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Treating Dyslipidemia in Adults: An Update

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Author's contribution

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ABSTRACT

Dyslipidemia is an important risk for the promotion of atherosclerosis and the development of cardiovascular disease (CVD). Currently available drugs can effectively lower the increased levels of blood cholesterol in most patients and prevent the development and progression of CVD. This paper focuses on the adverse cardiovascular effects produced by high blood cholesterols and the overall management of dyslipidemia in adults. Relevant guidelines and research papers published mainly after the year 2000 on the management of dyslipidemia were reviewed. High levels of low density lipoprotein cholesterol (LDL-C), or low levels of high density lipoprotein cholesterol (HDL-C), combined or independently are associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). Apolipoprotein B (ApoB), an atherogenic lipoprotein has emerged recently as the key factor in the pathogenesis of atherosclerosis. High triglyceride (TG) levels are associated with acute and recurrent pancreatitis. The purpose of treating lipid disorders is to prevent the development of ASCVD and pancreatitis. The treatment of dyslipidemia includes multifactorial life style intervention and pharmacotherapy with lipid modifying drugs. Reduction of LDL-C is substantially associated with reduction of risk of ASCVD and evidences show that "lower is better" for LDL-C reduction.

Keywords: Cholesterols; lipids; atherosclerosis; LDL-cholesterols; HDL-cholesterols; management.

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1. INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is an important health problem that causes increased morbidity and mortality worldwide [1, 2]. Its prevalence is higher in many countries with aging of the population combined with atherogenic lifestyles. The ASCVD includes coronary artery disease (CAD), cerebrovascular disease (stroke) and peripheral arterial disease (PAD) all of atherosclerotic origin. CAD encompasses acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary revascularization. Dyslipidemias, which are abnormalities in blood lipids consisting of elevations of low density lipoprotein cholesterol (LDL-C) and low levels of high density lipoprotein cholesterol (HDL-C) are important risk factors for cardiovascular disease (CVD). There is a strong link between elevated levels of LDL-C and atherosclerosis [3]. In people with established CVD, elevated LDL-C correlates with recurrent cardiovascular events (CVE) [4]. There is also substantial evidence that low levels of HDL-C are linked with increased CVE [5,6]. The role of elevated levels of triglyceride (TG) as a cardiovascular (CV) risk is controversial and not as robust as is with LDL-C [7]. Patients with substantially elevated levels of TG (>500 mg/dL) are at risk for acute pancreatitis. High levels of lipoprotein(a) ((Lp(a)) are recognized to be independent risk factor of ASCVD [8,9]. New evidences reveal that apolipoprotein B (ApoB), a component of atherogenic lipoprotein, plays crucial role in the development and progression of atherosclerosis [10,11]. The major goals in the clinical management of dyslipidemia are to prevent development of CVE and acute pancreatitis. Numerous randomized clinical trials have consistently shown that lowering total cholesterol (TC) and LDL-C reduces and prevents CVD [12,13].

This review focuses briefly on the role of different lipids in CVD and the clinical management of dyslipidemia in general. Relevant research papers and various national and international guidelines published since the year 2000, were reviewed. Detail management of special conditions and populations for lipid management has not been described in this paper.

2. DEFINING DYSLIPIDEMIA

Dyslipidemias are heterogeneous group of disorders characterized by abnormal levels of circulating lipids and lipoproteins. It is generally characterized by increased plasma levels of TC, LDL-C, TG, or reduced levels of HDL-C singly or in combination [14]. These are the major components of blood lipid measured to determine a patient's CV risk. The risk of developing CAD in relation to the elevated LDL-C and reduced HDL-C is well known; LDL-C levels are found to be directly associated with CVE; whereas HDL-C levels are found to be inversely related to risk of CVE [3-6,15]. The risk attributable to low HDL-C is independent of LDL-C levels [16].

A total cholesterol (TC) of >240 mg/dl (6.2 mmol/L) has been classified as elevated and associated with increased CVD risk, and optimal values are <200 mg/dL (5.2 mmol/L) [17]. An LDL-C value >160 mg/dL (4.1 mmol/L) has been classified as high, and an optimal value being <100 mg/dL (2.6 mmol/L). In patients with CVD an optimal value should be <70 mg/dL (1.8 mmol/L). In US adult population, studies suggest that optimal TC levels are about 3.8 mmol/L (150 mg/dL), which corresponds to an LDL-C level of about 2.6 mmol/L (100 mg/dL) [18,19]. Adult populations with cholesterol concentrations in this range manifest low rates of ASCVD [20]. HDL-C has been classified as low level if <40 mg/dL (1 mmol/L) in men, and <50 mg/dL (1.2 mmol/L) in women, while optimal values are >50 mg/dL in men and >60 mg/dL in women [17]. Triglycerides levels >200 mg/dL (2.3 mmol/L) have been classified as elevated, with optimal values being <150 mg/dL (1.7 mmol/L). Moreover, fasting TG levels >1,000 mg/dL have been classified as severe hypertriglyceridemia which is associated with an increased risk for developing acute and recurrent pancreatitis.

Patients with primary hypercholesterolemia with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L) have a high-risk of ASCVD with premature and recurrent CVE and this group has been considered to have severe hypercholesterolemia [21,22]. LDL-C levels of 160–189 mg/dL (4.1–4.8 mmol/L) has been considered as moderate hyper-cholesterolemia. LDL-C less than <160 mg/dL is considered acceptable level in low CVD risk individuals [23].

3. CAUSES OF DYSLIPIDEMIA

Dyslipidemia may be primary (due to genetic causes) or secondary. The majority of patients with dyslipidemia have some combination of genetic predisposition and environmental contribution (multifactorial). The environmental factors include unhealthy diet (excess saturated

fat or trans fat intake, heavy carbohydrate diet), sedentary life style and obesity. Causes of secondary dyslipidemia include diabetes mellitus (DM) [24], metabolic syndrome, chronic kidney disease (CKD) [25], nephrotic syndrome [26], cholestatic liver disease [27], hypothyroidism [28], Cushing's syndrome [29], drugs (β-blockers, thiazide diuretics, corticosteroids, oral contraceptives and bile acid sequestrants) [30], alcohol abuse [27] and pregnancy [31]. Metabolic syndrome is a risk factor for ASCVD. The diagnosis of metabolic syndrome is made by the presence of any 3 of the following: elevated waist circumference, elevated TG, reduced HDL-C, elevated blood pressure (BP) and elevated fasting glucose [32]. Definitions of elevated waist circumference as ≥102 cm in men and ≥88 cm in women were recommended by the 1998 National Heart, Lung, and Blood Institute Obesity Initiative Expert Panel [33]. The prevalence of metabolic syndrome increases with age and commonly occurs in patients with type 2 DM.

DM, metabolic syndrome, or CKD increases TG and decreases HDL-C levels. Heavy carbohydrate diet, alcohol intake, oral contraceptives, or bile acid binding resins increase blood TG. Diet rich in saturated and trans fat, nephrotic syndrome or hypothyroidism increases LDL-C. Obesity, cholestatic liver disease, pregnancy or drugs like β-blocker, thiazide diuretic and corticosteroid—increases LDL-C & TG. Primary (genetic) dyslipidemias include [34] primary or familial hypercholesterolemia, common hyper-cholesterolemia, familial combined hyperlipidemia, remnant hypercholesterolemia, and hyperchylomicronemia (TG levels are markedly increased). Genetic disorders of Lp(a) a highly atherogenic lipoprotein, are extremely rare.

4. MEASUREMENTS OF BLOOD LIPIDS

Blood lipid measurements are usually performed to screen for primary or secondary prevention of CVD, to investigate patients with clinical features of lipid disorders and to establish a baseline for monitoring response to lifestyle intervention and pharmacological therapy of dyslipidemia. Major components of blood lipids are measured for assessing ASCVD risk. A standard blood lipid profile to assess ASCVD risk includes TC, HDL-C, TG and LDL-C. Total cholesterol and TG values reflect cholesterol and TGs in all circulating lipids and lipoproteins; the lipoproteins are the vehicle of transport of the blood lipids, as lipids are water insoluble. TC is conventionally defined as the sum of HDL-C, LDL-C, and very low density lipoprotein (VLDL).

In many cases, a calculation rather than an actual measurement is used for the LDL-C. The Friedewald formula has long been used to calculate LDL-C from TC, TG and HDL-C provided the patient was sampled after an overnight fast and the triglyceride values are <4.5 mmol/L (400 mg/dL) [35]. This formula calculates LDL-C by subtracting the sum of HDL-C and VLDL from TC. The VLDL is estimated by dividing total blood TG by 2.2 if measured in mmol/L or 5 if measured in mg/dL. In most individuals, direct measurement of LDL cholesterol does not provide additional CVD risk information beyond calculated LDL-C. When TG levels are high (>400 mg/dL) the LDL-C is measured by direct assay using plasma ultracentrifugation. Non-HDL-C can be calculated as TC – HDL-C; non-HDL-C is a measure of total cholesterol present in all atherogenic lipoproteins. Studies have demonstrated that non-HDL-C is a better predictor of CV risk than is LDL-C [36]. Elevated non-HDL-C is associated with greater CV risk and lowering non-HDL-C has the potential to lower that risk.

Traditionally, blood sampling for lipid analysis has been recommended in the fasting state for maximum accuracy and consistency. Recent systematic studies suggest that the difference in the values between a fasting and non-fasting sample is small and has been shown to have no impact on CV risk estimation [37]. Fasting and nonfasting TC and HDL-C levels appear to have fairly similar prognostic value and associations with CVD outcomes. Indeed, a number of guidelines recommend non-fasting sampling [38-43].

Lipid testing may be postponed until after resolution of acute illness (e.g. fever) because TG and certain lipoprotein (e.g. Lp(a)) levels increase and cholesterol levels decrease in inflammatory states. Lipid testing may be deferred for at least 2 weeks after an acute illness [42].

Other CVD risk markers such as ApoB and Lp(a) are usually not routinely measured. Apo B is found in each of the atherogenic lipoprotein particles such as chylomicrons, VLDL, intermediate density lipoprotein cholesterol (IDL), LDL-C and Lp(a). ApoB thus provides an estimate of the total concentration of atherogenic

lipoprotein particles and represents the total atherogenic burden of an individual [44]. Lp(a) levels are genetically determined and especially, higher levels (>50 mg/dL) are associated with ASCVD [45]. For improvement of CV risk assessment in certain individuals, ApoB and Lp(a) measurements may be useful [36]. The 2019 European society of cardiology (ESC) and European atherosclerosis society (EAS) guideline [40] recommends measurement of ApoB as part of routine lipid analysis among patients with DM or high TG levels, and in patients with very low LDL-C levels considering the potential inaccuracy of LDL-C in dyslipidemia. The 2018 American heart association (AHA) and the American college of cardiology (ACC) 2018 guidelines [39] consider a relative indication for measurement of ApoB when TG ≥200 mg/dL. A persistent elevation of ApoB can be considered a risk-enhancing factor; a level ≥130 mg/dL corresponds to an LDL-C ≥160 mg/dL. The 2019 ESC/EAS guideline recommends to consider measurement of Lp(a) at least once in each person's lifetime, if available, to identify people who have inherited an extremely elevated level of Lp(a) and have a very high lifetime risk of ASCVD. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guideline considers a relative indication for measurement of Lp(a) when there is a family history (FH) of premature ASCVD; a Lp(a) ≥50 mg/dL constitutes a risk-enhancing factor.

5. SCREENING

Screening for dyslipidemia is performed according to country-specific guidelines and demographic conditions. The ESC/EAS guidelines [40], recommend risk factor screening including the lipid profile to consider in men >40 years old, and in women >50 years of age or post-menopausal. Singapore guidelines [42] in their country, recommend that clinicians should routinely screen men and women aged 40 years and older for lipid disorders. The Malaysian guideline 2017 [41], advocates screening all adults >30 years of age. Clinicians can routinely screen younger adults (men and women aged 18 and older) for lipid disorders if they have other risk factors for CAD. The risk factor for CAD includes individuals with a FH of premature CAD, a history suggestive of familial dyslipidemia, presence of metabolic syndrome, hypertension, DM and abdominal obesity [41,42]. Individuals who are at high risk of developing CVD or who have already developed CVD should have a lipid profile earlier in life. For individuals with screening results within the lipid target levels, lipid profile may be repeated at 3 yearly intervals unless they are at very high or high risk of CAD, in which case screening should be repeated annually [42]. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol, recommends that screening start at age 20 and be repeated every 4 to 6 years, regardless of risk factors [46]. In 2001, the US Preventive Services Task Force (USPSTF) recommended routine screening of all men aged 35 and older, women aged 45 and older for lipid disorders and treat abnormal lipids in people who are at increased risk of CAD [47]. The USPSTF recommended that clinicians routinely screen younger adults (men aged 20 to 35 years and women aged 20 to 45 years) for lipid disorders if they have other risk factors for CAD. In 2008, USPSTF updated the previous cholesterol screening guideline, and the major change in the recommendation was that adult women at any age should be screened only if other risk factors for CVD are present [48]. The other recommendations remain unchanged. The 2016 USPSTF recommended universal lipid screening in adults aged 40 to 75 years for identification of dyslipidemia and calculation of 10-year CVD event risk [49]. This recommendation replaces the USPSTF 2008 recommendation on screening for lipid disorders. The USPSTF recommends neither for nor against screening for dyslipidemia in adults aged 21 to 39 years. It found insufficient evidence that screening for dyslipidemia before age 40 years has an effect on either short- or longer-term CV outcomes.

6. ASSESSMENT OF THE PATIENT

Dyslipidemia is generally asymptomatic; however, the potential sequelae like CVD (e.g. CAD, stroke, PAD) and pancreatitis need consideration. Once the dyslipidemia is detected, efforts should be made to rule out any possible secondary causes [46]. Although many patients with dyslipidemia have a primary cause, secondary factors frequently contribute to the dyslipidemia. A careful medical, family, and social history should be obtained. Hypothyroidism is more prevalent in the elderly in whom a high index of suspicion may be necessary for diagnosis [28]. Cushing's syndrome including subclinical disease can lead to lipid abnormalities in 40-70% of patients [29]. Patients on exogenous steroids may also develop secondary dyslipidemia. While evaluating an individual with dyslipidemia, presence of other well established CV risk

factors (Table 1) need to be noted; the important ones include cigarette smoking, advancing age, obesity, physical inactivity, hypertension, diabetes, metabolic syndrome, CKD and FH of premature CVD. A FH of premature atherosclerotic disease may suggest primary dyslipidemia. The age of premature CVD varies slightly in various guidelines depending on the country specific demographic characteristics of population related to CVD. Some authors and guidelines consider age of premature CVD in men (father and/or brother) <55 years, and in women (mother and/or sister) <65 years [41,43, 50,51]. Singapore guideline [42], in their country, considers age of premature CVD in men <50 years, and in women <60 years.

BMI and waist circumference measurement should be done while clinical assessment (to determine central obesity and metabolic syndrome). Primary lipid disorders are also suspected when patients have physical signs of dyslipidemia that include xanthelasma (nodular lipid deposits around the eyelids), corneal arcus, tendon xanthoma, (located in tendons typically finger extensor, Achilles tendons), striae xanthoma, (palm creases), eruptive xanthoma, (buttocks, elbows) tuberous xanthoma (raised cutaneous cholesterol deposits), lipemia retinalis (opaque, white appearance of the retinal vessels, visible on fundoscopic examination giving a creamy appearance of the retina), acute pancreatitis, hepatomegaly (due to fatty liver), and lipemic blood/ plasma [34].

A fasting glucose needs to be done in the initial workup of all subjects with dyslipidemia. Nephrotic syndrome and CKD should be excluded by obtaining urine protein and serum creatinine. Liver function tests should be performed to rule out hepatitis and cholestasis. Hypothyroidism should be ruled out by measuring serum TSH and serum free T3.

7. CARDIOVASCULAR RISK STRATIFICATION

Dyslipidemia is an important risk factor for CVD. The intensity of lipid lowering treatment and target lipid level depends on the level of total CVD risk irrespective of cause. The higher the CV risk, the more intense is the treatment, the tighter is the lipid target and more is the benefit. CV risk refers to the likelihood of an individual developing a CVE, fatal or non-fatal in future, over a defined period of time. Many risk scoring systems (including online equations) are available that are prepared on population-based risk chart and observational epidemiological data. In addition to blood lipids, other multiple major risk factors are considered to calculate overall CV risk imposed by dyslipidemia in the various risk scoring systems; the major risks include the presence of ASCVD, DM, CKD, advancing age, gender, race, smoking and BP. The scoring systems combine these major risk factors to estimate a patient's probability for developing ASCVD.

Table 1. Risk factors for ASCVD

Cigarette smoking
Hypertension
Diabetes
Dyslipidemia (↑ TC, ↑ LDL-C, ↓ HDL-C)
Sedentary life style
Unhealthy diet: ↑saturated fat, ↑ trans fat, ↑ refined carbohydrates, lack of dietary fibres, oily fish, fresh vegetables and fruits
Lack of exercise
Obesity
Metabolic syndrome
Heavy alcohol consumption
Chronic kidney disease
Past history of ASCVD
Family history of premature CAD
Age—risk increases with age
Gender—more in male, in female after menopause risk is similar to male
High risk race/ ethnicity—South Asian ancestry are at increased risk

Abbreviations and symbols: ASCVD, atherosclerotic cardiovascular disease; ↑, high; ↓, low; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CAD, coronary artery disease

The Framingham General CVD risk score system has been used since long for primary care assessment of the 10-year risk of developing CVD. [52,53]. According to Framingham risk score, based on the 10-year CV risk, individuals may be at high CV risk (>20%), intermediate or moderate CV risk (10-20%) or low CV risk (<10%). Those individuals with a 10-year risk of CVD of >20% are either high risk or very high risk. They should be treated aggressively from the outset with life style intervention and pharmacological therapy to achieve treatment targets. Individuals who are low risk should be given advice to help them maintain the status. This is because, in low risk individuals, the absolute benefit of risk reduction by lipid lowering therapy may be less [54]. However, benefit from statin therapy may be seen in lower-risk individuals having other risk enhancing factors. For primary prevention, 2001 National Cholesterol Education Program Adult Treatment Panel III (ATP III) [17] identified four levels of risk for determining the intensity of LDL-C lowering. Risk for CAD was calculated using Framingham risk score system [52]. A 10-year risk >20% for CAD was called high risk, 10-19% as moderately high risk, 5%-<10% as moderate risk and <5% risk for CAD as low risk. The ACC/AHA 2013 guideline on the assessment of cardiovascular risk, employed a pooled cohort equation (PCE) developed from several large population groups in USA to estimate 10-year risk (and lifetime risk) for ASCVD events [39,55]. The PCE was an extension of the Framingham heart study risk equations. The 2013 ACC/AHA guideline, established and categorized a 10-year risk of ASCVD as low-risk (<5%), borderline risk (5% to <7.5%), intermediate risk (7.5% to <20%), and high risk (≥20%) in American populations. The 2013 ACC/AHA risk calculator is available online in the internet [56]. The ESC/EAS recommend the use of the SCORE system based on risk for ASCVD mortality in European populations [40, 57]. The ESC/EAS categorized a 10-year risk of ASCVD as low-risk (SCORE <1%), borderline risk (SCORE >1% to <5%), high risk (SCORE >5% to <10%), and very high risk (SCORE ≥10%). The UK's National Institute for Health and Care Excellence (NICE) has recommended QRISK2 as the preferred risk score assessment tool for assessing CV risk in people for primary prevention of CVD [38].

Certain individuals declare themselves to be at high or very high CVD risk without need of risk scoring, and all their risk factors require immediate attention. This is true for patients with documented CVD, severe hypercholesterolemia (LDL-C level ≥190 mg/dL), advanced CKD and older individuals with long-standing DM or diabetes with target organ damage [38-42].

AHA/ACC 2018 defines very high risk as a history of multiple ASCVD events or of one event plus multiple high-risk conditions (that includes age >65, current smoking, DM, hypertension, CKD stage 3 or 4, and history of congestive heart failure) [39]. ECS/EAS 2016 defines very high risk category with established CVD, DM with target organ damage, advanced CKD stage 4 or 5 (eGFR <30 mL/min/1.73 m^2), or FH with ASCVD with another major risk [57]. In people with established or clinical CVD, elevated LDL-C correlates with recurrent CVE and increased mortality [4]. In these patients, LDL-C should be reduced with high-intensity statin therapy or maximally tolerated statin therapy. The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction [39]. Patients with severe hypercholesterolemia have a high lifetime risk of ASCVD with premature and recurrent CVE, and decisions about statins in these patients do not require ASCVD risk scoring [21,39,40]. In Singapore, patients having familial hypercholesterolemia are categorized as very high risk [42]. These patients should be treated with high intensity statin therapy.

The ECS/EAS 2016 [54] defines a high risk category with markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP >180/110 mmHg, patients with FH without other major risk factors, patients with DM without target organ damage, or moderate (stage 3) CKD (eGFR 30-59 mL/min/1.73 m^2). There is a wide spectrum of risk among individuals with DM that varies with age, duration of DM, presence or absence of diabetes complications, and the presence of traditional risk factors common to the general population. The AHA/ACC recognizes most adults 40 to 75 years of age with DM at intermediate or high-risk of ASCVD as they develop multiple risk factors. The ECS/EAC considers diabetes with target organ damage (like nephropathy, neuropathy or retinopathy) as very high risk and diabetes without target organ damage as high risk. ESC/EAS 2016 considers stage 4-5 CKD very-high risk while stage 3 CKD as high risk for ASCVD [57].

All other individuals with dyslipidemia not declaring themselves as very high risk or high risk, should be risk stratified by estimating the

individual's 10-year CV risk at the beginning using one of the risk calculator (as recommended by the country) to determine if they are at high, intermediate (moderate) or low risk. In individuals with intermediate risk (moderate risk) or selected borderline-risk, other risk factors not included in the conventional CV risk calculators may be considered that will influence treatment decision (about initiation or intensification of statin therapy). These factors include [58] (a) FH of premature CVD, (b) ankle: brachial index (ABI) <0.9 - this indicates PAD, ABI <0.9 is a risk-enhancing factor, the lower the index, the more severe the disease [39-41], (c) hs-CRP levels ≥2 mg/L is a serum marker of atherosclerosis [39,41] and (d) coronary artery calcium (CAC) score which is also a measure of disease burden. Detection of CAC with non-contrast computed tomography (CT) gives a good estimate of the atherosclerotic burden and is strongly associated with CVE [59]. CAC deposition generally occurs as a result of atherosclerosis; the more the amount of calcium deposited in coronary arteries, the more is the total amount of atherosclerosis. A CAC score of zero identifies individuals at lower risk of ASCVD events. In a study, the risk for CAD was about 10 times higher in the group with a CAC score of 300 or more compared to the group without CAC [60]. Sometimes preventive therapy may remain uncertain for some individuals with borderline or intermediate estimated 10-year ASCVD risk, and some patients may be reluctant to take medical therapy without clearer evidence of increased ASCVD risk. For these individuals, the assessment of CAC score has been recommended by AHA/ACC 2018 guidelines [39] to refine CVD risk, as part of shared decision-making. In these patients (a) if the CAC score is zero, it is reasonable not to initiate statin therapy as long as other higher risk conditions are absent (DM, FH of premature coronary heart disease (CHD), cigarette smoking, etc.), (b) if CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; and (c) if CAC score is 100 or higher, it is reasonable to initiate statin therapy.

For those at moderate risk, some guidelines have also included additional factors such as increased ApoB, Lp(a), C-reactive protein; the presence of albuminuria; and the presence of atherosclerotic plaque in the carotid or femoral arteries, that may further refine ASCVD risk assessment and upgrade risk classification [39,40]. ApoB may be a better measure of an individual's exposure to atherogenic lipoproteins, and its use may be particularly helpful for risk assessment in people with high TG, DM, obesity, or very low LDL-C. Lp(a) measurement may help to identify people with very high inherited Lp(a) levels or in patients with a FH of premature CVD who have a substantial lifetime risk of ASCVD. Assessment of carotid or femoral plaque burden with ultrasound has been demonstrated to be predictive of CVE [61,62]. However, routine measurement of carotid or femoral plaque for risk assessment is not recommended.

8. MANAGEMENT OF DYSLIPIDEMIA

LDL-C has been considered as the primary target of therapy for dyslipidemia [39-43,46,57]. Randomized controlled trials (RCTs) have shown that lowering of LDL-C reduces CVE in both primary and secondary prevention in both gender [12,63,64]. Once the ASCVD risk level has been determined, the patient needs to be discussed about their risk level, management strategy, adherence to a healthy lifestyle, benefits and potential adverse effects of drugs, as well as the patient's personal preferences for a treatment decision. Most individuals at low risk and intermediate (moderate) risk can be managed by life style modification and non-pharmacological therapy alone. Occasionally, lipid modifying agents may be necessary to achieve target lipid levels. Once decided to initiate pharmacotherapy, it should be individualized following a mutual discussion with the patient. It is crucial to treat other CV risk factors and the underlying secondary causes of dyslipidemia if present which can lead to a substantial improvement in the lipid profile.

8.1 Life Style Intervention

Lifestyle interventions can reduce risk of CVD. This includes adhering to a healthy diet, regular exercise, avoidance of tobacco smoking, alcohol restriction and maintenance of standard body weight [38-43,46,57]. Appropriate lifestyle modifications are an integral part of dyslipidemia management.

8.1.1 Dietary interventions to reduce ASCVD risks

Good adherence to various LDL-lowering diets will reduce LDL-C levels by 10% to >15% [65]. Emphasis should be given for consuming a healthy pattern of diet with intake of vegetables, fruits, whole grains, legumes, low-fat dairy and poultry products, fish, nuts and vegetable oils.

These are cardioprotective foods, and should be consumed in sufficient amount. Intake of refined carbohydrates, sweets, sugar-sweetened beverages and red meats should be limited [66].

Regarding fatty food intake, the aim of dietary counselling is to reduce the content of saturated fats, cholesterols and trans fats in the diet. It has been recommended that dietary fat intake should be 20 – 25% with an upper limit of 30% of total energy [67]. As for saturated fat, its consumption should be <10% of the total caloric intake and should be further reduced (<7% of energy) in the presence of hypercholesterolemia [40-42,68,69]. Saturated fats have the greatest impact on LDL-C levels; they should be replaced to equivalent calorie with unsaturated fats (polyunsaturated and monounsaturated fats) [70]. Foods rich in unsaturated fat such as oils from safflower, sunflower, rapeseed, flaxseed, corn, olives, or soybean were shown to reduce LDL-C levels when used in substitution of saturated fat-rich foods [71]. Observational evidence indicates that consumption of food rich in omega-3 fatty acids (fish at least twice a week) is associated with lower risk of CV death and stroke, but has no major effects on plasma lipoprotein metabolism [72,73]. However, pharmacological doses of omega-3 fatty acids were found effective in reducing TG levels [40]. It should be kept in mind that low intakes of fats and oils increase the risk of inadequate intakes of fat soluble vitamins (such as vitamin E) and of essential fatty acids, and may contribute to a reduction of HDL-C [74]. The contribution of dietary cholesterols to blood cholesterol levels is however, more complex and the impact of dietary cholesterol (egg) intake on adverse CVE is controversial. Based on the findings from observational studies that do not support an association between dietary cholesterol and CVD risk, the most recent Dietary Guidelines for Americans from the US Department of Health and Human Services set no specific recommended limits for the amount of dietary cholesterol intake [75]. However, most of the high-cholesterol foods also contain high levels of saturated fats. For this reason, guidelines recommend limiting dietary cholesterol to <300 mg/day in secondary prevention particularly in people with high plasma cholesterol levels [40-42,68,76]. Another recent research revealed that higher consumption of dietary cholesterols is significantly associated with higher risk of CVD in a dose-dependent manner [77]. Trans-fat should be avoided or reduced to less than 1% of total energy [68,69]. Dietary trans fat increases LDL-C, decreases HDL-C and are associated with a high risk of ASCVD [67,70,74]. Partially hydrogenated fats of industrial origin represent the major source of trans fats in the diet.

ESC guideline 2019, [40] recommends carbohydrate intake that should range between 45–55% of total energy intake, since both higher and lower percentages of carbohydrate diets are associated with increased mortality. One study showed a U-shaped relationship between carbohydrate intake and mortality: diets associated with the highest mortality rate had carbohydrate intakes >70% and <40% of total energy, with minimal risk observed when carbohydrate intake was between 45–55% of total energy intake [78]. In another meta-analysis, low-carbohydrate diets were associated with a 31% higher risk of all-cause death, with increased cardiac mortality rate [79]. Some guidelines have recommended carbohydrates should be 50–60% of total energy in the form of unrefined carbohydrates [41,42]. Excessive intake of simple carbohydrates should be discouraged because insulin drives TG production in the liver thereby increasing TG levels. In presence of high TG and low HDL-C, total carbohydrate intake should be low. The detrimental effects of a high-carbohydrate diet on TG occur mainly when refined carbohydrate-rich foods are consumed, while they are much less prominent if the diet is based largely on fiber-rich, low-glycaemic index foods. Habitual consumption of significant amounts (>10% energy) of dietary fructose contributes to TG elevation, particularly in people with abdominal obesity [80,81].

Emphasis should be given on intake of foods rich in dietary fiber (25–40 gm/day) particularly of the soluble type (7—13 gm/day) which is present in fruits, green leafy vegetables, legumes, beans and wholegrain cereals [39-43]. The soluble dietary fiber has a hypocholesterolemic effect and minimizes the untoward effects of a high-carbohydrate diet on other lipoproteins [82].

8.1.2 Other life style interventions to reduce ASCVD risk

Interventions other than dietary advice are also important to reduce CV risk and control blood lipids. Tobacco smoking should be completely stopped and passive smoke should be avoided. Cigarette smoking increases the risk for dyslipidemia and remains a strong, independent risk factor for ASCVD and premature death [83]. Smoking cessation has clear benefits regarding

overall CV risk, and may contribute to HDL-C elevation, provided that weight gain is prevented [84]. Therefore, smoking cessation is strongly recommended and those who use tobacco should be assisted and advised to quit. Alcohol consumption should be reduced or avoided altogether; alcohol is associated with hypertriglyceridemia [85].

It is always appropriate to advise people with dyslipidemia to engage in regular physical exercise. The numerous health benefits of regular physical activity have been well established, and physical activity is a cornerstone of maintaining and improving CV health. In general, aerobic exercise decreases TG concentration while increasing HDL-C, with little changes to LDL-C concentration [86]. 150 minutes a week of moderate aerobic or 75 minutes a week of vigorous aerobic exercise or a mixed moderate and vigorous aerobic activity is recommended [87,88]. Shorter durations of exercise seem to be as beneficial as longer ones (e.g., ≥10 minute bouts), and thus the focus of physical activity counselling should be on the total accumulated amount [89]. Decreasing sedentary behavior in adults may be reasonable to reduce ASCVD risk [90]. Sedentary individuals starting an exercise program should initiate exercise at a lower intensity (e.g., slow walking) and duration and progressively increase gradually to recommended levels [91].

Overweight and obese people should reduce their body weight; obesity and overweight are related to dyslipidemia. Many studies with obese or overweight individuals found that TC, LDL-C, and TG concentrations decreased with weight loss [92]. Weight reduction increases HDL-C levels and improves insulin sensitivity. Therefore, guidelines recommend to achieve and maintain a country specific normal BMI or at least 5-10% of basal body weight reduction over 1-2 years [93]. For weight reduction, the consumption of energy-dense foods should be decreased to induce a caloric deficit of 300–500 kcal/day from the baseline, combined with exercise [94]. In the case of excess weight, body weight reduction, even if modest (5–10% of basal body weight), improves lipid abnormalities and favorably affects the other CV risk factors often present in dyslipidemic individuals [93].

Waist circumference, if increased, should be reduced to country specific norms. Increased waist circumference and central obesity has been associated with increased risk of ASCVD [95]. Waist circumference measurement is recommended for patients with BMI <35 kg/m^2 and is needed for the diagnosis of metabolic syndrome [96]. Guideline has recommended to maintain waist circumference of <94 cm for men <80 cm for women [40].

8.2 Pharmacological Measures

When lifestyle interventions alone are not enough to correct dyslipidemia, or those who are determined to be at sufficient ASCVD risk, lipid modifying drugs are used after a clinician–patient overall discussion. Before starting lipid modifying drugs, the individual should be checked with standard blood lipid profile to establish a baseline. The liver function tests (ALT, AST) and blood glucose levels are seen routinely. It is important to monitor the individual on a regular basis for response to therapy and achievement of lipid targets.

Currently there are 7 classes of lipid modifying agents: statins (e.g. atorvastatin, rosuvastatin, simvastatin, pravastatin), cholesterol absorption inhibitors (ezetimibe), bile acid sequestrant (colesevelam, cholestyramine), fibrates (fenofibrate, gemfibrozil), nicotinic acid derivatives (niacin), omega 3 fatty acids (fish oil supplements), and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab, alirocumab) [97]. Patient with predominant hypercholesterolemia (high LDL-C/TC/Non-HDL-C) can be treated with one or more of the cholesterol-lowering drugs that include statins, cholesterol absorption inhibitors, bile acid sequestrants, or PCSK9 inhibitors. Statin is the primary pharmacological agent for hypercholesterolemia [39-43]. In patients at very-high risk and with persistent high-risk despite being treated with a maximally tolerated statin, combination with ezetimibe or bile acid sequestrants is recommended and, if still not at goal, the addition of a PCSK9 inhibitor is recommended [39-40]. Addition of a PCSK9 inhibitor directly to a statin is also feasible [98, 99]. The decision to combine a statin and another lipid lowering agent must be individualized and should be initiated only when it is strongly indicated. Patients with predominant hypertriglyceridemia can be treated with one or more of drugs that include fibrates, nicotinic acids, or omega-3 fatty acids supplements [39, 41-42]. Statins and PCSK9 inhibitors are also useful to some extent. For individuals with a TG concentration of 500 mg/dL or higher, Korean guidelines recommend drug therapy and lifestyle modification with complete abstinence of alcohol to prevent acute pancreatitis [43]. Fibrates are

the first line of drug to reduce the risk of pancreatitis in these patients. Niacin or omega 3 fatty acids are often added for treatment when fibrates alone do not adequately lower the markedly elevated TG levels. For individuals with a TG concentration of 200–499 mg/dL, the primary treatment goal is to lower the LDL-C to the target level first with statin therapy. After achieving the LDL-C target level, if TG levels are still >200 mg/dL (2.3 mmol/L) and cannot be lowered by lifestyle measures, then pharmacological therapy should be considered to lower TG level. For TG concentration of 150 mg/dL to 200 mg/dL drug therapy is not given [40]. Secondary causes of hypertriglyceridemia should be sought and treated for each. For patients with diabetes, strictly blood glucose control is helpful. A meta-analysis of 10 trials included people treated with various agents that reduce serum TGs (fibrates, niacin, and omega-3 PUFAs) reported a 12% reduction in CVE [100]. In mixed dyslipidemia, statin therapy is initiated, adding ezetimibe, fibrate or niacin if lipids still not at target. Fibrates can be considered as add-on therapy to a statin in very high or high risk patients when TG is between 200 to 500 mg/dL in the presence of low HDL-C. In patients with low HDL-C levels, in the very high-risk or high-risk group, the use of agents that elevate HDL-C, such as fibrate or nicotinic acid, may be considered after controlling LDL-C [43]. However, there is no evidence from randomized trials that therapeutically increasing plasma HDL-C or directly infused HDL mimetic that increase plasma HDL-C concentrations, reduces the risk of CVE [101,102].

The primary goal of dyslipidemia treatment is to control LDL-C to or below the target [39-43]. Among the lipid modifying drugs, statins are the first line of therapy in addition to healthy lifestyle interventions. A stepwise approach to the management of high LDL-C is used until the LDL-C levels are lowered adequately. If statins alone do not sufficiently lower LDL-C, or patient has problems taking a statin, additional drug options are available. Seven types of stains, namely atorvastatin, simvastatin, rosuvastatin, lovastatin, pravastatin, fluvastatin, and pitavastatin, are currently used (Table 2). Intensity of statin therapy has been classified into [46] (a) high-intensity statin therapy where the daily dose lowers LDL-C by ≥50% (atorvastatin 40-80 mg or rosuvastatin 20-40 mg), (b) moderate-intensity statin therapy by 30 to 49% (atorvastatin 10-20 mg, rosuvastatin 5-10 mg or simvastatin 20-40 mg) and (c) low-intensity statin therapy lowers LDL-C by <30% (simvastatin 10 mg, pravastatin 10-20 mg, lovastatin 20 mg or fluvastatin 20-40 mg). High-intensity statin therapy is indicated for patients with severe hypercholesterolemia or clinical ASCVD. The first goal is to achieve a ≥50% reduction in LDL-C levels. The individuals in whom despite high intensive statin therapy have an LDL-C level ≥100 mg/dL (≥2.6 mmol/L) are likely to derive additional ASCVD risk reduction from ezetimibe add-on therapy through additional LDL-C lowering [103]. Furthermore, if LDL-C levels remain ≥70 mg/dL (≥1.8 mmol/L), adding a PCSK9 inhibitor is reasonable if the cost/benefit ratio is favorable. Nonetheless, adding bile acid sequestrants to otherwise maximal cholesterol-lowering therapy in patients who are not eligible for a PCSK9 inhibitor may be considered. The addition of a bile acid sequestrant or ezetimibe to a statin regimen increases the magnitude of LDL-C lowering by approximately 15% to 30% and 13% to 20%, respectively [104,105]. The addition of a PCSK9 inhibitor to a statin regimen has been shown to further reduce LDL-C levels by 43% to 64% [99,106,107]. Moderate-intensity statin therapy also reduces major vascular events and CHD deaths in patients with ASCVD [12,108].

Patients with severe hypercholesterolemia who are adherent to statins, achieve <50% reduction in LDL-C levels with high intensity statin therapy. Absolute benefit from statin therapy depends on baseline LDL-C levels; the greatest absolute benefit occurs in patients with the highest baseline LDL-C levels. In selected patients with severe hypercholesterolemia whose LDL-C is inadequately controlled with drug therapy, LDL apheresis is an option [109,110]. All patients with established CVD or experiencing a CVE should be prescribed a statin, regardless of the baseline LDL-C concentration. If a person has ACS, statin treatment should not be delayed. More patients are surviving their initial CVE and are at high-risk of recurrences. In people with established CVD, elevated LDL-C correlates with recurrent CVE. Peoples with established CVD have greater absolute benefit from LDL-C reduction. In a randomized controlled trial on 4,500 patients who experienced an acute MI, the incidence of CVD was lower in the group that received statin immediately after MI than in the group that did not receive statin immediately after MI [111]. Summary of secondary prevention in a patient with ASCVD is shown in Table 3. Adults with DM should start with a moderate-intensity statin, and as they develop multiple risk factors, a high-intensity statin may be considered to reduce the LDL-C level by ≥50% [112,113].

Table 2. Statins currently available and intensity of therapy

Statins	Daily dose used (mg)	High intensity, ≥ 50% ↓ LDL-C (mg)	Moderate intensity, 30-49% ↓ LDL-C (mg)	Low intensity <30% LDL-C (mg)
Atorvastatin	10—80	40—80	10—20	5
Rosuvastatin	5—20	20—40	5—10	
Simvastatin	20—40		20—40	10
Lovastatin	20—80		40—80	10--20
Pravastatin	10—40		40—80	10—20
Fluvastatin	20—80		80	20--40
Pitavastatin	1—4		1—4	

Abbreviations and symbols: LDL-C, low density lipoprotein cholesterol; ↓, reduction

Table 3. Summary of secondary prevention in patients with established CVD

High intensity statin therapy; if goals not achieved, addition of non-statin drugs
Goals of LDL-C are tight (<70 mg/dL)
Antiplatelets (aspirin/ clopidogrel)
Beta-blocker if no contraindication
ACE inhibitors or ARBs
Correction of risk factors
Life style modifications

Abbreviations: CVD, cardiovascular disease (CVD—defined as acute coronary syndrome, unstable or stable angina, myocardial infarction, history of coronary revascularization, ischemic stroke and transient ischemic attack); LDL-C, low density lipoprotein cholesterol; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

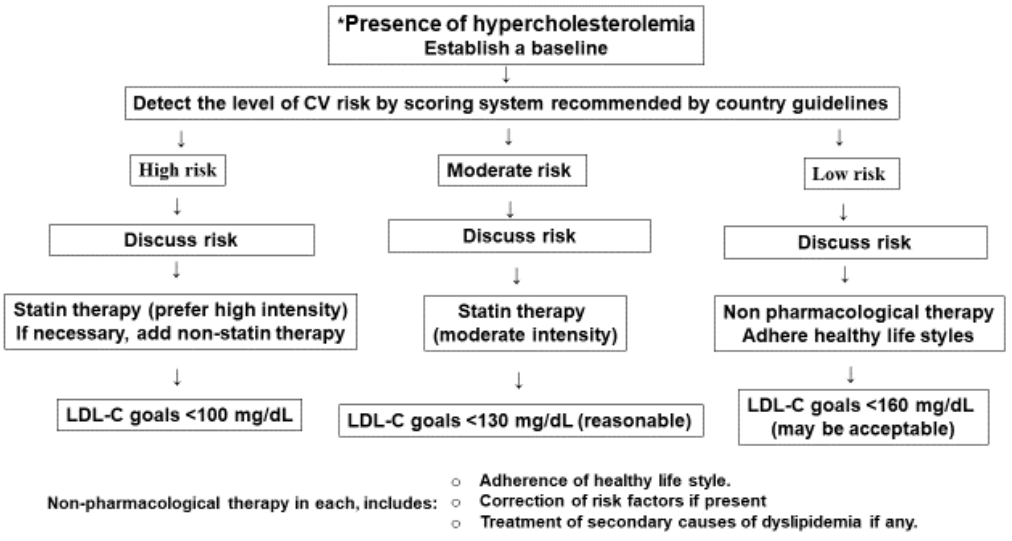

Fig. 1. Algorithm for primary prevention of dyslipidemia in adults

*Abbreviations: CV, cardiovascular; LDL-C, low density lipoprotein cholesterol. *This algorithm does not apply to patients with atherosclerotic cardiovascular disease, severe hypercholesterolemia (LDL-C >190 mg/dL), diabetes or advanced chronic kidney disease*

For primary prevention of CVD in adults with dyslipidemia (Fig. 1, see algorithm), the first step is to calculate the 10 year CVD risk and to look all the other risk factors not included in the risk calculator. Those individuals with high risk should be treated aggressively from the outset with life style intervention and pharmacological therapy to achieve treatment targets. In adults at moderate risk, after risk discussion, a moderate-intensity statin should be recommended [114]. When

decision regarding pharmacotherapy is uncertain (borderline), other risk-enhancing factors should be considered; their presence will favor initiation of statin therapy [115]. The low risk individuals, should be advised to adhere with healthy life styles; however, if lipid levels remain uncontrolled they may be advised low intensity statins. Risk factors related to dyslipidemia should be addressed in every cases.

In dialysis dependent end stage kidney disease (ESKD) patients, who are free of ASCVD, commencement of statin therapy is not recommended for primary prevention because of lack of studies to show beneficial effects of statin on prevention of CVD [116]. However, in adults who need dialysis for ESKD and are currently receiving statin therapy, statin is continued. Stage 3-5 CKD are considered to be at high or very-high risk of ASCVD. The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3-5 CKD. Initiation of lipid-lowering therapy is not recommended in patients with heart failure in the absence of other indications for their use [40]. Moderate-intensity statins may be considered in patients with heart failure due to ischemic heart disease [39]. Initiation of lipid-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD or other indications [40]. In patients >75 years of age with ASCVD, potential benefits versus adverse effects of statin therapy should be considered before initiating statin therapy.

9. TARGETS OF SERUM LIPIDS

There is a general agreement that LDL-C is the primary target of treatment [23,39,40,46]. The approach to lipid management is primarily aimed at reducing ASCVD risk by substantially lowering LDL-C to target or at lower levels which have shown to be associated with atherosclerotic regression. RCTs of cholesterol-lowering drugs in high-risk patients confirm that LDL-C lowering produces marked reductions in ASCVD [36]. This confirms the general principle that the greater the LDL-C reduction, the greater the CV risk reduction, the “lower is better” for LDL-C reduction. A one mmol/L (40 mg/dL) reduction in LDL-C reduces CV mortality by 22% [113]. No level of LDL-C below which benefit ceases, and no adverse effects of very low LDL-C concentrations (e.g. <1 mmol/L) has been defined [40]. However, depending on the patients’ ASCVD risk, targets have been defined by different guidelines with slight differences but almost similar for matching the intensity of lipid modifying therapies to the absolute ASCVD risks of a patient. In other words, patients who have highest risk should receive most intensive LDL-C reduction. Secondary goals have also been defined by inference for non-HDL-C and for ApoB [40].

9.1 LDL-C Targets

In those patient with very high risk, the 2019 ECS/EAS guidelines [40] recommend a therapeutic regimen that achieves ≥50% LDL-C reduction from baseline and an LDL-C goal of <55 mg/dL (1.4 mmol/L). Lowering of LDL-C beyond the goals is associated with fewer ASCVD [117]. Therefore, it seems appropriate to reduce LDL-C to as low a level as possible, at least in patients at very high CV risk. In the 2018 AHA/ACC guideline, no numerical targets are stated. High intensity or maximally tolerated statin should be used in people with very high risk to lower LDL-C levels by ≥50% from baseline, a LDL-C threshold of 70 mg/dL (1.8 mmol/L) is used to consider addition of non-statins to statin therapy [39]. The ATP III (updated 2004) [23], set a target LDL-C of 70 mg/dL (1.8 mmol/L) for very high risk individual. In people with high risk, the 2019 ESC/EAS guidelines recommend to use a high intensity or maximally tolerated statin to lower LDL-C levels by ≥50% from baseline and an LDL-C goal of <70 mg/dL (1.8 mmol/L). The ATP III, set a target LDL-C of <100 mg/dL (2.6 mmol/L) for high risk individual. In people with moderate risk, the 2019 ESC/EAS guidelines considers a LDL-C goal of <100 mg/dL (2.6 mmol/L). The ATP III, set a target LDL-C of <130 mg/dL (3.3 mmol/L) for moderate risk individuals. In people with low risk, the 2019 ESC/EAS guidelines considers a LDL-C goal of <116 mg/dL (3.0 mmol/L). The ATP III, set a target LDL-C of < 160 mg/dL (4.1 mmol/L) for low risk individuals.

In patients with severe primary hypercholesterolemia with LDL-C ≥190 mg/dL (4.9 mmol/L) without concomitant ASCVD, the AHA/ACC 2018, recommends high intensity statin therapy to achieve an LDL-C goal of <100 mg/dL (2.6 mmol/L) [39].

9.2 Targets of Lipids Other than LDL-C

The optimum levels of TC have been recommended to be <200 mg/dL (5.2 mmol/L) [17,41]. The levels of HDL-C that is associated with increased risk of ASCVD in male <40 mg/dL (1 mmol/L), and in female <50 mg/dL (1.2 mmol/L). Although increases in HDL-C predict

atherosclerosis regression, recent studies indicate that the currently available therapies for raising HDL-C do not reduce the risk of ASCVD [101,102,118]. ESC/EAS 2019 guideline gives no specific goals for HDL-C levels as they have not been determined in clinical trials [40]. TG level <150 mg/dL (1.7 mmol/L) indicates lower risk and if the TG levels are higher than that, other risk factors should be looked for and steps should be taken to correct them [40,41]. Non-HDL-C may be considered as a secondary target when treating patients with combined dyslipidemias, diabetes, cardio metabolic risk and CKD. Non-HDL-C goals are <85, 100, and 130 mg/dL (2.2, 2.6 and 3.3 mmol/L) for very-high, high, and moderate-risk people, respectively [119,120]. ApoB secondary goals are <65, 80 and 100 mg/dL for very-high, high, and moderate-risk people, respectively [119, 120].

10. MONITORING OF THERAPY AND MANAGEMENT OF ADVERSE EFFECTS OF DRUGS

Before starting lipid lowering pharmacotherapy, the individual should be checked with standard blood lipid profile, blood sugar level, liver function tests (ALT), renal function and eGFR routinely to establish a baseline [38-43,46]. The term 'baseline' refers to the lipid levels in a person not taking any lipid-lowering medication. Clinical efficacy is monitored by measurement of percentage reductions in LDL-C relative to baseline levels. Unless a baseline level is established, it will be difficult to evaluate response to therapy. Blood creatinine levels should also be measured before fibrate administration because fibrate therapy may be associated with renal dysfunction [121] Non-HDL-C or ApoB are measured, when used as a secondary treatment target [40]. The ESC guideline [40] also recommends creatine kinase (CK) measurement (a marker of muscle damage) at baseline to identify the limited number of patients where treatment is contraindicated. CK should be checked in the very elderly with comorbidities, patients with antecedents of muscle symptoms, or patients receiving interacting drugs. If baseline CK is >4 times upper limit of normal (ULN), it is recommended not to start drug therapy; and to recheck, re-evaluate indication for statin treatment. When statins are used, patients should be advised to report promptly to their doctors if they develop any significant liver or muscle symptoms [122].

In clinical practice, lifestyle and statin therapy are commonly introduced together. The maximum percentage change of lipid profile will occur by 1 to 3 months after starting a statin or combined therapy. Therefore, once lipid lowering pharmacotherapy has been initiated, the patient should be re-assessed after 1—3 months to see the response to pharmacotherapy and their side effects [38-43,46]. The patient should be clinically assessed for adherence with drug treatment, diet and exercise, with monitoring of weight and BP. At this stage a lipid profile is done and the dose is adjusted accordingly to achieve target LDL-C levels primarily.

Severe hepatitis (nausea, vomiting, loss of appetite, jaundice and liver tenderness) and progression to liver failure, associated with statin therapy is very rare [123,124]. A transient and mild elevation of alanine transaminase (ALT) is seen in about <3% of patients and normalization is seen with continuing therapy [124,125]. If sustained ALT elevation >3 times ULN that is not due to fatty liver, treatment should be stopped and the individual should be evaluated and monitored [126]. Lipid lowering drug can be cautiously reintroduced under monitoring after levels have returned to normal [126]. Guidelines do not recommend routine testing of liver enzymes (ALT) during long term treatment unless symptoms suggesting liver disease evolve or the individual is treated with fibrates [38-41, 43,46].

The incidence of statin induced myopathy (proximal muscle weakness, with or without elevation of CK), myositis (muscle inflammation, muscle pain, elevation of CK), rhabdomyolysis (elevation of CK ≥10 times ULN, severe muscle pain, muscle necrosis, myoglobinuria, dark urine, acute kidney injury) and autoimmune mediated necrotizing myositis (severe proximal muscle weakness, very high CK level, and histological evidence of muscle necrosis with minimal lymphocyte infiltration) are very low [127,128]. It is not necessary to perform routine monitoring of CK unless skeletal muscle symptoms occur [38-41,43,46]. If myalgia or weakness occurs in association with CK >5 times ULN, treatment should be discontinued and the individual should be evaluated [122]. The renal function should be checked, and the patient should be monitored with CK [46]. If CK falls <4 times ULN, if no muscle symptoms, statin can be restarted and continued but the patient should be alerted to report symptoms [40]. Patients who are troubled by muscle pain, stiffness and muscle knots, even in the absence of a raised serum CK, may

benefit from either stopping the statin therapy or reducing the dosage [122]. Statins have been associated with a small increase in the incidence of development of type 2 DM (9-12%) [129]. The CV risk reduction benefits seen with statins far outweigh the risk of developing diabetes; therefore, it is better to continue statin and make necessary lifestyle modification, such as exercise, and weight reduction [130]. Fibrates should be used with caution in patients with CKD as they can raise creatinine [121]. Blood creatinine levels should be measured 3 months of fibrate administration and patients should be followed-up every 6 months if there are no abnormal findings. The increase of serum creatinine by fibrate therapy seems to be fully reversible when the drug is stopped. An increased frequency of proteinuria has been reported for all statins which is of tubular origin, and not to glomerular dysfunction. As such, routine monitoring of renal function or proteinuria is not recommended [131].

Thereafter, the standard practice for subsequent follow-up monitoring is 3–12 months as needed depending on the patient's CV risk and degree of lipid reduction [39-41,43]. Periodic re-measurements will make it possible to confirm adherence to therapy. Once a patient has achieved the target or optimal lipid level, blood lipids may be tested annually [40].

11. CONCLUSION

LDL-C levels can now be markedly reduced and goals achieved in the most of patients with currently available drugs and thereby the risk of ASCVD reduced. Adherence to lifestyle intervention and pharmacotherapy is important. It should be emphasized that individuals with dyslipidemia will be on lifelong therapy. Blood LDL-C level rises within few months after cessation of therapy and reverts back to the pre-treatment levels. In addition, the CV protective effects of statin disappear rapidly after stopping administration, so it is important to continue taking the drug unless warranted by other circumstances.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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