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Review article

Dyslipidemia management for primary prevention of cardiovascular events: Best in-clinic practices

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ABSTRACT

Dyslipidemia is a fundamental risk factor for cardiovascular diseases (CVDs) and can worsen the prognosis, if unaddressed. Lipid guidelines are still evolving as dyslipidemia is affecting newer patient subsets. However, these guidelines are governed by regional demographics and ethnic data. Primary care practitioners (PCPs) are the first to offer treatment, and hence placed early in the healthcare continuum. PCPs shoulder a huge responsibility in early detection of dyslipidemia for primary prevention of future cardiovascular (CV) events. Therefore, as members of Cardiovascular RISk Prevention (CRISP) in Asia network, the authors intend to align and shape-up the daily clinical practice workflow for PCPs and have a goal-directed strategy for managing dyslipidemia. This paper reviews the major international lipid guidelines, namely the American and European guidelines, and the regional guidelines from Indonesia, Malaysia, Philippines, Thailand, and Vietnam to identify their commonalities and heterogeneities. The authors, with a mutual consensus, have put forth, best in-clinic practices for screening, risk assessment, diagnosis, treatment, and management of dyslipidemia, particularly to reduce the overall risk of CV events, especially in the Asian context. The authors feel that PCPs should be encouraged to work in congruence with patients to decide on best possible therapy, which would be a holistic approach, rather than pursuing a "one-size-fits-all" approach. Since dyslipidemia is a dynamic field, accumulation of high-quality evidence and cross-validation studies in the future are warranted to develop best in-clinic practices at a global level.

1. Introduction

Premature death due to cardiovascular diseases (CVD) is at an all-time high, globally (Gebreegziabiher et al., 2021). In Asia the number of CVD deaths have almost doubled from 5.6 million to 10.8 million over the last 30 years (Zhao et al., 2019). The risk of developing CVD increases two-fold when dyslipidemia sets in (Gebreegziabiher et al., 2021). Dyslipidemia is responsible for approximately 4 million CVD-related deaths across the globe. Asian countries such as Indonesia, Thailand, Malaysia, and China have witnessed the largest increases in cholesterol levels over the last few years and have already surpassed other western countries/continents including Europe and the United States (Zhao et al., 2019). Some country-based studies have shown increased levels in all the measured lipid parameters. (Fig. 1).

Dyslipidemia is a major modifiable risk factor for CVD. It can be classified into hypercholesterolemia, hypertriglyceridemia, and mixed hyperlipidemia, characterized by elevated levels of either total cholesterol (TC) or triglycerides (TG), or a combined pattern. This condition is linked to an underlying genetic or an acquired cause (Nelson, 2013). Genetic causes affect single or multiple genes involved in overall lipid metabolism. This may result in familial hypercholesterolemia (FH) with elevated TC levels (>7.7 mmol/L), combined (FH) with elevated TC (<6.5 mmol/L) and TG levels (>2.2 mmol/L) or familial hypertriglyceridemia (1.7-≥22.6 mmol/L) (Nelson, 2013; Luijten et al., 2019) resulting in premature ASCVD in younger individuals (20–40 years; Nelson RH, 2013). An in-depth discussion of all the genetic causes of hyperlipidemia and their clinical consequences is beyond the scope of this review. The genetic pattern, combined with modifiable risk factors namely central obesity, saturated and trans fats intake, excess cholesterol content can accelerate the hyperlipidemia occurrence. (Hill and

Abbreviations: CRISP, Cardiovascular RISk Prevention; CV, cardiovascular; CVD, cardiovascular diseases; PCPs, primary care practitioners.

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Bordoni, 2022; Nelson, 2013). Exogenous factors namely intake of drugs belonging to specific classes (thiazide diuretics, beta-blockers, oral contraceptives, and antiretrovirals), obesity, diabetes, chronic kidney disease (CKD), nephrotic syndrome, thyroid disorders can increase hyperlipidemia risk with disease progression. (Hill and Bordoni, 2022; Nelson, 2013).

Dyslipidemia alone or combined with other risk factors such as age, gender, cigarette smoking, physical inactivity, genetics, type 2 diabetes mellitus (T2DM), hypertension, metabolic syndrome (MetS), hormonal changes in women (polycystic ovarian syndrome [PCOS] and post-menopause), and obesity can increase cardiovascular (CV) morbidity and mortality (Francula-Zaninovic and Nola, 2018). In the absence of documented family history of premature CVD, children and adolescents with risk factors such as poor diet, sedentary lifestyle, hypertension, diabetes, smoking, overweight and obesity, are candidates for dyslipidemia screening (Kalra et al., 2009).

Multiple international guidelines have put forth strategies to prevent and manage dyslipidemia. However, these are mostly corroborated in the western population, which differ from their Asian counterparts with respect to lifestyle, diet type, eating habits, overall body mass index (BMI), smoking status, and genetics. The CVD risk is also substantially raised in Asians and can be attributed to urbanization, ethnic or genetic susceptibility, and/or comorbidities. Southeast Asia also has a high prevalence of T2DM with genetic predisposition towards dyslipidemia and related conditions such as, central obesity, to be precise (World Health Organization Regional Office for South-East Asia, 2011). Interestingly, accumulating evidence suggests that central obesity among Asians for a given BMI is greater vs. Caucasians. This combined with T2DM gives rise to higher CV mortality amongst Asians vs. Caucasians (Yu Chen et al., 2013). Ethnicity also tends to impact lipid profiles, even within the ethnic groups from the same country e.g., ethnic groups within Indonesia have large variation in their plasma lipid profiles (Alshamiri et al., 2018; Pu et al., 2016). Considering this variability, extrapolation of the international guidelines or for that matter, regional Asian guidelines that do not account for this variation is undesirable and potentially creates confusion.

Therefore, a common consensus between major international guidelines and local clinical practice guidelines becomes imperative to overcome the intriguing dilemma of providing clinical guidance in the view of such variations. Primary care practitioners (PCPs) in primary care settings are usually the first point of contact, attending all patients in general (including those with or without risk factors). Hence, they should have clear and practical knowledge regarding the risk factors, screening, diagnostic tools as well as management strategies to cater to the unique needs of the population (in both urban and rural areas) (Alshamiri et al., 2018). It could be a great opportunity for the PCPs to aim at primary prevention of impending CVD by targeting dyslipidemia early on. For this purpose, the medical practitioners in Cardiovascular RISk Prevention (CRISP) in Asia network, who are also serving as authors for this review, have come together to put forth the best in-clinic practices with regards to screening among varied age groups, risk assessment, diagnosis, drug strategies and overall management. The authors have considered seven dyslipidemia guidelines while crafting these best practices: America (American College of Cardiology/American Heart Association (ACC/AHA), Europe (European Society for Cardiology/European Atherosclerosis Society (ESC/EAS), Indonesia (Indonesian Heart Association Guidelines on Management of Dyslipidemia), Malaysia (Management of Dyslipidemia Guidelines), Philippines (Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines), Thailand (Clinical Practice Prevention on Pharmacological Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention) and Vietnam (Recommendations on Diagnosis and Treatment of Lipid Disorders) (Grundy et al., 2019; Mach et al., 2020; Erwinanto et al., 2017; Yusoff et al., 2017; Gonzalez-Santos et al., 2021; The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for

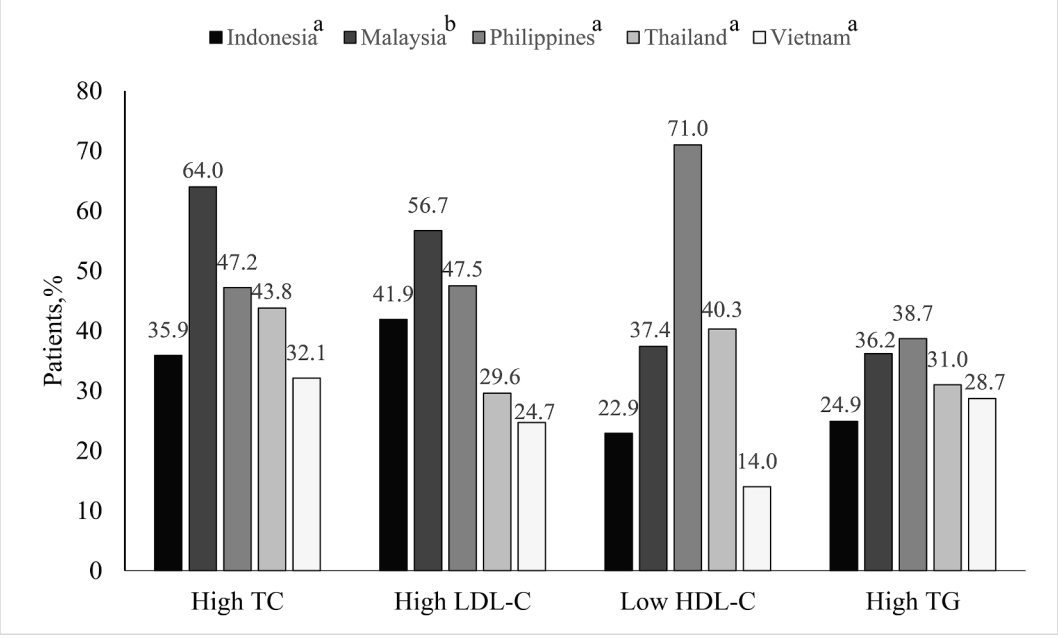


Fig. 1. The prevalence of plasma lipid disorders in Indonesia, Malaysia, Philippines, Thailand, Vietnam have been collated from various sources (Lee et al., 2021; Aekplakorn et al., 2014; Mohamed-Yassin et al., 2021; Dung et al., 2020).

HDL-C, high density lipoproteins-cholesterol; LDL-C, low density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides

Lipid cut-offs used for all five countries: TC ≥ 5.1 mmol/L [≥200 mg/dL]; LDL-C ≥ 4.9 mmol/L [≥185 mg/dL]; HDL-C, <1.0 mmol/L [<40 mg/dL]; TG ≥ 1.6 mmol/L [≥150 mg/dL]

[a]lipid parameters have been converted from mg/dL to mmol/L by multiplying LDL-C, HDL-C and TC with 38.67 and multiplying TG with 88.57

[b]lipid parameters have been converted from mmol/to mg/dL by multiplying LDL-C, HDL-C and TC with 0.02586 and multiplying TG with 0.01129 (Haney et al., 2007).

Atherosclerotic Cardiovascular Disease Prevention, 2016; Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015).

Following careful evaluations and assessments, the commonalities and heterogeneities across the guidelines are presented as pragmatic points for better risk prediction and decision making for managing dyslipidemia in primary care settings. The roadmap for the overall strategy is summarized in the below sections.

2. Screening and risk assessment for dyslipidemia

2.1. Screening

Dyslipidemia being asymptomatic, a routine screening becomes essential for its early identification and can prevent or delay ASCVD-related mortality.

Advanced age is an important risk factor for dyslipidemia. Annual or more frequent screening of risk factors, including plasma lipid profiles is essential in adults (men > 40 y; women > 45 y and/or post–menopausal) to assess the risk of coronary heart disease (CHD). Screening younger patients with risk factors for ASCVD, e.g., diabetes, hypertension, chronic inflammatory diseases, CKD, and those with FH is recommended (Mach et al., 2020; Jellinger et al., 2017).

Physiologically, cholesterol level usually peaks in late adolescence and young adulthood. Therefore, screening young adults for lipid abnormalities can flag future risk of CV events (Chou et al., 2016). It can also alert them to address risk factors (smoking, unhealthy eating, sedentary lifestyle) as much as possible. Children and adolescents are highly vulnerable to faulty eating habits, obesity, or genetic susceptibility. Hence, screening them at specific age intervals is essential. Going forward, it can also detect the risk of FH and avert adverse consequences.

Screening can be selective (to identify high-risk patients), universal (absence of risk factors) or based on clinical examination. Regardless of screening type, the cost incurred during clinic visits, lipid profile tests, analysis of secondary causes of dyslipidemia should be considered. Universal screening seems to be cost-effective in the purview of general dyslipidemia detection. A decision-analytic model undertaken using screening simulation, suggested an accrual cost of $1980 and $32170 with universal screening vs. selective screening for detecting general dyslipidemia and severe dyslipidemia, respectively. Although, large patient numbers can be tested (under universal screening), determining one severe case incurs huge procedural cost per patient vs. selective screening. Hence, economic implications of screening should be accounted in the treatment prioritization matrix (Smith et al., 2018).

Genetic and cascade screenings are specifically designed for FH confirmed cases (Lozano et al., 2016). Upon identifying a proband, cascade screening, through a systematic family tracing process, can screen a broader set of at-risk relatives. Further, an early diagnosis of FH in relatives is highly cost-effective to prevent ASCVD events in future. In fact, the expert panel for ACC advises cascade screening throughout the extended family including first- and second-degree relatives to test and diagnose all at-risk relatives for FH (Sturm et al., 2018). In cases of non-consenting or deceased at-risk relatives, cascade screening should be extended to their first-degree relatives. (Lee et al., 2019; Knowles et al., 2017). Additional to first-and second-degree relatives, National Institute for Health and Care Excellence guidelines recommend HCPs to screen third-degree relatives and inform them regarding potential risks of FH (NICE guidelines, 2021). Case scenarios, wherein a child is the index patient, reverse cascade screening can identify their affected parents or siblings. (Sturm et al., 2018).

Aggressive screening practices can help the PCPs to identify the 'red flags' responsible for unusual lipid profile. Some of the best in-clinic practices for screening that can be adopted by PCPs are illustrated in Table 1.

Table 1
Best in-clinic practices for dyslipidemia screening

Screening	Best in-clinic practices
Age group	
Men >40 y; women >50 y or post-menopausal, no other risk factors[a]	• Universal screening every one-two years (Grundy et al., 2019; Mach et al., 2020; Erwinanto et al., 2017; Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015)
<45 y; presence of other risk factors	• Selective screening frequently based on clinical judgement (Mach et al., 2020; Erwinanto et al., 2017; Gonzalez-Santos et al., 2021)
Special cases	
CKD (all stages including dialysis and renal transplant) HIV infections Erectile dysfunction Use of OCPs	• Selective screening for CV risk factors (Yusoff et al., 2017)
Women-related conditions	
Premature menopause (<40 y) History of pregnancy-related disorders (preeclampsia, SGA infants, preterm deliveries	• Selective screening frequently based on clinical judgement (Grundy et al., 2019)
Children, adolescents, and young adults	
≥ 5 y; suspected FH [b, c]	• In children, testing for FH is recommended from the age of 5 y, or earlier if HoFH is suspected (Grundy et al., 2019)
≥20 y; without a personal history of ASCVD, but with a family history of premature ASCVD or genetic hyperlipidemia	• Measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders (Grundy et al., 2019)
≤19 y, suspected FH	• Selective screening frequently based on clinical judgement (Gonzalez-Santos et al., 2021)
Special cases	
Adolescents with DM	• Screening every two years after attaining glycemic control (Mach et al., 2020)

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; FH, familial hypercholesterolemia; HIV, human immunodeficiency virus; HoFH, homozygous familial hypercholesterolemia; OCPs, oral contraceptives; SGA, small for gestational age; y, years
[a]include family history of premature CVD, genetic dyslipidemias, metabolic syndrome, DM and abdominal obesity, gender, smoker, hypertension ≥140/90mmHg, BMI 25 kg/m^2, postmenopausal women, HDL-C level <1.03 mmol/L
[b]children and adolescents found to have moderate or severe hypercholesterolemia. LDL-C ≥4.9 mmol/L family history of premature CVD
[c]include presence of premature CHD, tendon xanthomas or established risk factor in child/adult family member, presence of family history of early CVD, hypercholesterolemia, premature cardiac death in family members

2.2. Risk assessment

The next step after screening involves stratifying patients in appropriate risk categories (namely low, intermediate, high, and very high). Considering the grave risk of recurrent CV event in patients with history of acute coronary syndrome (ACS), classifying them in "extremely high risk" category can trigger an early intervention. Calculator tool is required for risk assessment and deciding on lipid lowering treatment. However, patients with established ASCVD, T2DM, CKD, severe hypertension, and suspected FH are already considered as high-or very-high or extremely high risk groups (Banach et al., 2021). Hence, the risk calculator tools are not required in these situations. Some well-known calculator tools are Framingham Risk Score (FRS), Pooled cohort equations (PCE) and Systemic Coronary Risk Estimation (SCORE), Reynolds Risk Score and QRISK have been formulated using robust population-based data (Chia et al., 2014). Despite this, certain limitations hinder their practical application and generalizability. Guidelines recommend using a CVD risk calculator that is appropriate for patient-

specific race and ethnic groups and geographic region. But the calculator tools have not been validated in many countries, and no single tool is hence applicable to all patients (Wilson et al., 2021) (Fig. 2).

With the above-mentioned limitations, identifying the underlying risk factors, along with risk assessment tools, can be fruitful in understanding overall true risk and aligning the therapy accordingly. This can be aided by risk–discussion and shared decision making among the clinician–patient (in this case, PCP–patient). Furthermore, identifying "risk–enhancing factors" can increase the specificity of 10–y ASCVD risk assessments, especially in "low–" and "intermediate–" risk patients (Agarwala et al., 2019). Risk enhancing factors include high–risk features like race and genetics, women-related conditions, lipid-related risks, high–risk comorbidities, and biomarkers. However, in cases where "low–" and "intermediate"–risk patients with risk–enhancing factors might wish to abstain from the drug therapy due to uncertainty of its benefits or prefer to avoid drug therapy altogether. In such scenarios, use of coronary artery calcium (CAC) scores becomes a viable option. CAC can further reclassify the CV risk on individual–basis. It involves directly visualizing calcified plaque in coronary arteries using computed tomography (CT) and designating scores accordingly. A CAC score ≥ 100 indicates greater CV risk and necessitates initiation of statin therapy (Berman and Blankstein, 2019).

After assessing the future ASCVD risk and their influencing factors, it is important for both PCPs and patients to have a clear communication to promote trust and healthy debate. This can also help both parties to strictly monitor and manage the risk factors in a better way. PCPs can also address patient concerns with regards to future ASCVD risk as well as queries regarding management strategies. Additionally, managing the risk also plays a major role in preventing otherwise healthy patients to fall within "at–risk stratum." Risk assessment, monitoring, and management, along with effective risk communication form the four essential pillars of primary prevention. (Table 2).

3. Diagnosis of dyslipidemia

Lipid profile is the standard diagnostic test for dyslipidemia, which is done either in fasting or fed state (Halawani et al., 2019). Although, both sampling techniques have minimal differences in their clinical values, non-fasting sampling is far more simplified with high screening compliance in general population (Erwinanto et al., 2017; Yusoff et al., 2017). In hypertriglyceridemia (TG > 4.5 mmol/L, test results are confirmed using fasting samples as non-fasting TG samples are not standardized in this scenario and can falsely indicate low calculated LDL-C levels (Robert et al., 2018). The results that read TC ≥ 6.2 mmol/L, LDL- C ≥ 4.8 mmol/L, TG ≥ 1.7 mmol/L and HDL < 1.0 mmol/L either in isolation or combination is usually alerting (Halawani et al., 2019). In children and adolescents, single or clustered elevations with TC ≥ 5.1 mmol/L, LDL-C ≥ 3.3 mmol/L, TG ≥ 1.1 mmol/L (0–9 y), ≥1.4 mmol/L, (10–19 y) and HDL-C < 1.0 mmol/L should trigger management interventions (Yoon, 2014). Typically, an LDL-C level in the range of ≥ 5.0–10.0 mmol/L in children, with a family history of premature ASCVD, is indicative of HeFH or homozygous familial hypercholesterolemia (HoFH) (Reiner, 2018; Reiner and Sahebkar, 2020).

Advanced lipid testing (ALT) that reclassify patients falling between "intermediate"– "high"–risk seems to be a reasonable option (Mach et al., 2020). ALTs can further refine ASCVD risk assessments and resultant management strategies by measuring lipoprotein subpopulation, lipoprotein (a) or Lp(a), apolipoprotein B (ApoB) (Mach et al., 2020). Lp(a) being highly stable, display tighter binding to intimal arterial walls vs. LDL molecules resulting in higher cholesterol entrapment, accelerates atherosclerotic progression (Nordestgaard et al., 2010). ALTs can be value–added diagnostic tools that can detect these pro-atherogenic biomarkers, responsible for poor prognosis of atherosclerosis. Although promising, adoption of ALT in clinics is challenging due to lack of reference goals especially for Lp(a) as their measurements require isoform-insensitive assays kits, standardized secondary reference Lp(a) preparations, reproducible methodologies and validated procedures for blood, plasma, and serum collection and lastly, cross-validated risk thresholds across various ethnicities. Above all, PCPs may find it difficult to therapeutically justify the prognostic superiority of these tests over standard lipid profile with corresponding high costs (Harada et al., 2014).

FH patients are at 22–fold higher cardiac risk than patients without FH (McGowan et al., 2019). Such patients can experience major CV

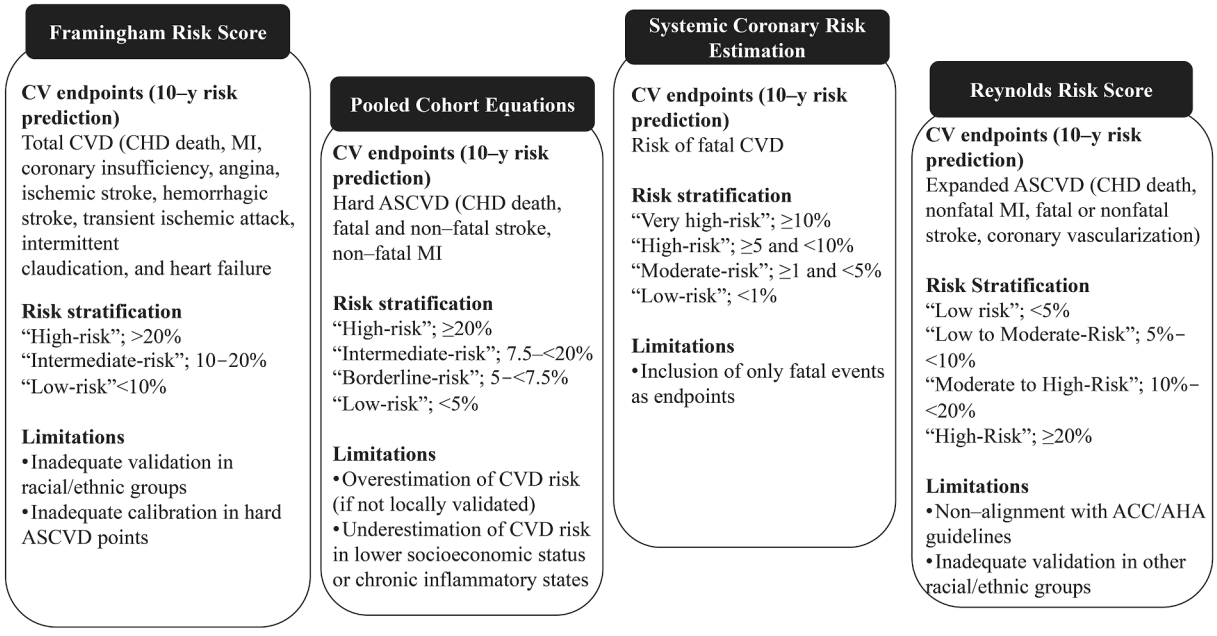


Fig. 2. Few examples of well-known risk assessment tools with risk stratifications and their limitations (Lloyd-Jones et al., 2019, Jahangiry et al., 2017, Khera et al., 2020, Mach et al., 2020, Ridker et al., 2007).

ACC/AHA, American College of Cardiology/ American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CHD, congestive heart disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease.

Table 2
Best in-clinic practices for managing cardiovascular risk factors

Four essential pillars	Best in-clinic practices
Risk assessment	
Stratifying risk	• **Extremely high-risk:** Recurrent MI with previous vascular event in the last 2 years; ACS with either MVD or polyvascular disease or FH; ACS with DM and ≥one additional risk factor[a] (Banach et al., 2021) • **Very high-risk:** History of ≥ one major ASCVD events[b] ischemic stroke, DM with target organ damage[c], severe CKD (eGFR <30ml/min/1.73m^2, FH with ASCVD, SCORE ≥10%; FRS-CVD >30% (Yusoff et al., 2017) • **High-risk:** Combined or isolated elevated factor (TC >8 mmol/L OR LDL-C >4.9 mmol/L OR uncontrolled BP, >160/110 mm Hg), DM (≥10 y duration) without target organ damage, moderate CKD (eGFR >30 -<60 mL/min/1.73 m^2), FH (Simon Broome criteria, LDL >4.9 mmol/L; TC >7.5 mmol/L, SCORE ≥5% and <10%; FRS-CVD >20% (Mach et al., 2020; McGowan et al., 2019; Jahangiry et al., 2017) • **Intermediate-risk:** Patients with DM (<10 y) without other risk factors, SCORE ≥1 % and <5%; FRS-CVD score 10-20% • **Low-risk:** SCORE <1%; FRS-CVD score <10% (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017; Gonzalez-Santos et al., 2021; Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015)
Using risk assessment tools	• Using tools preferably validated with ethnic data of the local population. • Using PCE in young adults (<40 y), and those suspected FH should be avoided since it can underestimate risk in this population and postpone drug therapy (Berman et al., 2019)
Risk-discussion	Discussion between PCP-patients reviewing: • Major risk factors • Emphasizing the importance of lifestyle changes • Benefits, and potential AEs of drug therapies • Understanding individual preferences and cost (Grundy et al., 2019)
Risk enhancing factors	• Considering "risk enhancing factors[d]" during risk-discussion (Grundy et al., 2019)
Use of CAC scores	• Considering use of CAC scores when PCP–patients discussion is unable to arrive at a consensus. CAC is scored as 0; 1-99; ≥100. Higher the score, higher is calcifications in coronary arteries (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017; Berman et al., 2019)
Risk communication	
Communication	• Using simple lay languages, graphical representation, or handouts to explain meaning of cholesterol, heart diseases • Digital platforms such as internet–based education and audiovisual aids can be effective means of communication (Mentrup et al., 2020)
Risk monitoring	
Monitoring	• Monitoring of lipid profile, glycemic status, blood pressure, dietary changes, weight gain, smoking and physical activity goals (Chauhan, 2007)
Risk management	
Management	• Accessing digital platforms and electronic records for updated lipid guidelines • Using prompt reminders/alerts for lipid testing as part of risk assessments • Using targeted efforts in high-risk patients for further risk assessments (Chauhan, 2007)

AEs, adverse events; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; FRS, Framingham risk score; FRS-CVD, Framingham risk score- Cardiovascular disease; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; MVD, multivessel disease; PCE, pooled cohort equations; PCP, primary care physicians; SCORE, systemic coronary risk estimation; TC, total cholesterol; y, years
[a] hsCRP ≥3.0 mg/L and/or chronic kidney disease with eGFR < 60 ml/min/1.73 m^2 and/or lipoprotein(a) >50 mg/dl (Banach et al., 2021)
[b]previous acute coronary syndrome (MI or unstable angina), stable angina, coronary revascularization (percutaneous interventions or coronary artery bypass, and other arterial revascularization procedures)
[c]microalbuminuria, retinopathy, or neuropathy
[d]family history of premature ASCVD, South Asian ethnicity, women-related conditions such as preeclampsia, premature menopause (<40 y), hypercholesterolemia (LDL-C ≥4.1-4.8 mmol/L); hypertriglyceridemia (TG ≥2.0 mmol/L), high-risk conditions such as arterial brachial index, ABI <0.9, inflammatory conditions, elevated biomarkers such as high-sensitivity C-reactive protein, (hs-CRP ≥2.0 mg/L) (Grundy et al., 2019; Agarwala et al., 2019)

events such as angina pectoris or MI as early as in their second or third decade (Cuchel et al., 2014). FH is classified into HoFH (characterized by absence of normal-functioning LDL-R caused by genetic mutations) and heterozygous FH (HeFH; characterized by only 50% of normal-functioning LDL-R due to mutational changes) (Anna and Frank, 2010). Compared to HoFH, HeFH is highly prevalent (one out of every 200 individuals are diagnosed with FH) with symptomatology including high LDL-C levels, a family history of hypercholesterolemia or premature ASCVD, with/without presence of tendon xanthomas (Cao et al., 2021). Though, lipid profile analysis is one of the strategies for cascade screening, some at-risk relatives may carry LDL-C lowering alleles or display minimal LDL-C elevation due to 'reduced penetrance'. This can hinder clinical differentiation between the FH and non-FH patients, affecting the sensitivity of the test results. In such situations, genetic analysis of proband and at-risk relatives can impart higher sensitivity to the test results. Nonetheless, cost-benefit ratio should be factored in, while including such analysis. A definitive diagnostic criterion such as US Make Early Diagnosis to Prevent Early Death (MEDPED), the UK Simon Broome system, Dutch Lipid Clinic Network criteria (DLCN), National Lipid Association expert panel recommendations can help in definitive diagnosis of FH. This includes high-risk population such as obese, diabetic children, or those with strong family history of early onset coronary artery disease (CAD) in parents, grandparents, aunt, uncle, or siblings (McGowan et al., 2019). Simon Broome is an economically feasible tool since it considers only clinical features, risk factors and lipid profile. Likewise, the Japanese FH criteria also considers clinical features and family history. Although, these criteria are easy to use, genetic testing can make the diagnosis of FH more accurate. The DLCN criteria have an option of using clinicals or identified genetic defects associated with LDL receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9) and ApoB in the diagnostic criteria. Genetic testing is becoming cheaper and can be more accessible in the near future. MEDPED compares TC in patients and their first-, second- or third-degree relatives with general population. Since, it does not account for clinical features or genetics, results can be less reliable (Al-Rasadi et al., 2014; Tada et al., 2020).

An accurate and timely diagnosis of dyslipidemia is the key for primary prevention of ASCVD events (Table 3).

4. Treatment and management strategies

4.1. Lowering low-density lipoprotein (LDL)-cholesterol: Hitting the bull's eye in dyslipidemia management

Increased plasma LDL-C continues to get accumulated in the arterial intima, ultimately leading to progressive atherosclerotic plaque development (Ference et al., 2017). With each passing decade, the chance of an MI event nearly doubles in a patient with high LDL-C levels (Ference et al., 2018). Hence, lowering LDL-C as early as possible yields a substantial risk reduction for future ASCVD. Every mmol/L reduction in LDL-C gradually stabilizes the plaque and achieves an overall 20–25% reduction in ASCVD risk in first five years (Ference et al., 2017). Mendelian randomization studies, notoriously known as "naturally randomized trials", further reiterate that low LDL-C exposure for long time

Table 3
Best in-clinic practices for diagnosis of dyslipidemia

Diagnostic tools	Best in-clinic practices
Fasting/non-fasting samples	• Both fasting and non-fasting samples may be used for lipid screening in general population (Alshamiri et al., 2018; Grundy et al., 2019; Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015) • Fasting samples are preferred in patients with non-fasting TG >4.5 mmol/L, familial hypertriglyceridemia, concomitant drugs increasing TG levels, and/or FBG (Alshamiri et al., 2018; Grundy et al., 2019; Erwinanto et al., 2017) • Caution should be exercised while interpreting LDL-C results from non-fasting samples in patients with MetS and DM (Mach et al., 2020) • Fasting samples should be preferred in children and adolescents with risk factors. (Mach et al., 2020)
Advanced lipid testing	• Can be used to reclassify patients falling between intermediate–and high–risk (Mach et al., 2020) • Lp(a) can be measured in patients having parents, siblings with premature ASCVD, risk factors (-) (Mach et al., 2020) • Lp(a) should be measured in patients with or suspected of having FH • Lp(a) should be measured for advanced age but low 10-y ASCVD risk • Lp(a) should be measured at least once in adults to identify very-high inherited Lp(a) levels >180 mg/dL who may have a lifetime risk of ASCVD and family history of premature CVD (Mach., et al 2020) • Lp(a) should be measured in cases of recurrent CVD despite statin treatment • 10-y risk SCORE of ≥3% of fatal CVD • 10-y risk of ≥10% of fatal and /or non-fatal CHD as per FRS • Non-HDL-C (difference between TC and HDL-C) or ApoB should be measured in patients with high TG, DM, obesity, MetS, or very–low LDL-C levels, and who have already achieved target LDL-C (Mach et al., 2020; Yusoff et al., 2017) • Patients' need, test availability and cost factor should be borne in mind before ordering tests (Mach et al., 2020; Yoon, 2014)
Tools for FH diagnostic criteria	• The need for diagnostic criteria tools should be gauged as per availability of tests and severity of risk factors in patients suspected of FH • The Dutch Lipid Clinic Network criteria has genetic testing as one of components to confirm diagnosis (Al-Rasadi et al., 2014) • Simon Broome may or may not include genetic testing to confirm diagnosis (Al-Rasadi et al., 2014) • For cost–effective tools, Japanese FH criteria or MEDPED can be considered as former considers clinical features and lipid profile, while latter considers only lipid profile (Al-Rasadi et al., 2014; Tada et al., 2020)

ASCVD, atherosclerotic cardiovascular disease; Apo B, apolipoprotein B; CVD, cardiovascular disease; CHD, coronary heart disease; DM, diabetes mellitus; FBG, fasting blood glucose; FH, familial hypercholesterolemia; FRS, Framingham risk score; LDL-C, low density lipoproteins cholesterol; Lp(a), lipoprotein(a); MEDPED, Make Early Diagnosis to Prevent Early Deaths; MetS, metabolic syndrome; non-HDL-C, non-high density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

Table 4
Target LDL-C goals in various patient subsets

Patient subset	Target LDL-C goals (mmol/L)
Very high-risk	• 1.4 - <1.0 (Mach et al., 2020); (Yusoff et al., 2017); (Gonzalez-Santos et al., 2021)
Very high-risk with FH	• <1.4 (Mach et al., 2020)
With ASCVD experiencing second vascular event (can be a different event) within two years	• <1.0 (Mach et al., 2020)
High-risk	• <1.8 (Mach et al., 2020; Yusoff et al., 2017; Gonzalez-Santos et al., 2021; The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)
DM	• ≤2.6 (Yusoff et al., 2017)
CKD with eGFR 30-<60 mL/min/1.73 m^2	• ≤2.6 (Yusoff et al., 2017)
Intermediate–risk	• <2.6-3.0 (Mach et al., 2020; Yusoff., et al 2017; The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)
Low–risk	• <3.0 (Mach et al., 2020; Yusoff et al., 2017; The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney diseases; DM, diabetes mellitus; FH, familial hypercholesterolemia; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol

brings about three–fold greater reduction in ASCVD risk (Ference et al., 2018). Therefore, lowering LDL-C remains a primary target in dyslipidemia management (Table 4).

Treatment and management strategies that is meticulously planned and executed well can indeed meet the above LDL-C goals.

4.2. Adopting therapeutic lifestyle changes

Therapeutic lifestyle changes (TLC) play a pivotal role in achieving the target LDL-C. Healthy diet regimens (for e.g., Mediterranean diet, Dietary Approaches to Stop Hypertension [DASH]) are crucial in achieving healthy lipid profile. Additionally, aerobic physical activity enhance cardiorespiratory fitness and ameliorate dyslipidemia. High intensity intermittent aerobic training can reduce myocardial oxygen demand and help control exercise intensity, increase HDL-C levels vs. moderate intensity continuous aerobic training. (Vanhees et al., 2012). Aerobic training can bring about an approximate 30–40% reduction in TG and 20% increase in HDL-C levels in patients with moderate hypertriglyceridemia. Strict avoidance of smoking (including e-cigarettes, vaping) with moderate alcohol consumption can amplify the positive effects of healthy diet and exercises (Grundy et al., 2019; Mach et al., 2020).

Although the importance of TLC in dyslipidemia management is proven, adaptation is an uphill task. Changing ingrained lifestyle habits appears scary for most people and some of them may even prefer drug therapy rather than indulging in regular physical activity. This reluctance can be dealt with educational interventions such as in–person training sessions, educational writing tools, frequent follow-ups (both telephonic and home visits) that continually encourages people to engage in self-management behavior. Alongside, post–discharge programs that provide information regarding diet, exercise, symptom monitoring, and reporting can optimize TLC (Salahodinkolah et al., 2020). Table 5 presents best practices for TLC.

4.3. Statins: Cornerstone of dyslipidemia therapy

LDL-C is the prime focus in dyslipidemia management, and statins with their ability to inhibit enzyme, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, have remained the mainstay therapy for dyslipidemia. Statins inhibit the reductase enzyme that is originally utilized for *de novo* cholesterol synthesis. In addition, statins enhance LDL clearance from the systemic circulation because of the upregulation of LDL receptors. This decreases the plasma concentration of LDL-C and along with it, other ApoB-containing lipoproteins. Pleiotropic benefits of

Table 5
Best practices to promote TLC

Lifestyle tool	Best in-clinic practices
Diet	• Healthy diet comprising of fruit, non-starchy vegetables, nuts (unsalted), legumes, fish, vegetable oils, yoghurt, and wholegrains. Lower consumption of red and processed meats, refined carbohydrates, and salt (Mach et al., 2020) • Replacing animal fat with vegetable fat with PUFAs and extra-virgin olive oil (Mach et al., 2020) **Limits for individual diet components** • Caloric intake (1200–1500 kcal/d, men; 1500–1800 kcal/d, women) (Grundy et al., 2019) • Salt intake (sodium <1500 mg; potassium 3500–5000 mg/d) (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017) • Cholesterol (<300 mg/d; for high TC patients) (Mach et al., 2020; Yusoff et al., 2017) • Dietary fiber (20-40 gm) (Mach et al., 2020) • Added sugar (<10% of total energy gained from additional sugar) (Mach et al., 2020; Yusoff et al., 2017) • Using dietary supplements and functional foods such as phytosterols (2 gm), red yeast rice (2.5–10 mg), omega3 fatty acids (2–3 gm/d) (Mach et al., 2020) • Adopting regional diet designed as per ethnic population (for e.g., Pinggang Pinoy[a] for Filipinos; QuarterQuarterHalf plate[b] for Malaysians) (Yusoff et al., 2017; Gonzalez-Santos et al., 2021)
Physical activity	• **Low-intensity exercises**: Short durations with slow increments; slow walking, yoga, stretching, pilates; suitable for sedentary individuals. (Grundy et al., 2019; Yusoff et al., 2017) • **Moderate-intensity exercises**: 75–150 min/week; for additional benefit >300 min/week brisk walking, jogging [<10 min], cycling, swimming); suitable for most patients (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017) • **Vigorous-intensity exercises**: 75 min/week; jogging/ running (>8km/h), vigorous swimming; suitable for patients with DM and other ASCVD risk factors (Grundy et al., 2019) • Shorter bouts of exercise (≥10 min) should be preferred than longer ones (Grundy et al., 2019) • Increase in overall daily physical activity (taking stairs, walking/cycling to work, avoiding sitting for long hours) (Mach et al., 2020)
Smoking and Alcohol	• Complete cessation of smoking (all types; e- cigarette, vaping) (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017; Gonzalez-Santos et al., 2021) • Moderate alcohol consumption (≤10 g/day [1 unit]) (Mach et al., 2020)

ASCVD, atherosclerotic cardiovascular disease; PUFAs, polyunsaturated fatty acids; TC, total cholesterol

[a] serves green leafy vegetables (1/4 portion), meat (1/4 portion) and fiber-rich carbohydrates (remaining portion)

[b] carbohydrates such as rice, noodles, bread, cereals (1/4 portion), protein such as fish, poultry, meat, legumes (1/4 portion), fruits and vegetables (1/2 portion) and plain water

statins such as improving endothelial functioning, stabilizing the plaques with subsequent reduction in platelet aggregation makes it a suitable candidate for primary prevention of ASCVD (Singh et al., 2020). Evidence from the *meta*-analysis of statin randomized controlled trials (RCTs) observed reduced risk of MI, major coronary events, revascularization, and angina with overall relative risk (RR < 1) (Baigent et al., 2005).

Early initiation of statins in children with FH aged 8–18 years resulted in decreased mean LDL-C levels (32% from the baseline) upon follow-up over 20 years. Moreover, the mean progression difference in carotid intima thickness (IMT) was −0.0001 mm/year between FH patients vs. control group with minimal or no new CV events or deaths over 20 years (Luirink et al., 2019). Statins (atorvastatin and rosuvastatin) when administered in HeFH children (aged 6-<18 years), produced a mean LDL-C reduction by ~ 45% by end of three years, and non-significant difference (p = 0.2) in carotid IMT among HeFH children vs. control group over two years. (Langslet et al., 2016; Braamskamp et al., 2017). The American Academy of Pediatrics and the National Heart, Lung, and Blood Institute recommends early statin use in children (8–10 years) with elevated LDL-C levels uncontrolled by TLC (de Ferranti et al., 2017). In children and adolescents with FH, moderate–intensity statins should be initiated immediately when diagnosed. Up–titration of the dose can be according to the LDL–C lowering response (reduction by 50%) of the statins (Pang et al., 2020). Non-statins such as ezetimibe or BAS can be added to the existing therapy, in case, 50% reduction in LDL-C levels are not achieved (de Ferranti et al., 2019).

Statins have been grouped as "high-intensity," "moderate-intensity," and "low-intensity" statins according to their LDL-C lowering intensity. "High-intensity" statins such as atorvastatin 40–80 mg and rosuvastatin 20–40 mg lowers LDL-C by ≥ 50%. "Moderate intensity" statins like atorvastatin 10–20 mg; rosuvastatin 5–10 mg; simvastatin 20–40 mg; pravastatin 40–80 mg; lovastatin 40–80 mg; fluvastatin 80 mg, pitavastatin 1–4 mg lowers LDL-C by 30–<50%. Finally, "low–intensity" statins include simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg. Most guidelines recommend moderate to high–intensity statin, based on the level of risk, for primary prevention of CV events (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017; Gonzalez-Santos et al., 2021).

4.4. Non-statins: As an add-on therapy in patients not reaching their low-density lipoprotein (LDL)-cholesterol goals with statin monotherapy

Although, statins have proven their mettle in lowering LDL-C, there can be a subset of high-risk patients, who are unable to achieve their target lipid goals with statin monotherapy. In such cases, addition of non-statin drugs can aid statins in achieving the desired results (Zhan et al., 2018). Non-statins namely ezetimibe (a selective cholesterol absorption inhibitor), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (inhibits PCSK9 protein that expresses LDLR), fibrates like fenofibrate (regulates transcription factors involved in lipid metabolism), omega-3 and BAS such as cholestyramine and colestipol (prevents cholesterol reabsorption into blood) have been recommended by major lipid guidelines (Grundy et al., 2019; Mach et al., 2020; Yusoff et al., 2017; Gonzalez-Santos et al., 2021). Ezetimibe added to high–intensity statins significantly reduced LDL-C from the baseline (P < 0.001) (Thongtang et al., 2012). In yet another study, significantly higher number of patients achieved LDL-C < 2.5 mmol/L (from baseline; ≥ 3.3 mmol/L with ezetimibe and statin combinations vs. statin monotherapy (P < 0.001) (Feldman et al., 2004). On the other hand, drugs like fibrates and bile acid sequestrants (BAS) have a weak LDL-C lowering activity. However, fibrates and omega-3 significantly lower TG levels (P < 0.001) while BAS is preferred in pregnancy due to its safety (Ginsberg et al., 2010); (Lent-Schochet and Jialal, 2021). Lastly, PCSK9 inhibitors are recommended as an add-on treatment in high-risk patients requiring additional LDL-C lowering with statin treatment. They lower LDL-C by 50–60% when used in combination with statins or even as monotherapy (Pokhrel et al., 2021). Treatment and management strategies tailored as per the risk factors, and comorbidities with TLC in the background are illustrated in Table 6.

The Fig. 3 indicates a clinical practice workflow for PCPs that can help them in decision-making for managing dyslipidemia.

4.5. Handling of adverse events owing to statin therapy

Statin-associated AEs include myalgias, elevated liver enzymes, and isolated cases of new onset DM (NODM) in high-risk patients (Grundy et al., 2019). In an AE, the statin dose and frequency can be tapered or combined with a non-statin. Creatine phosphokinase should be checked if muscle symptoms occur while on statin treatment. However, routine monitoring of creatine phosphokinase is not recommended. Transaminitis can occur at the start of the statin or after up–titration of the dose. Hence, transaminases should be assessed at baseline, after two–three months of statin initiation, and after adjusting/increasing statin

Table 6
Best in-clinic practices for prescribing statins and non-statins

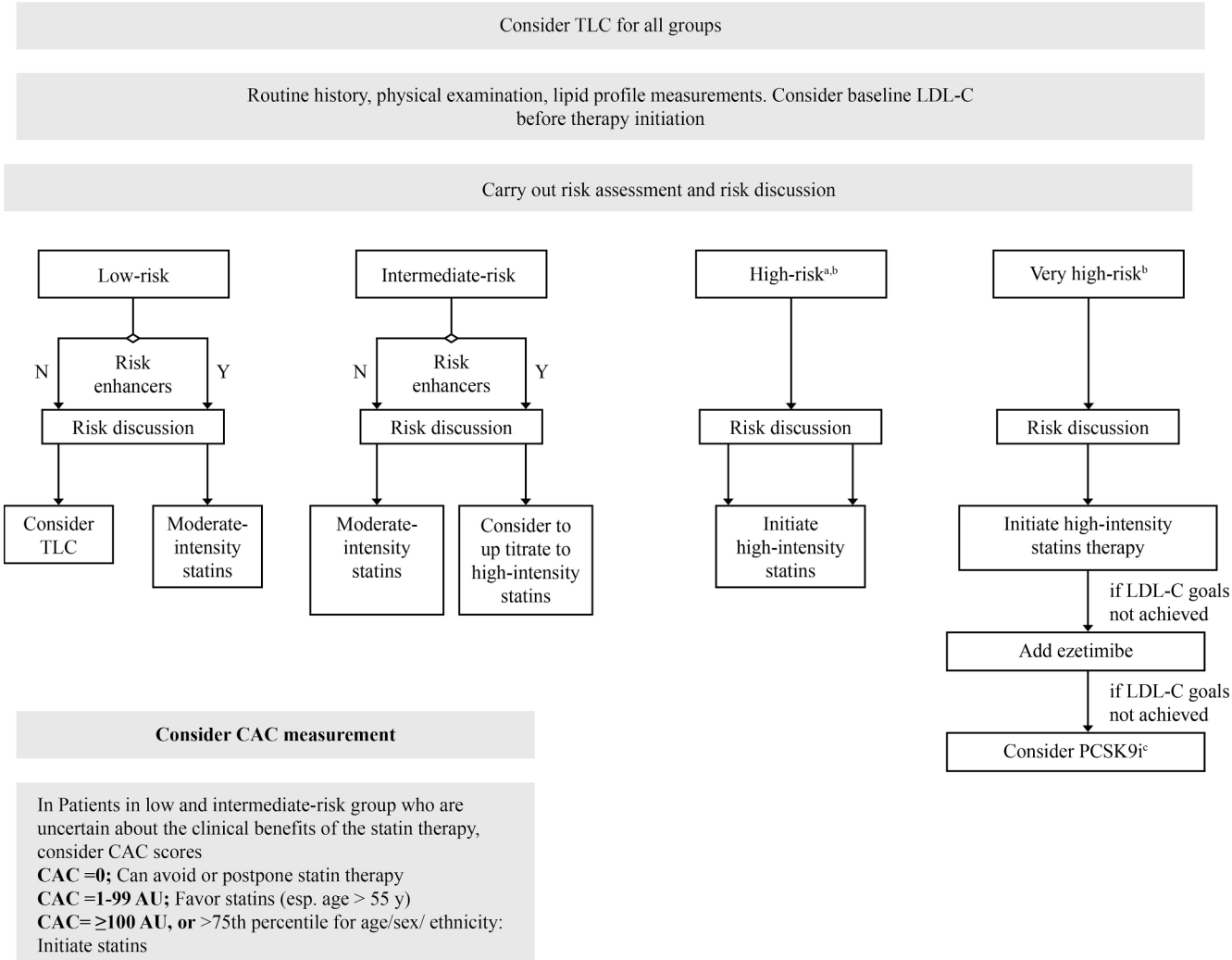
Patient subset	Best in-clinic practices
• 0-19 y; without ASCVD risk	• Consider TLC (Grundy et al., 2019)
• 0-19 y; with ASCVD risk and FH	• Initiate statins (Grundy et al., 2019; Yusoff et al., 2017)
• 20-39 y; without ASCVD risk	• Consider TLC, estimate lifetime risk with risk assessment tools (Grundy et al., 2019)
• >21 y; LDL-C ≥4.91 mmol/L	• Initiate moderate–intensity statins and then up–titrate to achieve 50% plasma LDL–C reduction from the baseline (Grundy et al., 2019)
• >35 y; LDL-C ≥4.91 mmol/L, Thai CV Risk SCORE ≥10%	• Low[a]- to Moderate[b]-intensity statins
• <40 y; with DM	• Consider TLC for 3-6 months. If LDL-C still ≥2.58 mmol/L, initiate low-to moderate-intensity statins
• FH patients	• Initiate high–intensity[c] statins (The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016) or use maximally tolerated statin therapy (Grundy et al., 2019)
40-75 y; LDL-C ≥1.8 - <4.9 mmol/L; Risk enhancing factor (+)	
• Low-risk (<10%)	• Moderate-intensity statin (Grundy et al., 2019)
• Intermediate-risk (10-20%)	• Moderate-intensity statin; consider risk enhancers to up–titrate to high-intensity statins (Grundy et al., 2019)
• High-risk (>20%)	• High–intensity statin (Grundy et al., 2019)
• DM (+); Multiple ASCVD risk factors (+)	• High–intensity statins (Grundy et al., 2019)
• DM (+); Multiple ASCVD risk factors (-)	• Initiate statins (Gonzalez-Santos et al., 2021)
CAC (Grundy., et al 2019)	
• Score 0	• Consider avoiding or postponing statins and reassess CAC within 5-10 y[d]
• Score 1-99 AU; ≥55 y	• Favors statins (Moderate–intensity statin)
• Score ≥100 AU; or >75th percentile for age/sex/race/ethnicity	• Initiate statins (Moderate–intensity statin)
Elderly	
• >75 y	• Initiate statins if at high risk, can continue with statins, if tolerable. Non–statins can be considered case-by-case basis if unable to tolerate statins (Grundy et al., 2019; Mach et al., 2020; Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015)
• ≤75 y	• High–intensity statins initiated as per risk levels (Grundy et al., 2019; Mach et al., 2020)
Indications for adding non-statins	
• Very-high risk; ASCVD risk factors (+); failure to achieve LDL-C goals with monotherapy	• Ezetimibe can be added to maximally tolerated statin therapy • PCSK9 inhibitor may be considered. (if LDL-C remains ≥1.8 mmol/L with statins and ezetimibe) (Grundy et al., 2019; Mach., et al 2020; Yusoff., et al 2017)
• DM (+) with TG >2.3 mmol/L	• Statin combined with EPA 4 gm/d should be considered (Mach et al., 2020)
ACS and PCI	
• ACS	• High-intensity statins. If treatment goal not reached, consider adding ezetimibe (Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015)
• PCI	• High-intensity statins before intervention (Vietnam recommendations on diagnosis and treatment of lipid disorders, 2015)
Indications for statins in specific conditions	
• Asymptomatic atherosclerotic disease[e]	• High-intensity statins (Yusoff et al., 2017)
• Hypertension with elevated TC	• Initiate statins (Yusoff et al., 2017)
• Chronic inflammation (e.g., psoriasis, rheumatoid arthritis, HIV infection)	• Low-to moderate-intensity statins (The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)
• Cerebral ischemia or transient ischemic attack	• LDL-C ≥2.58 mmol/L, high-intensity statins; LDL-C <2.58 mmol/L, consider moderate-intensity statins (The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)
CKD	
• CKD ≥50 y; eGFR <60 mL/min/1.73 m^2; not on dialysis; LDL-C ≥2.58 mmol/L	• Low-to Moderate-intensity Statins or Ezetimibe/moderate-intensity statins can be initiated (Mach et al., 2020; Yusoff et al., 2017; The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)
• Dialysis	• Statin should not be commenced. If already on statins or ezetimibe/statin, therapy to be continued (Mach et al., 2020; Yusoff et al., 2017)
• Renal replacement therapy already on statins	• Continue statins with dose adjustments (The Royal College of Physicians of Thailand Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention, 2016)

Lipid profile to be obtained in 4 to 12 weeks, and then every 3 to 12 months, post-initiation, or adjustments, to assess statin effect, adherence, and safety
ABI, ankle brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; AU, Agatston units; CAC, coronary artery calcium; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; FH, familial hypercholesterolemia; HIV, human immunodeficiency virusLDL-C, low density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TG, triglycerides; TLC, therapeutic lifestyle changes; y, years
[a]simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg, pitavastatin 1 mg
[b]atorvastatin 10-20 mg; rosuvastatin 5-10 mg; simvastatin 20-40 mg; pravastatin 40-80 mg; lovastatin 40-80 mg; fluvastatin 80 mg
[c]atorvastatin 40-80 mg; rosuvastatin 20-40 mg
[d]If the patient is diabetic or a smoker or has a family history of premature CHD, statins should NOT be avoided or postponed
[e]Significant plaques (>50% narrowing); ankle brachial index: <0.9 or >1.4

dose (Yusoff et al., 2017). In patients with advanced CKD (stage 3–5) who are not on dialysis, statin use with dosing adjustments are warranted. However, if the same subset of patients undergo dialysis but are without risk of ASCVD, statins may not be initiated (Yusoff et al., 2017). Statin benefits outweigh NODM risk, but PCPs ought to be careful, especially in elderly or obese patients. Once on statins, TLC are recommended, and glycemic parameters in these patients should be checked annually for early detection (Yusoff et al., 2017). The overall impact of AEs should be discussed in detail along with their management strategies to ensure adherence to the therapy (Grundy et al., 2019).

4.6. Handling drug-drug interactions

Statin metabolism is usually mediated by cytochrome P450



Notes:

For patients in all age-groups who do not achieve target LDL-C goals despite maximally tolerated statin, consider intensification of therapy by addition of non-statin

[a]For young patients (0-19 y) with FH; initiate moderate-intensity statins

[b]For elderly patients (≥70 y), it is recommended that the statin is started at a low dose especially if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals

[c]Consider adding PCSK9i in select group of patients

Fig. 3. Decision tree for dyslipidemia management as a primary prevention of ASCVD.
AU, Agatston units; CAC, coronary artery calcium; LDL-C, low density lipoprotein cholesterol; N, no; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; TLC, therapeutic lifestyle changes; Y, yes; y, years.

(CYP450) isoenzymes and by glucuronidation. The CYP3A4 isoenzyme metabolizes lovastatin, simvastatin, and atorvastatin, whereas CYP2C9 is responsible for metabolism of fluvastatin, pitavastatin, and rosuvastatin. Pravastatin is the only statin that is not metabolized by the CYP isoenzyme family (Newman et al., 2019). Statins can be cleared rapidly from systemic circulation when administered alongside CYP inducers (dexamethasone, omeprazole, rifampin) causing suboptimal effect. A CYP inhibitor (itraconazole, azithromycin, cyclosporine) may slow down the statin metabolism, increasing its systemic levels leading to AEs such as myopathy. In the same vein, some statins can inhibit other drugs (anticoagulants like warfarin) from utilizing similar CYP isoenzyme for their metabolism thereby causing minor increase in the international normalized ratio (INR). Atorvastatin, on the other hand does not interact with warfarin and can be a preferred in warfarin users (Andrus, 2004). Although the clinical relevance of statin interaction with warfarin is limited, PCPs should increase INR monitoring frequency especially when warfarin is used concomitantly along with statins (Engell et al., 2021). In case of an interaction, careful maneuvering in terms of dose adjustments, changing to alternate statin or temporary stopping of therapy is essential (Mukherjee, 2016).

5. Dyslipidemia management in special cases

As dyslipidemia continues to rise, it is difficult to have an umbrella protocol for dyslipidemia management, especially when there is variability in patient characteristics and risk factors. Hence, PCPs should be aware of nuances to be considered while managing patients in special cases so that the prognosis is not affected.

5.1. Counselling reproductive age women while prescribing statins

A growing number of young women are on statins to ameliorate CV

risk due to PCOS, obesity or bad obstetric history. A major proportion of these women wish to become pregnant or are with an on-going pregnancy while still on statins. Statins are contraindicated in pregnant and breastfeeding mothers, though US FDA has requested removal of this contraindication owing to lack of birth defect reports from multiple RCTs featuring statins. Nevertheless, PCPs should discontinue statin therapy in most of the pregnant patients. They may consider the ongoing therapeutic needs on case-by-case basis, particularly those at very high risk for CV events during pregnancy. Breastfeeding patients on statins, should switch to infant formula (Food and Drug Administration, 2021).

BAS as an alternate lipid lowering therapy can be used during pregnancy (Lent-Schochet and Jialal, 2021). Birth control strategies such as oral contraceptive pills (OCPs) preferably third generation with low dose estrogen-progestin should be considered in young females on statins. In patients with high risk of thrombotic events, OCPs should be avoided, and other contraceptive options should be considered (Mach et al., 2020).

5.2. Managing elderly population (>75 y)

The statin utility in elderlies (>75 y) can be marred due to several comorbidities, polypharmacy, progressive fragility and decreased physiologic reserve. Furthermore, age-related decline in hepatic function can reduce statin clearance exposing them to increased AEs risk. However, deprescribing statins due to fear of AEs can up the risk of CV-related hospitalizations by 33% as reported by a French cohort study in over 5000 elderlies (Giral et al., 2019). PCPs should gauge the CV risk factors and weigh the benefit-risk ratio before prescribing or deprescribing statins in elderlies. Initiation of a low–dose statin with slow up-titration can be opted for elderlies to ensure safety followed by risk discussion and shared decision making. Statins may be avoided in frail adults due to limited life expectancy (Saeed and Mehta, 2020).

5.3. Managing patients with co-morbidities and other risk factors

5.3.1. Coronavirus disease

Besides impacting multiple organs, the acute inflammatory state in coronavirus disease (COVID-19) infection can also interfere with lipid metrics by decreasing HDL-C and apo-A-1 levels and significantly increasing TG levels (Sun et al., 2020). Infected patients with ASCVD risk factors can experience acute cardiac complications such as acute cardiac injury, MI, acute onset of heart failure (HF). Hence, COVID-19 positive patients can continue using statins. In case AE occurs (severe myositis or hepatitis), statins can be temporarily discontinued till the AE is resolved and resumed when the patient condition is better (Virani, 2020). Since remdesivir and lopinavir are metabolized by CYP 450, statin dose should be lowered or temporarily withheld during treatment. In addition, statin should be temporarily withheld during tocilizumab treatment. Patients receiving dexamethasone, should continue with statin therapy (Iqbal et al.,2020).

5.3.2. Metabolic syndrome

Metabolic syndrome (MetS) is an amalgamation of CV risk factors namely dyslipidemia (with low HDL-C and high TG levels), obesity, hyperglycemia, hypertension, T2DM and insulin resistance (Yusoff et al., 2017). Patients with MetS might have higher fatality rate due to CV events and T2DM, compared with those without the disorder.

Adopting TLC is the first step towards managing MetS. A Mediterranean diet in addition to low-glycemic index foods with high fibers can lower overall TG levels. Physical activity should focus on reducing abdominal adiposity and waist circumference to increase insulin sensitivity. PCPs should also screen for CV and T2DM risk factors once MetS diagnosis is firmly established with non-fasting blood samples. Optimum reductions in HDL-C (<2.2 mmol/L) and ApoB < 65 mg/dL in very-high risk patients should be targeted (Mach et al., 2020).

6. Hindrances in dyslipidemia management and possible solutions

Despite having multiple time-tested evidence for drug therapies and management strategies in place, prevention and management of dyslipidemia remains an unmet need, globally. This is attributed to certain hindrances that PCPs and patients face while diagnosing and managing dyslipidemia.

Apprehension to prescribe high-dose statins: Resistance may occur among some PCPs to up titrate statin dose, especially in elderlies due to statin-associated AEs.

Possible solution: An attractive option for the PCPs can be to clearly set a lipid goal for patients belonging to various risk strata, discussing possible AEs and their management with shared decision making. There is a need to increase PCPs' access to the revised lipid guidelines, possibly by providing access to condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards and digital applications for abridged and quick information (Mach et al., 2020). Additionally, mapping patient characteristics to different risk–benefit aspects of diagnosis and management, especially from regional and ethnic aspects, may address this unmet need.

Drug reimbursement constraints: Appropriate medical reimbursement policies can reduce the economic burden of dyslipidemia and encourage therapy adherence. However, in countries like Indonesia, national health insurance formulary allows reimbursements only for low– and moderate–intensity statins. This forces people to pay out of their pockets to buy high-intensity statins that limits their adherence to the therapy and hence warrants amendment to the policy (Irawati et al., 2020).

Lack of standardized guidelines: Given the huge disparities pertaining to local risk factors, ethnicity and individual circumstances, an umbrella treatment and management for each patient becomes questionable (Alshamiri et al., 2018). It is also a major obstacle in achieving goal-driven treatment strategy. Moreover, CV risk calculators have not been cross validated in multiethnic groups that blunts their risk prediction potential and ultimately, statin prescription pattern.

Possible solution: An engaging and informed dialog, discussing risk factors and overall drug strategy between PCPs and patients against the backdrop of guidelines is important. PCPs can also train the patients for periodic self-monitoring of drug response and reporting (in case of an AE). As a long-term plan, obtaining high-quality evidence with various patient pools, gathering real-world data for developing global CV risk estimators can be attempted to bridge the gap across guidelines (Cook et al., 2012).

Limited access to clinics due to geographical make-up: Patients often tend to postpone or forego follow-ups owing to difficulties in reaching clinics or busy schedules. This can be a missed opportunity for PCPs to evaluate drug response or ordering laboratory tests in case of an AE (Lee et al., 2021).

Possible solution: Patients can resort to teleconferencing or videoconferencing or can simply avoid procrastinating clinic visits, which is very viable solution considering the current situation due to COVID-19.

7. Conclusion

Managing dyslipidemia early on is a giant leap towards preventing CV events. Hence, commonalities across major guidelines, i.e., US, European and Asian guidelines have been selected, consolidated with best clinical practices, and translated into some recommendations by the authors. This might help to enhance the actual clinical practice in local reference. In summary, in the ever-changing landscape of dyslipidemia, having hands-on access to primary prevention tools, i.e., screening, risk assessment, diagnosis, TLC, statin and non-statin therapy can help PCPs nip dyslipidemia in the bud. Moreover, the possible solutions to overcome major barriers to dyslipidemia management can improve adherence and help patients achieve their target LDL-C goals. The main

limitation of this review is the use of different risk estimators (validated in their respective population) depending on varied risk factors across geographies and their interpretation of ASCVD risk. Nevertheless, efforts must be made in future to obtain high-quality evidence and cross-validation studies to improve on the consistency across the guidelines.

8. Authors' contributions

This set of best in–clinic practices are the result of critical intellectual content, shaped by all authors, bringing together best from their clinical practice and expertise. This would not have been possible without their contribution and active participation. The collective thoughts from all authors have been represented through the paper. All authors have provided their critical review, feedback, additions, further references, and guidance.

9. Additional contributions

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10. Ethical compliance

This paper did not utilize any research data from human or animal subjects and have utilized data from previously published studies available publicly in anonymized databases. Hence, ethical approval was not necessary.

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