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Review

Consensus clinical recommendations for the management of plasma lipid disorders in the Middle East

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ABSTRACT

Background: Plasma lipid disorders are key risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) and are prevalent in the Middle East, with rates increasing in recent decades. Despite this, no region-specific guidelines for managing plasma lipids exist and there is a lack of use of guidelines developed in other regions.
Methods: A multidisciplinary panel of regional experts was convened to develop consensus clinical recommendations for the management of plasma lipids in the Middle East. The panel considered existing international guidelines and regional clinical experience to develop recommendations.
Results: The panel's recommendations include plasma lipid screening, ASCVD risk calculation and treatment considerations. The panel recommend that plasma lipid levels should be measured in all at-risk patients and at regular intervals in all adults from the age of 20 years. A scoring system should be used to calculate ASCVD risk that includes known lipid and non-lipid risk factors. Primary treatment targets include low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol. Lifestyle modifications should be first-line treatment for all patients; the first-line pharmacological treatment targeting plasma lipids in patients at moderate-to-high risk of ASCVD is statin therapy, with a number of adjunctive or second-line agents available. Guidance is also provided on the management of underlying conditions and special populations; of particular pertinence in the region are familial hypercholesterolaemia, diabetes and metabolic dyslipidaemia.
Conclusions: These consensus clinical recommendations provide practicing clinicians with comprehensive, region-specific guidance to improve the detection and management of plasma lipid disorders in patients in the Middle East.

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, Africa Middle East Cardiovascular Epidemiological; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CK, creatine phosphokinase; CKD, chronic kidney disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; ESRD, end-stage renal disease; FCHL, familial combined hyperlipidaemia; FDA, Food and Drug Administration; FH, familial hypercholesterolaemia; FRF, Framingham Risk Factor; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IAS, International Atherosclerosis Society; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MetS, metabolic syndrome; RA, rheumatoid arthritis; TC, total cholesterol; TG, triglyceride; ULN, upper limit of normal; VLDL, very low-density lipoprotein; WC, waist circumference.

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1. Background

Disorders of plasma lipids are key risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) [1,2], which is a leading cause of morbidity and mortality worldwide [3]. Typical disorders of plasma lipids include elevated levels of low-density lipoprotein cholesterol (LDL-C), elevated non-high-density lipoprotein cholesterol (non-HDL-C), elevated plasma triglyceride (TG), and low levels of high-density lipoprotein cholesterol (HDL-C) [1]. These plasma lipid disorders may be primary, occurring due to the interaction of genetic susceptibility and environmental risk factors or secondary [4,5], occurring as a result of other disorders (e.g. diabetes, hypothyroidism, nephrotic syndrome) [5–7].

Disorders of plasma lipids are a well-known problem in the Western world [8], and are an issue of increasing importance in the Middle East. Although estimates are hampered by a lack of clinical studies in the region and by inconsistencies in the definitions and thresholds used in those studies that have been conducted, the prevalence of plasma lipid disorders in the region is high [9]. Available data vary in their estimates [10–16], with prevalence as high as 50% or more in some areas. A literature review assessing the prevalence of plasma lipid disorders in Gulf countries, using studies published from 1987 to 2010, found that reported rates ranged from 3% to 52% across varying population types [10]. Similarly a further study of hypercholesterolaemia in the Gulf region, evaluating data from 1990 to 2014, found the prevalence range to be 17–55% in males and 9–54% in females [11]. A large ($n = 4378$) study in the Middle East and Africa found that 70% of stable outpatients who attended general practice clinics had disorders of plasma lipids; in all countries in the study, the prevalence of these disorders in this population was >50% [16]. Of these, only 16% of subjects were receiving lipid-lowering medications and many subjects were not achieving LDL-C goals recommended in international guidelines [16]. Large ($n > 6000$) prospective registries of patients with acute coronary syndrome conducted in Gulf countries (GULF RACE and GULF RACE-2) estimated the prevalence of plasma lipid disorders to be 31–32% [12,13].

In addition to these high prevalence rates, the profile of plasma lipid disorders observed in the Middle Eastern population differs somewhat to that seen in many other regions, with metabolic dyslipidaemia (high TG, low HDL-C and high or normal LDL-C) being one of the most common types [9]. The presentation of high TG and low HDL-C levels has also been observed among patients in the region who are already receiving chronic statin treatment; the DYSIS Middle East study ($n = 2182$) found that 62% still have high LDL-C levels, 56% have low HDL-C levels, and 49% have high TG levels [17]. A number of key risk factors for metabolic dyslipidaemia are common among the population, including type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) [9]. There is also a high prevalence of heterozygous and homozygous familial hypercholesterolaemia (FH), possibly secondary to a high prevalence of consanguineous marriages [9]. The prevalence of many of these factors has increased in the region over recent decades [18,19]. A further characteristic of the Middle Eastern population is an earlier onset of ASCVD compared with populations in Western countries. The INTERHEART study, a case-control study conducted in 52 countries, found that the Middle East has the lowest average age to first myocardial infarction (51 years) [20].

International guidelines exist and all agree on most key recommendations [2,4,5,21], however there is lack of awareness and adherence to these international guidelines by local healthcare professionals [9]. This paper aims to provide practical recommendations for the management of plasma lipid disorders, specifically for Middle Eastern populations [9].

1.1. Aim

A multidisciplinary panel of regional experts in plasma lipid disorders was convened with the aim of developing consensus clinical recommendations for the management of plasma lipids in the Middle East.

The panel considered a number of existing international guidelines, including:

- *American College of Cardiology* (*ACC*)/*American Heart Association* (*AHA*): Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. 2013 [5].
- *European Society of Cardiology* (*ESC*)/*European Atherosclerosis Society* (*EAS*): Guidelines for the Management of Dyslipidaemias. 2011 [4].
- *International Atherosclerosis Society* (*IAS*): Global Recommendations for the Management of Dyslipidemia. 2013 [21].
- *National Lipid Association*: Recommendations for Patient-Centered Management of Dyslipidemia. 2015 [2,22].
- *Kidney Disease Improving Global Outcomes* (*KDIGO*): KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. 2013 [23].
- *American Association of Clinical Endocrinologists* (*AACE*): Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. 2012 [24].

There is a high degree of agreement in the recommendations proposed in these international guidelines. In cases where the international guidelines disagreed, or did not make specific recommendations of relevance to the Middle East, the panel came to consensus based on comprehensive literature searches and regional clinical experience.

The recommendations from the panel are detailed in the following sections.

2. Screening

Screening for plasma lipid disorders should be performed in all patients with T2DM [4,22], evidence of ASCVD [4,22], arterial hypertension [4], central obesity [4], chronic inflammatory autoimmune disease [4], chronic kidney disease (CKD) [4,22], a family history of ASCVD, and in the offspring of patients with severe disorders of plasma lipids (e.g. FH) [4] (Box 1). These patients are considered to be at high risk for plasma lipid disorders and the development of ASCVD. Screening should also be considered in all adults ≥20 years old and should be repeated every five years [22].

2.1. Screening endpoints

2.1.1. Assessment of lipids

Screening should include the measurement of lipid levels including LDL-C, plasma total cholesterol (TC), TG, HDL-C and non-HDL-C. Either fasting [4] or non-fasting [22,25] measurements may be used.

Direct methods for measuring LDL-C should be used if available. Calculation of LDL-C is also possible using Friedewald's formulae, although this method is subject to a number of assumptions and limitations and cannot be used if TG levels are high [4].

Measurement of non-HDL-C provides an estimate of the concentration of cholesterol in all atherogenic lipoproteins in the plasma (very low-density lipoprotein [VLDL], intermediate-density lipoprotein and LDL). Non-HDL-C is calculated by subtracting HDL-C levels from plasma TC levels [4,21,22]. Commercially available assays should be used for measuring HDL-C, TC and TG levels, including assay validation with reference and control agents [4].

Elevated plasma lipoprotein(a) (Lp(a)) levels are also indicative of an increased ASCVD risk [4,26,27] and elevated levels require a specific treatment approach (see Section 7.2). Therefore, measurement of Lp(a) should be considered in high-risk patients [4]. Lp(a) can be measured using a commercially available, size-insensitive assay – it is important to ensure assay standardisation [4].

Box 1
Patient populations recommended for plasma lipid screening

- Once every five years in patients ≥20 years old [22,24]
- T2DM [4,22]
- Arterial hypertension [4]
- Manifest ASCVD [4,22]
- Central obesity [4]
- Chronic inflammatory autoimmune disease [4]
- CKD [4,22]
- Family history of ASCVD [4]
- Offspring of patients with severe disorders of plasma lipids (e.g. FH) [4]

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; FH, familial hypercholesterolaemia; T2DM, type 2 diabetes mellitus

2.1.2. Genetic testing

A number of plasma lipid disorders, such as FH, familial combined hyperlipidaemia (FCHL), dysbetalipoproteinaemia [4] and hypertriglyceridaemia [28] have genetic components. Assessment of family history is therefore an integral part of diagnosis and the panel recommend that genetic testing may be considered, although data are currently somewhat limited in this regard.

There are currently no consensuses among guidelines for the diagnosis of FH and different criteria exist to diagnose FH cases, including the use of biochemical, clinical, genetic and radiological investigations. Nevertheless, genetic testing should be considered in families with FH [4]. Elevated LDL-C in FH is present from birth and there is evidence that the prognosis of both heterozygous and homozygous FH is improved with early treatment [4]. Detection of FH via clinical assessment alone can be particularly challenging in patients where LDL-C elevation is less marked [29] and the CVD risk levels of patients with FH may not accurately be predicted by the use of multivariate risk scoring (see Section 3) [4]. Therefore, genetic screening should be considered to identify common mutations causing FH in the region for new-borns with LDL-C elevation or clinical signs suggestive of FH. This genetic confirmation, which could be incorporated into the analysis of the blood sample taken in the new-born heel prick test, may help to differentiate FH from FCHL and polygenic hypercholesterolemia with increased Lp(a). A systematic literature review identified 57 mutations in the Middle East and North Africa [30]; Table 1 summarises those reported in Middle Eastern countries. To date, the availability and uptake of genetic testing for FH in the Middle East has been limited [29].

3. Calculation of CVD risk

3.1. Estimating CVD risk

Assessment of ASCVD risk should take account of both lipid and non-lipid risk factors [2,4,24]. A number of patient groups should automatically be considered to be at high or very high risk of developing ASCVD, and should receive pharmacological therapy targeting plasma lipids. These include patients with known ASCVD [2,4,21,22], FH (due to a high risk of premature ASCVD, in absence of other risk factors) [4,21,29], T2DM [2,4,21,22] and CKD [2,4,21,22]. For other patients outside of these high-risk groups, the patient's global risk of ASCVD should be estimated using a scoring system (see Section 3.2) [4].

3.2. Key scoring systems

A number of different ASCVD risk scoring systems are recommended in existing international guidelines. Some scoring systems permit the calculation of lifetime CVD risk, while others calculate 10-year risk. Lifetime risk calculations may be of greater clinical relevance in the Middle East, due to the earlier onset of ASCVD in this population. Whichever scoring system is used, it should be remembered that ASCVD risk exists on a continuum, with thresholds for risk classification being somewhat arbitrary [4].

3.2.1. Ethnicity and scoring systems

Of the available scoring systems, the Framingham Risk Factor (FRF) has been assessed most widely in different ethnic groups, including in Middle Eastern populations, and is discussed in Section 3.2.2. The QRISK2 [40] also includes adjustment for ethnicity and has been compared with the FRF in an ethnically diverse UK population. One study found both systems to underestimate ASCVD risk in South Asian females [41], while another found the QRISK2 to underestimate ASCVD risk in South Asian males [42]. The SCORE risk chart, developed for European countries, has both a low- and high-risk version for use in different countries in the region, but the high-risk version may still underestimate risk in some Eastern European and Central Asian countries [43]. The Reynolds Risk Score, which incorporates measurement of additional risk factors such as levels of high-sensitivity C-reactive protein, was developed and validated using data from 24,558 initially healthy American women who were followed over a 10-year period for the development of heart attack, stroke, angioplasty (balloon surgery to open an artery), coronary artery bypass surgery, or death related to heart disease [44]. The Reynolds Risk Score for men was similarly developed using data from 10,724 initially healthy non-diabetic American men [45]. However, the score has since been examined in a US race-balanced, multi-ethnic (white African American, Hispanic and Chinese participants) population study and found to be predictive of ASCVD risk in males, but to underestimate risk in females [46]. However, a further study comparing the Reynolds Risk Score with the FRF in a multi-ethnic female population found the Reynolds Score to be better calibrated and to better discriminate between black and white females [47]. In 2013, the ACC/AHA published race-specific algorithms for the calculation of 10-year and lifetime CVD risk in non-Hispanic African American and white populations and recommended that the non-Hispanic white population version of the algorithms be used in other ethnic groups [48].

Table 1
FH-related genetic mutations reported in the Middle East.

Country	Reported FH-related mutations
Bahrain	*LDLR* c.1706-2A>T [30]
Iran	*LDLR* c.1478_1479delCT or *LDLR* c.1476_1478delCT (**FH-Yrmeih**); *LDLRAP1* c.71dupG; *LDLR* 2140 + 5G>A; *LDLR* 1773C>T; *LDLR* 1413G>A; *LDLR* 1725C>T [30]
Lebanon	LDLRAP1 c.406C>T; LDLRAP1 p.P202H/ LDLRAP1 c.747 + 744G>A; LDLRAP1 c.89-1G>C; LDLRAP1 c.748-608G>A [30], p.W249ins62* [31]; LDLR c.2043C>A; LDLR p.Q254P; LDLR p.D356Y; LDLR p.C358Y; LDLR c.1329G>A; LDLR p.I451T; LDLR p.P826S; LDLR p.T726I [30]; LDLRc.1171G>A, p.A391T [30,32]; LDLR c.980dupA [30]; PCSK9 L21dup [30]
Oman	*LDLR* c.272delG; *PCSK9* p.V474I [30]
Saudi Arabia	*LDLR* c.2439G>A [30], p.W813* [33]; LDLR c.2027delG, p.(G676Afs*33) [34]; LDLR c.2026delG, p.(G676Afs*33) [35]; LDLR c.1332dup, p.(D445*) [36]; LDLR c.313C>T, p.P105S [37]; LDLR c.498C>T, p.A166 = [37]; LDLR c.1171G>A, p.A391T [37]
Syria	*LDLR* c.2043C>A [30]; *LDLR* p.C667R [30]; LDLR c.1999T>C, p.C646R [38]; *LDLR c.1027G>A, p.G343S* [39]; *LDLR c.2483A>G, p.Y828C* [39]; *LDLRAP1* c.89-1G>C [30]

3.2.2. Framingham Risk Factor (FRF) scoring system

The Framingham ASCVD risk calculator (Framingham Risk Factor) is widely established and is commonly cited in existing international guidelines [4,21,22]. It incorporates various factors (Box 2) into multivariable sex-specific algorithms for the prediction of first cardiovascular (CV) event in patients [49].

This calculator is predictive of general ASCVD risk, rather than a specific disorder, thereby increasing utility in primary care and optimising ease of use for primary care physicians [49]. Two versions exist that either incorporate laboratory parameters (i.e. lipid levels) or replace these with inclusion of the patient's body mass index (BMI) (office-based version). The office-based version of this scoring system may have particular practical value in developing countries [51].

The FRF has its drawbacks, however. Limitations include a lack of TG level assessment [21] (high levels of TGs are a common feature of plasma lipid disorders in the Middle East) and limited predictive value in CKD patients [52]. In addition, the FRF calculates 10-year risk rather than lifetime risk. As mentioned in Section 3.2, lifetime risk calculations may be of greater clinical relevance in the Middle East. This means that clinicians may wish to choose an alternative scoring system, depending on the specific needs of their clinic.

Nevertheless, an advantage of the FRF is that validation and recalibration studies have been conducted in Middle Eastern populations. A Turkish study of patients undergoing coronary angiography for the assessment of coronary artery disease (CAD) due to chest pain and ischaemia ($n = 227$), found that a FRF score calculated before angiography was in general predictive of the presence, extent and severity of CAD. The score was more predictive in patients with hypertension, obesity or a family history of the disorder and less predictive in male patients and in those with diabetes [53]. A large Iranian study ($n = 46{,}674$) reported the performance of the office-based version of the FRF in predicting fatal CVD events to be comparable with that of previously tested models [51]. A further Iranian study ($n = 6224$) also confirmed clinical utility in this country's population, concluding that it may be more useful in males than in females [54].

Overall, it should be remembered that no scoring system is perfect for estimating ASCVD risk. Nonetheless, the use of a scoring system is important for approximating a patient's ASCVD risk and the need for pharmacological therapy. In this regard healthcare professionals in the Middle East may select those that they feel most appropriate to their own clinical practice. If healthcare professionals are unsure as to which scoring system is most appropriate for their clinic, then the FRF is a reasonable choice.

3.3. Other considerations when estimating CVD risk

Family history is an important component of ASCVD risk and should be assessed in all patients [2], in particular to identify the risk of heterozygous and homozygous FH [4]. This is of particular importance in the Middle Eastern population, where both forms of FH have an increased prevalence [29,55] and are underdiagnosed [29,55].

Women are at increased risk for some ASCVD risk factors (e.g. diabetes [4]), yet are generally under-managed in the Middle East and underrepresented in clinical trials [2,4]. It is important to initiate ASCVD risk assessment and subsequent treatment for dyslipidaemia in all eligible patients, regardless of gender.

Box 2
Factors incorporated into the Framingham 10-year ASCVD risk calculator [49,50].

- Sex (M/F)
- Age (years)
- Systolic blood pressure (mmHg)
- Treatment for hypertension (Y/N)
- Current smoker (Y/N)
- Diabetes (Y/N)
- HDL-C level (mg/dL)
- TC level (mg/dL)

HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol

4. Treatment goals

Risk levels for ASCVD should be used to inform treatment targets, treatment goals and treatment selection in patients with disorders of plasma lipids [4,5,22]. Pharmacological interventions should be initiated in all patients with a moderate or high risk of an ASCVD event. The treatment goals for these patients are outlined below.

4.1. Primary treatment target: LDL-C

High LDL-C levels (Box 3) are an independent predictor of ASCVD events [56], with risk being directly proportional to the level of LDL-C [57,58]. Reduction of LDL-C levels reduces the risk of having an ASCVD event [4,57]. The importance of reducing LDL-C levels is highlighted by the well-documented effects of statin therapy, with a number of pivotal clinical trials confirming that statin treatment reduces ASCVD risk [59–67]. Further evidence for the importance of LDL-C as a treatment target exists in the markedly increased ASCVD risk associated with FH [68].

A meta-analysis of clinical trials of statin therapy concluded that for every 1.0 mmol/L reduction in LDL-C there is an approximate 20% decrease in the risk of having a major ASCVD event. The authors of this analysis recommended that LDL-C goals should therefore exceed the one-third reduction that is currently commonly used in clinical practice [69].

Box 3
Classifications of cholesterol and triglyceride levels [22].

Lipid levels (mmol/L)	Lipid levels (mg/dL)	Classification
Non–HDL-C		
3.4	<130	Desirable
3.4–4.1	130–159	Above desirable
4.1–4.9	160–189	Borderline high
4.9–5.7	190–219	High
>5.7	≥220	Very high
LDL-C		
<2.6	<100	Desirable
2.6–3.3	100–129	Above desirable
3.3–4.1	130–159	Borderline high
4.1–4.9	160–189	High
>4.9	≥190	Very high
HDL-C		
<1.0	<40 (males)	Low
<1.3	<50 (females)	Low
TG		
<1.7	<150	Normal
1.7–2.2	150–199	Borderline high
2.2–5.6	200–499	High
>5.6	≥500	Very high

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
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4.1.1. High-risk patients

The ESC/EAS [4] and the IAS [21] guidelines recommend that, in high-risk patients, LDL-lowering therapy should be used to achieve an LDL-C < 1.8 mmol/L (<70 mg/dL). The ACC/AHA guidelines [5] recommend the use of high-intensity statin therapy to reduce LDL-C by >50%, with consideration of an adjunctive non-statin therapy to further reduce LDL-C if required [70]. We recommend that clinicians should aim for BOTH a 50% reduction in LDL-C levels (initial goal) AND an LDL-C < 1.8 mmol/L (<70 mg/dL) (after 50% reduction is achieved) in high-risk patients (Box 4). Clinicians should initially aim to reduce a patient's LDL-C by 50%. If after that goal is reached the patient has levels above 1.8 mmol/L (<70 mg/dL), then further management is needed to reduce this level until it is below this LDL-C goal.

4.1.2. Moderate risk patients

The ESC/EAS [4] and the IAS [21] guidelines recommend LDL-lowering therapy to achieve an LDL-C < 2.6 mmol/L (<100 mg/dL) in patients at moderate risk of developing ASCVD. The ACC/AHA guidelines [5] recommend the use of moderate-intensity statin therapy to reduce LDL-C by >30%%, with consideration of an adjunctive non-statin therapy to further reduce LDL-C if required [70]. We recommend that clinicians should aim for BOTH a 30% reduction in LDL-C (initial goal) AND an LDL-C < 2.6 mmol/L (<100 mg/dL) (after 30% reduction achieved) (Box 4).

4.2. Primary treatment target: non-HDL-C levels

A number of authors and international guidelines report non-HDL-C levels (Box 3) to be more predictive of ASCVD risk than are LDL-C levels [4,21,22,72]. Several international guidelines have recommended non-HDL-C as a co-primary treatment target [4,21,22]. Reductions in non-HDL-C levels by a range of lipid-lowering drug classes are associated with decreased ASCVD events, with an approximately 1:1 relationship between non–HDL-C decrease (%) and coronary heart disease reduction [73]. Non-HDL-C levels are a particularly useful measure in people with hypertriglyceridaemia, diabetes, CKD or MetS, where this value may provide a more accurate indication of ASCVD risk than is provided by the level of LDL-C alone [4]. Non-HDL-C levels may be of particular clinical relevance in Middle Eastern populations. We therefore recommend non-HDL-C as a primary treatment target, alongside LDL-C. Treatment goals should be non-HDL-C levels 0.8 mmol/L (30 mg/dL) higher than LDL-C targets for all patients [4] (Box 4).

4.3. Secondary treatment targets

In terms of secondary treatment goals, clinicians should consider HDL-C and plasma TG [4,21].

Box 4
Plasma lipid treatment goals.

Primary treatment goal: LDL-C

High-risk patients

- A 50% reduction (initial goal) AND <1.8 mmol/L (<70 mg/dL) (after 50% reduction achieved)

Moderate-risk patients

- A 30% reduction (initial goal) AND <2.6 mmol/L (<100 mg/dL) (after 30% reduction achieved)

Primary treatment goal: Non-HDL-C

- 0.8 mmol/L (30 mg/dL) higher than LDL-C target [4,71]

HDL, high-density lipoprotein; LDL-C, low-density lipoprotein; TG, triglyceride.

4.3.1. HDL-C

There is long-standing, well-documented and robust evidence showing that the concentration of HDL-C is an independent inverse predictor of the risk of having an ASCVD event [74]. The risk associated with a low level of HDL-C (Box 3) remains apparent even when the level of LDL-C has been reduced to low levels by treatment with a statin [75]. Furthermore, increasing the concentration of HDLs in mice and rabbits, whether by intravenous infusions of HDLs or by overexpressing the main HDL apolipoprotein, apoA-I, markedly decreases susceptibility to atherosclerosis in these animals [76,77]. However, despite these consistent observations, there is still no firm evidence in humans that interventions designed to increase the concentration of HDLs translate into a reduced risk of having a clinical ASCVD event [78].

Overall, the evidence base for targeting HDL-C to prevent ASCVD is not sufficient to recommend HDL-raising therapy as a strategy to reduce ASCVD risk. Rather, given that the presence of a low level of HDL-C is associated with a high ASCVD risk, it should be considered as an indication for more aggressive LDL-C lowering therapy to reduce this risk.

4.3.2. Plasma TG

An elevated level of plasma TG (Box 3) has been shown in several population studies to be associated with an increased ASCVD risk [79]. ESC and AACE guidelines report levels of <150 mg/dL (1.7 mmol/L) to be desirable [4,24], and the ESC recommends that pharmacotherapy is considered in high-risk patients with levels >200 mg/dL (2.3 mmol/L), if lifestyle modifications are not successful alone [4]. AACE guidelines report patients with TG levels ≥200 mg/dL to have a greatly increased ASCVD risk [24]. Very high levels (> 880 mg/dL [10 mmol/L]) of plasma TG are associated with acute pancreatitis [4]. It should be emphasised, however, that there is still no robust, consistent evidence that reducing the level of plasma TG translates into a reduction in ASCVD risk. As with a low level of HDL-C, an elevated plasma TG is associated with an increased ASCVD risk [80]. As a consequence, the presence of an elevated plasma TG should be considered as an indication for more aggressive LDL-C lowering therapy to reduce this risk. It should be noted that subgroup analyses of several trials with fibrates have provided a consistent finding that having an elevated plasma TG level identifies people who have a significant reduction in ASCVD risk when treated with a fibrate [81,82]. It is not known whether the reduction in risk is a consequence of a fibrate-induced reduction in plasma TG level or whether the presence of an elevated TG identifies people in whom a fibrate reduces risk by some other (unknown) mechanism. Despite the absence of direct evidence and despite uncertainty of what level of plasma TG should be aimed for, we recommend reducing elevated plasma TG levels as a secondary treatment goal. We recommend that a TG level > 200 mg/dL (2.3 mmol/L) warrants treatment.

5. Pharmacological treatment of plasma lipid disorders

5.1. General principles

The initiation of pharmacotherapy for the management of plasma lipids should be underpinned by patient education regarding the potential benefits and side effects of such therapy, the importance of long-term adherence to therapy, and the treatment goals to be achieved [22]. Following initiation, ongoing monitoring is important in all patient groups, and should include the assessment of lipid levels and adherence to both lifestyle advice and pharmacotherapy [5,22].

5.2. First-line treatment of plasma lipid disorders

Due to their proven benefits in reducing both fatal and non-fatal ASCVD events in large clinical outcome trials, statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors [83]) should be considered the first-line pharmacotherapy for lowering levels of LDL-C to reduce ASCVD risk [4,5,21,22]. The use of statins has been

shown to reduce LDL-C by 25–55% [21] (Table 2). Despite this, studies of patients in the Middle East revealed that the majority of high-risk patients requiring high intensity lipid lowering therapy were not receiving treatment that would enable them to meet the recommended target LDL-C reduction [84–86]. This contrasts with findings from Europe, which show that statin use has increased steadily over the past decade in both high-risk (i.e. Sicily) and low-risk (e.g. Stockholm) regions [87]. Nevertheless, even in Europe, a recent study showed that a sizeable portion of high-risk patients receiving lipid-lowering medication fail to achieve LDL-C target reduction and require more intensive lipid management [88].

The choice of statin should be based on the lipid-lowering target of the patient [4] (Table 3), statin–drug interactions (cytochrome pathway statins) and underlying renal function. If the maximum tolerated dose is not efficacious, then an alternative, more potent statin should be used. If, after switching, the treatment goal is still not achieved then another pharmacological agent should be added [4,5,22] (see Section 4.3), after first assessing patient adherence to treatment (including to lifestyle modifications) [5]. Statins are generally well tolerated, with serious side effects a rare occurrence. The most clinically important adverse effect associated with statin treatment is myopathy (occurring in <1/1000 patients), which, in rare cases, can lead to rhabdomyolysis and subsequent renal failure. Statin-induced myopathy can be measured via creatine phosphokinase (CK) levels, with an increase of five to ten times the upper limit of normal (ULN), measured on two occasions, requiring further evaluation [4,100] and levels greater than ten times the ULN suggesting myopathy [100]. Myalgia without CK elevation can occur in 5–10% of patients [4]. Dose-dependent increases in hepatic transaminases also occur in 0.5–2% of statin patients, although statin-induced liver failure is extremely rare [4]. If hepatic transaminases are more than three times the ULN on two occasions a few days or weeks apart, consideration should be given to reducing the dose of the statin or even stopping the statin and using an alternate LDL-lowering therapy. If a patient is found to be truly intolerant to statin therapy, this indicates a switch to an alternative pharmacotherapy (see below) [22,70].

5.3. Add-on, or second-line therapy to manage plasma lipids

Several classes of LDL-lowering agents are available as add-on therapy to statins – or as second-line therapy in cases of statin intolerance [4,21,70]. These include cholesterol absorption inhibitors, bile acid sequestrants, niacin and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (Table 2).

Table 2
The effects of currently available drug classes on low-density lipoprotein cholesterol levels when used for the general management of dyslipidaemia.

Pharmacological class	Reported decrease in LDL-C levels
Statins	25–55% [21]
Cholesterol absorption inhibitors (ezetimibe)	15–20% as monotherapy [4] Addition to a statin: 15–20% further reduction, beyond statin alone [89]
Bile acid sequestrants	18–25% as monotherapy [4] Addition to a statin: 10–20% further reduction, beyond statin alone [4]
Niacin	15–18% as a monotherapy [4] Addition to a statin/ezetimibe: 38% further reduction, beyond statin/ezetimibe combination alone [90]
PCSK9 inhibitors	47–57% as monotherapy [91–94] Addition to a statin/ezetimibe: 44–75% further reduction, beyond statin or ezetimibe alone [4,93,95–99]

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type

Table 3
Selecting a statin based on LDL-C treatment goals[a] [22].

High-intensity daily dosage ↓ LDL-C ≥ 50%	Moderate-intensity daily dosage ↓ LDL-C 30% to <50%
Atorvastatin, 40–80 mg Rosuvastatin, 20–40 mg	Atorvastatin, 10–20 mg Fluvastatin, 40 mg bid Fluvastatin XL, 80 mg Lovastatin, 40 mg Pitavastatin, 2–4 mg Pravastatin, 40–80 mg Rosuvastatin, 5–10 mg Simvastatin, 20–40 mg

bid, twice daily; LDL-C, low-density lipoprotein cholesterol.

[a] Individual responses to statin therapy should be expected to vary in clinical practice. Moderate- or high-intensity statin therapy is preferred unless not tolerated. Reprinted from J Clin Lipidol, Vol 9, Jacobson et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1—full report, pp. 129-–169, Copyright (2015), with permission from Elsevier.

5.3.1. Cholesterol absorption inhibitors

The cholesterol absorption inhibitor, ezetimibe, has been used both as add-on therapy to statins and as monotherapy in cases of statin intolerance [4,21]. When used as a monotherapy, ezetimibe reduces LDL-C by 15–20% [4]. When added to a statin, ezetimibe provides an average 15–20% further reduction in LDL-C, beyond that of the statin alone [89] (Table 2). Addition of ezetimibe to a statin reduces ASCVD events (IMPROVE-IT trial) [101,102]; this indication is now approved in Europe [103,104], although the US Food and Drug Administration (FDA) did not approve a proposed label change based on these findings [105]. A recent consensus document from the ACC suggests the use of ezetimibe as a second-line add-on to statin therapy, including in patients with comorbidities or baseline LDL-C ≥ 4.9 mmol/L (≥190 mg/dL) [70]. No major side effects have been reported with ezetimibe use [4,70].

5.3.2. Bile acid sequestrants

Bile acid sequestrants (cholestyramine, colestipol and colesevelam [106]) were the first class of drugs to show a reduction in ASCVD risk related to LDL-C lowering [106,107]. When used as a monotherapy, bile acid sequestrants reduce LDL-C by 18–25% [4]. Addition to a statin provides an average 10–20% further reduction in LDL-C levels, beyond that of the statin alone [4] (Table 2). In cases of statin intolerance, clinicians may wish to consider combining a bile acid sequestrant with ezetimibe [4]. The 2016 ACC consensus report also highlights their use as an alternative to ezetimibe in patients with TG <3.4 mmol/L (<300 mg/dL) and baseline LDL-C ≥ 4.9 mmol/L (≥190 mg/dL) [70]. Bile acid sequestrants can cause gastrointestinal side effects that may limit their use. These adverse effects may be reduced by initiating treatment at a low dose and increasing the dose gradually, and also by ensuring that the patient consumes ample amounts of fluid at the time of drug administration [4]. Clinicians should also be aware that TG may increase in patients treated with bile acid sequestrants [4].

5.3.3. Niacin

Niacin monotherapy reduces LDL-C by 15–18% (Table 2) and TG by 20–40%. Niacin also increases HDL-C in a dose-dependent manner by up to 25% [4]. Extended-release niacin may be used in combination with statins [4], and produces a larger increase in HDL-C and decrease in TG than statin alone or statin in combination with ezetimibe [108]. Further reductions (38%) in LDL-C, beyond those of statin/ezetimibe combination alone, have been reported [90] (Table 2), although other studies have found no additional reduction [108]. Side effects associated with niacin include skin reactions, hyperuricaemia and hepatotoxicity [4] and concerns exist regarding niacin side effects. In the HPS2-THRIVE study, 25% of patients receiving combined extended release niacin and laropiprant (compared with 17% receiving placebo) stopped

study treatment, with the most common reasons cited as skin, gastrointestinal, diabetes and musculoskeletal side effects. The treatment was also associated with increased risk of myopathy in Chinese patients [109].

5.3.4. PCSK9 inhibitors

Two monoclonal antibodies that inhibit PCSK9 were approved by the FDA [110] and European Medicines Agency [95,96] in 2015: alirocumab and evolocumab. When used as monotherapy, PCSK9 inhibitors reduce LDL-C levels by 47–57% [91,92]. PCSK9 inhibitors are more efficacious than ezetimibe in lowering LDL-C [91,92]. When added to a statin or ezetimibe, PCSK9 inhibition provides a further 44–75% reduction in LDL-C, beyond that achieved by the statin or ezetimibe alone [4,93,95–99] (Table 2). PCSK9 inhibitors should be considered for high-risk patients in whom LDL-C levels remain higher than the recommended goals despite taking maximal tolerated doses of a statin [95,96,111]. PCSK9 inhibitors can also be used in combination with other lipid-lowering agents [2,95,96]. The 2016 ACC consensus document highlights the potential of PCSK9 inhibitors as an adjunctive therapy to statins including when baseline LDL-C ≥ 4.9 mmol/L (≥190 mg/dL), and also as a potential replacement for statins, including in cases of statin intolerance or of comorbidities [70]. The NLA 2015 guidelines recommend that PCSK9 inhibitors be used as an adjunct to statin therapy in patients with ASCVD and LDL-C levels ≥2.6 mmol/L (100 mg/dL) or non-HDL-C levels ≥3.4 mmol/L (130 mg/dL), in high-risk patients with ASCVD with LDL-C and HDL-C levels that exceed their treatment goals, and in high- or very high-risk patients who are statin-intolerant [2]. The Canadian Consensus Working Group have also listed PCKS9 inhibitors as a pharmacotherapeutic option in patients with statin intolerance [112]. To date, no serious adverse effects have been reported with the use of PCSK9 inhibitors. Minor adverse effects include injection-site reactions [113] and respiratory effects [95,96].

Large clinical ASCVD outcomes trials of PCSK9 inhibitors are ongoing [110,111]. However, there are some preliminary, post-hoc shorter-term CV data available suggesting that these agents may reduce ASCVD risk [111]. In a post-hoc analysis comparing the addition of evolocumab to standard therapy, 1-year ASCVD events were reduced (0.95%, vs 2.18% for standard therapy alone, $p = 0.003$) [114]. A post-hoc analysis of a 78-week trial assessing the addition of alirocumab to statin therapy demonstrated a lower rate of major CV events compared with statin alone (1.7% vs 3.3%, $p = 0.02$) [94].

6. Lifestyle modifications

Lifestyle modification is an essential component of the management of patients with disorders of plasma lipids [4,5,21,22]. Information on lifestyle modifications should be provided to all patients at moderate or high risk of ASCVD, whether or not they are receiving pharmacotherapy [4]. It is critical to encourage adherence to a healthy lifestyle (which has traditionally been an issue in the Middle East). To this end, structured programmes are required for long-term effectiveness [4] and ongoing support is known to be valuable in maintaining weight loss [2]. The beneficial effects of lifestyle modifications on lipid levels are shown in Table 4.

Table 4
The beneficial effects of lifestyle modifications on lipid levels.

Lifestyle modification	Effect on lipid levels
Nutrition	
↓ trans fats (e.g. margarine, processed foods)	↓LDL-C +++, ↓TG, ↑HDL-C+++ [2,4,21]
↓ saturated fats (e.g. palm or coconut oil, beef, lamb, processed foods, ghee)	↓LDL-C+++, ↓TG + [2,4,21]
↓ carbohydrates (e.g. wheat flour, white rice, potato)	↓TG++, ↓VLDL, ↑HDL-C++ [4,21]
↓ mono and disaccharides (e.g. sugar-heavy desserts and drinks)	↓TG+++ [2,4,21], ↑HDL-C+ [4]
↑ fibre (e.g. wholegrain carbohydrates, fruit, vegetables, nuts and seeds)	↓LDL-C++, ↓TG [2,4,21]
Phytosterols intake	↓LDL-C+++, ↓TG [2,4,21]
n-3 polyunsaturated fats supplements/foods intake (e.g. oily fish)	↓TG++ [2,4,21]
Exercise	
↑ regular exercise	↓LDL-C+, ↓TG++, ↑HDL-C+++ [4,21]
Body weight	
↓ excess weight	↓LDL-C+, ↓TG+++, ↑HDL-C++ [2,4,21]
Other modifications	
Alcohol cessation	↓TG+++ [4,22]
Smoking cessation	↓TG+ [4,21,22], ↑HDL-C + [4]

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein; +++ = general agreement on the effects on lipid levels; ++ = less pronounced effects on lipid levels; weight of evidence/opinion is in favour of efficacy; + = conflicting evidence, efficacy is less well established by evidence/opinion [4].

6.1. Nutrition

There has been a worldwide shift towards a more energy-dense diet, which contains fewer high-fibre foods and greater levels of processed foods. This transition is contributing to an increase in obesity worldwide and is driven by factors including economic growth, urbanisation and globalisation [115]. Many countries in the Middle East have been undergoing development and urbanisation at a rapid rate over recent years, and this has been reflected in nutrition transition in the region. Food supply has increased over the last decade in many Middle Eastern countries [116] and has altered such that an increase in overall daily energy consumption has occurred. Protein and fat consumption in the Middle Eastern diet has also increased, including increased consumption of meat products. A decrease in consumption of cereals, fruit and vegetables has occurred in richer countries in the region, along with a dramatic increase in fat consumption in some countries and a high sugar intake in some regions due to local dietary customs [117]. The Western diet, which is increasing in prevalence in the Middle East, is known to be associated with several ASCVD risk factors (including high plasma TG and low HDL-C, MetS, T2DM and obesity) [118,119]. Some traditional Middle Eastern diets are also linked to plasma lipid disorders. For example, the Iranian diet (including high levels of refined grains, potato, hydrogenated fats, and broth) has been demonstrated to be significantly associated with low HDL-C and high TG levels [119].

Patients in the Middle East should be advised to modify their diet to reduce trans fats [2,4,21], saturated fats [2,4,21], carbohydrates [4,21] and mono- and disaccharides [4], and to increase fibre [2,4,21] and intake of phytosterols [2,4,21] and foods/supplements rich in $n-3$ polyunsaturated fats [2,4,21].

6.2. Exercise recommendations

Patients should be advised to participate in regular, moderate-intensity exercise, aiming for at least 30 min daily [4,21]. Moderate intensity can be considered as aerobic exercise at 40–75% of the patient's aerobic capacity. Patients aiming to reduce body weight can increase exercise levels gradually up to 250–300 min per week [5]. Regular exercise has proven benefits on plasma lipid levels (Table 4) and is particularly important in those with obesity, MetS and T2DM [4] (which are all highly prevalent in the Middle East).

6.3. Body weight recommendations

There is a high prevalence of overweight and obesity in the Middle East, with up to 40% of males and 30% of females being overweight, and 30% of males and 40% of females being obese [120]. Challenges exist with respect to the measurement of obesity and its relation to

ASCVD risk in Middle Eastern populations. There is some evidence that BMI may not be as predictive of ASCVD risk in this population compared with Western countries [20,51], and that BMI risk thresholds calculated in European populations may not be appropriate to use in Middle Eastern populations [121]. Instead, it is thought that values adapted for use in individuals of a specific ethnic origin may give a higher prediction of mortality in upper centiles of BMI [122].

A number of studies suggest that measurements of abdominal obesity, such as waist circumference (WC) values, may be more appropriate for use in the Middle East and that threshold values for abdominal obesity should be adapted for use in Middle Eastern populations. For example, in the INTERHEART Middle East study, abdominal obesity (measured by waist-to-hip ratio) (but not BMI) was significantly associated with the risk of acute myocardial infarction [20]. However, the IDEA study, which assessed 168,000 primary care patients in 63 countries, found that BMI may be more predictive of CVD than WC in Middle Eastern males [120]. WC thresholds for abdominal obesity have been calculated in Middle Eastern populations, with a threshold of >78.5 cm for males and >84.5 cm for females suggested in a study of an Omani Arab population [123]. Thresholds have also been calculated in Iran for ASCVD risk with a threshold of ≥90 cm indicative of patients at risk for ASCVD and requiring lifestyle modifications and ≥95 cm indicative of high risk patients who require immediate intervention [121].

Despite these difficulties in determining precise thresholds for overweight and obese subjects, it is important that all patients should be advised to reduce excess body weight [2,4,21] (Table 4).

6.4. Other lifestyle recommendations

Where alcohol is legally available, patients should be advised to keep intake to a minimum [4] (Table 4). Smoking cessation should also be recommended to all patients who smoke [4,21,22] (Table 4), including shisha and waterpipe tobacco smoking. Smoking prevalence in the Middle East is somewhat variable. A 2012 systematic analysis of surveys and databases in the region calculated that 52 million people in the Middle East and North Africa were smokers, with prevalence in Middle Eastern countries ranging from 8 to 27% [124].

7. Management of underlying conditions

A number of underlying conditions exist that predispose to abnormal plasma lipid levels. Here we review those most pertinent to clinicians in the Middle East: metabolic dyslipidaemia, elevated Lp(a), diabetes mellitus, CKD, FH, human immunodeficiency virus (HIV) and rheumatoid arthritis (RA).

7.1. Patients with high plasma TG and low HDL (metabolic dyslipidaemia)

Patients presenting with high levels of plasma TG and low levels of HDL-C are common in the Middle East [9]. This is important as there is increasing evidence that hypertriglyceridaemia is associated with elevated CVD risk [80]. In patients with mild-to-moderate hypertriglyceridaemia, lifestyle modifications alone may be sufficient [28], while statin therapy should be considered for all patients in whom additional risk factors are present.

Add-on fibrate (e.g. fenofibrate, bezafibrate, or ciprofibrate) therapy should be considered an option in patients with elevated levels of plasma TG and low levels of HDL-C despite taking statins [22,28]. When used as an add-on therapy to statins [2], fibrates are associated with a greater reductions in TG levels, and a greater increase in HDL-C (compared with either used as a monotherapy) [125]. Subgroup analyses of fibrate trials have consistently demonstrated that fibrates decrease ASCVD events in those with elevated levels of plasma TG and low levels of HDL-C [4,126]. Fibrates are generally well tolerated. Gastrointestinal side effects occur in around 5% of patients and skin rash occurs in around 2% of patients. Other clinically important side effects are myopathy (<1% increased risk [127]), cholelithiasis (<1% increased risk [127]) and increases in liver enzymes (<1%) [4].

In addition to statins, fibrates and lifestyle modifications, there is some evidence that $n-3$ fatty acids may have utility in patients with high levels of plasma TG and low levels of HDL-C – with up to 25–30% dose-dependent decreases reported in fasting and post-prandial TGs [4,28]. Clinical trials are ongoing to further investigate the effects of $n-3$ fatty acids on ASCVD risk [128]. PCSK9 inhibitors may also be of value in this patient population [99,129–132]. Further studies are ongoing [129].

7.2. Patients with elevated Lp(a)

An elevated Lp(a) level is a causal risk factor for ASCVD [4,26,27]. The mechanism by which raised levels of Lp(a) increase ASCVD risk is not known, but may relate to pro-thrombotic/anti-fibrinolytic effects [26]. Few efficacious treatment options exist; niacin lowers Lp(a) levels by up to 30% [4]. PCSK9 inhibitors may represent a new therapeutic option in these patients, with Lp(a)-reducing effects seen in post-hoc analyses of both evolocumab [133] and alirocumab [134] clinical trials. LDL apheresis is considered the most efficacious method to reduce Lp(a) and should be considered as a treatment option for patients with elevated Lp(a) [4]. This specialised technique removes LDL and Lp(a) from the plasma during extracorporeal circulation, once every 1–2 weeks [4,21,22]. However, LDL apheresis is of limited availability in the Middle East. Finally, oestrogen and oestrogen replacement therapies also decrease Lp(a) by up to 10% [26], therefore the panel suggest that these may be considered in female patients, if not contraindicated.

7.3. Diabetes mellitus

The Middle East and North Africa region has one of highest diabetes prevalence rates globally (9–11%), with T2DM predominating [19,135]. In a World Health Organization 2007 report, four of the five countries where diabetes was most prevalent were Middle Eastern countries (United Arab Emirates, Saudi Arabia, Bahrain and Kuwait) [136] and diabetes rates are predicted to rise significantly in Middle Eastern countries by 2030 [136,137] (Table 5). A 2015 International Diabetes Federation Report estimates that over 9% of adults (20–79 years) in the Middle East and North Africa have diabetes, with over 40% of these undiagnosed [135]. Seven to 8% of the Middle East and North Africa population is estimated to suffer from impaired glucose tolerance, and to be at an increased risk of diabetes [19,135], and MetS prevalence is approximately 25% [18].

7.3.1. Type 2 diabetes (T2DM)

An elevated level of plasma TG combined with a low level of HDL-C and an LDL fraction characterised by small dense particles is frequently encountered in people with T2DM [138,139]. This lipid profile may partly account for the high ASCVD risk in patients with T2DM [138,139]. Management of both glucose levels and the metabolic dyslipidaemia is integral to minimising CVD risk [22], and appropriate glycaemic control reduces TG levels [28]. The current management of dyslipidaemia and glycaemic control in T2DM in the Middle East is suboptimal [19,140].

Middle Eastern countries suffer from a high prevalence of other T2DM risk factors (e.g. obesity) due to changing lifestyles, exercise levels and diets in recent decades [10,19]. Therefore, to manage plasma lipids in patients with T2DM, lifestyle modifications are essential for all patients [4,139,141], and individualised dietary advice is important [4]. For all patients, statin therapy should be considered and individualised, including with respect to age and LDL-C levels [4,5]. In patients aged 40–75 years with LDL-C ≥ 70 mg/dL, moderate-intensity statin therapy should be initiated [5]. The panel also recommends that statins should be initiated in patients <40 years of age if T2DM duration ≥10 years. The UK NICE guidelines recommend statin initiation in patients with T2DM with a ≥10% 10-year risk of developing ASCVD [142].

Table 5
Predicted prevalence of diabetes in Middle Eastern countries in 2030, compared with those reported in 2000 [137].

Country	2000	2030
Arab World	7,814,000	22,157,000
Bahrain	37,000	99,000
Egypt	2,623,000	6,726,000
Iraq	668,000	2,009,000
Jordan	195,000	680,000
Kuwait	104,000	319,000
Lebanon	146,000	378,000
Oman	113,000	343,000
Qatar	38,000	88,000
Saudi Arabia	890,000	2,523,000
Syria	627,000	2,313,000
United Arab Emirates	350,000	684,000
Yemen	327,000	1,286,000

If the maximal statin dose is not efficacious then other medications may be added. Ezetimibe, or alternatively bile acid sequestrants, can be added to statin therapy in patients aged 40–75 years with LDL-C 1.8–4.9 mmol/L (70–189 mg/dL) [70]. Addition of fibrates may be beneficial in some groups. Fibrates have been found to reduce ASCVD event rates in T2DM patients with elevated plasma TG and low HDL-C levels [126,143]. Data regarding the beneficial effects of fibrates on ASCVD risk in diabetic patients with normal levels of plasma TG and HDL-C have been disappointing [143].

As an alternative to fibrates, colesevelam (a bile acid sequestrant) may be considered as an add-on to statin therapy as it has been shown to improve HbA1c levels in T2DM [144,145]; however, it is not widely available in the region. PCSK9 inhibitors may also be considered, as these are efficacious in patients with T2DM, with LDL-C reductions of approximately 60% [146–148], which is much greater than observed with ezetimibe [146]. The American Diabetes Association recommends that PCSK9 inhibitors are considered as an adjunct to statin therapy in diabetic patients with high risk for ASCVD who have not attained their LDL-C goals, and as an option in those intolerant to statins [149]. Furthermore, niacin could be considered in those patients for whom fibrates are contraindicated, although it may worsen glycaemic control [4,109,150].

7.3.2. Type 1 diabetes

Type 1 diabetes is associated with increased CVD risk [151]. Patients typically have lower than normal levels of TG and LDL-C and higher than normal levels of HDL-C, thought to be due to insulin treatment, with atherogenic changes in particle composition. Statins are the first-line treatment for managing plasma lipids in patients with type 1 diabetes, with an LDL-C goal of 30% reduction regardless of baseline LDL-C levels [4]; the panel recommends a goal of 50% reduction in LDL-C in patients with type 1 diabetes if established ASCVD is also present.

7.4. Chronic kidney disease (CKD)

CKD is a major risk factor for ASCVD [152,153] and is associated with an 8 to 10-fold increase in cardiovascular mortality [136]. Abnormalities of plasma lipids are common in people with CKD [23], including increased TG and non-HDL-C levels, and decreased levels of HDL-C [4]. Abnormalities of plasma lipids increase with worsening glomerular filtration rate (GFR) [4] as do CKD-related ASCVD risk factors, such as inflammation, oxidative stress and vascular calcification [154]. The level of vascular calcification in CKD patients is also predictive of ASCVD risk [155–158] and is increased in patients with concomitant diabetes and CKD [158–160]. These CKD-related ASCVD risk factors are distinct from those in the general population [154]. All newly diagnosed CKD patients should be screened for plasma lipid disorders [23]. Other ASCVD risk factors present in patients with CKD include obesity, diabetes and hypertension [153], which are all prevalent in Middle Eastern countries [16,136]. ASCVD can be complex in CKD patients, and is often underdiagnosed and undertreated [153].

The global prevalence of CKD is 5–7% [152] – with higher prevalence rates in developing countries [152] – and is rapidly increasing worldwide [4]. Accurate data and large epidemiological studies on the prevalence of CKD in the Middle East are somewhat lacking [136,161,162] and prevalence is likely under-reported [136]. There may also be a population of undiagnosed and untreated patients [136]. Nevertheless, some data are available, which suggest that the incidence in the Middle East may be higher than global levels. A large ($n = 10{,}748$) Turkish study reported CKD prevalence of 16% [163]. In the same population the prevalence of hypertension, diabetes, dyslipidaemia, obesity, and MetS were 33%, 13%, 76%, 20%, and 31% respectively [163]. Large ($n > 10{,}000$) Iranian studies estimate CKD prevalence to be approximately 11–13% [164,165]. Another Iranian study ($n = 3313$) reported incidence density rates 285 and 133 per 10,000 person-year (women and men, respectively) [166], suggesting that >2% population develops CKD each year. End-stage renal disease (ESRD) incidence is estimated at 100–140 cases per million in the Middle East [161], and this may be increasing according to data from one country (Saudi Arabia) [162]. A literature review of data from ten Middle Eastern countries estimated average incidence rates of ESRD as 93 patients per million, with an average prevalence of 352 patients per million [167].

While LDL-C is not as predictive of ASCVD risk in CKD patients as in the rest of population [168], LDL-C lowering by the combination of simvastatin plus ezetimibe has been shown to reduce ASCVD risk [23,169]. However, there is no evidence to date that statins reduce CVD risk in patients receiving dialysis. The choice of treatment should be based on GFR [4,23] and where possible, it is recommended that prescribed pharmacotherapies should be those cleared by hepatic routes [4]. It is also important to note that CKD patients may be receiving multiple medications, therefore the potential for drug–drug interactions with lipid-lowering medications should be carefully considered (e.g. many statins undergo significant cytochrome P450 metabolism [4,170]). The recommended treatments for dyslipidaemia in patients with CKD are outlined in Table 6 and statin doses in Table 7. These recommendations are aligned with the 2013 KDIGO clinical practice guideline for lipid management in CKD [23].

7.5. Familial hypercholesterolaemia

FH confers a greatly increased risk of ASCVD [4,68,171]. It is characterised by high LDL-C levels [4,29,68,171]. If untreated, FH results in premature ASCVD and premature death [4,29,68,171]. FH is inherited in an autosomal dominant manner, and can be either heterozygous or homozygous (with homozygous being the more severe form) [4,68,171].

Heterozygous FH is the more common form, affecting 1 in 250 people in European populations [172,173], with homozygous FH affecting 1 in approximately 300,000 people [174]. Both heterozygous and homozygous FH are important in the Middle East due to a higher level of consanguineous marriages [29,30]. Surprisingly, however, FH prevalence data in the Middle East are lacking. Nevertheless, extrapolation of global data and the local data available suggest that rates of homozygous FH are higher in the Middle East than in the West [29].

FH is underdiagnosed in the Middle East [29,30]. Diagnosis of FH should include a number of components, including the assessment of LDL-C levels, xanthomas and family history. Useful diagnostic criteria that encompass these various elements are available, including the WHO criteria [175], Dutch criteria [176] and Simon-Broome criteria [177], which has been used successfully in an Omani Arab population [178]. Adulthood LDL-C levels in untreated FH are typically 5–10 mmol/L (200–400 mg/dL) in heterozygous FH [4] and >13 mmol/L (500 mg/dL) in homozygous FH, although levels can be lower [29]. Xanthomas may be present in patients with homozygous FH (although not in every case) [4,29] and tendon xanthomatas may present in cases of heterozygous FH [4]. To differentiate FH from other conditions where

Table 6
Recommendations for managing plasma lipids in patients with chronic kidney disease [23].

Patient type (adults)	Treatment recommendation
≥50 years eGFR <60 mL/min/1.73 m^2 Not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5)	Statin or statin/ezetimibe
≥50 years CKD and eGFR > 60 mL/min/1.73 m^2 (GFR categories G1-G2)	Statin
18–49 years CKD Not treated with chronic dialysis or kidney transplantation One or more of following present • known coronary disease (myocardial infarction or coronary revascularisation) • diabetes mellitus • prior ischaemic stroke • estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%	Statin
Kidney transplant recipient	Statin
Dialysis-dependent CKD	Do not initiate statin (if already receiving at time of dialysis initiation, continue)
CKD and high TG	Lifestyle modifications

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; TG, triglyceride.

elevated LDL-C levels may be within a similar range, assessment of family history is critical [4,29,178] and genetic testing should be considered (in the case of homozygous FH in particular) [29]. However, genetic testing is of limited availability in the Middle East currently [29]. Patients with FH should also be screened for other potential underlying dyslipidaemia risk factors (e.g. diabetes) [29].

In addition to lifestyle modifications [4,178], statins should be first-line treatment for dyslipidaemia in FH [4,29]. However, even the most potent statins may be insufficient to achieve recommended LDL-C levels [4,29,178]. In such cases, the addition of another medication (e.g. ezetimibe [4,21], a PCSK9 inhibitor [2,95,96,148]), or bile acid sequestrants [4] should be considered; the 2016 ACC consensus statement recommends that a PCSK9 inhibitor may be considered as a first-line adjunct [70]. In the case of homozygous FH, which is a complex disorder that should be treated under the guidance of a specialist and include careful medication monitoring, LDL apheresis should be used alongside statin therapy where available [4]. The panel recommend that the LDL-C time-averaged mean for apheresis in homozygous FH patients should be <2.6 mmol/L (<100 mg/dL). The microsomal transfer protein inhibitor lomitapide is also now available in the Middle East and is indicated as an adjunct to other pharmacotherapies in the treatment of homozygous FH [179,180]. Lomitapide reduces LDL-C by up to 50% and TG by 45% when administered as an adjunct therapy [181]. In some countries, the oligonucleotide mipomersen [182] is also approved as an add-on to statins for the treatment of homozygous FH. This medication is associated with an incremental LDL-C reduction of 25–36% [183,184]. Evolocumab can also be considered as an adjunct therapy in homozygous FH patients [96,185,186], and is efficacious in LDL-receptor-defective patients [185].

Table 7
Recommended statin doses (mg/d) in adults with chronic kidney disease [23].

Statin	eGFR G1–G2	eGFR G3a–G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	ns
Fluvastatin	GP	80
Atorvastatin	GP	20
Rosuvastatin	GP	10
Simvastatin/ezetimibe	GP	20/10
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GP, general population; ns, not studied.

7.6. HIV

HIV is associated with an increased prevalence of CVD, thought to be due in part to HIV-associated inflammatory and immune activity and in some cases related to antiretroviral therapy. HIV should however be considered a CVD risk factor and patient education on this topic is important. In general, patients with HIV and plasma lipid disorders should be treated with pharmacotherapy in the same way as other patients, although consideration should be given to the possibility of drug–drug interactions [2].

7.7. Rheumatoid arthritis (RA)

The systemic inflammation present in RA confers an increased risk of CVD [2,187] and CVD is the leading cause of death in RA patients [188]. Lipid levels vary depending on RA treatment and the level of inflammation present, and can be lower than those in the general population despite an overall increased CVD risk. Some RA medications (e.g. methotrexate) may undergo drug–drug interactions with lipid-lowering drugs. These should be considered when selecting treatment and monitoring may be required [2].

8. Management of special populations

Sub-populations of patients with plasma lipid disorders require special management: here we provide guidance on the management of plasma lipids in pregnancy and lactation, and in children.

8.1. Pregnancy and breastfeeding

Lipid levels increase during pregnancy, peaking as the woman approaches term. In a 'normal' pregnancy neither TC and TG levels should exceed 250 mg/dL; if these levels are exceeded this may indicate a pre-pregnancy plasma lipid disorder, which may lead to an increased risk of obstetrical and foetal complications (hypertriglyceridaemia may also indicate undiagnosed pre-pregnancy diabetes). This pregnancy-related increase in lipid levels represents an additional risk factor for CVD in patients with FH. If pre-pregnancy lipid levels are unknown, evaluation may be incorporated into routine pregnancy blood tests and conducted again six weeks post-natally [2].

In general, women receiving lipid-lowering medication, with the exception of bile acid sequestrants, are advised to stop pharmacotherapy in preparation for, and during, pregnancy [70], although preliminary

Box 5
Summary of recommendations.

Screening
Every five years in patients ≥20 years old [22].
In all patients with T2DM [4,22]; arterial hypertension [4]; manifest ASCVD [4,22]; central obesity [4]; chronic inflammatory autoimmune disease [4]; CKD [4,22]; family history of ASCVD [4].
Offspring of patients with severe plasma lipid disorders (e.g. FH) [4].
Screening endpoints
LDL-C, TC, TG, HDL-C, non-HDL-C, Lp(a) (in high-risk patients) [4]; family history [2]; genetic testing (dependent on family history) [4]; ASCVD risk scoring system [4].
Primary treatment goals
LDL-C
High-risk patients: 50% reduction AND <1.8 mmol/L (<70 mg/dL) (after 50% reduction achieved).
Moderate-risk patients: 30% reduction AND <2.6 mmol/L (<100 mg/dL) (after 30% reduction achieved).
Non-HDL-C
0.8 mmol/L (30 mg/dL) higher than LDL-C target [4,71].
Treatment
Pharmacotherapy
First-line [4,5,21,22]: statins.
Second-line/adjuncts [4,21,70]: cholesterol absorption inhibitors (ezetimibe); bile acid sequestrants (cholestyramine, colestipol and colesevelam); niacin; PCSK9 inhibitors.
Lifestyle modifications
↓ trans fats [2,4,21], saturated fats [2,4,21], carbohydrates [4,21] and mono- and disaccharides [4].
↑ fibre [2,4,21] and intake of phytosterols [2,4,21] and foods/supplements rich in *n*−3 polyunsaturated fats [2,4,21].
Regular, moderate-intensity exercise (30 min daily) [4,21]; ↓ excess body weight [2,4,21].
Alcohol (where legally available) kept to a minimum [4]; smoking cessation [4,21,22].
Patient with underlying conditions
Metabolic dyslipidaemia: mild-to-moderate: lifestyle modifications [28]. Additional risk factors: consider statin therapy. If dyslipidaemia persists: add-on fibrates [22,28]. *n*−3 fatty acids and PCKS9 inhibitors may be useful [4,28,99,129–132] (studies ongoing [128,129]).
Elevated Lp(a): few efficacious treatments. LDL [4]; niacin [4]; possibly PCSK9 inhibitors [133,134]; oestrogen and oestrogen replacement [26] in female patients, if not contraindicated.
T2DM: Lifestyle modifications [4,139,141] and individualised dietary advice [4]. Statins [4]: moderate-intensity [5] in patients aged 40–75 years with LDL-C ≥ 70 mg/dL. Individualise with respect to age and LDL-C levels in other patients [5]. Initiate statins in patients <40 years of age if T2DM duration ≥10 years.
Add-on therapies (if statin alone not efficacious): ezetimibe, or bile acid sequestrants, in patients aged 40–75 years with LDL-C 1.8–4.9 mmol/L (70–189 mg/dL) [70]; fibrates (in patients with elevated plasma TG and low HDL-C levels) [126,143]; colesevelam as an alternative to fibrates [144,145]; PCSK9 inhibitors may also be considered [146,147]; Niacin could be considered if fibrates contraindicated; may worsen glycaemic control [4,109,150].
T1DM: first-line pharmacotherapy: statins [4].
CKD [23]: dialysis-dependent: do not initiate statins. High TG: lifestyle modifications. Other CKD patients: statins. ≥50 years, GFR categories G3a–G5: also consider add-on ezetimibe.
FH: Lifestyle modifications [4,178]; statins are first-line pharmacotherapy [4,29]. Add-on therapies (if statin alone not efficacious): ezetimibe [4,21], PCSK9 inhibitor [95,96]), or bile acid sequestrant [4]. Also lomitapide for homozygous FH [179,180]. In some countries, mipomersen [182] for homozygous FH.
HIV: consider drug–drug interactions [2].
RA: consider drug–drug interactions, monitoring may be required [2].
Special populations
Pregnancy and breastfeeding: lifestyle modifications; stop pharmacotherapy (with the exception of bile acid sequestrants) in preparation for, and during, pregnancy [70].
Hypertriglyceridaemia (≥500 mg/dL)*: n*-fatty acids and/or fibrates (fenofibrate or gemfibrozil) into the second trimester, based on clinical judgement [2,191].
FH: colesevelam and LDL apheresis [2].
Pharmacotherapy and breastfeeding: FH: colesevelam [2,191,192]; hypertriglyceridaemia: pharmacotherapy [2,191,192]; statin and ezetimibe may be resumed after completion of breastfeeding [70].

Children: Monitoring of lipid levels and ASCVD risk factors [2]; lifestyle modifications [2]; avoid lipid-lowering pharmacotherapy, except in FH [4].

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); non-HDL-C, non-high-density lipoprotein cholesterol; RA, rheumatoid arthritis; TC, total cholesterol; TG, triglyceride; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; PCSK9, proprotein convertase subtilisin/kexin type.

data regarding statin use in pregnancy are now available [189]. Data on the use of lipid-lowering medications in pregnancy from human studies are somewhat lacking and animal studies have elicited mixed data [2,190]. The safety of PCSK9 inhibitors during pregnancy has not yet been determined [2]. Lifestyle modifications should be continued throughout pregnancy.

8.1.1. Pharmacotherapy in pregnancy: special circumstances

Hypertriglyceridaemia (≥500 mg/dL) may be treated with *n*-fatty acids and/or fibrates (fenofibrate or gemfibrozil) into the second trimester, based on clinical judgement [2,191]. Women with FH may be treated with colesevelam and LDL apheresis during pregnancy. In women with gestational diabetes or pre-existing diabetes good glycaemic control is also critical [2]. Currently no safety and efficacy data are available regarding the use of mipomersen [70] or PCSK9 inhibitors in pregnancy [70,95,96].

8.1.2. Pharmacotherapy and breastfeeding

Breastfeeding women should continue with lifestyle modifications. Those with FH may continue colesevelam. Medications for hypertriglyceridaemia may also be continued. Breastfeeding, including duration of lactation, has a beneficial effect on future ASCVD risk [2,191,192]. Statin and ezetimibe may be resumed after completion of breastfeeding [70]. Currently, safety and efficacy data are not available regarding the use of PCSK9 inhibitors in breastfeeding [95,96].

8.2. Children

With the exception of conditions such as FH, ASCVD is rare in childhood [2,4]. Nevertheless, accumulation of ASCVD risk factors can occur, for example obesity and insulin resistance [2], and conditions such as diabetes mellitus and Kawasaki disease can lead to childhood plasma lipid disorders [2]. Therefore, in children with these conditions, monitoring of lipid levels and ASCVD risk factors and management with lifestyle modifications are integral to improved outcomes in adulthood [2]. Lipid-lowering pharmacotherapy should generally be avoided in children with increased lipids, with the exception of those with FH [4].

9. Future directions

The recommendations presented here represent the first set of clinical recommendations for the management of plasma lipid disorders in the Middle East (summarised in Box 5). To continue to improve patient management in the region there is a need for further research in the management of disorders of plasma lipids in the Middle East. Such research should focus on: the development of a region-specific risk scoring system for calculating cardiovascular risk; incorporating a comprehensive and cost-effective FH screening program in the region that includes assessment of family history for all patients and routine screening of children at risk of FH; large and accurate regional epidemiological studies of plasma lipid disorders – particularly metabolic dyslipidaemia, as it is the most prevalent form of lipid disorder in the region – and FH; and developing increased patient awareness of, and adherence to, lifestyle advice and modifications. Additionally, as new treatments continue to be examined (e.g. long-term CV outcome trials with PCSK9 inhibitors) and developed (e.g. microsomal transfer protein inhibitors [193,194]), there will be a need to update the current recommendations at an appropriate time point in the future. Finally, there is a need for lipid clinic networks and regional lipid societies in the Middle East to develop lipid educational programs to improve the awareness of lipid disorders among physicians, allied health professionals, patients and the public.

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All authors attended and participated in the expert panel meeting where the discussions for these recommendations took place. Dr. Al Sayed, Professor Al-Rasadi and Professor Barter contributed to the development of the initial draft of the recommendations. All authors critically reviewed and revised this draft. All authors approved the final version of the manuscript.

Conflicts of interest

Over the past 2 years, Dr. Al Sayed has received honoraria from AstraZeneca and Sanofi and sat on advisory boards for Aegerion and Sanofi.

Dr. Al-Nouri and Dr. Sabbour sit on advisory boards for Aegerion, Amgen and Sanofi.

Dr. Al-Rasadi has received educational grants from Pfizer, honoraria from AstraZeneca, Pfizer and Sanofi, and has sat on advisory boards for Aegerion, AstraZeneca and Sanofi.

Dr. Hassanein reports receiving speaker honoraria from Merck and Sanofi, and has sat on advisory boards for Merck and Sanofi.

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