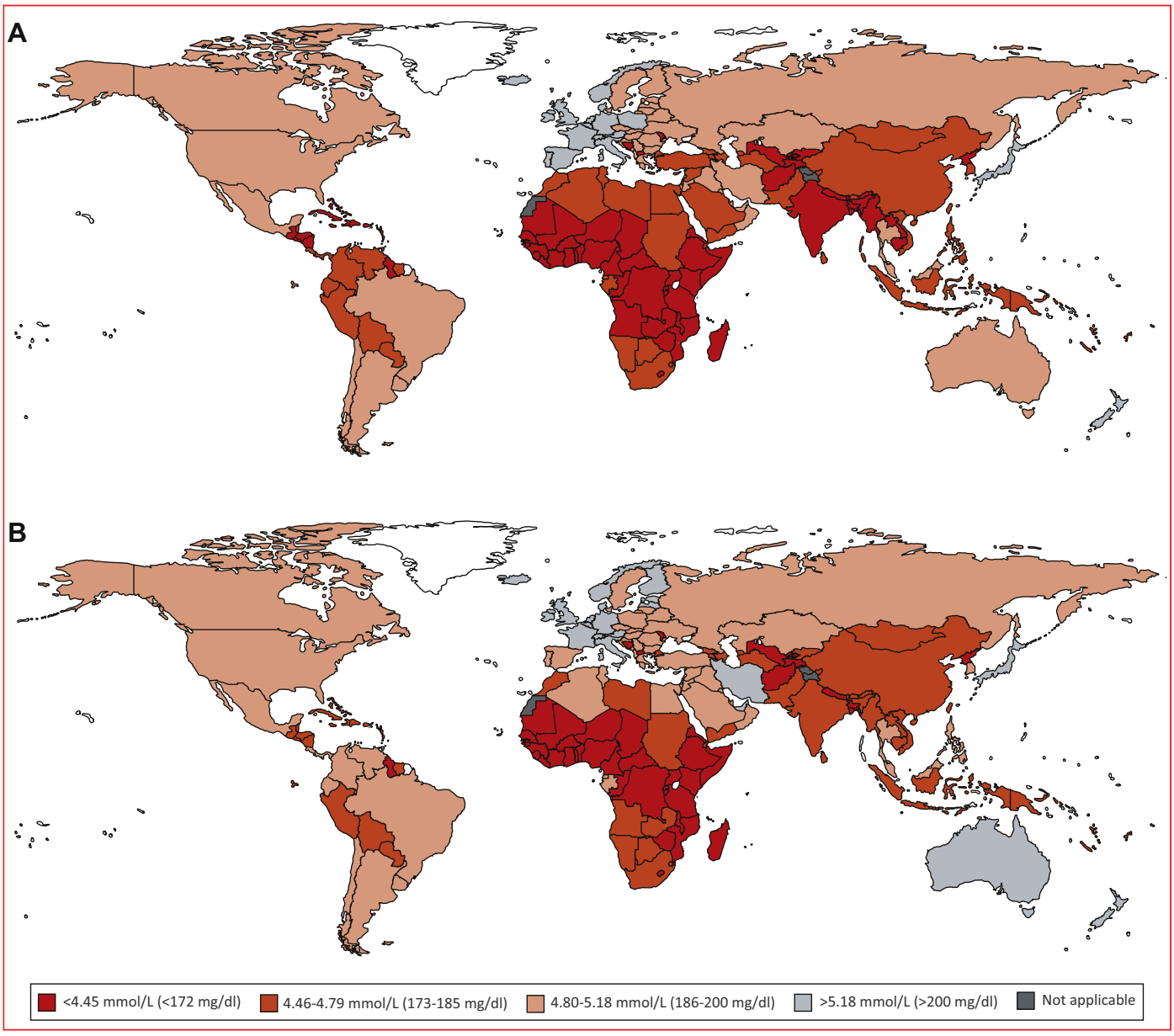

FIGURE 1. Mean total cholesterol (mmol/l) by country. (A) Male and (B) female subjects, 2008 (conversion to mg/dl is approximate).

applicable. The INTERHEART risk score is another example and was developed from a case-control study in 52 high-, middle-, and low-income countries and was subsequently validated in cohorts from 21 countries [40]. Another recent effort to develop an adaptable risk prediction equation for CVD is the Globorisk score [41]. To develop the Globorisk score, data from 8 prospective cohort studies were used to estimate risk of fatal and nonfatal CVD associated with smoking, blood pressure, diabetes, and TC, allowing the effect of sex and age to vary between cohorts and countries. The resulting risk prediction equation can be recalibrated for application in different countries using locally available mortality and prevalent risk factor data. Whatever approach is used, risk score charts are only a guide to assessment of CVD risk, and resulting scores should be interpreted in light of the clinician's knowledge of the patient and his or her family history, taking account of other factors that may increase risk such as level of social deprivation and psychosocial stress [42].

Although the Total Risk Score approach is more comprehensive than a single risk approach, it is heavily influenced by age and sex, risk factors for CVD that are nonmodifiable, and to a much lesser extent by LDL-C, blood pressure, smoking, and diabetes, CVD risk factors that can be successfully modified by treatment. For

TABLE 1. Examples of guidelines for risk assessment, risk thresholds for treatment, and targets

Guideline	Groups to Be Treated Without Requiring Risk Stratification	Risk Assessment Tool for Others	Threshold for Treatment	Treatment Target	Pharmacological Treatment Options
2016 ESC/EAS guidelines for the management of dyslipidemias	Very high risk Subjects with any of the following: • Documented CVD • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension, or dyslipidemia • Severe chronic kidney disease (GFR <30 ml/min/1.73 m^2)	• The SCORE system estimates the 10-year cumulative risk of a first fatal atherosclerotic event. (Charts for high- and low-risk regions in Europe.)	• A calculated SCORE ≥10% for 10-year risk of fatal CVD (very high risk) • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD	• Very high-risk: LDL-C <1.8 mmol/l (70 mg/dl) or a reduction of ≥50% if the baseline is between 1.8 and 3.5 mmol/l (70 and 135 mg/dl) • High risk: LDL-C < 2.6 mmol/l (100 mg/dl) or a reduction of ≥50% if the baseline is between 2.6 and 5.2 mmol/l (100 and 200 mg/dl)	• Statin up to the highest recommended or highest tolerable dose to reach the goal • Ezetimibe or bile acid sequestrants in the case of statin intolerance • PCSK9 inhibitor may be considered
2016 ACC expert consensus (endorsed by the National Lipid Association)	Secondary prevention • Established clinical CVD Primary prevention • LDL—C ≥190 mg/dl (4.9 mmol/l) • Diabetes type 1 or 2 (age 40—75 years; LDL-C 70—189 mg/dl [1.8—4.8 mmol/l])	• Pooled Cohort Equations is recommended to estimate 10-year CVD	• ≥7.5% estimated 10-year fatal and nonfatal CVD risk and age 40—75 years • 5% to <7.5% 10-year fatal and nonfatal CVD risk on an individualized basis	• ≥50% LDL-C reduction, but may consider LDL-C target (<100 mg/dl [2.5 mmol/l] or <70 mg/dl [1.8 mmol/l], according to clinical situation)	• Consider nonstatin medication such as ezetimibe and PCSK9 inhibitor when patient is out of target despite maximal tolerated statin dose. (See Appendix 6.)
2013 ACC/AHA guidelines	Same as for 2016 ACC	Same as for 2016 ACC	Same as for 2016 ACC	• No LDL-C target. Treatment choice is based on percentage of LDL-C reduction.	• High-intensity statin therapy (lowers LDL—C on average, by approximately ≥50%) or moderate-intensity statin therapy (lowers LDL—C on average, by approximately 30% to <50%)
2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult	• Clinical atherosclerosis • Abdominal aortic aneurysm • Diabetes mellitus — Age ≥40 years — 15-year duration for age ≥30 years (type 1) — Microvascular disease	• Modified FRS	• All individuals at high risk (>20% risk) • Individuals at intermediate risk (modified FRS 10% to 19%) with: — LDL-C > 3.5 mmol/l • LDL-C < 3.5 mmol/l but with apo B 1.2 g/l	• In high-risk patients, a target of LDL-C level consistently <2.0 mmol/l or >50% reduction of LDL-C • -Alternative target variables are apo B <0.8 g/l or	• Statin as first option (treat to target approach) • Ezetimibe as first-line add-on therapy (bile acid sequestrants as an alternative) • PCSK9 inhibitors as second-line therapy

(continued)

TABLE 1. Continued

Guideline	Groups to Be Treated Without Requiring Risk Stratification	Risk Assessment Tool for Others	Threshold for Treatment	Treatment Target	Pharmacological Treatment Options
	• Chronic kidney disease (age ≥50 years) • Estimated GFR <60 ml/min/1.73 m^2 or ACR >3 mg/mmol — LDL-C >5.0 mmol/l		or non—HDL-C 4.3 mmol/l or in men ≥50 years and women ≥60 years with >1 CV risk factor	non—HDL-C <2.6 mmol/l • For patients with LDL-C >5.0 mmol/l, a >50% reduction of LDL-C is indicated • On the basis of the IMPROVE-IT trial, for those with a recent acute coronary syndrome and established coronary disease consideration should be given to more aggressive targets (LDL-C <1.8 mmol/l or >50% reduction)	
2015 NICE guidelines Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of CVD	• **Chronic kidney disease with an estimated GFR <60 ml/min/1.73 m^2 and/or albuminuria** • **People with CVD** • **Adults with type 1 diabetes who:** — **are older than 40 years** — **have had diabetes for >10 years or** — **have established nephropathy or** — **have other CVD risk factors or FH**	• **QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people ≤84 years**	• **>10% 10-year risk of developing fatal and nonfatal CVD**	• **No lipid target**	• **Atorvastatin 20 or 80 mg, according to risk**
2016 China guidelines on the prevention and treatment of dyslipidemia in Chinese adults	Very high risk: • Patients with established atherosclerotic CVD High risk: • LDL-C ≥4.9 mmol/l (or TC ≥7.2 mmol/l) • Patients with diabetes, age ≥40 years and LDL-C ≥1.8 mmol/l and	• Risk assessment equations based on (CMCS) • Estimate 10-year cumulative risk of a first fatal or nonfatal atherosclerotic events • Estimate lifetime risk of a first fatal or nonfatal atherosclerotic event for	• 10-year risk of fatal or nonfatal atherosclerotic events ≥10% • 10-year risk 5% to 9% but lifetime risk ≥30% and age 35—55 years	• Low- and moderate-risk LDL-C <3.4 mmol/l Non—HDL-C < 4.1 mmol/l • High-risk LDL-C <2.6 mmol/l	• Statins • Consider combination treatment like Ezetimibe when z is out of target despite titration of statin doses, or statin intolerance

	<4.9 mmol/l (or TC ≥ 3.1 mmol/l and <7.2 mmol/l)	individual aged 35–55 years		Non-HDL-C <3.4 mmol/l • Very high-risk LDL-C<1.8 mmol/l Non–HDL-C <2.6 mmol/l	
2013 Brazilian guidelines on dyslipidemias and prevention of atherosclerosis	• **Established atherosclerotic CVD** • **Extensive subclinical atherosclerosis** • **Diabetes (types 1 and 2)** • **Chronic kidney disease** • **FH**	• **General Cardiovascular Risk Score (from Framingham Heart Study)**	• **> 10% for women** • **>20% for men**	• **LDL-C <70 mg/dl for high-risk patients** • **LDL-C <100 mg/dl for intermediate- risk patients**	• **Statin in the maximal tolerated dose as first option, but ezetimibe may be added to reach the goal**
2012 South African dyslipidemia guidelines consensus statement	• Established atherosclerotic disease • Type 2 diabetes • Type 1 diabetes with microalbuminuria or proteinuria • Genetic dyslipidemia (e.g., FH) • Chronic kidney disease (GFR < 60 ml/min/ 1.73 m^2)	• FRS	• Immediate drug treatment for all very high-risk patients (>30%). In this category, even if LDL-C <1.8 mmol/l, drug treatment may be considered. • Immediate drug treatment for all high-risk patients (15% to 30%) if LDL-C ≥2.5 mmol/l. If <2.5 mmol/l, drug intervention may be considered. • Consider drug intervention if uncontrolled in the following situation: moderate risk (3% to 15%) and LDL-C ≥2.5 mmol/l; low risk (<3%) with LDL-C ≥5.0 mmol/l	• Low and moderate risk: <3.0 mmol/l • High risk: <2.5 mmol/l • Very high risk: <1.8 mmol/l	• Statins as first option, with potency of treatment depending on target • (Rosuvastatin 40 mg or atorvastatin 80 mg for very high risk) patients (goal <1.8 mmol/l)
2007 WHO guidelines for assessment and management of cardiovascular risk	• **Patients with established angina pectoris, coronary heart disease, myocardial infarction, transient ischemic attacks, stroke, or peripheral vascular disease, or who have had coronary revascularization or carotid endarterectomy**	**WHO/ISH risk prediction charts specific for different regions, considering whether measurement of cholesterol level is possible or not**	• **All individuals with a 10-year fatal and nonfatal risk of cardiovascular event >30%** • **Adults >40 years with 10-year risk of cardiovascular event 20% to 30% and with persistently high serum cholesterol**	• **Lowering LDL-C (to <3.0 mmol/l or 115 mg/dl). In very high-risk patients, a TC <4.0 mmol/l (152 mg/dl) and LDL-C < 2.0 mmol/l (77 mg/dl), or a reduction of 25% in TC and 30% in LDL-C, whichever achieves the lower absolute**	**Statins**

(continued)

TABLE 1. Continued

Guideline	Groups to Be Treated Without Requiring Risk Stratification	Risk Assessment Tool for Others	Threshold for Treatment	Treatment Target	Pharmacological Treatment Options
	• Individuals without established CVD who have TC ≥8 mmol/l (320 mg/dl) or • LDL-C ≥6 mmol/l (240 mg/dl) or • TC/HDL-C ratio >8; • Patients with type 2 diabetes, >40 years of age		(>5.0 mmol/l or 193 mg/dl), and/or LDL-C >3.0 mmol/l or 115 mg/dl, despite a lipid-lowering diet should be given a statin.	level, may be desirable goals	

ACC, American College of Cardiology; ACR, albumin to creatinine ratio; AHA, American Heart Association; apo B, apolipoprotein B; CMCS, Chinese Multiprovincial Cohort Study; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerotic Society; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; FRS, Framingham Risk Score; GFR, glomerular filtration rate; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; ISH, International Society for Hypertension; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, Systemic Coronary Risk Evaluation; TC, total cholesterol; WHO, World Health Organization.
Country-specific decisions on who to treat should be guided by national policy, local risk profiles, and available resources.

example, one-half of cardiovascular events in men and one-third of all cardiovascular events in women in the United States occur before age 65 years [43]. Given the dominance of age and sex in the calculation of risk, few of these individuals would qualify for preventive therapy according to the Total Risk Score approach. Risk calculated according the Total Risk Approach only becomes substantial in men after age 60 and in women after age 70 years. Therefore, relatively few men or women cross the risk threshold before these ages. The result is that primary prevention based on exceeding the risk threshold is uncommon before these ages but extremely common thereafter [44]. Missed opportunities to treat younger individuals who would benefit more even within the first decade from therapy are likely to be even more common in regions where coronary disease rates increase earlier in life, such as has been suggested in South East Asia. The Total Risk Approach also fails to take account of the treatment benefits for some young people who have a low total risk based on their age, but are at high lifetime risk and would benefit significantly from early treatment that is sustained over many years. An alternative approach that has emerged is the Benefit Model of Cardiovascular Prevention [45]. The Benefit model incorporates the baseline risk information from the Total Risk Approach but also adds the estimated benefit to that individual from the decrease in risk expected from statin therapy. This estimate is based on their baseline level of LDL-C or apo B and the potency of the statin that is used [45]. The Benefit model expands the number who would be eligible for statin primary prevention therapy by including younger individuals with higher levels of LDL-C or apo B, thus preventing more CVD events over a lifetime. This approach will address some of the criticisms of the Total Risk Approach but to the best of our knowledge it has not yet been implemented, and an Individual Benefit Approach calculator is currently being developed to make individual recommendations.

Statin therapy. The effectiveness of statin therapy for reducing CVD risk is supported by very strong evidence. The Cholesterol Treatment Trialists' Collaboration established that a 1 mmol/l (38.66 mg/dl) reduction in LDL-C is associated with a 22% relative risk reduction in major vascular events, a 14% reduction in risk of death from vascular causes, and a 10% reduction in overall risk of death [46]. A Cochrane review of the effectiveness of statins for primary prevention of CVD events found that statins reduce all-cause mortality, fatal and nonfatal events, and the need for revascularization [47]. The efficacy and safety of statins is also supported by a recent review of evidence from randomized controlled trials, which highlighted the benefits of statins in almost all subgroups irrespective of primary or secondary prevention, lipid levels, sex, risk level, and other subgroups [48]. The effect of treatment with statins on reductions in major vascular events and LDL-C reduction in randomized trials is shown in Figure 2.

After assessing CVD risk, the recommended threshold for initiating statin treatment varies among available guidelines and these are outlined in Table 1. Countries should look to their national or regional guidelines to guide initiation of statin therapy and these should be informed by the resources available and the effectiveness of treatment in that setting. As an example, based on the Total Risk Approach, WHO recommends that the 10-year CVD risk threshold for determining whether to initiate statin therapy should be 20% in high-resource, 30% in medium-resource, and 40% in low-resource settings. However, these risk thresholds were set many years ago and do not reflect current scientific evidence for CVD risk reduction with statins or the availability of generics for this class of drug. From the more recent evidence from HIC, the ACC/AHA and the National Institute for Health and Care Excellence (NICE) in the United Kingdom have both recommend lower 10-year risk thresholds (≥7.5% and ≥10%, respectively) [28,49]. It is likely that given the decreasing cost of statins and the updated data on effectiveness and safety [29], global risk thresholds for treatment will also be lowered. This is nevertheless a matter for national policy because of the costs of detecting those at any given risk threshold in a given population and the costs of all treatments, including statins, to reduce total CVD risk. For those diagnosed with FH (FH detection is described in the Familial Hypercholesterolemia section), or who are asymptomatic but at very high risk for other reasons, statin therapy should be initiated as soon as possible.

There are several approaches recommended in guidelines regarding choice of statin, statin dosage, and whether or not to achieve targeted reductions in LDL-C, the latter depending on resources being available for follow-up monitoring. Monitoring of patient response to treatment is desirable, especially in cases when LDL-C is high to begin with (>190 mg/dl), for example, and is also important given the high interindividual variation in the effect of statins on LDL-C and other atherogenic lipoproteins such as non−HDL-C. Without monitoring the effectiveness of the chosen statin and dose, the effect will not be known [50]. Therefore, the impact of treatment on LDL-C levels should be monitored after 3 months to make sure dosage is appropriate, and dose titration may be necessary if the intention is to achieve a targeted reduction (percentage of LDL-C reduction or LDL-C goal). In addition to LDL-C as a target, non−HDL-C is also recommended in some guidelines, and this may be more appropriate in countries where the prevalence of insulin resistance and atherogenic lipoproteins are high. Targets recommended by different guidelines are included in Table 1. Although monitoring is desirable, it may not be feasible in resource-limited settings. In such settings when monitoring is not feasible, a low- to moderate-intensity dose of statin may be used for primary prevention. The NICE and AHA/ACC guidelines do not recommend

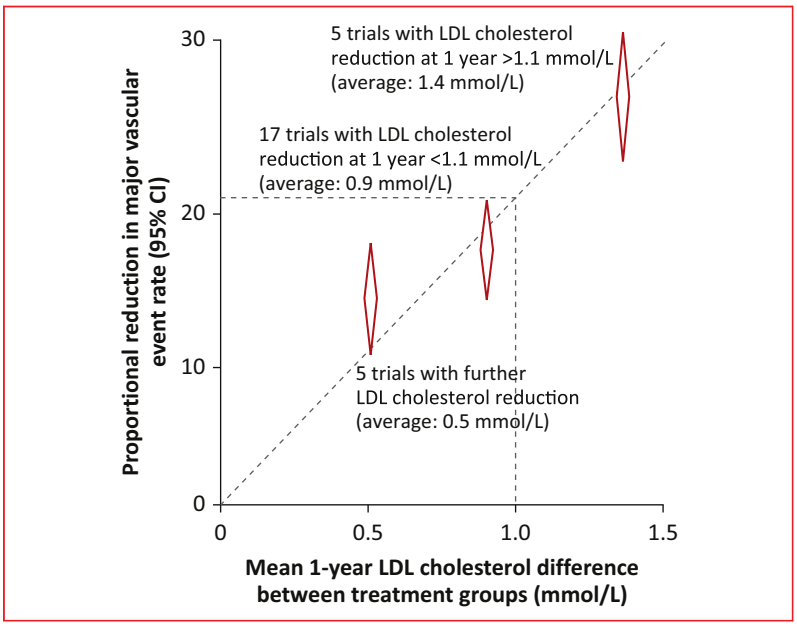

FIGURE 2. Proportional major vascular event reductions versus absolute low-density lipoprotein cholesterol (LDL-C) reductions in randomized trials of routine statin therapy versus no routine statin use and of more intensive versus less intensive regimens. Reproduced with permission from Collins et al. [48]. CI, confidence interval.

targeted reductions in LDL-C but rather the choice of high-, moderate-, or low-intensity statins depending on the patients' level of risk. A simpler approach recently validated in the HOPE-3 (Heart Outcomes Prevention Evaluation 3) trial [29], is to provide a moderate-intensity statin treatment (without dose adjustments or lipid targets) to patients at intermediate risk (i.e., expected risk of 1% per year or 10% over 10 years, without a formal assessment of risk but defined by the presence of other cardiovascular risk factors) [29].

Even where monitoring of cholesterol levels is not feasible, patients should be followed to monitor for any side effects of statin treatment. Although most statin-induced myopathy (muscle weakness and raised concentrations of creatine kinase) occurs in the first 3 months after treatment initiation, delayed onset symptoms are possible. For patients who do not respond, or do not tolerate high-dose statins, lower doses of statins or non-statin treatments can be considered, including ezetimibe and resins. Recent findings from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial show that the new class of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors) is effective in lowering LDL-C and reducing risk of major cardiovascular events in patients with established CVD who are already taking an optimized regimen of lipid-lowering therapy [51] and may be suitable for such patients if cost-effective [52].

A description of nonstatin options and current evidence regarding the effectiveness of each are included in Appendix 6 [53-58]. Regardless of whether statin or nonstatin treatment is selected, drug treatment of cholesterol is life-long and must be accompanied by advice and support toward lifestyle modifications such as maintaining a healthy diet (Mediterranean diet), exercising regularly, and refraining from smoking.

Primary prevention pathway. Figure 3 outlines the pathway for primary prevention of CVD, including treatment of cholesterol. WHF recommendations for addressing other risk factors such as raised blood pressure or tobacco are outlined in previous WHF roadmaps [4,5].

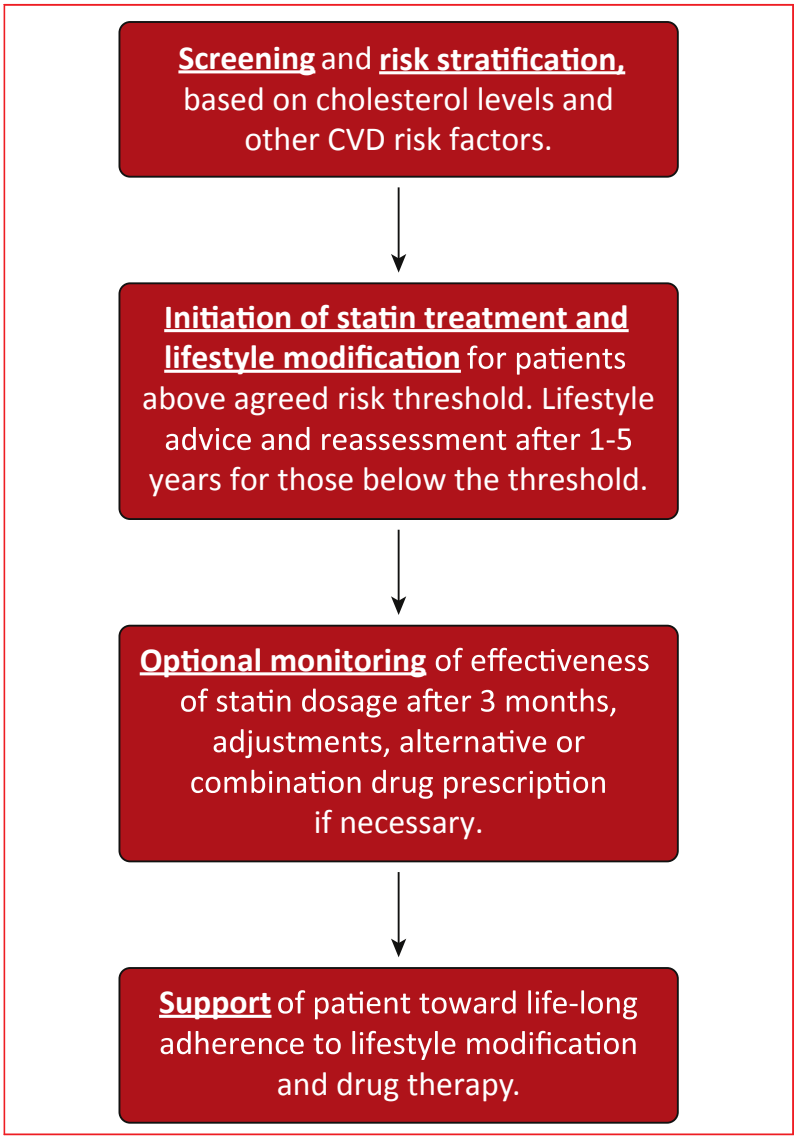

FIGURE 3. Patient pathway of cholesterol treatment for primary prevention of cardiovascular disease (CVD).

Secondary prevention

As mentioned, those with established CVD do not require risk stratification to determine treatment initiation. All patients who have had a CVD event (i.e., MI or ischemic stroke) should be considered at risk of recurring CVD event, regardless of LDL-C levels, and should be treated with statins. There is clear evidence that reducing LDL-C levels among MI and ischemic stroke patients improves patients' outcomes and reduces mortality [18,46] and most major national cardiology societies and international health organization guidelines recommend including statins as part of an evidence-based strategy for secondary prevention of CVD (along with aspirin and other antiplatelet therapies, angiotensin-converting enzyme inhibitors, and beta blockers [post MI]) [59-61]. The WHF Roadmap for secondary prevention of CVD [3] highlights the role of statin therapy as an integral part of effective secondary prevention of CVD and thus vital to achieving targets for reducing CVD mortality globally.

The patient pathway for treatment of cholesterol as part of a secondary prevention of CVD strategy is outlined in Figure 4. In secondary prevention, patients should be put on treatment with a high-intensity statin (atorvastatin or rosuvastatin) at an appropriate dose. As with primary prevention, while monitoring of treatment is desirable, in may not be feasible in some resource-limited settings. When monitoring is not feasible for secondary prevention, a high (or intermediate) dose of statin may be used. Depending on available resources for follow-up, statin dosage should either be maintained without change, or adjusted according to targeted reductions in LDL-C (or TC if more feasible to measure), and the effect of treatment should continue to be monitored after 3 months to ensure dosage is appropriate and adherence to treatment is maintained. In secondary prevention of CVD, treatment with statins should be continued for life. Patients will also require prevention and rehabilitation programs for lifestyle modification and for the effective management of all other risk factors, including adherence to all cardioprotective medications.

Familial hypercholesterolemia

Although the onset of atherothrombotic events most often takes place when individuals are 40 years of age or older, early exposure to hyperlipidemic environments may lead to lipid deposition in artery walls very early in life, leading to premature cardiovascular risk. This is what occurs in individuals with FH, a genetically inherited defect that impedes proper LDL clearance, leading to accumulation of LDL in the blood [62,63]. The prevalence of FH has generally been thought to be around 1:500, but newer studies show that the prevalence may be as high as 1:200 in several populations [62,64]. The prevalence of FH is as high as 1:70 in populations with founder effects [65].

One set of criteria for diagnosing FH, called the Dutch Clinic Network Criteria, are shown in Table 2 [62,63].

Other commonly used criteria for diagnosis of FH are those from the Simon Broome register [66]. FH leads to increased risk of CVD, particularly CAD.

Diagnosis of FH is primarily based on clinical assessment. Clinical diagnosis can be supported by genetic testing where resources allow, but the nonavailability of genetic testing should not preclude the detection and management of FH. FH should be suspected when untreated LDL-C or non−HDL-C levels are at or above LDL-C =190 mg/dl (4.9 mmol/l) or non−HDL-C = 220 mg/dl (5.7 mmol/l) for those aged 20+ and LDL-C = 160 mg/dl (4.1 mmol/l) or non−HDL-C = 190 mg/dl (4.9 mmol/l) for those aged <20 years. When FH is diagnosed by specific clinical criteria, cascade screening of all first-degree relatives is the most cost-effective approach to detection of further FH cases [67]. Children with at least 1 parent with FH have a 50% chance of inheriting the condition [68], and therefore such children and young people require genetic testing as well as intensive lifestyle intervention. While some experts recommend universal screening for FH, in particular among children [69], the cost-effectiveness of this approach is not clear [69-71].

This risk of CVD associated with FH can be reduced with treatment with statins and lifestyle modifications. FH patients should be treated with a high-intensity statin at maximum tolerable dose, ezetimibe, and, if appropriate, bile acid binding resins to reach LDL-C of <3.5 mmol/l (<135 mg/dl) for children, <2.5 mmol/l (<100 mg/dl) for adults, and <1.8 mmol/l (<70 mg/dl) for adults with known CVD or diabetes [63]. For patients whose cholesterol levels do not respond sufficiently to treatment with statins, other treatment options have been limited in the past. However, new therapies such as PCSK9 inhibitors should be

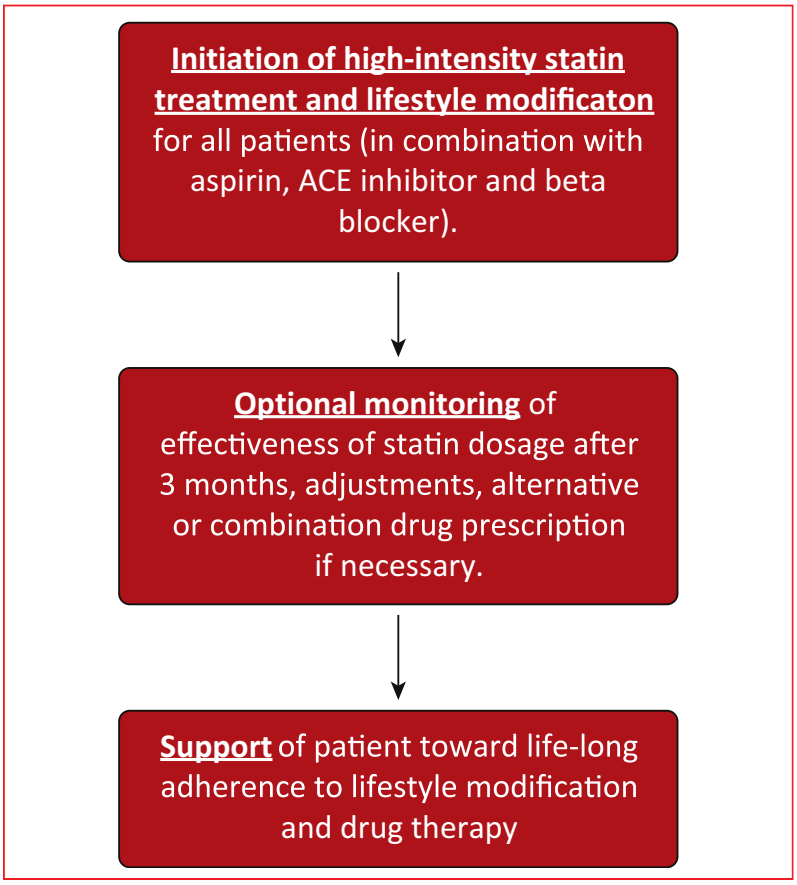

FIGURE 4. Patient pathway of cholesterol treatment for secondary prevention of cardiovascular disease (CVD). ACE, angiotensin-converting enzyme.

TABLE 2. Dutch Clinic Network Criteria for clinical diagnosis of FH [62,63]

	Criteria	Score
Family history	**First-degree relative known with premature CAD or first-degree relative with LDL-C >95th centile**	**1**
	First-degree relative with tendon xanthoma and/or children <18 years with LDL-C >95th centile	**2**
Clinical history	Patient has premature CAD (male before 55, female before 60 years of age)	2
	Patient has premature cerebral/peripheral vascular disease	1
Physical examination	**Tendon xanthoma**	**6**
	Arcus cornealis <45 years	**4**
LDL-C	>8.5 mmol/l (>∼330 mg/dl)	8
	6.5−8.4 mmol/l (∼250−329 mg/dl)	5
	5.0−6.4 mmol/l (∼190−249 mg/dl)	3
	4.0−4.9 mmol/l (∼155−189 mg/dl)	1
Diagnosis		
Definite FH		**>8**
Probable FH		**6−8**
Possible FH		**3−5**
No diagnosis		**<3**

CAD, coronary artery disease; other abbreviations as in Table 1.

considered for all FH patients. Adoption of these therapies in LMIC will depend on their affordability. While there is a strong body of evidence showing the cost-effectiveness of statin therapy in adults with FH, more research is needed on the efficacy and safety of newly emerging drug therapies [72]. The ideal patient pathway for detecting, treating, and managing FH is outlined in Figure 5.

KNOWLEDGE-PRACTICE GAPS

Despite strong evidence of the importance of cholesterol levels in primary or secondary prevention of CVD, and the effectiveness of statin therapy for cholesterol lowering and reduction of CVD risk, gaps exist in the detection, treatment, and management of high cholesterol globally.

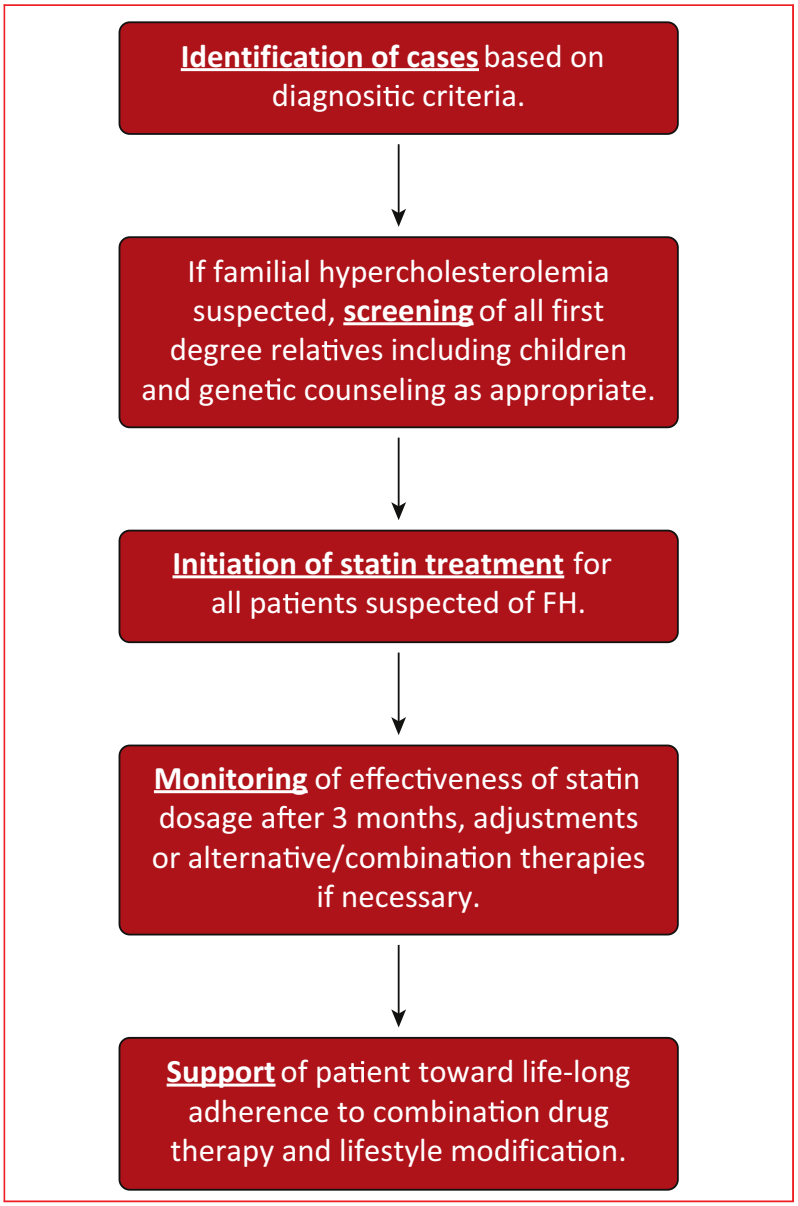

FIGURE 5. Patient pathway of cholesterol treatment for familial hypercholesterolemia (FH).

Primary prevention

Primary prevention of CVD using a Total Risk Approach requires detection and management of high cholesterol, but in many LMIC, CVD risk factors in general often go undetected [73]. Levels of undetected CVD risk factors are higher in poorer countries [74]; however, knowledge-practice gaps in primary prevention of CVD are not restricted to LMIC. Research has revealed high rates of undiagnosed high cholesterol in countries at all stages of development. A study of 8 countries showed high levels of undiagnosed high cholesterol in both HIC and LMIC, although levels varied between countries from, for example, 16% in the United States to 78% in Thailand. The proportion of those diagnosed who were being treated also varied between countries, ranging from 47% in Japan to 91% in Thailand, as did the proportion of those treated whose cholesterol levels were controlled, from only 4% in Germany to 58% in Mexico [75]. Within countries, levels of undetected high cholesterol and other CVD risk factors are higher among poorer populations within countries, as these populations are least likely to be informed about CVD risk and make contact with a health professional [76,77]. For example, the Brazilian Longitudinal Study of Adult Health found that while levels of awareness, treatment, and control of high LDL-C are low overall in Brazil (58.1%, 42.3%, and 58.3%, respectively), they are particularly so among men, individuals of mixed race and blacks, the poorer and less educated, and those without private health insurance [78].

Secondary prevention

Various national and international guidelines provide evidence-based recommendations regarding the inclusion of statins in an effective secondary CVD prevention strategy and include suggested treatment targets. However, despite international consensus on the effectiveness of secondary prevention of CVD with a drug regimen including statins, major evidence-practice gaps exist globally. The EUROASPIRE (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) study, a study of 24 HIC and MIC in Europe found that, among those with CAD on lipid-lowering medication, prevalence of LDL-C <2.5 mmol/l (100 mg/dl) was approximately 65% among men and 55% among women, and prevalence of LDL-C <1.8 mmol/l (70 mg/dl) was only 22% among men and 17% among women. Roughly 13% of patients were not on lipid-lowering medication, suggesting gaps in management of cholesterol treatment [79]. The PURE (Prospective Urban and Rural Epidemiological) study also found a low average level of treatment of CVD patients with statins globally (14.6%). This level was markedly lower in LIC (3.3%) than in HIC (66.5%) [80].

Familial hypercholesterolemia

While the prevalence of potential FH among coronary patients is high [81], FH is underdetected and undertreated worldwide [37,69]. Earlier work estimated that 80% of FH patients in Western countries go undetected [82], and a recent consensus paper estimated that in Mexico, Brazil, and Chile, as well as in other HIC, <1% of FH cases are diagnosed [63]. This figure is likely to be as high if not higher in LMIC, but sufficient data do not exist. To effectively address the care gap in FH in LMIC, more research is needed on the extent of this care gap and specific barriers to achieving effective detection and treatment of FH.

EXISTING ROADBLOCKS TO ADDRESSING CVD RISK ASSOCIATED WITH CHOLESTEROL

The significant variation in levels of awareness, treatment, and control of cholesterol among countries and regions highlights the essential role of country health systems in implementing known cost-effective strategies for the reduction of CVD risk. As emphasized by a recent systematic review of research on barriers to effective secondary prevention of CVD [83], high-quality evidence of health system barriers and CVD in LMIC is lacking. More research is needed to inform appropriate policy responses is these settings. Through consultation with an expert committee, composed of global experts in cholesterol management and health systems research in LMIC, we identified potential roadblocks to effective treatment of cholesterol for primary and secondary prevention of CVD and FH (Box 1). This is not intended to be an exhaustive list of barriers but aims to capture the main health system challenges that may be encountered in addressing cholesterol in LMIC. Many of these relate to detection, management, and treatment of other cardiovascular risk factors such as hypertension [5] or diseases, such as rheumatic heart disease [6]. Those that relate to cholesterol alone are italicized.

A main barrier to effective detection of CVD risk due to elevated cholesterol or FH is the absence of facilities and resources for cholesterol measurement. Figure 6 from WHO shows countries where facilities for testing blood samples are available at the primary health care level. Countries that do not have such facilities are predominantly in Sub-Saharan Africa or South and Southeast Asia, where distances to secondary or tertiary facilities with testing labs may be prohibitively long, acting as a major challenge to effective cholesterol screening of at-risk populations. Effective screening for cholesterol and initiation of treatment may also be compromised by the absence of clear national guidelines on who and how to screen for and treat increased CVD risk due to elevated cholesterol or FH. While not a LMIC, research from the United States also reported low rates of cholesterol screening among women of reproductive age (49% of women with no CHD risk factors, 52% of women with 1 risk factor, and 69% of women with CHD or CHD equivalent risk) and pointed to inconsistency in national recommendations as a possible cause [84].

In terms of uptake and adherence to lipid-modifying treatment, 2 major roadblocks are the low affordability and availability of statins. Data from 18 countries in the PURE study suggest that the 4 drugs required for

BOX 1. Roadblocks to effective detection, management, and treatment of cholesterol levels for primary and secondary prevention of CVD and patients with FH

Patient-level roadblocks
- **Low access to health facilities among poor or remote populations**
- ***Statins unaffordable for patients***
- ***Lack of awareness among patients regarding importance of adherence to statin treatment***
- ***Undue patient fear of side effects of statin treatment***
- **Infrequent access to follow-up or support for treatment adherence**
- ***Lack of awareness of FH and FH risk factors among general population***

Physician-level roadblocks
- **Lack of awareness among physicians about the importance of CVD risk screening and prevention**
- **Lack of education/training among physicians regarding treatment**
- **Poor capacity among physicians for monitoring treatment, especially with competing disease priorities**
- **Poor patient access to health professionals for follow-up and support toward adherence**
- ***Lack of awareness of FH and FH risk factors among physicians and general population***
- ***Low capacity among physicians for diagnosing and managing statin treatment among FH patients***

Health system-level roadblocks
- **Lack of screening programs or suboptimal screening programs**
- ***Shortage of facilities for large-scale measurement of blood cholesterol levels, especially in rural areas***
- ***Environmental barriers to lifestyle modification (e.g., food insecurity, few options for physical activity, tobacco marketing)***
- **Multiple, complex (and sometimes contradictory) clinical guidelines**

Roadblocks that relate to cholesterol alone are italicized.
CVD, cardiovascular disease; FH, familial hypercholesterolemia.

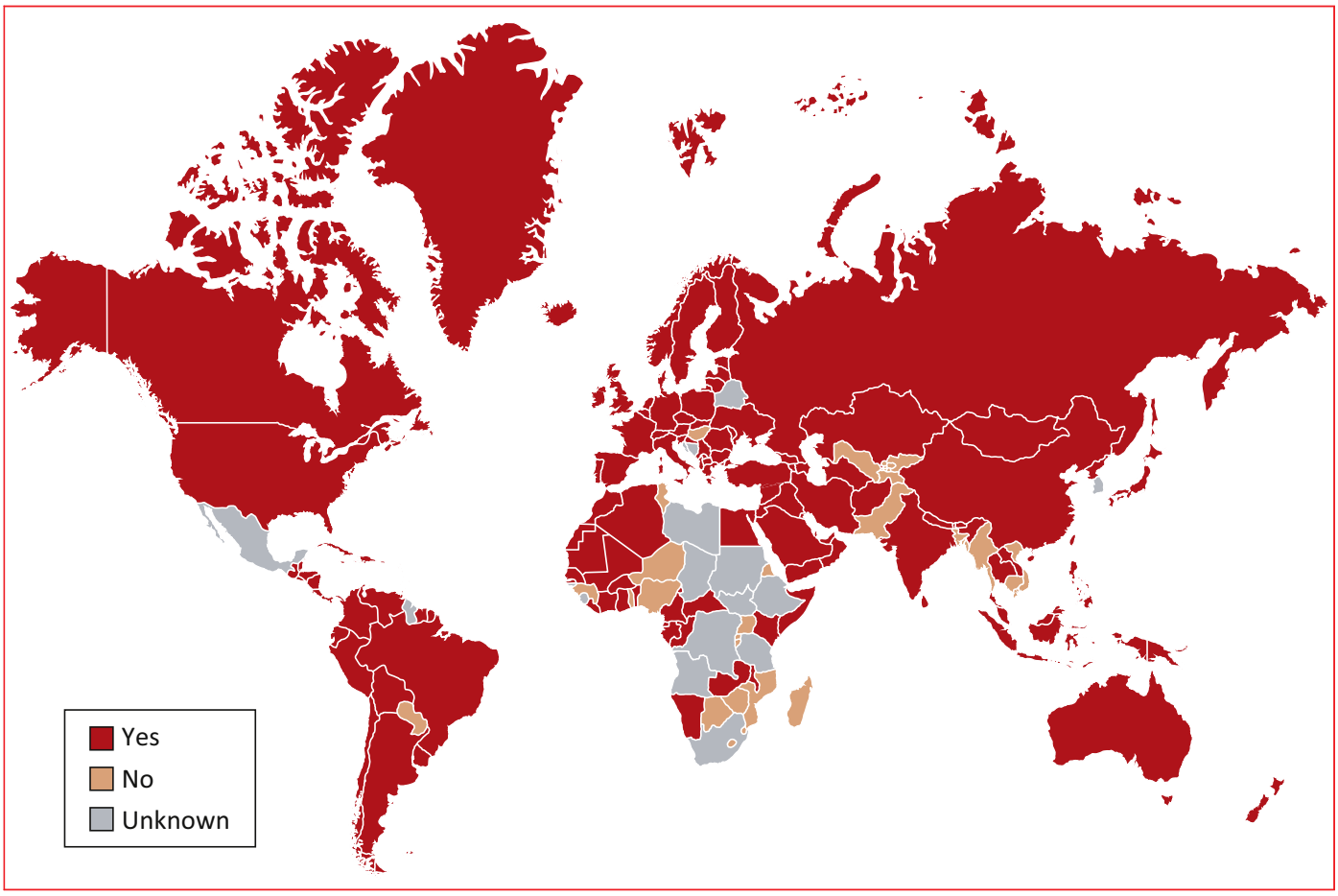

FIGURE 6. Countries with facilities for testing blood samples at the primary health care level, World Health Organization.

secondary prevention of CVD, including statins, are potentially unaffordable for 0.14% of households in HIC, 25% in upper MIC, 33% of lower MIC, and 60% in LIC. In communities in which all 4 medicines were available, patients were less likely to use medicines if the household potentially could not afford them (odds ratio = 0.16; 95% confidence interval: 0.04 to 0.55) [85]. Where copayments are required to purchase drugs, adherence is also likely to be negatively affected [86]. Equally as important as affordability is availability of medications. Whereas statins are officially on the essential medicine list of most countries, they are not always widely available. Although the drugs for secondary prevention of CVD are licensed and distributed in all the countries of the PURE study, in both branded and generic forms, they were found less likely to be stocked by retailers based in rural and poor communities [85]. Even when statins are affordable and available, roadblocks exist to effective adherence to statin treatment such as lack of health literacy or awareness of the importance of treatment adherence [87-89]. A recent study commissioned by the British Heart Foundation to investigate adherence to statins specifically found that media influence, fear of side effects, skepticism of medicine, and lack of confidence in doctors act as barriers to statin adherence among patients, which in turn affected doctors' comfort with prescribing statins. Unfavorable news reports, specifically, caused 5% of patients to discontinue statins, of whom nearly one-third were at high risk of CVD [90,91]. Finally, with respect to FH, although there is no published research on the roadblocks that are specific to the effective detection and treatment of FH, the documented high prevalence of undetected FH in countries at all levels of development points to very low physician and population awareness of FH and FH risk factors.

POTENTIAL SOLUTIONS

Point-of-care testing

Addressing the problem of poor access to laboratory facilities for cholesterol testing, research has shown that non-laboratory-based CVD risk score charts (i.e., risk score excluding cholesterol levels but including other CVD risk factors) perform well when predicting overall CVD risk [15]. However, it is important to remember that non-laboratory-based methods will fail to identify risk in those with FH who may be lean, normotensive, and have

no other risk factors. To improve identification of those at risk of CVD due to elevated cholesterol in resource-limited settings where lab facilities are scarce, point of care (PoC) testing devices have emerged as a potential solution. PoC testing is conducted at or near the site of patient care and can greatly reduce the cost and delays associated with laboratory tests. PoC devices now exist for a range of medical conditions and diseases [92]. For cholesterol, specifically, PoC devices that take a finger prick blood sample have been shown to produce accurate and reproducible results [93-95] and may also reduce dependence on highly trained health professionals for cholesterol testing [95]. The appropriateness of these devices for cholesterol testing in different resource-limited settings needs to be formally evaluated [92].

Availability and affordability of medicines

While PoC testing devices may improve detection of those at risk of CVD due to elevated cholesterol, to treat this risk effectively, lipid-lowering medications must be affordable. Strategies that have been advocated to improve the affordability of medicines include eliminating duties and taxes on medicines and monitoring to ensure these savings are passed on to patients [96,97], the provision of free or significantly subsidized medicines, and the use of generic versus innovator brand drugs [98,99]. WHO has recommended pooled procurement of drugs to reduce prices [99]. This may involve pooling of multiple hospitals, centralized procurement at the state or country level, such as was done in Delhi State in India, or even international pooling such as has been practiced in the Maghreb countries, Eastern Caribbean countries, and Gulf States [99].

South Africa provides one example where government has employed some of these strategies to achieve "access to quality, affordable medicines" for all, which it has declared a right [100]. It is important to note though that these strategies must be accompanied by efforts to inform physicians and consumers regarding the quality of free or generic medicines, as these medicines may be perceived to be of lower quality or less effective than brand name products [100]. Equally important is to ensure that these medicines are in stock at even remote pharmacies and health centers. While South Africa has made large strides in improving the affordability of essential medicines, stock outages of these medicines are common, leading to nonadherence or long

BOX 2. Potential solutions to address roadblocks in the screening, treatment initiation and long-term management of cholesterol

Screening and risk stratification

- **Campaigns to raise awareness among health professionals and the public of the importance of screening for elevated cholesterol and possible FH**
- **Development of simplified national guidelines for whom and how to screen for CVD risk using cholesterol measurement**
- **Adaptation of risk score charts to ensure appropriateness for specific populations**
- **Point of care testing with inexpensive and easy to use technologies (e.g., cholesterol test strips)**
- **Risk stratification by trained community health workers, using non–lab-based risk scores where necessary, to improve screening rates and reduce workload of highly trained health professionals**

Initiation of treatment for cholesterol management

- **Development of simplified guidelines on whom and how to treat CVD risk through cholesterol management (e.g., clear indications for low-, moderate-, and high-dose statins; all secondary prevention patients prescribed statins but primary prevention based on local and personal resources/affordability)**
- **Continuing medical education for general practitioners and nonlipid specialists to improve skills and confidence in prescribing statin treatment, including for FH**
- **Campaigns to provide balanced information to public and health professionals of the safety and efficacy of cholesterol treatment with statins**
- **Limit number of available statins to avoid misconceptions surrounding dose and cholesterol-lowering efficacy**
- **Engage the patient in treatment initiation decisions (shared-decision making)**

Life-long adherence to treatment for cholesterol management

- **Ensure affordability of statin and nonstatin therapies through free or subsidized drug provision, eliminating taxes on pharmaceuticals**
- **Ensure availability of cholesterol management therapies in pharmacies and health facilities through local generic drug manufacture, monitoring stock outages**
- **Reduce wait times for repeat prescriptions by increasing supply dispensed to patient at each visit**
- **Explore novel interventions using text messaging to remind and support patients toward treatment adherence**
- **Engage pharmacists and nonphysician health workers in patient support and counseling for adherence to drug therapy**
- **Explore use of polypill (combination pill including aspirin, a beta-blocker, a statin, and an ACE inhibitor) among certain high-risk groups (e.g., post-MI, diabetics)**

ACE, angiotensin-converting enzyme; MI, myocardial infarction; other abbreviations as in Table 1.

wait times for medicines at facilities that do have stock. For example, a 2015 report found that over 1 in 3 facilities experienced stock outages of antiretroviral or tuberculosis medicines in the 3 months preceding contact (an increase from 2014 figures) [101]. A mix of private and public drug supply, including private sector involvement in decentralized storage and distribution, has been identified as crucial to ensuring continuous availability of these medicines, but the precise solutions for addressing drug supply will depend on specific contexts [94].

Adherence support

Even when drugs are available and affordable however, long-term and persistent adherence to drug treatment must be addressed to ensure the effective reduction of CVD risk. This is especially important in patients with CVD or CVD risk factor conditions such as elevated cholesterol, who may not have symptoms and therefore forget to take medications or feel it is unnecessary. Adherence to statins is a problem not only in LIC, but worldwide. A recent Cochrane review of interventions to improve adherence to lipid-lowering medication concluded that intensified patient care that includes reminders (e.g., calendar, text message, or phone call reminders) and patient education by health care professionals can improve adherence. Novel interventions that use text messaging to remind patients to take their hypertension medication are currently being tested in South Africa [102] and will provide further important insights toward improving patient adherence to chronic medication for CVD prevention in low-resource settings. The applicability of these interventions to different LMIC settings needs to be assessed.

This discussion outlines only some of the potential solutions for addressing roadblocks to effective detection, treatment, and management of cholesterol-related CVD risk. Box 2 outlines further potential solutions, based on consultation with experts in cholesterol management and health systems in low-resource settings. These have been grouped according to the corresponding step on the patient pathway: screening and risk stratification; initiation of treatment for cholesterol management; and life-long adherence to treatment for cholesterol management. As with the roadblocks, this list of potential solutions is not intended to be exhaustive, and the effectiveness and feasibility of these in specific LMIC settings is not yet known. Any potential solution would have to be adapted to and tested in local contexts. Many of these interventions—for example, those that employ text message medication reminders or nonphysician health worker support—may simultaneously address detection, treatment, and management of other cardiovascular conditions such as hypertension [5] or atrial fibrillation [7], providing opportunities for more integrated, efficient CVD care.

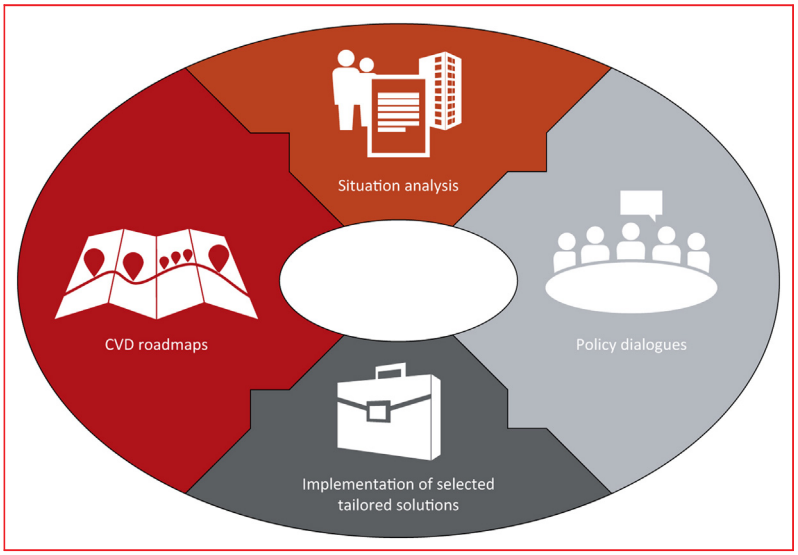

FIGURE 7. Adapting the World Heart Federation (WHF) Roadmaps at the national level. Reproduced with permission from Perel et al. [103]. CVD, cardiovascular disease.

Adapting to national roadmaps

The WHF Roadmaps are essential tools to identify known effective interventions for the reduction of premature CVD mortality and to identify potential roadblocks to implementing these interventions. However, to be effective, they will need to be adapted to local contexts, identifying local roadblocks and local solutions. Previous Roadmaps have outlined steps for adapting these at the national level, which are depicted in Figure 7 [103].

Applying these steps to the context of cholesterol may include (1) convening a stakeholder coalition (ministries of health care and finance, health care and pharmaceutical industry, patient and caregiver interest groups [including FH patients and caregivers], health nongovernmental organizations, scientific societies, and academia) to work together on the following steps toward developing an adapted national Roadmap; (2) conducting a situation analysis of the local cardiovascular epidemiological profile (e.g., prevalence of CVD, average cholesterol levels, prevalence and treatment of elevated cholesterol and FH), relevant policies and health system arrangements that might affect cholesterol management (e.g., national screening guidelines, essential medicine lists, existence of laboratory capacities), and exploring through qualitative research the perceived roadblocks to effective detection and treatment experienced by local patients and health practitioners; (3) conducting policy dialogues with stakeholders from step (1) to identify feasible solutions that could be implemented to address the roadblocks identified in step (2), including estimated costs, effects, timelines, and resources required for implementation (based on international or local research); and (4) develop a plan for evaluating the proposed policies and interventions using concrete indicators to evaluate the impact of the new policies.

Many of the existing roadblocks (and potential solutions) are common to patients with hypertension and

secondary prevention and countries should tackle these issues jointly in a common "cardiovascular prevention" roadmap. WHF provides tools to facilitate these roadmap adaptation processes (available at the WHF Roadmap webpage) and in addition as the global convener on cardiovascular health provides the global forum to share experiences and lessons learned from around the globe on overcoming existing roadblocks and achieving the goal of reducing global premature cardiovascular mortality.

ACKNOWLEDGMENTS

The authors thank the World Heart Federation, Sanofi/Regeneron, and Amgen, as well as the World Heart Federation members and partners who provided feedback throughout the Roadmap development.

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APPENDIX

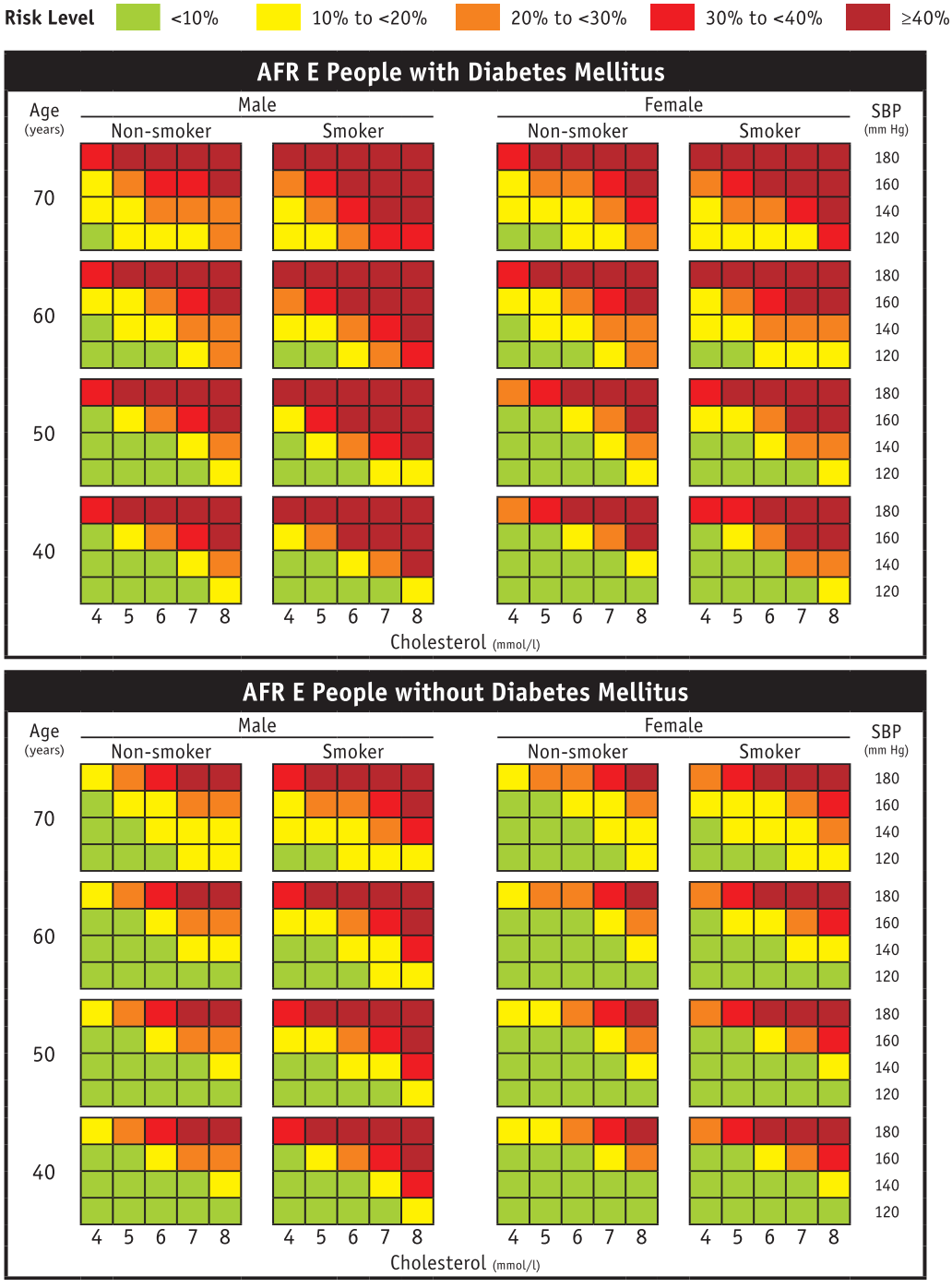
APPENDIX 1. Dietary guidelines from the European Society of Cardiology 2016 guidelines for the management of dyslipidemias [19]

	To Be Preferred	To Be Used With Moderation	To Be Chosen Occasionally in Limited Amounts
Cereals	**Whole grains**	**Refined bread, rice and pasta, biscuits, corn flakes**	**Pastries, muffins, pies, croissants**
Vegetables	Raw and cooked vegetables		Vegetables prepared in butter or cream
Legumes	**All (including soy and soy protein)**		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles	
Sweets and sweeteners	**Noncaloric sweeteners**	**Sucrose, honey, fructose, glucose, chocolate, candies**	**Cakes, ice creams**
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork, or veal; seafood; shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	**Skimmed milk and yogurt, egg white**	**Low fat milk, low fat cheese, and other milk products**	**Regular cheese, cream, egg yolk, whole milk, and yogurt**
Cooking fat and dressings	Vinegar, ketchup, mustard, fat-free dressing	Vegetable oils, soft margarines, salad dressing, mayonnaise	Butter, solid margarines, trans fats, palm and coconut oils, lard, bacon fat, dressings made with egg yolks
Nuts/seeds		**All**	**Coconut**
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

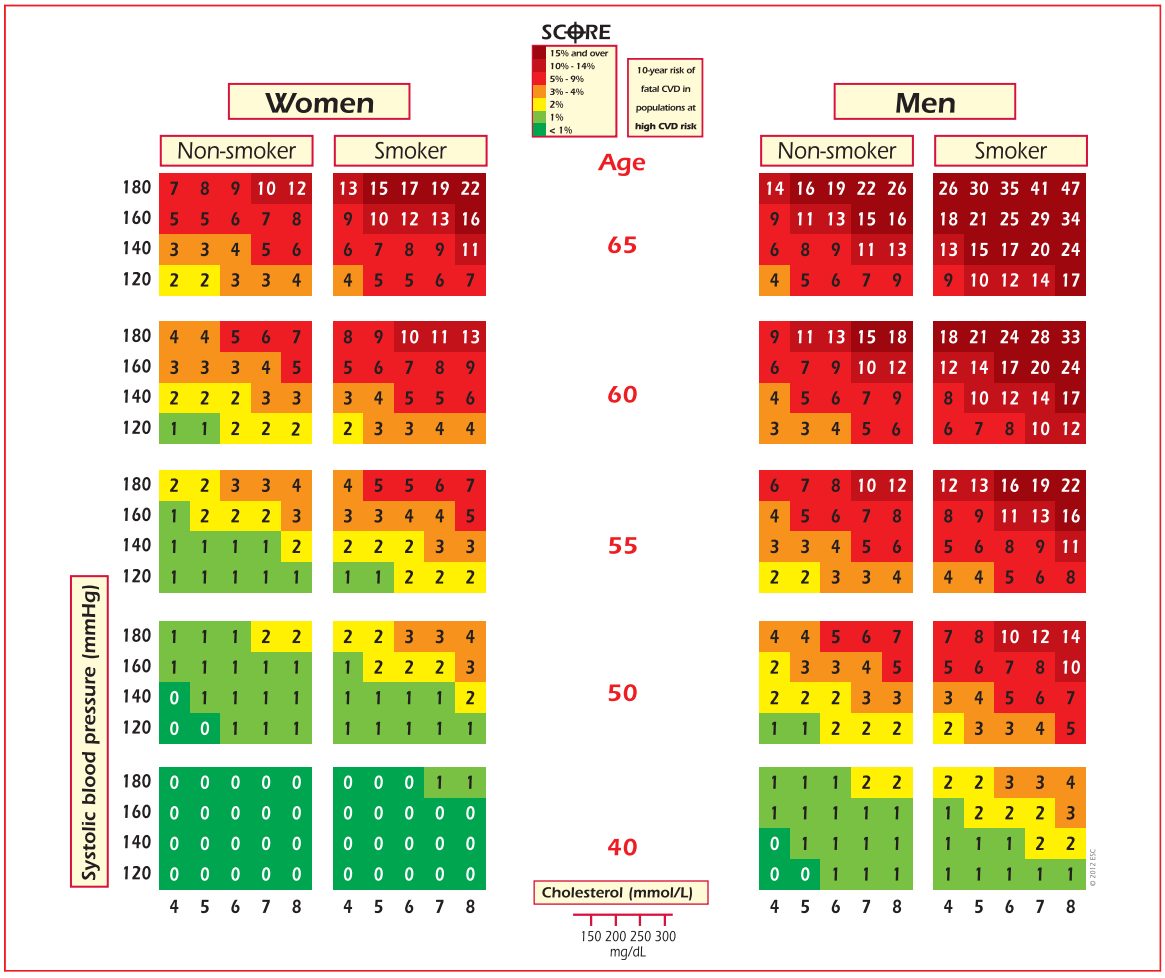
APPENDIX 2. Mediterranean style diet adapted to various regions of the world [25]

Mediterranean Style Dietary Pattern Component	Region-Specific Food Choices						
	East Asia	South Asia	Middle East	Africa	South America	North America	Europe
Fruits	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**
Vegetables (non-starchy)*	Chard, kale, bok choi, pak choi	Beetroot, spinach, cabbage, green leafy vegetables	Lettuce, spinach, carrots	Beetroot leaf, spinach, pumpkin leaf	Beetroot, spinach	Lettuce, kale, other dark leafy vegetables	Spinach, lettuce, cabbage, beetroot, chard
Legumes (beans, lentils)	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**
Whole grain cereals (brown rice, whole grain breads, maize, whole-wheat pasta)	Sorghum, millet	Chapathi, paratha, roti from whole grains	Whole grain bread	Oats, *sadza*† from sorghum, whole grain bread	Brown rice, whole grain bread	Whole grain bread (e.g., rye bread)	Whole grain bread (e.g., rye bread)
Fatty fish‡	**Any type (e.g., tuna, sardine, mackerel)**	**Any type (e.g., sardines, queen fish, mackerel)**	**Any type (e.g., tuna, trout)**	**Any type (e.g., tuna)**	**Any type (e.g., tuna, salmon, sardine, trout)**	**Any type (e.g., salmon, tuna, trout, herring sardines, mackerel)**	**Any type (e.g., salmon, tuna, trout, herring, mackerel)**
Reduce meats,§ increase meat alternatives	*Meats*: poultry, lean beef, pork without fat *Alternatives*: tofu, legumes (e.g., mung beans, adzuki beans, broad beans), seitan	Vegetarians should emphasize legumes and nuts	*Meats*: any type of poultry, lamb or beef without fat *Alternatives*: foul (fava beans), chickpeas (falafel), lentils, and pulses of all kinds	*Meats*: poultry, lean beef, pork without fat *Alternatives*: legumes in general and nuts, soy beans, peanuts	*Meats*: poultry, lean beef, pork without fat *Alternatives*: burritos, kidney, romano beans, and all dried pulses	*Meats*: poultry, lean beef, pork without fat *Alternatives*: legumes in general and nuts, soy beans, peanuts	*Meats*: poultry, lean beef, pork without fat *Alternatives*: legume (baked beans on toast), bean stews, tofu and foods from other cultures
Low-fat dairy‖	**Plain milk**	**Plain milk, yogurt**	**Plain milk, yogurt**	**Plain milk, yogurt**	**Plain milk, low-fat yogurt**	**Plain milk, low-fat yogurt**	**Plain milk, low-fat yogurt**
Cooking oil¶	Grape seed oil, soybean oil	Sunflower oil	Mixed vegetable oils, olive oil	Sunflower oil	Canola oil, olive oil	Canola oil, olive oil	Soybean oil, sunflower oil
Nuts	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**	**Any type**

*Following WHO classification, starchy tubers such as potatoes are not included in the vegetable group.
†Sadza is a staple food in Zimbabwe.
‡Fatty fish are a good source of omega-3 fatty acids. Those populations that do not consume fish may obtain omega-3 fatty acids from plant sources, such as flaxseed, soybean, rapeseed, or walnuts.
§Meat is not an essential component of the healthy dietary pattern; populations that consume meat are advised to do so sparingly, especially red meats; generally, plant-based protein sources (e.g., legumes, nuts, soy) are preferred over animal sources.
‖Those populations that do not consume dairy may obtain protein from other sources, such as nuts, legumes, whole grains, etc.; and calcium from fortified tofu, almonds, or kale.
¶It is advised to avoid clarified butter, lard, or tallow for food preparation.



APPENDIX 3. WHO/ISH risk prediction chart for AFR-E.* Ten-year risk of fatal or nonfatal cardiovascular event by sex, age, systolic pressure, total blood cholesterol, smoking status, and presence or absence of diabetes mellitus. Reproduced with permission from the World Health Organization [34]. AFR-E = sub-region Africa E; ISH = International Society for Hypertension; WHO = World Health Organization. *WHO AFR-E includes Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe.



APPENDIX 4. Score Risk Chart for 10-year risk of fatal CVD in high risk regions of Europe. Reproduced with permission from the European Society of Cardiology [27]. CVD, cardiovascular disease.

APPENDIX 5. Performance of cholesterol measures as markers of cardiovascular risk

	apo B	TC	Non−HDL-C	LDL-C (F)	LDL-C (DM)
Marker of CV risk	+++	+	++	+	+
Marker CV risk on Rx	++		++	++	++
Marker of benefit with Rx	+++		++	+	+
Fasting necessary	No	No	No	Yes	No
Analyte performance	++	+++	+	+	+
Cost	++	+++	++	++	++

Marker CV risk is the summary of conventional observation epidemiological studies and discordance analyses for relative value as marker of CV risk. Marker of CV risk on Rx is the value as measure of CV risk on statin therapy. Marker of benefit with Rx is the value as a measure of benefit with statin therapy. Analyte performance is the accuracy and standardization of laboratory measurement.
apo B, apolipoprotein B; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C(DM), low-density lipoprotein cholesterol by direct measurement; LDL-C(F), low-density lipoprotein cholesterol determined by the Friedewald equation; Rx, prescription/medication; TC, total cholesterol; +, least good; ++, intermediate; +++, best.

APPENDIX 6. Nonstatin drugs for the treatment of cholesterol

Drug	Mechanism of Action	Effect on Lipids	Evidence of Benefit on MACE/ Outcomes Studies
Ezetimibe	**Reduces cholesterol absorption in small intestine by inhibition of NPC1L1 protein**	**18% of LDL-C reduction in monotherapy; 25% incremental reduction in combination therapy with statins**	**In the IMPROVE-IT trial [54], the addition of ezetimibe 10 mg to moderate-intensity statin (simvastatin 40 mg) in patients with recent ACS (preceding 10 days) resulted in a 2.0-percentage-point lower rate of the primary composite endpoint of CV death, major coronary events, or nonfatal stroke (HR: 0.936; 95% CI: 0.89 to 0.99; p = 0.016)**
PCSK9 inhibitors (monoclonal antibodies to PCSK9) • Alirocumab • Evolocumab	PCSK9 binds to LDLR and induces its lysosomal catabolism. By inhibiting PCSK9, these monoclonal antibodies increase the expression of LDLR at the cell surface, increasing the clearance of circulating LDL-C that reduces circulating levels	Reduction of LDL-C levels by ~50% to 60% independently of the background lipid-lowering therapy [55]. This effect is attenuated in patients with homozygous FH [56].	The FOURIER trial [51] found that evolocumab decreased LDL-C levels by 59% in comparison to placebo and reduced the risk of the primary endpoint (composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization) by 15% (HR: 0.85; 95% CI: 0.79 to 0.92; p < 0.001). The ongoing ODYSSEY Outcomes trial [57] is evaluating Alirocumab in 18,600 post-ACS patients.
Bile acid sequestrants **• Cholestyramine** **• Colestipol** **• Colesevelam**	**These polymers bind bile acids in the intestines and impede their reabsorption. The decrease in bile acid returned to the liver leads to up-regulation of key enzymes responsible for bile acid synthesis from cholesterol. The increase in cholesterol catabolism to bile acids results in a compensatory increase in hepatic LDLR activity, clearing LDL-C from the circulation and thus reducing LDL-C levels.**	***Colesevelam:* Monotherapy—15% (6 tablets daily); combination with low- to moderate intensity statin—additional 10% to 16% reduction in LDL-C (data from simvastatin 10 mg, atorvastatin 10 mg).** ***Cholestyramine:* Monotherapy—10.4% vs. placebo.** ***Colestipol:* In dose-ranging RCT with monotherapy, doses of 5 g, 10 g, and 15 g resulted in 16.3%, 22.8%, and 27.2% reduction in LDL-C, respectively.**	**The LRC-CPPT trial [58], a multicenter, randomized, double-blind study, tested the efficacy of cholesterol lowering with cholestyramine in the reduction of CHD risk in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia treated for an average of 7.4 years. The cholestyramine group experienced a 19% reduction in risk (p < 0.05) of the primary endpoint—definite CHD death and/or definite nonfatal MI. The effects of colesevelam and colestipol on CV morbidity and mortality have not been determined. This study was performed before the statin era.**
Phytosterols	These are in part related to displacement of cholesterol from the micellar phase, reducing its absorption.	Consumption of 2 g/day of phytosterols decreases LDL-C by 5% to 15%. No additional effect on doses above 3 g/day.	There is no existing evidence on the effect of phytosterols on major acute coronary events.

ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; FH, familial hypercholesterolemia; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HR, hazard ratio; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; MACE, major adverse cardiovascular events; MI, myocardial infarction; ODYSSEY, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial; UA, unstable angina.

Adapted from Lloyd-Jones et al. [53].