

Expert opinion on the applicability of dyslipidemia guidelines in Asia and the Middle East

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Abstract: Cardiovascular disease (CVD) is a growing burden across the world. In Asia and the Middle East, in particular, CVD is among the most prevalent and debilitating diseases. Dyslipidemia is an important factor in the development of atherosclerosis and associated cardiovascular events, and so effective management strategies are critical to reducing overall cardiovascular risk. Multiple dyslipidemia guidelines have been developed by international bodies such as the European Society of Cardiology/European Atherosclerosis Society and the American College of Cardiology/American Heart Association, which all have similarities in practice recommendations for the optimal management of dyslipidemia. However, they differ in certain aspects including pharmacological treatment, lifestyle modification and the target levels used for low-density lipoprotein cholesterol. The evidence behind these guidelines is generally based on data from Western populations, and their applicability to people in Asia and the Middle East is largely untested. As a result, practitioners within Asia and the Middle East continue to rely on international evidence despite population differences in lipid phenotypes and CVD risk factors. An expert panel was convened to review the international guidelines commonly used in Asia and the Middle East and determine their applicability to clinical practice in the region, with specific recommendations, or considerations, provided where current guideline recommendations differ from local practice. Herein, we describe the heterogeneous approaches and application of current guidelines used to manage dyslipidemia in Asia and the Middle East. We provide consensus management recommendations to cover different patient scenarios, including primary prevention, elderly, chronic kidney disease, type 2 diabetes, documented CVD, acute coronary syndromes and family history of ischemic heart disease. Moreover, we advocate for countries within the Asian and Middle East regions to continue to develop guidelines that are appropriate for the local population.

Keywords: Asia, dyslipidemia, guidelines, Middle East, cardiovascular disease

Cardiovascular disease and dyslipidemia in Asia and the Middle East

The increase in urban spread in developing countries has been accompanied by a rising burden of chronic non-communicable diseases, such as cardiovascular disease (CVD). Developing countries account for approximately 80% of the global mortality related to CVD;^{1,2} in Asia and the Middle East, CVD is among the most prevalent and debilitating diseases.^{2,3} It is well established that dyslipidemia is an important cardiovascular risk factor, with the failure to attain optimal lipid levels contributing significantly to the residual risk of CVD.⁴ According to Global Health Observatory

data of the World Health Organization (WHO), 2.6 million deaths each year are attributable to dyslipidemia, which in 2008 had a global prevalence of 37% in males and 40% in females.⁵ Due to the role of dyslipidemia in the development of atherosclerosis and associated cardiovascular events, the effective management of dyslipidemia is a high priority in cardiovascular prevention. A 10% reduction in serum cholesterol in males aged 40 years old has been reported to reduce the risk of ischemic heart disease by 50%, with this risk reduction achieved within 5 years.⁶

Multiple dyslipidemia guidelines developed by international bodies have been published; these share the goal of providing clinical guidance on the optimal management of dyslipidemia, but differ in their emphasis on pharmacotherapy, stratification of patient groups, lifestyle modification and use of a fixed target or percentage reduction in low-density lipoprotein cholesterol (LDL-C).⁷ Importantly, these guidelines have been developed for Western populations, and their applicability to the geographically diverse and ethnically and culturally heterogeneous populations of Asia and the Middle East is largely untested. Only recently, regional guidelines have been published specifically for the management of dyslipidemia in the Middle East,⁸ and no equivalent region-wide guidelines for Asia have been published to date. As a result, regional societies and practitioners within Asia and the Middle East continue to rely on international evidence despite population differences.⁹

Dyslipidemia prevalence and groups at increased risk in Asia and the Middle East are summarized in Table 1.^{2,10–21} Unlike in Western populations where dyslipidemia is predominantly characterized by high levels of LDL-C, in Asia and the Middle East there is evidence of a predominance of low levels of high-density lipoprotein cholesterol (HDL-C), as well as an increased prevalence of hypertriglyceridemia.^{2,14,18,22–27} The relevance of this phenotype is currently unknown, but the expression of low levels of HDL-C has been implicated as a CVD risk factor.^{27,28} Further research needs to be undertaken to determine whether or not HDL-C should be a therapeutic target in such individuals. In the interim, such findings suggest a need for comprehensive screening in affected groups.²⁹

In the Middle East in general, patients present with cardiovascular events, including myocardial infarction, at a younger age on average than patients elsewhere, with an associated high prevalence of diabetes mellitus, obesity, hypertension and smoking.^{30,31} Compared with Western countries, the prevalence of diabetes mellitus is markedly higher in Asian countries and is linked with a high rate of strokes and ischemic heart diseases, with population-attributable risk highest for high blood pressure, total cholesterol, obesity and smoking.³² However, the epidemiology of CVD within these regions shows considerable variation. For example, in Saudi Arabia, which has a large number of itinerant workers, CVD is associated with smoking, high fat and low fiber intake, lack of exercise and sedentary lifestyle, in addition

Table 1 Dyslipidemia prevalence and groups at increased risk in Asia and the Middle East

	Asia						Middle East		
	People's Republic of China	Indonesia	Malaysia	Philippines	Taiwan	Thailand	Egypt	Saudi Arabia	UAE
Overall prevalence in adults	54% overall	High TC, 43%; high TG, 26%; high LDL-C, 83%; low HDL-C, 23%	48% overall	High TC 46.9%; high LDL-C 47.2%; low HDL-C 71.3%; high TG 38.6%	High TC, 13% males, 10% females; high TG, 21% males, 8% females	66.5% overall; high LDL-C 29.6%; high TG 38.6%; low HDL-C 47.1%	76% overall	High TC, 8.5%; high TG, 8.5%; high LDL-C, 7.4%; low HDL-C, 48.7%	44–75% overall
Groups at increased risk	Han Chinese, males, age, family history, college education, current smoker, overweight and obesity, HYT and DM	Minangkabau females >40 years, and Sundanese males <40 years	Risk is increased in females vs. males	Risk is increased in females vs. males	Increased risk of high TG in males vs. females	Female sex, increasing age, urban living	–	Increasing age	Male sex, increasing age
References	10–13	14,15	16	17	18	19	2	20	2,21

Abbreviations: DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HYT, hypertension; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UAE, United Arab Emirates.

to a predominance of low HDL-C and high levels of triglycerides.^{2,23,25,33} An unusually high prevalence of low HDL-C has also been observed in the Philippines,¹⁷ which presents an intriguing dilemma for possible treatment strategies. In Indonesia, one study showed the tremendous variation in lipid profiles among the Minangkabau, Sundanese, Javanese and Buginese ethnic groups.¹⁵ In a rural Chinese population, smoking, lower education, obesity and low HDL-C predicted increased cardiovascular risk.¹³

Owing to the lack of region-specific guidelines, practitioners in the Asian and Middle East regions are attempting to bridge the gap between major international guidelines and the unique needs of local populations regarding the optimal management of dyslipidemia. To this end, a number of countries throughout these regions have developed, or are in the process of developing, local clinical practice guidelines in an effort to improve the management of dyslipidemia among local populations (Table 2).^{34–39} Rather than developing such guidelines from first principles, existing guidelines such as those issued by the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and the American College of Cardiology (ACC)/American Heart Association (AHA) inevitably form the basis for a review intended to guide the development of optimized local guidelines. The aim of this article is to review these updated guidelines to determine their applicability to local clinical practice. Herein, we summarize the expert opinion of practitioners involved in the care of patients with dyslipidemia in the People's Republic of China, Egypt, Indonesia, Malaysia, the Philippines, Saudi Arabia, Taiwan, Thailand and the United Arab Emirates. Professor Philip Barter from Australia served as an expert advisor to the group.

Current guidelines on dyslipidemia

Major dyslipidemia clinical practice guidelines approach primary prevention with the common aim of providing

guidance on the optimal management of dyslipidemia; yet confusion often persists among physicians due to differences between these guidelines.⁷ This appears to have been the case since the ACC/AHA published its 2013 guidelines on the treatment of blood cholesterol,⁴⁰ which considered evidence from randomized controlled trials (RCTs) only when formulating recommendations. The 2013 ACC/AHA guidelines emphasize statin monotherapy on the basis that the addition of non-statin had not been shown to reduce risk in RCTs that were available at that time. Furthermore, they do not specify an LDL-C goal to be achieved on the same grounds that a precise level has not been identified in RCTs. The 2013 ACC/AHA guidelines also adopt a new cardiovascular risk calculator (Table 3).⁴⁰ By contrast, both the ESC/EAS and the National Institute for Health and Care Excellence (NICE) in the UK have published guidelines that consider sources of data other than RCTs as a valid way of translating evidence to clinical practice.^{41–44} The International Atherosclerosis Society (IAS) similarly adopts a broader view of evidence in order to make recommendations other than those pertaining to pharmacotherapy and to answer critical questions in clinical intervention.^{41,45} Rather than focusing on these differences, it is helpful to acknowledge that a divergent methodological approach to evidence likely explains a major part of the dissimilarities between 2013 ACC/AHA guidelines and other clinical practice guidelines, but overall there are only minor points of disagreement. In brief, these differences can be summarized in terms of cardiovascular risk algorithm, identification of LDL-C target levels and emphasis on the use of non-statin drugs, as well as lifestyle intervention.

The 2016 ESC/EAS guidelines differ from the earlier 2011 guidance in giving greater emphasis to the role of healthy lifestyle as a strategy to reduce cardiovascular risk while also revising the recommendations regarding LDL-C goals for different risk groups (Table 3).⁷ When comparing the new ESC/EAS guidelines with ACC/AHA 2013,

Table 2 Clinical practice guidelines applicable to the management of dyslipidemia among local populations in Asia and the Middle East

	Asia						Middle East		
	People's Republic of China	Indonesia	Malaysia	Philippines	Taiwan	Thailand	Egypt	Saudi Arabia	UAE
National guidelines	2016 Prevention and Treatment Guideline of Dyslipidemia in Chinese Adults	2015 Indonesian Dyslipidemia Management Guidelines	2017 Malaysian Dyslipidemia Guidelines	2015 Philippine CPG in the Management of Dyslipidemia	2017 Taiwan Lipid Guideline for High Risk Patients	2016 RCPT Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention	No national guidelines currently available	No national guidelines currently available	No national guidelines currently available
References	34	35	36	37	38	39	–	–	–

Abbreviations: CPG, Clinical Practice Guideline; RCPT, Royal College of Physicians of Thailand; UAE, United Arab Emirates.

Table 3 Major features of international dyslipidemia guidelines

	ACC/AHA 2013	NICE 2014	IAS 2013	ESC/EAS 2016
Risk score	Pooled cohort equations to estimate 10-year risk of fatal and non-fatal CHD and CVA	QRISK2 to estimate 10-year risk of fatal and non-fatal CHD, CVA and PAD	FRS to estimate lifetime risk of non-fatal and fatal CVD	SCORE chart to estimate 10-year risk of fatal CVD
Step 1	Identify statin benefit groups, eg: ASCVD history; <ul style="list-style-type: none"> LDL-C \geq190 mg/dL, age \geq21 years DM, age 40–75 years, LDL-C \geq70 mg/dL \geq7.5% ASCVD risk, age 40–75 years, LDL-C \geq70 mg/dL 	Identify statin benefit groups, eg: <ul style="list-style-type: none"> T1DM CKD stage III Risk score $>$10% Age $>$85 years Familial hyperlipidemia 	Stratify CVD risk, eg: <ul style="list-style-type: none"> High: \geq45% lifetime risk of CVD; DM with major risk factor; familial hyperlipidemia; CKD Moderately high: 30–44% lifetime risk of CVD; DM alone; MS; CKD 	Stratify CVD risk, eg: <ul style="list-style-type: none"> Very high: documented CVD; DM with target organ damage; severe CKD; SCORE \geq10% High: markedly elevated single risk factors; moderate CKD; SCORE \geq5% and $<$10% Moderate: SCORE \geq1% and $<$5% Low: SCORE $<$1%
Step 2	Determine adequacy of treatment effect: <ul style="list-style-type: none"> High-intensity statin: $>$50% reduction of LDL-C Moderate-intensity statin: 30–50% reduction of LDL-C 	Determine adequacy of treatment effect: <ul style="list-style-type: none"> $>$40% reduction of non-HDL-C 	Determine target: <ul style="list-style-type: none"> High to moderately high: LDL-C $<$100 mg/dL or non-HDL-C $<$130 mg/dL (may be lower for very high risk) Moderate to low: LDL-C $<$130 mg/dL or non-HDL-C $<$160 mg/dL 	Determine target: <ul style="list-style-type: none"> Very high: LDL-C $<$70 mg/dL or \geq50% reduction if baseline LDL-C is between 70 and 135 mg/dL High: LDL-C $<$100 mg/dL or \geq50% reduction if baseline LDL-C is between 100 and 200 mg/dL Moderate-low: LDL-C $<$115 mg/dL
Step 3	Follow-up lipids: <ul style="list-style-type: none"> 1–3 months after initiation of therapy; every 3–12 months as indicated thereafter 	Follow-up lipids: <ul style="list-style-type: none"> 3 months after initiation of therapy; annually when target achieved 	Treat according to risk: <ul style="list-style-type: none"> High: statin therapy and lifestyle change Moderately high: lifestyle change, consider initiating statin therapy Moderate: lifestyle change, consider statin therapy if LDL-C $>$160 mg/dL Low: lifestyle change only 	Treat according to risk: <ul style="list-style-type: none"> ESC/EAS 2016 and 2011 guidelines differ in that the latest guidelines show a considerable increase in the emphasis given to the importance of healthy lifestyle as a strategy to reduce cardiovascular risk; however, a statin and dose should be chosen that can provide required reduction in LDL-C to reach goal
Step 4	Options if treatment effect inadequate: <ul style="list-style-type: none"> Reinforce lifestyle changes, adherence to medication Exclude secondary causes Add non-statin agent 	Options if treatment effect inadequate: <ul style="list-style-type: none"> Reinforce lifestyle changes, adherence to medication Up-titrate statin dose 		Follow-up lipids and options if target not reached: <ul style="list-style-type: none"> 8 ± 4 weeks after initiation; 8 ± 4 weeks after adjusting treatment until within target range; annually when target met Up-titration of statin dose, consider drug combinations

Note: Adapted with permission from Hendrani AD, Adesiyun T, Quispe R, et al. Dyslipidemia management in primary prevention of cardiovascular disease: current guidelines and strategies. *World J Cardiol.* 2016;8(2):201–210.⁷

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; IAS, International Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; NICE, National Institute for Health and Care Excellence; PAD, peripheral artery disease; SCORE, systematic coronary risk evaluation; T1DM, type 1 diabetes mellitus.

NICE and IAS guidelines, there are 10 points of general agreement:

1. The decision to use lipid-lowering drugs should be based on an assessment of overall cardiovascular risk rather than on any perceived need to treat an abnormal lipid level.
2. High-risk patients include those with manifest atherosclerotic CVD (ASCVD), familial hypercholesterolemia (FH) and diabetes.
3. In people without ASCVD, FH or diabetes, global risk should be calculated and used to guide treatment decisions.
4. Calculation of global risk should take account of both lipid and non-lipid risk factors.
5. There should be a major emphasis on lifestyle intervention whether or not drug therapy is used.
6. LDL-C should be a primary therapeutic target.
7. Statins are indicated in proven high-risk conditions.
8. When cardiovascular risk is high, treatment should be intensive.
9. When cardiovascular risk is moderately high, treatment should be moderately intensive.
10. Non-HDL-C should be considered as an alternative therapeutic target to LDL-C.

Consensus clinical recommendations for the management of dyslipidemia in the Middle East have recently been published.⁸ These are regional recommendations that show similarities particularly with the ESC/EAS 2011 guidelines and include recommendations for plasma lipid screening, ASCVD risk calculation and treatment. Primary treatment targets include LDL-C and non-HDL-C, with an emphasis on lifestyle modification as first-line treatment of all patients.

Applicability of current dyslipidemia guidelines to Asia and the Middle East

Due to a paucity of local data in the Asian and Middle East regions, physicians often must refer to major international guidelines. The expert panel agreed that the 2016 ESC/EAS guidelines are generally applicable to the management of dyslipidemia in Asia and the Middle East. On a 6-point Likert scale where “0” represents “not applicable” and “5” represents “directly applicable”, most panel members scored the 2016 ESC/EAS guidelines as either a 4 or 5. The 2013 ACC/AHA guidelines were also considered to be applicable in Asia and the Middle East, with panel scoring ranging from 3 in Taiwan and Thailand to a score of 5 in Malaysia, the United Arab Emirates, Saudi Arabia, Egypt and Indonesia. 2014 NICE guidelines were considered applicable in Malaysia (4), the United Arab Emirates, the Philippines, Thailand, Egypt and Indonesia (all 3), but not in the People’s Republic of China, Saudi Arabia or Taiwan.

Screening

The 2016 ESC/EAS guidelines state that “screening for dyslipidemias should be considered in all adult males ≥ 40 years of age and in females ≥ 50 years of age or postmenopausal, particularly in the presence of other risk factors”, as well as in the offspring of patients with severe dyslipidemia (with follow-up in specialist clinics) and family members of patients with premature CVD.⁴⁴ The panel members for countries in Asia generally endorse this guideline; however, certain countries have specific screening criteria defined by national guidelines or reimbursement policies. A scientific rationale is often absent, with an emphasis on reimbursement. For example, the Taiwanese reimbursement system does not permit routine screening for dyslipidemia in males ≥ 40 years of age and in females ≥ 50 years of age. Nonetheless, to further reduce the prevalence of CVD, widespread screening for patients with multiple CVD risk factors, including old age, hypertension, diabetes and/or smoking, is endorsed in Taiwan. Both the Philippines and Thailand recommend lipid

screening for all adults aged ≥ 45 years old,^{37,46} but they differ in that the Thai guidelines also endorse screening younger adults with at least one risk factor, while two risk factors are required in the Philippines. The Indonesian guidelines promote screening for dyslipidemias for males aged ≥ 45 years and females ≥ 55 years, those who are active smokers, people with a family history of early coronary artery disease (CAD) and those with hypertension or HDL-C level < 40 mg/dL.³⁵

In the Middle East, the panel members recommend screening to begin at an earlier stage because of the high prevalence of diabetes, obesity, sedentary lifestyle, smoking and premature CAD. Physicians in the Middle East should aim to align their screening practice with the recent Middle East clinical consensus recommendations, which propose plasma lipid screening in patients ≥ 20 years old, once every 5 years.⁸

In the absence of scientific evidence to support local screening programs, it is difficult to achieve a consensus regarding a shared approach to the screening of dyslipidemia in Asia and the Middle East. However, participation in a screening program in itself does not lead to improved clinical outcomes since gaps in the program such as those related to treatment availability and willingness to prescribe may limit any benefit.⁴⁷ As a panel, we therefore advocate for further research to provide an evidence-based rationale for screening local and regional populations.

Risk calculation

Development of an appropriate and validated tool for assessing cardiovascular risk is an essential aspect of dyslipidemia management where the aim is to reduce cardiovascular events. Current guidelines use different models for assessing cardiovascular risk. For example, the ESC/EAS recommends the Systematic Coronary Risk Evaluation (SCORE), whereas ACC/AHA guidelines use the Pooled Cohort Equations for ASCVD. The Framingham Risk Score (FRS) is another risk tool calculator. The cardiovascular risk scoring systems recommended by international guidelines differ principally in terms of whether they calculate lifetime CVD risk (ie, IAS)⁴⁵ or 10-year risk (ie, ACC/AHA, NICE, ESC/EAS 2011 and 2016).^{40,42–44}

One of the key concerns with adopting existing risk calculation models is their applicability to local populations. Among members of the expert panel, there was agreement that current cardiovascular risk calculators including SCORE, ASCVD, FRS and QRISK2 may not be applicable to Asia and the Middle East. Whereas the SCORE chart provides a relatively straightforward method for calculating

cardiovascular risk, and its focus on fatal CVD events allows for simple recalibration for use in different populations after adjustment for secular changes in CVD mortality and risk factor prevalence,⁴⁴ it also overlooks the occurrence of total CVD, which occurs at a frequency approximately 3- to 4-fold greater than fatal CVD. The aim of risk calculation should be to prevent cardiovascular events altogether rather than reducing the risk of fatal cardiovascular events. In a diverse South Asian population⁴⁸ and in Pakistan,⁴⁹ the QRISK2 calculator has demonstrated utility in the assessment of cardiovascular risk. However, a systematic search of risk assessment tools applied to Asian populations found that just two were derived from an Asian population, suggesting limited real-world applicability.⁵⁰ The development of new risk calculators that are optimized to the local population, and that include all important factors underlying CVD including non-traditional risk factors, is a challenge that needs to be met.⁵¹

Given the lack of local cardiovascular risk models in many countries in Asia and possible concerns about the validity of existing risk calculators in local populations, the methods used to assess cardiovascular risk in Asia and the Middle East are a significant point of departure from international guidelines. Of the countries represented, Egypt, Indonesia, Malaysia and the United Arab Emirates advocate for the use of the SCORE risk chart as laid out in the 2016 ESC/EAS guidelines. However, due to concerns regarding its lack of validation in local populations, all other panel members representing the Asian and Middle East regions indicated reliance on local guidance and risk calculator methodologies. For example, the 2016 Thai lipid guidelines³⁹ recommend that physicians use the Thai CV Risk Score (available from: https://med.mahidol.ac.th/cardio_vascular_risk/thai_cv_risk_score/tcvrs_en.html), which was developed from a cohort of Thai patients, as other cardiovascular risk calculators using the Framingham data had been shown to overestimate risk

in Asian patients.⁵²⁻⁵⁴ As for the ACC/AHA ASCVD risk calculator, the Thai CV Risk Score includes coronary heart disease and stroke. Although it uses a cutoff of 10% for intervention, this is only for reimbursement purposes, with an intervention at the 7.5% threshold requiring out-of-pocket expenditure on the part of the patient (Table 4).

In Taiwan, the Health Insurance Reimbursement guidelines offer a simplified risk calculator that counts only the number of risk factors, such as established CVD, diabetes, age, sex, hypertension, low HDL-C levels, family history of premature CAD and smoking. In the Philippines, most physicians similarly use a risk counting method or refer to the ACC/AHA guidelines, which use the 10-year ASCVD risk calculator based on the pooled cohort equations and lifetime risk prediction tools. In the Middle East, lifetime cardiovascular risk calculators may be more relevant in clinical practice because of the increased prevalence of early ischemic heart disease.

One study in Malaysia used the 2006 National Health and Morbidity Survey population data to assess the validity of the SCORE (high and low risk), FRS and WHO/International Society of Hypertension (ISH) – Western Pacific Region risk scores in their local population.⁵² The investigators concluded that the FRS and SCORE high-risk models, but not the WHO/ISH model, can be used to identify high cardiovascular risk patients among the Malaysian population. However, the SCORE high-risk model had a tendency to underestimate risk in females. A retrospective study in 967 multiethnic patients in a primary care clinic in Malaysia further assessed the FRS and deemed it a reasonable alternative for use in a multiethnic group of patients in the absence of local risk prediction charts, although it tended to overestimate cardiovascular risk in females.⁵³ Taken together, these studies suggest that existing cardiovascular risk calculators may be useful tools in the absence of local population cardiovascular risk models,

Table 4 Typical patient scenarios and management recommendations by the expert panel

Patient scenarios	Recommendations by expert panel
Primary prevention	All adults ≥ 18 years old with a 10-year risk of ASCVD $\geq 7.5\%$ (or 10% according to the Thai CV risk score) or LDL-C ≥ 190 mg/dL are candidates for primary prevention
Elderly (>75 years)	Statins may be prescribed, with caution, taking into consideration polypharmacy and comorbidities in this population
Chronic kidney disease	Statin therapy is beneficial in pre-dialysis patients. The statin dose should be adjusted according to eGFR
Type 2 diabetes	All type 2 diabetes patients should receive statin therapy
Documented CVD	Statin therapy with a target LDL-C ≤ 70 mg/dL or $\geq 50\%$ reduction
Patient with ACS	Maximum tolerated dose of statin with a target LDL-C ≤ 70 mg/dL. If the target is not achieved, add ezetimibe. In case of intolerance, decrease the statin dose and add ezetimibe
Family history of premature IHD with LDL-C < 190 mg/dL	Family history is an important additional risk factor and thus treatment with statin therapy should be considered

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol.

but careful assessment and validation are necessary first to determine their accuracy.

Despite disparities on which cardiovascular risk calculator to use across the countries represented, the panel advocated the value of using such tools in order to accurately assess cardiovascular risk in patients. Cardiovascular risk tools that are relevant to the local population should be used in routine clinical practice to ensure all patients are adequately assessed and managed. Other countries in Asia and the Middle East are encouraged to follow the example set by Thailand and develop their own risk calculators based on their local populations. We propose that all adults ≥ 18 years old with a 10-year risk of ASCVD $\geq 7.5\%$ (or 10% according to the Thai CV Risk Score) or LDL-C ≥ 190 mg/dL are candidates for primary prevention (Table 4).

Statin therapy and LDL-C target level

There was consensus among the expert panel that lifestyle adjustment is a key component of reducing cardiovascular risk. However, many patients are unable or unmotivated to change their lifestyle through diet and exercise. Moreover, in those countries with a high prevalence of dyslipidemia, many patients at screening already have a high cardiovascular risk consistent with the general population. Panel members considered LDL-C target levels to be important for clinical practice guidelines; setting LDL-C goals offers the benefit of flexibility to physicians to choose the statin and dose they believe will achieve the goal. However, there is evidence that Asian populations may have a heightened response to statins compared with Caucasian populations, suggesting that high statin dose intensity may not be needed to achieve target LDL-C levels.^{55–58} Functional variants of the *PCSK9* gene have been proposed to account for ethnicity-related differences in response to LDL-C response to statins,⁵⁹ but current evidence is limited. Despite the lipid improvements achieved with lower statin doses in Asian populations, no safety issues have been identified even when statins are given at equivalent doses to Asian and non-Asian populations.^{55,60} Studies have not found evidence of an increased risk of serious statin toxicities in Asian patients, including older adults, compared with their non-Asian counterparts.^{60,61} By contrast, epidemiological and experimental data have shown pleiotropic and organ-protective benefits for statins with proven safety in Asian populations.⁶²

Panel members broadly agreed with the LDL-C target levels recommended in 2016 ESC/EAS guidelines as follows:

1. In patients at very high cardiovascular risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of $\geq 50\%$ if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.
2. In patients with high cardiovascular risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL) or a reduction of $\geq 50\%$ if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.
3. In patients at low or moderate risk, consider an LDL-C goal of <3.0 mmol/L (115 mg/dL).

Non-statin therapies may be added to a statin in situations where the patient has reached the maximum tolerated dose of a statin without achieving target levels.

Special cases: diabetes and acute coronary syndrome (ACS)

The panel members agreed that statins should be given to all patients with diabetes, except where local policies dictate otherwise. For example, in Taiwan statins should only be administered in patients with LDL-C >100 mg/dL because of cost/reimbursement constraints. In addition, the 2017 Taiwan Lipid Guideline for High Risk Patients also recommends an LDL-C target of <100 mg/dL for patients with diabetes who do not have overt CVD (Class I, Level A) and a target of <70 mg/dL for patients with diabetes with overt CVD (Class I, Level B).³⁸ In Thailand, national guidelines recommend statin therapy in patients with diabetes over the age of 40 years.³⁹ The panel acknowledged that the evidence on the benefits of statins in patients with diabetes with LDL-C <40 mg/dL is currently limited.

For patients with ACS, there was a general consensus among the panel members that ezetimibe should only be added to maximum tolerated dose of statin if the LDL-C target level is not achieved with a statin alone. If the patient is intolerant of maximum dose of statin, then the statin dose should be decreased and ezetimibe added. This recommendation also applies to ACS patients with concomitant diabetes mellitus.

Patient scenarios and treatment recommendations

In order to provide practical guidance to physicians who are managing dyslipidemia patients on a daily basis, the expert panel identified a range of typical patient scenarios that are particularly pertinent to Asia and the Middle East, and provided specific considerations or recommendations in these cases (Table 4).

Discussion

Guidelines of the ESC/EAS and ACC/AHA are the two most prominent international guidelines and, as such, have formed the basis for the recommendations we have made herein. The 2013 clinical practice guidelines of the ACC/AHA on the treatment of blood cholesterol to reduce cardiovascular risk recommend high-intensity statin therapy for the prevention of cardiovascular events.⁴⁰ The ACC/AHA guidelines deliver the unambiguous message to treat high-risk patients with high-intensity statins; however, these guidelines have abandoned the use of LDL-C target levels, while also constraining the role of lifestyle intervention and non-statin lipid-lowering drugs. By contrast, updated 2016 guidelines of the ESC/EAS have introduced specific LDL-C goals for different risk groups while placing greater importance on implementing a healthy lifestyle.⁴⁴ Our expert opinion is that the ESC/EAS 2016 guidelines are more in line with the needs of patients from Asia and Middle East in whom less-intensive statin therapy may be adequate to achieve LDL-C targets despite high cardiovascular risk status at screening. By clearly defining targets, LDL-C can be better controlled in clinical practice, with the additional benefit of improved physician–patient communication as a result. Patients who receive long-term statin therapy and fail to achieve target LDL-C levels may benefit from combination therapy. In addition, patients who achieve maximum tolerated statin doses and fail to achieve target LDL-C may benefit from non-statin therapies.

Limitations

Our review has some limitations. Asia and the Middle East are geographically diverse, and ethnically and culturally heterogeneous regions. These recommendations intend to provide broad guidance to clinicians in the regions, but local circumstances, risk factors and health care service provisions need to be taken into consideration when managing patients. Additionally, the limited data available from Asia and the Middle East required the referral to evidence from Western populations in some instances, supplemented by small, local studies and expert opinion. Further large-scale studies in Asia and the Middle East are required to generate a stronger evidence base for regional guidelines.

Conclusion and future perspectives

Far from being prescriptive, clinical practice guidelines aim to provide evidence-based recommendations that are relevant to a defined population. Until there are more local data from which to guide clinical practice in Asia and the Middle East,

the challenge for individual countries will be to continue to review international guidelines for relevance and adopt those recommendations that are deemed to be applicable and implementable in local populations. In this regard, referral to a broad evidence base, together with the formulation of expert opinion, will be helpful in optimizing the local management of dyslipidemia. Future research endeavors may focus on the development of country-specific scoring systems for calculating cardiovascular risk, incorporating a cost-effective screening program, particularly for all patients at risk of FH, and promoting patient awareness of dyslipidemia and the benefits of lifestyle change. Finally, as new treatments continue to become available, current recommendations will continue to evolve.

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References

1. Kelly BB, Narula J, Fuster V. Recognizing global burden of cardiovascular disease and related chronic diseases. *Mt Sinai J Med.* 2012;79(6):632–640.
2. Alsheikh-Ali AA, Omar MI, Raal FJ, et al. Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East Cardiovascular Epidemiological (ACE) study. *PLoS One.* 2014;9(8):e102830.
3. Yang ZJ, Liu J, Ge JP, Chen L, Zhao ZG, Yang WY; China National Diabetes and Metabolic Disorders Study Group. Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007–2008 China National Diabetes and Metabolic Disorders Study. *Eur Heart J.* 2012;33(2):213–220.
4. Gao F, Zhou YJ, Hu DY, et al. Contemporary management and attainment of cholesterol targets for patients with dyslipidemia in China. *PLoS One.* 2013;8(4):e47681.
5. World Health Organization. Global Health Observatory (GHO) data. Available from: http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/. Accessed March 14, 2018.
6. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ.* 1994;308(6925):367–372.
7. Hendrani AD, Adesiyun T, Quispe R, et al. Dyslipidemia management in primary prevention of cardiovascular disease: current guidelines and strategies. *World J Cardiol.* 2016;8(2):201–210.
8. Al Sayed N, Al Waili K, Alawadi F, et al. Consensus clinical recommendations for the management of plasma lipid disorders in the Middle East. *Int J Cardiol.* 2016;225:268–283.

9. Al Rasadi K, Almahmeed W, AlHabib KF, et al. Dyslipidaemia in the Middle East: current status and a call for action. *Atherosclerosis*. 2016;252:182–187.
10. Gu D, Gupta A, Muntner P, et al. Prevalence of cardiovascular disease risk factor clustering among the adult population of China: results from the International Collaborative Study of Cardiovascular Disease in Asia (InterAsia). *Circulation*. 2005;112(5):658–665.
11. Cai L, Zhang L, Liu A, Li S, Wang P. Prevalence, awareness, treatment, and control of dyslipidemia among adults in Beijing, China. *J Atheroscler Thromb*. 2012;19(2):159–168.
12. Luo JY, Ma YT, Yu ZX, et al. Prevalence, awareness, treatment and control of dyslipidemia among adults in northwestern China: the cardiovascular risk survey. *Lipids Health Dis*. 2014;13:4.
13. Ge P, Dong C, Ren X, et al. The high prevalence of low HDL-cholesterol levels and dyslipidemia in rural populations in Northwestern China. *PLoS One*. 2015;10(12):e0144104.
14. Soebardi S, Purnamasari D, Oemardi M, Soewondo P, Waspadij S, Soegondo S. Dyslipidemia in newly diagnosed diabetes mellitus: the Jakarta primary non-communicable disease risk factors surveillance 2006. *Acta Med Indones*. 2009;41(4):186–190.
15. Hatma RD. Lipid profiles among diverse ethnic groups in Indonesia. *Acta Med Indones*. 2011;43(1):4–11.
16. Institute for Public Health (IPH) 2015. National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable Diseases, Risk Factors & Other Health Problems; 2015. Available from: <http://iku.moh.gov.my/index.php/research-eng/list-of-research-eng/iku-eng/nhms-eng/nhms-2015>.
17. Food and Nutrition Research Institute. 8th National Nutrition Survey (Philippines). 2013. Available from: <http://122.53.86.125/NNS/8thNNS.pdf>. Accessed March 14, 2018.
18. Pan WH, Wu HJ, Yeh CJ, et al. Diet and health trends in Taiwan: comparison of two nutrition and health surveys from 1993–1996 and 2005–2008. *Asia Pac J Clin Nutr*. 2011;20(2):238–250.
19. Aekplakorn W, Taneepanichskul S, Kessomboon P, et al. Prevalence of dyslipidemia and management in the Thai population, National Health Examination Survey IV, 2009. *J Lipids*. 2014;2014:249584.
20. Basulaiman M, El Bcheraoui C, Tuffaha M, et al. Hypercholesterolemia and its associated risk factors – Kingdom of Saudi Arabia, 2013. *Ann Epidemiol*. 2014;24(11):801–808.
21. Hajat C, Harrison O, Al Siksek Z. Weqaya: a population-wide cardiovascular screening program in Abu Dhabi, United Arab Emirates. *Am J Public Health*. 2012;102(5):909–914.
22. Iqbal SP, Dodani S, Qureshi R. Risk factors and behaviours for coronary artery disease (CAD) among ambulatory Pakistanis. *J Pak Med Assoc*. 2004;54(5):261–266.
23. Al-Nozha MM, Arafah MR, Al-Maatouq MA, et al. Hyperlipidemia in Saudi Arabia. *Saudi Med J*. 2008;29(2):282–287.
24. Basit A, Shera AS. Prevalence of metabolic syndrome in Pakistan. *Metab Syndr Relat Disord*. 2008;6(3):171–175.
25. Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Sabico SL, Chrousos GP. Decreasing prevalence of the full metabolic syndrome but a persistently high prevalence of dyslipidemia among adult Arabs. *PLoS One*. 2010;5(8):e12159.
26. Sy RG, Morales DD, Dans AL, et al. Prevalence of atherosclerosis-related risk factors and diseases in the Philippines. *J Epidemiol*. 2012;22(5):440–447.
27. Rutherford JN, McDade TW, Feranil AB, Adair LS, Kuzawa CW. High prevalence of low HDL-c in the Philippines compared to the US: population differences in associations with diet and BMI. *Asia Pac J Clin Nutr*. 2010;19(1):57–67.
28. Rosenson RS, Brewer HB Jr, Barter PJ, et al. HDL and atherosclerotic cardiovascular disease: genetic insights into complex biology. *Nat Rev Cardiol*. 2018;15(1):9–19.
29. Jain A, Puri R, Nair DR. South Asians: why are they at a higher risk for cardiovascular disease? *Curr Opin Cardiol*. 2017;32(4):430–436.
30. Motlagh B, O'Donnell M, Yusuf S. Prevalence of cardiovascular risk factors in the Middle East: a systematic review. *Eur J Cardiovasc Prev Rehabil*. 2009;16(3):268–280.
31. Almahmeed W, Arnaout MS, Chettaoui R, et al. Coronary artery disease in Africa and the Middle East. *Ther Clin Risk Manag*. 2012;8:65–72.
32. Nguyen HN, Fujiyoshi A, Abbott RD, Miura, K. Epidemiology of cardiovascular risk factors in Asian countries. *Circ J*. 2013;77(12):2851–2859.
33. Mahmood D, Jahan K, Habibullah K. Primary prevention with statins in cardiovascular diseases: a Saudi Arabian perspective. *J Saudi Heart Assoc*. 2015;27(3):179–191.
34. Joint Committee for Revision of Chinese guidelines for prevention and treatment of dyslipidemia in adults. [Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (2016 edition)]. *Chin Circulation J*. 2016;10:937–953. Chinese.
35. Perkumpulan Endokrinologi Indonesia. Panduan Pengelolaan Dislipidemia di Indonesia. [Guidelines for management of dyslipidemia in Indonesia]. PB PERKENI; 2015. ISBN 978-979-19388-5-3. Indonesian.
36. Malaysian Ministry of Health. Management of Dyslipidaemia Guidelines 2017 (5th edition). Available from: [http://www.moh.gov.my/penerbitan/CPG2017/CPG%20Management%20of%20Dyslipidaemia%202017%20\(5th%20Edition\).pdf](http://www.moh.gov.my/penerbitan/CPG2017/CPG%20Management%20of%20Dyslipidaemia%202017%20(5th%20Edition).pdf). Accessed March 14, 2018.
37. Guerrero AE, Gonzalez-Santos LE, Caole-Ang IV, et al. 2015 Clinical practice guidelines for the management of dyslipidemia in the Philippines – executive summary: dyslipidemia guidelines 2015. *ASEAN Heart J*. 2016;24(1):106–111.
38. Li YH, Ueng KC, Jeng JS, et al; Writing Group of 2017 Taiwan Lipid Guidelines for High Risk Patients. 2017 Taiwan lipid guidelines for high risk patients. *J Formos Med Assoc*. 2017;116(4):217–248.
39. The Royal College of Physicians of Thailand. 2016 RCPT Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention. Available from: <http://www.thaiheart.org/download/2016-RCPT-Dyslipidemia-Guideline.html>. Accessed March 14, 2018.
40. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1–S45.
41. Giner-Galvañ V, Esteban-Giner MJ, Pallarés-Carratalá V. Overview of guidelines for the management of dyslipidemia: EU perspectives. *Vasc Health Risk Manag*. 2016;12:357–369. eCollection 2016.
42. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, et al; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32(14):1769–1818.
43. Rabar S, Harker M, O'Flynn N, Wierzbicki AS; Guideline Development Group. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ*. 2014;349:g4356.
44. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis*. 2016;253:281–344.
45. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia—full report. *J Clin Lipidol*. 2014;8(1):29–60.
46. Thai Atherosclerosis Society. Guidelines for the Primary Prevention of Atherosclerosis. Available from: http://www.thaiathero.org/download/guidline_Thai_atherosclerosis_Update_16_07_50.pdf. Accessed May 15, 2017.

47. Ahn E, Shin DW, Yang HK, et al. Treatment gap in the National Health-Screening Program in Korea: claim-based follow-up of statin use for sustained hypercholesterolemia. *J Korean Med Sci.* 2015;30(9):1266–1272.
48. Robson J, Hippisley-Cox J, Coupland C. QRisk superior in diverse South Asian groups. *Int J Clin Pract.* 2012;66(7):722.
49. Kalra S. Health risk calculators for Pakistan. *J Pak Med Assoc.* 2016;66(12):1669–1670.
50. Liao SY, Mohamed Izham MI, Hassali MA, Shafie AA. A literature review of the cardiovascular risk-assessment tools: applicability among Asian population. *Heart Asia.* 2010;2(1):15–18.
51. Hussain SM, Oldenburg B, Wang Y, Zoungas S, Tonkin AM. Assessment of cardiovascular disease risk in South Asian populations. *Int J Vasc Med.* 2013;2013:786801.
52. Selvarajah S, Kaur G, Haniff J, et al. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. *Int J Cardiol.* 2014;176(1):211–218.
53. Chia YC, Gray SY, Ching SM, Lim HM, Chinna K. Validation of the Framingham general cardiovascular risk score in a multiethnic Asian population: a retrospective cohort study. *BMJ Open.* 2015;5(5):e007324.
54. Asia Pacific Cohort Studies Collaboration, Barzi F, Patel A, Gu D, et al. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health.* 2007;61(2):115–121.
55. Liao JK. Safety and efficacy of statins in Asians. *Am J Cardiol.* 2007;99(3):410–414.
56. Gupta M, Martineau P, Tran T, et al; ACTFAST investigators. Low-density lipoprotein cholesterol and high-sensitivity C-reactive protein lowering with atorvastatin in patients of South Asian compared with European origin: insights from the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study. *J Clin Pharmacol.* 2012;52(6):850–858.
57. Thongtang N, Sitthananun C, Sriussadaporn S, Nitiyanant W. Efficacy of low- and moderate-intensity statins for achieving low-density lipoprotein cholesterol targets in Thai type 2 diabetic patients. *J Diabetes Metab Disord.* 2017;16:6.
58. Lee B, Dumrongkitchaiporn K, Sriussadaporn S, Thongtang N. Statin intensity regimens in Thai type 2 diabetic patients who achieved LDL-C targets. *J Med Assoc Thai.* 2017;100(5):603–611.
59. Feng Q, Wei WQ, Chung CP, et al. The effect of genetic variation in PCSK9 on the LDL-cholesterol response to statin therapy. *Pharmacogenomics J.* 2017;17(2):204–208.
60. Chan JC, Kong AP, Bao W, Fayyad R, Laskey R. Safety of atorvastatin in Asian patients within clinical trials. *Cardiovasc Ther.* 2016;34(6):431–440.
61. Li DQ, Kim RB, McArthur E, et al. Statin safety in Chinese: a population-based study of older adults. *PLoS One.* 2016;11(3):e0150990.
62. Lau TW, Tan KEK, Choo JCJ, Ng TG, Tavintharan S, Chan JCN. Regional evidence and international recommendations to guide lipid management in Asian patients with type 2 diabetes with special reference to renal dysfunction. *J Diabetes.* 2018;10(3):200–212.

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