



An Update on Pharmacotherapy of Dyslipidemia for Adults

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Author's contribution

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ABSTRACT

Dyslipidemia is an important cause of atherosclerotic cardiovascular disease (ASCVD) worldwide that leads to increased risk of morbidity and mortality; treating dyslipidemia to goal reduces the risks. This article reviews the pharmacological therapy of dyslipidemia which is often required in addition to life style intervention to achieve target lipid levels. Currently, there are seven types of approved lipid modifying drugs which are effective in treating dyslipidemia when used singly or in combination. Statins are considered as first line drug and have been used extensively in the primary and secondary prevention of ASCVD. Ezetimibe is used as a first line add-on drug for patients already on a statin who have not reached their low density lipoprotein (LDL-C) goals; however, ezetimibe can be used as initial drug in statin intolerant patients. Bile acid sequestrants are a useful alternative to statins or ezetimibe in pregnant women or patients with liver disease. They also lower blood glucose and are useful in diabetes mellitus (DM). The PCSK9 inhibitors are powerful lipid modifying drugs, are expensive, need injection for delivery, and are used when statin in maximum doses with other drugs cannot lower the LDL-C level to targets in patients with very high CV risk. Fibrates have recently shown to slow the progression of microvascular diseases and are found beneficial for DM with hypertriglyceridemia and microvascular complications. Currently, niacin use is markedly decreased due to development of more effective alternative drugs for managing dyslipidemia and because of the adverse effects related to niacin use. Recent trials

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reveal that, ω -3 fatty acids, when added in pharmacological doses to statin therapy (after controlling LDL-C), are effective in reducing CV events in patients having moderate hypertriglyceridemia with high or very high CV risks.

Keywords: Cholesterol lowering drugs; ezetimibe; fibrates; LDL-C lowering drugs; PCSK9 inhibitors; statins; triglyceride lowering drugs; treatment (drugs).

1. INTRODUCTION

Dyslipidemia is an abnormality in blood lipids consisting of high levels of low density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglyceride (TG) or low levels of high density lipoprotein cholesterol (HDL-C) singly or in combination [1]. These are the 4 different lipids usually measured in a standard lipid profile to determine a patient's cardiovascular (CV) risk. Apolipoprotein B (Apo B) is a key structural component of all the atherogenic lipoprotein particles, including LDL, very low density lipoprotein (VLDL), and intermediate density lipoprotein (IDL). Lipoproteins are vehicles of transmission of lipids as the latter is insoluble in blood. Some expert panels have proposed using ApoB in conjunction with standard lipid testing to get a more accurate picture of a patient's risk of CV events [2]. High levels of lipoprotein(a) ((Lp(a)) are recognized to be independent risk factor of ASCVD [3,4]. However, ApoB and Lp(a) are not included in the routine measurement of standard lipid profile [5]. Dyslipidemia, is an established and important risk factor for atherosclerotic cardiovascular disease (ASCVD) [6,7]. LDL-C is the dominant form of atherogenic cholesterol. Patients with markedly elevated TG are (\geq 500 mg/dL) also at risk of acute and recurrent pancreatitis [8]. The higher the TG level, the greater is the risk. Excess TGs are carried in VLDL which are believed to be atherogenic. In marked hypertriglyceridemia, most patients have elevated VLDL plus chylomicrons. Chylomicronemia per se may not be atherogenic, but they impose the risk of acute pancreatitis. The purpose of treating lipid disorders is to prevent the development of ASCVD and pancreatitis.

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. In most patients, currently available lipid modifying drugs are effective in bringing the lipid levels to goal thereby reducing the risk of CV events. The decision to treatment with lipid modifying drugs must be individualized

and should be initiated only when it is indicated. The general criteria for the choice of drug and dose include the clinical condition of the patient, concomitant medications, drug tolerability, local treatment tradition, and drug costs [9]. Before starting lipid modifying drugs, the individual should have a base investigation with standard blood lipid profile, liver function tests, renal function tests, and fasting blood glucose levels. It is important to monitor the individual on a regular basis for response to therapy and the achievement of lipid targets [5]. It should be emphasized that individuals with dyslipidemia will be on lifelong therapy. Blood LDL-C level rises again a few months after cessation of statin therapy and reverts to the pre-treatment levels. In addition, the CV protective effects of statin disappear within several days after stopping administration, so it is crucial to continue taking the drug.

This paper focuses on the pharmacotherapy of dyslipidemia describing the current drugs available with their role in the management of various lipid disorders. With aging populations, the prevalence of dyslipidemia and cardiovascular disease (CVD) will continue to rise throughout the world, therefore the importance of drug therapy will remain; and more people will require the addition of drugs to control their dyslipidemia. The details of pharmacotherapy for specific population are out of scope in this review paper.

2. PHARMACOLOGICAL MEASURES

Currently, there are 7 classes of lipid modifying agents in use (Fig. 1), these include: statins, cholesterol absorption inhibitors, bile acid sequestrants, fibrates, niacin, ω -3 fatty acids (fish oil) supplements, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [5]. A stepwise approach to the management of dyslipidemia is used until the lipid levels are controlled adequately. The primary goal of dyslipidemia treatment is to control LDL-C at target values. Among the lipid modifying drugs, statins are the cornerstone of therapy in addition to healthy lifestyle adherence. If a statin alone

doesn't sufficiently lower LDL-C, or a patient has problems taking a statin, additional drug options are available. The use, adverse effects, contraindications, and safety profile of different lipid modifying drugs are summarized in Table 1.

2.1 Drugs Used in Predominant Hypercholesterolemia

Hypercholesterolemia has been defined as high levels of LDL-C, TC, or non-HDL-C, singly or in combination. It is associated with an increased risk of development of ASCVD and CV events. Treating hypercholesterolemia eventually decreases the risk. Other than primary or familial, secondary causes of hypercholesterolemia include nephrotic syndrome, Cushing syndrome, hypothyroidism, drugs (e.g., corticosteroids, beta-blockers), and consumption of a diet rich in saturated and trans fats [5,10]. Patients with predominant hypercholesterolemia are 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. In patients at very-high risk and despite being treated with a maximally tolerated statin, combination with

ezetimibe or a bile acid sequestrants is recommended and, if still the goal is not achieved, the addition of a PCSK9 inhibitor is recommended [9,11]. The addition of a PCSK9 inhibitor directly to a statin is also feasible [12, 13].

2.2 Drugs Used in Predominant Hypertriglyceridemia

Most cases of severe hypertriglyceridemia have a genetic component, but secondary factors may contribute. Heavy carbohydrate diet consumption, excess refined sugar intake, alcohol, obesity, DM, hypothyroidism, oral contraceptives, and many drugs including bile acid sequestrants, all can increase blood TG [5]. Because of the increased risk of acute pancreatitis, it is imperative to lower TG levels in patients having marked hypertriglyceridemia. Patients with predominant hypertriglyceridaemia can be treated with one or more of drugs that include fibrates, niacin, or ω -3 fatty acids supplements [11,14,15]. Statins and PCSK9 inhibitors are also useful to some extent. Fibrates are the first line of drugs, while niacin or ω -3 fatty acids are often added for treatment when fibrates alone do not adequately lower the markedly elevated TG levels.

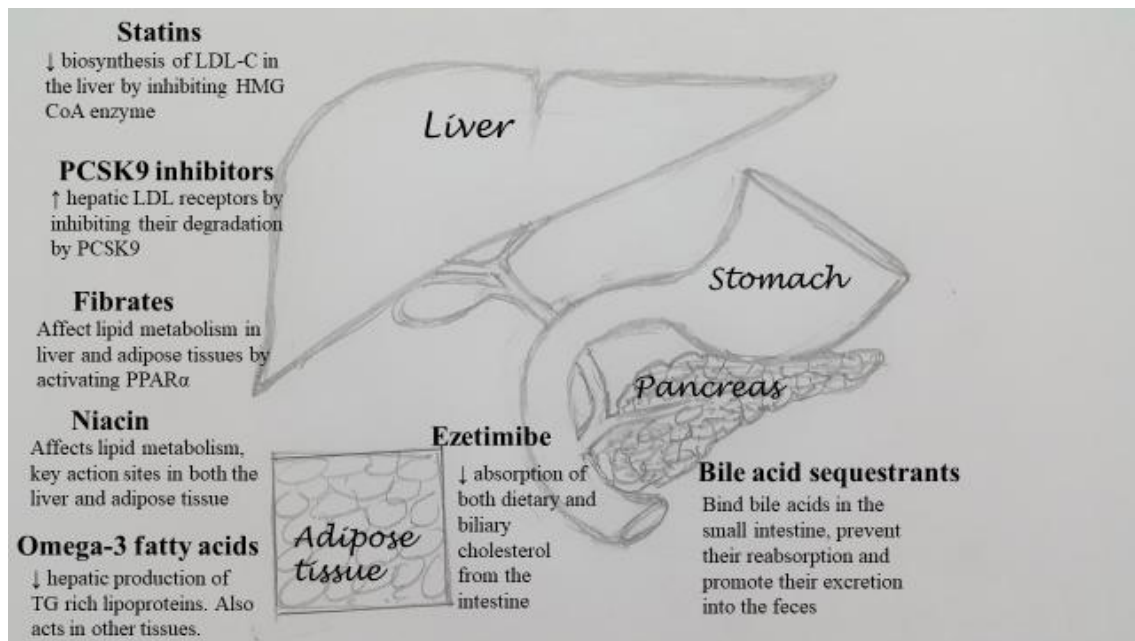


Fig. 1. Lipid modifying drugs and their main site of action

Abbreviations: LDL, low density lipoprotein; HMG CoA, hydroxy-methyl-glutaryl coenzyme A; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR α , peroxisome proliferator activated receptor- α ; TG, triglyceride

Table 1. Lipid modifying drugs currently used for treating dyslipidemia

Drug class	Example of drugs	Major use	Dose	Adverse effects	Contraindications	Safety profile
Statins	Atorvastatin, Simvastatin, Rosuvastatin, Lovastatin, Pravastatin, Fluvastatin, Pitavastatin	To ↓ LDL-C To ↓ TC and non HDL-C	Atorvastatin, 10-80 mg; Rosuvastatin, 5-20 mg; Simvastatin, 20-40 mg; Lovastatin; 20-80 mg; Pravastatin: 10-40 mg; Fluvastatin, 20-80 mg; and Pitavastatin, 1-4 mg. <i>All the drugs are used orally and daily</i>	GI upset: nausea, indigestion, heartburn, and abdominal pain. Skeletal muscle adverse effects: myalgia, myositis, myopathy, rhabdomyolysis and autoimmune necrotizing myopathy. ↑ liver enzymes, rarely hepatitis and hepatic failure. Small risk of developing DM.	Active or CLD (except stable liver disease e.g., NAFLD), pregnancy and lactation	Usually safe.
Cholesterol absorption inhibitors	Ezetimibe	To ↓ LDL-C To ↓ TC and non HDL-C	10 mg/day orally	GI upset: abdominal discomfort, pain, indigestion, flatulence, diarrhoea and anorexia. ↑ of liver enzymes, muscle pain, arthralgia, and fatigue.	Acute or CLD, pregnancy, lactation and hypersensitivity to Ezetimibe	Usually safe
Bile acid sequestrants	Cholestyramine, Colesevelam	To ↓ LDL-C To treat pruritus in patients with CLD	Cholestyramine, 8-24 gm/day orally; Colesevelam, 3.75 gm/day orally	GI upset: abdominal discomfort, bloating, flatulence, nausea and constipation. ↓ absorption of fat soluble vitamins. ↑ in plasma TGs	Patients with TG >400mg/dL (4.5 mmol/L)	Safe during pregnancy and lactation. Improves glycemic control
PCSK9 Inhibitors	Alirocumab and Evolocumab	Powerful LDL-C lowering agent	Alirocumab, 75-150 mg SC every 2 weeks or 300 mg SC once a month; Evolocumab, 70 mg SC every 2 weeks or 420 mg SC once a month.	Flu-like symptoms, myalgia, arthralgia, lethargy and nausea. At the site of injection: itching and swelling.	Hypersensitivity to the drug	Long-term safety profile remains unknown. Very expansive
Fibrates	Fenofibrate, Gemfibrozil	To ↓ TG levels in marked hypertriglyceridemia (>500 mg/dL)	Fenofibrate (micronized), 160 mg/day orally; Gemfibrozil, 600-1500 mg/day orally	GI upset, ↑ liver enzyme & creatinine, muscle symptoms, and cholelithiasis	Severe liver disease, CKD stage 4 & 5, gall stone, and hypersensitivity to fibrate	Protective effect against diabetic microvascular disease
Niacin	Niacin or nicotinic acid	To ↓ TG levels in	150-300 mg/day orally	Skin redness itching, tingling and	Active PUD, GERD, poorly	Use of niacin is

Drug class	Example of drugs	Major use	Dose	Adverse effects	Contraindications	Safety profile
		marked hypertriglyceridemia. To lower LDL-C		burning. Other: hepatotoxicity, hyperglycemia, hyperuricemia, dyspepsia, heartburn, indigestion, nausea, diarrhea and abdominal discomfort.	controlled DM, gout, pregnancy and lactation.	gradually declining as explained in the text
Omega-3 fatty acids	Omega-3 fatty acids	To ↓ TG levels in hypertriglyceridemia	2-4 gm/day orally	GI upset: nausea, vomiting, fish-smelling, fishy taste in mouth, diarrhea, dyspepsia, abdominal discomfort and acid eructation. Other: ↑ liver enzymes, ↑ blood glucose, arthralgia, itching, and headache.	Hypersensitivity to drug	Safe and well tolerated

Abbreviations: LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; GI, gastrointestinal; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; CLD, chronic liver disease; DM, diabetes mellitus; SC, subcutaneously

For individuals with a marked elevation of TG concentration of ≥ 500 mg/dL (5.6 mmol/L), the primary goal of treatment is to reduce the risk of pancreatitis. Guidelines consider the correction of secondary factors, and if still, TG remains high or if there are no secondary causes, to consider treatment with drugs [14,16,17]. There have been no randomized controlled trials demonstrating that treatment diminishes pancreatitis [17]. For individuals with a TG concentration of 200–499 mg/dL, the primary goal of treatment is to reduce CV risk. For those individuals with high LDL-C levels, the initial treatment goal is to lower the LDL-C to the target level first with statin therapy. In addition to lowering LDL-C levels, statins are also very effective in lowering TG levels particularly when the TGs are elevated. After achieving the LDL-C target level, if TG levels are still high and cannot be lowered by correcting secondary causes, pharmacological therapy that primarily lowers TG should be considered [9,11,18]. Some authors use non-HDL-C in high risk patients when statins have lowered the LDL-C levels to goal but the non-HDL-C levels are above goal due to elevated TG levels [17,19]. In CV outcome trials of fibrates, the risk reduction appeared to be proportional to the degree of non-HDL-C lowering [20]. A meta-analysis of 10 trials reported a 12% reduction in CV events; the trial included people who were treated with various agents (fibrates, niacin, and ω -3 fatty acids) that reduced serum TGs [21].

For primary prevention, some authors do not consider fibrates, niacin or ω -3 fatty acids for TG concentration of 150 mg/dL (1.7 mmol/L) to <200 mg/dL (2.3 mmol/L) [9,16]. Recently, the Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT), which tested the effect of high dose icosapent ethyl (2 gm twice daily) in patients with elevated fasting TG levels between 135-499 mg/dL who were at high or very risks for CV events, demonstrated an 18.3% decrease in TGs and a 25% reduction in CV events over a median follow-up of 4.9 years [22]. Therefore, in high-risk (or very high risk) patients with TG levels between 135-499 mg/dL despite statin treatment, guidelines consider EPA (2 gm twice daily) in combination with a statin [9,22,23].

2.3 Drugs for Low Levels of HDL-C

A low level of HDL-C is an established risk factor for coronary heart disease (CHD). Drugs that increase HDL-C include niacin and fibrates; a small increase in HDL-C is achieved with statins

[24]. In patients with low HDL-C levels, in the very high-risk or high-risk group for ASCVD, the use of HDL-C elevating agents, may be considered after controlling LDL-C [14,16]. However, there is no evidence from randomized control trials (RCTs) that therapeutically increasing plasma HDL-C or directly infused HDL mimetic that increases plasma HDL-C concentrations, reduces the risk of CV events [25,26].

2.4 Mixed Dyslipidemia

Diabetes, prediabetes, metabolic syndrome, and chronic kidney disease (CKD) commonly increases TG and decreases HDL-C levels. Obesity, cholestatic liver disease, or drugs like β -blocker, thiazide diuretic, and corticosteroid—increases LDL-C & TG [5]. In mixed dyslipidemia, statin therapy is initiated, adding ezetimibe, fibrate, or niacin if lipids still not at target. A recent study has shown that the use of fenofibrate as an add-on to statin treatment reduced significantly major CV events in adults with metabolic syndrome then with statin treatment alone [27]. In addition to high levels of TG and low levels of HDL-C, lipid abnormalities in patients with DM and prediabetes are typically characterized by high levels of LDL-C [28,29,30]. Because of the high risk of CV events in DM due to atherosclerosis, statin therapy is the preferred drug of choice. In addition to statin therapy, fibrates can be recommended as add-on therapy to statin if TG remains high or HDL remains low [31]. Addition of fenofibrate to a statin may benefit diabetic patients with a mixed dyslipidemic pattern, particularly those with microvascular complications [32]. In mixed dyslipidemia, if TGs are > 500 mg/dL guidelines consider initial therapy to direct at lowering TG levels [14,16,17].

2.5 Drugs to Reduce Lp(a)

Very high levels of Lp(a) are genetically determined and, when elevated, are a risk factor for CVD and aortic stenosis. Drugs that have been seen to reduce Lp(a) include PCSK9 inhibitors and niacin [33]. Other LDL-C lowering drugs (statins, ezetimibe, and bile acid sequestrants) do not lower Lp(a) levels [34]. However, at present, there are no data indicating that lowering Lp(a) lowers CV risk. There are no approved pharmacologic therapies to lower Lp(a) levels. PCSK9 inhibitors can significantly reduce Lp(a) level [33]. Targeting Lp(a) by PCSK9 inhibitors may provide an additive benefit beyond

LDL-C lowering, according to recent data from a randomized, controlled trial [35]. Further studies are needed to evaluate and to determine the effects of lowering Lp(a) on CV outcomes.

3. STATINS

Statins are the main drugs of choice for LDL-C and TC reduction and are most widely used to reduce the risk of CVD and death for both primary and secondary prevention of coronary artery disease (CAD). Currently, seven statins named, atorvastatin, simvastatin, rosuvastatin, lovastatin, pravastatin, fluvastatin, and pitavastatin, are used (Table 1). The major effect of statins is lowering LDL-C levels. The degree of LDL-C reduction is dose-dependent and varies between the different statins. Atorvastatin, rosuvastatin, and pitavastatin are more potent statins. Statins can lower LDL-C levels by a maximum of 60% as seen with rosuvastatin 40 mg/day [34]. The magnitude of LDL-C lowering with statin treatment also varies widely among individuals which may be genetically determined [36]. Statins have a moderate effect in lowering TG and in elevating HDL-C. Statins usually reduce TG levels by 10–20% from baseline values [37]. The percent reduction in plasma TG levels is dependent on the baseline TG levels [38]. In most studies, HDL-C levels increase between 5-10% with statin therapy [39,40]. Therefore, statin therapy can be effective in improving the lipid profile with mixed dyslipidemia (e.g., DM) unless the TG levels are markedly elevated. Statins have the ability to lower ApoB levels, but they do not lower Lp(a) levels [33].

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which is necessary for hepatic cholesterol biosynthesis. The reduction in intracellular cholesterol promotes increased LDL-receptor expression at the surface of the hepatocytes. Therefore, there is increased clearance of low density lipoprotein (LDL) which accounts for the reduction in plasma LDL-C. In addition to lowering LDL levels by clearance, some study has also shown that statins reduce the production and secretion of VLDL particles by the liver [41]. This could contribute to a decrease in TG levels.

Dose recommended for atorvastatin, 10 to 80 mg/day; rosuvastatin, 5 to 20 mg/day; simvastatin, 20 to 40 mg/ day; lovastatin; 20 to 80 mg/day; pravastatin: 10 to 40 mg/ day; fluvastatin, 20 to 80 mg/day; and pitavastatin, 1

to 4 mg/day. The choice of statin and their dose will depend on several factors including the intensity, tolerance, individual choice, price and response to therapy. The approximate equipotency of the different statins is as follows: 10 mg atorvastatin = 5 mg rosuvastatin = 20 mg simvastatin = 40 mg lovastatin / pravastatin = 80 mg fluvastatin [39,42]. Treatment is initiated especially with atorvastatin or simvastatin at the recommended starting dose with the evening meal per orally or at bed time [43]. In patients who prefer to take their statin in the morning should use a long-acting statin (atorvastatin, rosuvastatin, and pitavastatin) [44]. Statin therapy should be started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals [9]. The degree of lowering of LDL-C level depends on the intensity of statin therapy and varies between the different statins. Intensity of statin therapy has been classified into [45] (a) high-intensity statin therapy where the daily dose lowers LDL-C by $\geq 50\%$ (atorvastatin 40-80 mg/ rosuvastatin 20-40 mg), (b) moderate-intensity statin therapy by 30 to 49% (atorvastatin 10-20 mg/ rosuvastatin 5-10 mg/ 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/ fluvastatin 20-40 mg). High-intensity statin therapy is indicated for patients with severe hypercholesterolemia or clinical ASCVD and moderate intensity statin therapy, in patients with DM without CAD or CKD [45].

The main adverse effects of statin include gastrointestinal (GI), skeletal muscle and hepatic. Common GI adverse effects of statin therapy are indigestion, heartburn, nausea, and abdominal pain which occur in 4% [46]. The most common skeletal muscle adverse effect is muscle pain (myalgia) where creatine kinase (CK) is normal. Myalgia occurs in 5-10% of patients in clinical practice [47] and often result in nonadherence. If the symptoms are not tolerable or are progressive, the dose of statin should be reduced or the drug stopped and alternate drugs given. In clinical practice, it is often very difficult to know if the myalgia is actually secondary to statin therapy; in fact, many patients the myalgia is not due to statin therapy. Myalgia is more likely to be statin associated if it is bilateral, involves proximal muscles, has its onset within weeks to months after initiation of statins, and resolves after discontinuation of statins [48]. The incidence of other skeletal muscle adverse effects such as 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 upper limit normal (ULN), severe muscle pain, muscle necrosis, myoglobinuria, dark urine or acute kidney injury) and autoimmune necrotizing myositis/myopathy (severe proximal muscle weakness, high CK levels, presence of HMG CoA reductase antibodies, and histological evidence of muscle necrosis with minimal lymphocyte infiltration) are very low [48,49,50]; but the presence of those adverse effects require prompt statin cessation and evaluation [49]. The most severe form of statin-induced muscle damage is rhabdomyolysis which may lead to acute renal failure and death [46]. The risk of statin-associated myopathy or rhabdomyolysis is increased by the presence of older age, frailty, liver disease, renal disease, high dose statin, use of drugs interacting with statin, and co-administration of drugs like fibrates particularly gemfibrozil; therefore, in these patient high dose of statin should be carefully prescribed [49]. Most patients with autoimmune necrotizing myositis will need treatment with immunosuppressive therapy (glucocorticoids plus methotrexate, azathioprine, or mycophenolate mofetil) [50,51].

Guidelines do not recommend performing routine monitoring of CK unless skeletal muscle symptoms (muscle cramps, muscle pain, tenderness and weakness) occur [9, 14, 16, 45]. If myalgia or weakness occurs in association with CK > 5 times ULN, treatment should be discontinued and the individual should be evaluated [52]. The renal function should be checked, and the patient should be monitored with CK [45]. 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 [9]. 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 [52]. Some patients who experience muscle symptoms without elevations of CK may experience a reduction in symptoms when switched to an alternative statin.

The most common hepatic adverse effect is a mild elevation of alanine transaminase (ALT); it occurs in $< 3\%$ of patients on statin treatment, more commonly with potent statins or at high doses [53, 54]. The incidence of severe hepatitis (nausea, vomiting, loss of appetite, jaundice, and liver tenderness) and progression to liver failure

associated with statin therapy is very rare [46, 54]. Severe hepatitis associated with statins although very rare may be fatal [46]. In most cases, the elevation of ALT is mild and transient, and normalization is seen with continuing therapy [55]. 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. After levels have returned to normal, statin can be cautiously reintroduced under monitoring with a low dose or another agent may be considered [56]. Guidelines do not recommend routine testing of liver enzymes (ALT) during long term treatment unless symptoms suggest liver disease (e.g., fatigue, weakness, loss of appetite, jaundice) [9,14,16, 45,52].

All statins appear to increase the risk of developing DM (9-12%) [57]. Older persons, obese, and with prediabetes are at a higher risk of developing DM while on statin therapy. A fasting blood glucose or HbA1C should be done before initiating statin. Screening for DM with measurement of fasting glucose levels or HbA1c levels should be considered at 6-12 monthly intervals in patients at high risk of developing DM. It may take many years for an elevated blood glucose to induce diabetic complications while the reduction in CV events with statin therapy occurs relatively quick. The CV risk reduction benefits seen with statins far outweigh the risk of developing DM [58]. Therefore, it is better to continue statin and make necessary lifestyle modification, such as exercise, and weight reduction [58]. An increased frequency of proteinuria has been reported for all statins. The proteinuria is of tubular origin and is not to glomerular dysfunction [59].

Some statins including atorvastatin, simvastatin, and lovastatin are metabolized by certain cytochrome enzymes in the liver. Drugs such as itraconazole, ketoconazole, erythromycin, clarithromycin, amiodarone, diltiazem, verapamil, and cyclosporine that are also metabolized by the same enzyme pathway may elevate the serum level of these statins when administered concomitantly and therefore may increase the risk of toxicity [60]. It should be noted that grapefruit juice contains compounds that inhibit those cytochrome enzymes and the consumption of grapefruit juice can significantly increase statin blood levels [61]. Other statins such as rosuvastatin or pravastatin are not affected as they are metabolized by other pathways [62].

Statin therapy is contraindicated in active or chronic liver disease [63]. However, statins are not contraindicated in patients with increased ASCVD risk with chronic, stable liver disease (e.g., non-alcoholic fatty liver), and limited data suggest potential benefit [64]. Statin therapy is contraindicated in pregnancy and lactation. A woman who is planning pregnancy or is already pregnant, should stop statins if she is taking statins. In a recent prospective study, statins did not adversely affect memory, cognition, or brain volumes in people aged 70 and older [65]. A small increased risk of hemorrhagic stroke with statin use in secondary stroke prevention populations is possible, but the absolute risk is very small, and the benefit in reducing overall stroke and other vascular events greatly outweighs that risk [9, 66, 67].

4. CHOLESTEROL ABSORPTION INHIBITORS

Ezetimibe is the approved cholesterol lowering drug in this class. Because of its synergistic effect, ezetimibe is primarily used in combination with statin therapy when statin treatment alone does not lower LDL-C levels sufficiently to achieve target levels. Ezetimibe is extremely useful in further lowering LDL-C in patients who can only take low doses of a statin. It may be used as monotherapy to lower LDL-C levels in patients with statin intolerance [68]. Ezetimibe and bile acid sequestrants are also co-administered for LDL-C reduction. Ezetimibe has negligible effects on reducing TG and increasing HDL-C levels and has no effect on Lp(a) levels.

Ezetimibe monotherapy lowers LDL-C levels by approximately 15–22% [69]. A meta-analysis of RCTs that included over 2700 people treated with ezetimibe monotherapy (10 mg/day) showed an 18.5% reduction in LDL-C as compared with placebo [70]. In addition, there was a 3% increase in HDL-C, an 8% reduction in TGs, and a 13% reduction in TC with ezetimibe as compared with placebo. In patients with established CAD, ezetimibe, when added to a statin, produces further lowering of LDL-C and CV events [68]. The addition of ezetimibe to a statin regimen increases the magnitude of LDL-C lowering by approximately 13% to 20% [68]. The combination of a high dose potent statin (rosuvastatin 40 mg/day) plus ezetimibe (10 mg/day) can lower LDL-C levels by 70% which will allow many patients to reach their LDL-C goal [71]. Co-administration of ezetimibe and bile acid sequestrants has been reported to result in

an additional reduction of LDL-C levels by 10–20% when compared with the stable bile acid sequestrant regimen alone [72]. A meta-analysis of the effect of ezetimibe on Lp(a) revealed that with either monotherapy or combination with statin there were no change in Lp(a) levels [73].

Cholesterol absorption inhibitor selectively blocks intestinal absorption of both dietary (approximately 25%) and biliary cholesterol (approximately 75%) [74,75]. Thus, the majority of cholesterol is derived from bile [74]. Absorption of fat-soluble vitamins, TGs, fatty acids, bile acids, are unaffected. As a consequence, even in patients that have very little cholesterol in their diet, ezetimibe will decrease cholesterol absorption. When intestinal cholesterol absorption is decreased the chylomicrons formed by the intestine contain less cholesterol and thus the delivery of cholesterol from the intestine to the liver is diminished [76]. In response to reduced cholesterol delivery, there is an increase in hepatic LDL-receptor expression, which in turn leads to increased clearance of LDL from the blood. Ezetimibe binds to Niemann-Pick C1-Like 1 (NPC1L1) protein in the intestine and inhibits cholesterol absorption [74,75]. Cholesterol balance is achieved both by synthesis in the body and by absorption in the GI tract. Cholesterol synthesis and absorption are also critical determinants of plasma LDL-C concentrations. When cholesterol absorption is inhibited by drugs, hepatic cholesterol synthesis increases, and this may offset the effect of ezetimibe. The addition of a statin blocks the compensatory upregulation in cholesterol synthesis and may contribute to the potency of LDL-C lowering attributable to the combination of these two agents. Inhibitors of synthesis and inhibitors of absorption are both effective methods of lowering LDL-C concentrations and therefore often utilized in combination.

The recommended dose of ezetimibe is 10 mg daily orally which can be administered in the morning or evening irrespective of food intake. Adverse effects are GI disturbances (abdominal discomfort, pain, indigestion, flatulence, diarrhea, anorexia), moderate elevations of liver enzymes, muscle pain, arthralgia, and fatigue. Life-threatening liver failure with ezetimibe is extremely rare. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated CK levels beyond what is noted with statin treatment alone [77]. Ezetimibe does not appear to have adverse effects on fasting glucose levels or HbA1c levels [78]. It is

reasonable to obtain baseline hepatic transaminases before initiation of ezetimibe. When ezetimibe is coadministered with a statin, transaminase levels should be monitored as clinically indicated, and ezetimibe discontinued if persistent ALT elevations ≥ 3 times ULN occur [45]. Ezetimibe is contraindicated in patients with acute or chronic liver disease, in pregnant and lactating women, and individuals who show hypersensitivity to this agent.

5. BILE ACID SEQUESTRANTS

Bile acids sequestrants commonly used are cholestyramine, and colesevelam. Bile acid sequestrants are very effective in lowering LDL-C levels. These drugs can be used as monotherapy or in combination with other drugs that lower LDL-C levels. They are typically used in combination with statin therapy as a second line drug or as an addition to statin plus ezetimibe therapy as a third line drug. This combination is particularly useful in patients with familial hypercholesterolemia who have very high LDL-C levels at baseline. In statin intolerant patients the combination of a bile acid sequestrant and ezetimibe is frequently employed. Bile acid sequestrants can also reduce glucose and HbA1c levels in hyperglycemic patients [79]. It has been used for improving glycemic control in patients with type 2 DM.

The decrease in LDL-C ranges from approximately 5 to 30% depending on the drug and dose [80,81]. The addition of a bile acid sequestrant to a statin regimen further lowers LDL-C level by approximately 15% to 30% [19]. High doses of potent statins if combined with high doses of bile acid sequestrants can result in a total 60% reduction in LDL-C levels. Bile acid sequestrants will also further lower LDL-C levels by as much as 18% when added to statins and ezetimibe [82]. In patients who are statin intolerant, the combination of a bile acid sequestrant and ezetimibe results in an additional 10-20% decrease in LDL-C compared to either drug alone [63,83]. The drugs also reduce non-HDL-C and ApoB, but results in no change in Lp(a). Bile acid sequestrants may increase HDL-C slightly ranging from 3-9% [80, 81].

Bile acids are synthesized in the liver from cholesterol and are released into the intestinal lumen, but most of the bile acid is returned to the liver from the terminal ileum via active absorption. Bile acid sequestrants bind bile acids

in the small intestine, prevent their reabsorption in the terminal ileum, and promote their excretion into the feces [84]. As a result of decreased bile acids from the gut for re-use, the liver has to synthesize more bile acids from cholesterol to compensate for the loss. Due to an increase in the hepatic demand for cholesterol, the hepatic LDL-receptor expression is increased, which results in a decrease of circulating LDL. Bile acid is necessary for lipid digestion and cholesterol absorption from the intestine. The bile acid sequestrants prevent the absorption of cholesterol into the blood, and remove a large portion of the bile acids from the enterohepatic circulation. Bile acid sequestrants are not absorbed from the intestine, thus their primary effects are localized to the intestine [80,81]. The mechanism by which bile acid sequestrants improves glycemic control is not clear.

Cholestyramine is available as a powder and the dose ranges from 8-24 grams per day in divided doses given with meals. The recommended starting dose of cholestyramine is 4 g/d increased at weekly intervals to decrease GI side effects. The dose of colesevelam is 3.75 grams per day and can be given as tablets, or oral suspension (powder to dissolve in liquid). Colesevelam has increased affinity for bile acids compared to cholestyramine and therefore can be used in much lower doses reducing some side effects [81]. The major effect of bile acid sequestrants is to lower LDL-C levels in a dose dependent fashion.

Adverse effects of bile acid sequestrants are GI disturbance (commonly abdominal discomfort, bloating, flatulence, nausea, dyspepsia, and constipation) and reduced absorption of fat soluble vitamins [80, 81]. Because of GI disturbances that occur even at low doses, a significant number of patients will discontinue therapy with bile acid sequestrants. The GI adverse effects can be attenuated by beginning treatment at low doses and ingesting ample fluid with the drug. The dose should be increased gradually. Constipation is a very common side effect and can be severe with aggravation of hemorrhoids. The use of bile acid sequestrants is also contraindicated in patients with a history of recent intestinal obstruction. One of the other important adverse effect is that they can increase plasma TGs [85]. They are discouraged in individuals with baseline fasting TG levels ≥ 300 mg/dL (3.4 mmol/L) because severe TG elevations might occur [86]. Bile acid sequestrants are contraindicated in patients with

TG >400mg/dL (4.5 mmol/L) [80]. Patients need to follow-up with fasting lipid profile at 3 months after initiation of the drug, and every 6 to 12 months thereafter [45]. In patients with normal TG levels, bile acid sequestrants increase TG levels by a small amount. However, as baseline TG levels increase, the effect of bile acid sequestrants on plasma TG level increase becomes greater. The bile acid sequestrants may also interfere with the absorption of fat-soluble vitamins. Taking vitamins 4 hours before or after these drugs can reduce the likelihood of a vitamin deficiency. Bile acid sequestrants can impair the absorption of many other drugs from the intestine (L-thyroxine, glimepiride, glipizide, glyburide, phenytoin, olmesartan, warfarin, oral contraceptives) [80]. It is, therefore recommended that these medications should be taken either 4 hours before or 4 hours after taking bile acid sequestrants. Colesevelam has fewer interactions with other drugs; it does not interfere with the absorption of statins, fenofibrate, or ezetimibe.

As bile acid sequestrants are not well-absorbed from the gut they are safe during pregnancy or lactation (placed in category B) [87]. In women of child bearing age who are planning to become pregnant bile acid sequestrants can be a good choice to lower LDL-C levels. However, by interfering with vitamin absorption, they could cause vitamin deficiencies that may affect the fetus. So, vitamin supplementation should be considered, with appropriate intervals between dosing of the vitamins and bile acid sequestrants. In chronic liver diseases such as cirrhosis, bile acids may deposit in the skin, causing pruritus (itching). Hence, bile acid sequestrants may be used for the prevention of pruritus in patients with chronic liver disease.

6. PCSK9 INHIBITORS

PCSK9 inhibitors are powerful LDL-C lowering drugs and have shown to reduce major adverse CV events. Currently used PCSK9 inhibitors are alirocumab and evolocumab. The PCSK9 inhibitors can be used in combination with other lipid modifying drugs or alone in statin intolerant patients. They are used mainly for patients with a very high-risk group with ASCVD or severe familial hypercholesterolemia where LDL-C do not reach to target levels despite statin mono or combination therapy with other drugs in maximum dose [88,89]. The addition of a PCSK9 inhibitor to a statin regimen has been shown to further reduce LDL-C levels by 43% to 64% [13,

89]. The efficacy appears to be largely independent of any background therapy. The use of PCSK9 inhibitors has been associated with a decrease in non HDL-C, Apo B, and Lp(a) [34]. There is a small increase in HDL-C, and a small decrease in TG levels. A meta-analysis of 24 studies comprising 10,159 patients reported an increase in HDL of 5-8% [88]. Notably, in 12 RCTs with 6,566 patients, Lp(a) levels were reduced by 25-30% [88]. The mechanism by which PCSK9 inhibitors reduce Lp(a) levels is unclear. It should be noted that most LDL-C lowering drugs (statins, ezetimibe, and bile acid sequestrants) do not lower Lp(a) levels.

PCSK9 is an enzyme that can bind and degrade the hepatic LDL-receptor. PCSK9 is predominantly expressed in the liver and secreted into the circulation. Once extracellular, PCSK9 can bind to the hepatic LDL-receptor, decrease their number, and interfere with LDL clearance leading to elevations in plasma LDL-C levels [90]. The PCSK9 inhibitors target the PCSK9, inhibiting the binding of PCSK9 to the LDL-receptors on the surface of hepatocytes. The higher expression of LDL-receptors at the hepatic cell surface leads to increased clearance of LDL with resulting decrease in their blood levels [17,91]. When the LDL particle binds to the LDL-receptor, the complex formed, is taken into the liver cell by endocytosis for clearance [17]. PCSK9 monoclonal antibodies are eliminated primarily by cellular endocytosis, phagocytosis, and target-mediated clearance [34]. They are not metabolized or cleared by the liver or kidneys and therefore there is no need to adjust the dose in patients with either liver or kidney disease.

These drugs are administered subcutaneously (sc) at 2 weeks or a one-month interval. Alirocumab is administered as either 75 mg or 150 mg sc every 2 weeks or 300 mg once a month while evolocumab is administered as either 70 mg sc every 2 weeks or 420 mg sc once a month. Among the most frequently reported side effects are itching at the site of injection and flu-like symptoms [92]. Other adverse effects are injection-site swelling, myalgia, arthralgia, lethargy, and nausea. PCSK 9 inhibitors are not known to cause hepatotoxicity or muscle injury. There are no drug-drug interactions. Hypersensitivity to the drug is an absolute contraindication; there are currently no other contraindications [34]. They are not metabolized or cleared by the liver or kidneys and therefore there is no need to adjust the dose in patients with either liver or kidney disease.

They are generally being well tolerated, but the long-term safety profile remains unknown. The major limitation is the very high expense of these drugs and their use may not be possible in some countries with limited healthcare resources. The cost value may be beneficial only for a very specific group of only those people at very high-risk of ASCVD not controlled by other drugs [9].

7. FIBRATES

Fibrates are effective drugs in reducing TG levels and modestly increase HDL-C levels. The drugs in this class include fenofibrate, gemfibrozil, bezafibrate, and ciprofibrate. Fibrates are indicated for the treatment of marked hypertriglyceridemia (> 500 mg/dL) when life style interventions are ineffective to reduce TG levels. [93]. It is also used in moderate hypertriglyceridemia (< 500 mg/dL), when statin and non-pharmacological therapy are unable to lower the TG levels inspite of normal LDL-C levels. In patients with DM, fibrates appear to slow the progression of microvascular complications. Addition of fenofibrate to a statin may benefit certain patients with Type 2 DM with both high TG and low HDL-C dyslipidemic pattern, particularly those with microvascular complications [32]. In a study, the combination of statins and fibrates provided significantly greater reductions in TC, LDL-C and TGs, and a significantly greater increase in HDL-C than treatment with statins alone [94].

Fibrates are agonists of peroxisome proliferator activated receptor- α (PPAR α) a nuclear hormone receptor, influencing various steps in lipid and lipoprotein metabolism. PPAR α highly expressed in the liver and other tissues is important in fatty acid metabolism. Activation of PPAR α reduces the substrate available for the synthesis of TGs and the formation of VLDL [95]. PPAR α activation also facilitates the increased clearance of TG rich lipoproteins. Moreover, PPAR α activation leads to the increased production of HDL [96].

Fibrates reduce serum fasting and postprandial TG levels by 25-50% [97,98,99]. The magnitude of the reduction in TGs is dependent on the baseline TG levels. Patients with marked elevations in TGs have a greater reduction in TG levels [97,98,99,100]. Fibrates increase HDL-C levels by 5-20% [97,98]. The increase in HDL-C levels is more robust if the TG levels are elevated and/or if the HDL-C levels are low [100]. The effect on LDL-C is variable. If the TG levels

are very high (> 500 mg/dl), fibrate therapy may result in a paradoxical increase in LDL-C levels, whereas if TGs are not markedly elevated fibrates decrease LDL-C by 10-30% [99]. Fibrates also reduce ApoB, and non-HDL-C levels [98]. Fibrates do not have any major effects on Lp(a) levels [101].

Current evidence suggests that the fibrates may have a protective effect against diabetic microvascular complications by slowing their progression. Studies have shown that fibrates decrease diabetic retinopathy [102,103]. Studies also suggest that fibrates have a beneficial effect on diabetic kidney disease by producing albuminuria regression [104,105]. In a study, fenofibrate therapy acutely increased plasma creatinine levels and decreased estimated glomerular filtration rate (eGFR) [106]. However, over the long term, plasma creatinine rise was decreased in the fenofibrate group compared to the placebo group. In a trial, fenofibrate reduced uric acid levels by 20% and reduced episodes of gout by approximately 50% compared to placebo [107].

Recommended dose of fenofibrate (micronized) is 160 mg daily; gemfibrozil is given 600-1500 mg daily in divided doses 30 minutes before meal; bezafibrate, starting at 200 mg/day titrated to a maximum dose of 200 mg thrice daily; and ciprofibrate 100 mg daily. The most common adverse reaction is GI disturbances, being reported in <5% of patients [108]. Liver enzyme elevations, muscle symptoms, and cholelithiasis represent the other most well-known adverse effects associated with fibrate therapy [108]. Fibrates can be given in patients whose transaminase levels are elevated <3 times ULN range, but at a lower starting dosage with careful monitoring. The risk of serious muscle disease appears to be increased in patients with renal failure, hypothyroidism, and in the elderly [108]. Combination therapy with gemfibrozil and statin further increases the risk for myopathy [109]. Therefore, gemfibrozil should not be initiated in patients on statin therapy because of increased risk for muscle symptoms and rhabdomyolysis. Fenofibrate is the preferred agent for combination therapy with a statin, as it does not relatively increase the risk for myopathy. Skin rashes is reported in 2% with fibrate use [108]. Fibrates are all excreted by the kidneys and thus the excretion of fibrates is decreased in patients with renal dysfunction [108]. Fibrate therapy leads to an increase in serum creatinine [8,108]. In patients with CKD (stage 1 to 3) fibrates

should be used with caution and at lower doses, with appropriate monitoring for side effects, especially myopathy [108]. Renal function should be assessed with both a serum creatinine and eGFR before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter [45]. If during follow-up, the eGFR decreases persistently to ≤ 30 mL/min/1.73 m², fenofibrate should be discontinued. The increase of serum creatinine by fibrate therapy seems to be fully reversible when the drug is stopped. Studies of renal function in patients with DM actually suggests that treatment with fibrates may be protective [104,105].

Fibrates are absolutely contraindicated in severe liver disease, CKD stage 4 & 5 (eGFR < 30 ml/min), presence of gall stone, and hypersensitivity to fibrate [8]. Fenofibrate and gemfibrozil are pregnancy category C drugs and should only be used if the potential benefit justifies the potential risk to the fetus. Fibrates, may potentiate the action of anticoagulants (warfarin) and certain oral hypoglycemic agents [8]. Fibrates are associated with a slightly increased risk of pancreatitis perhaps via increasing gallstone formation [110].

Whether fibrate administration as monotherapy or in combination with a statin is effective in preventing CVD and reducing all-cause mortality from CV events remains controversial. In a meta-analysis of RCTs to investigate the effects of medications for dyslipidemia on mortality, statin significantly decreased CV mortality, while fibrate did not significantly lower mortality compared to placebo [111]. However, some studies have shown that fibrates when used as monotherapy appear to reduce CVEs in patients with high TG and low HDL-C levels [112,113]. Whether the addition of fibrates to statin therapy will reduce CVD is uncertain. Clearly additional studies are required that specifically focus on patients with high TGs and low HDL-C levels.

8. NIACIN

Niacin, a vitamin B3, is an important nutrient and is also known as nicotinic acid. Pharmacological doses of niacin are effective in decreasing TG, TC, LDL-C, ApoB, or Lp(a) and increasing HDL-C levels [114,115]. Niacin is the oldest drug used for reducing cholesterol level [116]. Niacin may be considered either as monotherapy or in combination with other drugs in individuals with markedly elevated TG (> 500 mg/dL) to reduce

the risk of pancreatitis. However, fibrates and ω -3-fatty acids are the initial choices in this situation. In a meta-analysis of 30 trials with 4,749 subjects, treatment with niacin decreased TG by 20%, decreased LDL-C by 14%, decreased TC by 10%, and increased HDL-C by 16% [117]. Niacin can also be useful in statin intolerant patients, in combination with other drugs to lower LDL-C levels. The addition of colesevlam to niacin therapy results in a further decrease in LDL-C by 7.8% and non-HDL-C by 4.9% [118]. In this combination, the increases in plasma TG levels induced by colesevlam are often reversed by niacin treatment. Addition of niacin to statin therapy typically results in further reductions in atherogenic lipoprotein particles and an increase in HDL-C levels. However, the addition of niacin to statin therapy was not found to decrease CV events in some renowned studies [25,119].

Nicotinic acid has key action sites in both the liver and adipose tissue. It suppresses lipolysis and decreases the mobilization of free fatty acids from adipose tissues to the liver for lipoprotein synthesis. In the liver, nicotinic acid inhibits the key enzyme required for TG synthesis; as a result, the availability of TG for VLDL assembly and secretion is reduced [120]. Hence there will be a reduction in VLDL and LDL formation and secretion by the liver [120,121]. Nicotinic acid raises HDL-C by stimulating ApoA1 production in the liver [121]. Niacin decreases the rate of synthesis of Lp(a) [122].

The effect of niacin is dose dependent with higher doses having a greater effect on plasma lipid levels [123]. Recommended starting dose of niacin is 150-300 mg daily in divided doses, titrated up to the usual dose of 2 g/day. The most common adverse effect of niacin is flushing of the skin characterized by redness and warmth due to vasodilation of the blood vessels in the skin [114]. Itching can occur and a tingling and burning sensation may also be noted. Niacin induced flushing is usually not accompanied by diaphoresis. The cutaneous flushing usually lasts for approximately one hour and in some patients is extremely annoying. To avoid cutaneous flushing, niacin therapy is generally started at lower doses and gradually titrated up to higher doses. Niacin can cause dyspepsia, heartburn, indigestion, nausea, diarrhea, and abdominal discomfort. Niacin can exacerbate gastroesophageal reflux and peptic ulcer disease. Niacin should be taken with meals to reduce GI side effects.

Because of the potential for hepato-toxicity, serum transaminase levels should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Muscle symptoms like myalgia and myopathy have not been a significant effect with niacin monotherapy [117]. In combination with statins, there is an increased risk of muscle symptoms. Other adverse effect is hyperglycemia. It has been recognized that niacin induces insulin resistance [124]. However, niacin is usually well tolerated without significantly affecting blood glucose in diabetic subjects who are in good glycaemic control [125]. In patients with poor glycaemic control, niacin is more likely to adversely impact glucose levels. Niacin can raise plasma levels of uric acid and precipitate gouty attacks in susceptible patients [114]. Baseline hepatic transaminases, fasting blood glucose or HbA1c, and uric acid should be obtained before initiation of niacin, and again during up-titration to a maintenance dose and every 6 months thereafter. Niacin should not be used if hepatic transaminase elevations are >3 times ULN, and in patients with persistent severe cutaneous symptoms, persistent hyperglycemia, or unexplained abdominal pain or GI symptoms. Treatment with niacin frequently results in side effects and these side effects are a major limitation of niacin therapy [126]. There are a substantial number of contraindications for niacin therapy that include active peptic ulcer disease, gastro-esophageal reflux disease, poorly controlled DM, acute or uncontrolled gout, pregnancy and lactation.

Currently, there is a decreased trend in the use of niacin for treating dyslipidemia, due to (a) availability of more efficient cholesterol lowering drugs like ezetimibe and PCSK9 inhibitors (b) the annoyance side effects of niacin (e.g., cutaneous flushing with burning skin, heart burn, GI symptoms, elevated blood glucose) (c) unavailability of niacin in some countries and importantly (d) the two large randomized trials (AIM-HIGH HPS-2 Thrive) that failed to show a decrease in CV events when niacin was added to statin therapy [25,119]. No medication containing nicotinic acid is currently approved in Europe [9].

9. OMEGA-3 FATTY ACIDS (FISH OIL) SUPPLEMENTS

Omega-3 fatty acids are present in dietary PUFAs commonly found in oily fish and marine oils [10]. Observational evidence indicates that

consumption of fish (at least twice a week) and vegetable foods rich in ω -3 fatty acids is associated with a lower risk of CV death and stroke, but has no major effects on plasma lipoprotein metabolism [127]. Pharmacological doses (2-4 gm/day) of two ω -3 fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are used to treat dyslipidemia. The ω -3 fatty acid supplements (2–4 gm/day) are effective in reducing TGs [128]. They can be used alone or in combination with other lipid modifying drugs for hypertriglyceridemia. The ω -3 fatty acid supplements are used in marked hypertriglyceridemia (≥ 500 mg/dL) to reduce the risk of development of acute and recurrent pancreatitis. In patients with marked hypertriglyceridemia, a single drug is often not sufficient to lower triglycerides into the desired range. ω -3 fatty acid supplements should be added in severe hypertriglyceridemia, where fibrates alone may not adequately lower the markedly elevated TG levels [129]. Studies have shown that the addition of ω -3 fatty acids to fenofibrate or niacin in marked hypertriglyceridemia further decreases TG levels [130, 131]. The ω -3 fatty acids are also used in moderate hypertriglyceridemia (< 500 mg/dL) as an adjunct to maximally tolerated statin therapy to reduce the risk of CVD in adults with established ASCVD or DM. In people with high TGs, ω -3 fatty acid supplements lower TG upto 50% depending on dose as well as baseline TG levels [132]. The reduction in plasma TG levels is directly related to baseline plasma TG levels (i.e. the higher the baseline TG level the greater the reduction in TGs). Additionally, the higher the dose of EPA/DHA, the greater the reduction in plasma TGs [133]. The effects of ω -3 fatty acid supplements on other lipids are trivial [128]. They do not affect significantly TC, HDL-C or Lp(a) levels. A meta-analysis by Balk and colleagues of 21 studies found minimal effects of fish oil supplements on the total LDL-C, and HDL-C levels (< 5% change) with significant decreases in plasma TG levels [134]. LDL-C levels may increase with fish oil supplementation treatment when the TG levels are markedly elevated (>500 mg/dL) [18,129].

Fish oil is also sold over the counter as a food supplement in many countries and is much less expensive than prescription ω -3 fatty acid drugs; however, they are not approved by the US FDA for treating high TG, as the amount of EPA and DHA can vary greatly and there may be other constituents like saturated fatty acids [17]. Many

people without known CVD take fish oil supplements to prevent adverse CV events, but the benefit has been less conclusive in recent trials. Studies on the effect of low dose ω -3 fatty acids (around 850 mg of EPA and DHA per day) on CV outcomes have failed to demonstrate a benefit [135,136]. However, a very recent large population based cohort study indicates that habitual use of fish oils is associated with a marginal benefit for CVD events in the general population, supporting their use for the prevention of mortality from CVD [137].

In the REDUCE-IT trial, high doses of EPA (icosapent ethyl 2 gm twice daily) was found to reduce TG levels (18% decrease) and also reduce CV events by approximately 25%, conducted in 8179 patients with either established CVD or with high CV risks (DM plus one risk factor), having TG levels of 135- 499 mg/dL and who were on stable statin therapy [22]. The results demonstrate that EPA treatment reduces CV events. Whether the beneficial effects of EPA are due to TG lowering or other effects of EPA are not clear. Recent guidelines recommend that patients aged \geq 45 years with clinical ASCVD, or aged \geq 50 years with DM requiring medication plus \geq 1 additional risk factor, with fasting TGs 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (\pm ezetimibe), to be treated with icosapent ethyl as an adjunct therapy for ASCVD risk reduction [9,22,23].

The TG lowering effect of ω -3 fatty acid is produced by decreased hepatic production and secretion of TG rich lipoproteins. The underlying mechanism is poorly understood, although it may be related to their ability to interact with PPARs and to the decreased secretion of Apo B. Omega-3 fatty acids activate PPAR alpha, which stimulates fatty acid oxidation in the liver and other tissues [138,139]. Studies in animal models have demonstrated that ω -3 fatty acids inhibit fatty acid synthesis and stimulate fatty acid oxidation in the liver, which would reduce the availability of fatty acids for TG synthesis [138,139]. The recommended doses of total EPA and DHA to lower TGs have varied between 2–4 gm/day in divided dose.

Omega-3-fatty acids have few side effects. The major adverse effect being GI side effects (nausea, vomiting, fish-smelling, fishy taste in mouth, diarrhea, dyspepsia, abdominal discomfort, and acid eructation). Other adverse reactions are elevated liver enzymes, elevated

blood glucose, arthralgia, itching, and headache. Liver function tests and fasting blood sugar should be done every 6 months. At very high doses, ω -3-fatty acids can inhibit platelets and prolong bleeding time. The antithrombotic effects may increase the tendency for bleeding, especially when given in addition to aspirin/clopidogrel. However, at the recommended doses this has not been a clinical problem but when patients are on anti-platelet drugs one should be alert for the possibility of bleeding problems. A recent review found no evidence for discontinuing the use of ω -3 fatty acid treatment before invasive procedures or when given in combination with other agents that affect bleeding [140]. Drug interactions have not been seen with ω -3-fatty acids. Omega-3 fatty acid appears to be safe and well tolerated. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, as TG \geq 500 mg/dL, it is reasonable to evaluate the patient for GI disturbances, skin changes, and bleeding [45]. Contraindication to the use of ω -3 fatty acids is hypersensitivity to drug. Omega-3 fatty acids (either from marine sources or supplements) are not considered to increase adverse effects during pregnancy and are not contraindicated. They are pregnancy category C drugs, and they should only be used if the benefits to the mother outweigh the potential risks to the fetus.

10. LIPID MODIFYING DRUGS IN DIFFERENT CONDITIONS

All patients with established CVD or experiencing a CV event should be prescribed a statin, regardless of the baseline LDL-C concentration [14,16]. More patients are surviving their first CV event and are at high-risk of recurrences. Peoples with established CVD have greater absolute benefit from LDL-C reduction. In a RCT on 4,500 patients who experienced an acute myocardial infarction (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 [141]. Patients with severe hypercholesterolemia should be treated with high intensity statin therapy; they may receive add on therapy with ezetimibe, bile acid sequestrants or PCSK9 inhibitors to achieve target cholesterol level. In selected patients with severe hypercholesterolemia whose LDL-C is inadequately controlled with drug therapy, LDL apheresis is an option [142]. 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 $\geq 50\%$. [11,67,104,105]. There are growing evidences that fibrates have a protective effect against diabetic microvascular complications by slowing their progression [102, 103,105,104,143]. In CKD the starting dose of statins should be low. During therapy, serum CK and renal function should be carefully monitored [15]. In dialysis dependent end stage kidney disease (ESKD) patients, who are free of ASCVD, the 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 [144]. However, in adults who need dialysis for ESKD and are currently receiving statin therapy, the 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. In patients with heart failure initiation of lipid-lowering therapy is not recommended in the absence of other indications for their use [9]. Moderate-intensity statins may be considered in patients with heart failure due to CAD [11]. In patients with aortic valvular stenosis without CAD initiation of lipid-lowering treatment is not recommended unless indicated for other reasons [9]. For primary prevention of CVD in adults with dyslipidemia, the first step is to calculate the 10 year CVD risk by country specific risk scoring system and to look at all the other risk factors not included in the risk calculator [5]. 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 [145]. When the decision regarding pharmacotherapy is uncertain (borderline), other risk-enhancing factors should be considered; their presence will favor initiation of statin therapy [146].

11. CONCLUSION

Currently available lipid modifying drugs can treat dyslipidemia efficiently in most patients and thereby reduce the risk of ASCVD. The decision to treat with lipid modifying agents must be individualized and should be initiated only when it is indicated. So far, statin is found to be best among the lipid modifying agents; it has been used extensively due to its efficacy and tolerability. The potential beneficial effects of a

drug should be considered when deciding on treatment choices. Fibrates may be considered in a patient with DM, microvascular complications, and hypertriglyceridemia because of their potential beneficial effects on slowing the progression of microvascular disease. In a high or very high CV risk patient with moderate hypertriglyceridemia, ω -3 fatty acids are found to be beneficial when added to statin therapy after controlling LDL-C, and therefore should be considered.

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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