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Chapter

Dyslipidemia in Special Populations, the Elderly, Women, HIV, Chronic Kidney Disease and ESRD, and Minority Groups

Amarpali Brar, Jeans M. Santana, Moro O. Salifu and Clinton D. Brown

Abstract

This chapter discusses the management of dyslipidemia in special patient populations: the elderly, woman and pregnancy, renal disease, human immunodeficiency virus (HIV), and different racial/ethnic groups. In the elderly, dyslipidemia is often underdiagnosed and undertreated. Consideration for potential atherosclerotic risk-reduction benefits, risk of adverse effects, drug-drug interactions, and patient preferences should precede the initiation of statin therapy. Data on pregnant women are lacking and need future research. Dyslipidemia and its effects on the cardiovascular system in chronic kidney disease (CKD), end-stage renal disease (ESRD), and HIV are dynamic and multimodal. These conditions are states of chronic inflammation, where it is difficult to associate quantities of cholesterol types with outcomes. Among all racial groups, Asian Indians, Filipinos, and Hispanics are at a higher risk for dyslipidemia. Genetic differences in statin metabolism may explain this racial/ethnic difference.

Keywords: dyslipidemia, elderly, women, racial disparity, gender disparity

1. Introduction

Dyslipidemia, defined as high levels of low-density lipoprotein cholesterol (LDL-C) (≥130 mg/dl), total cholesterol (≥200 mg/dl), and triglycerides (TG) (≥150 mg/dl), or low levels of high-density lipoprotein cholesterol (HDL-C) [<40 (men) and < 50 (women) mg/dl], is a major risk factor for cardiovascular disease (CVD). Significant heterogeneity in patterns of dyslipidemia exists in these special populations. There is confusion among health-care providers regarding selection and implementation of appropriate guidelines, particularly for special patient populations. Patients in special populations may not clearly fall into one of the four statin-benefit groups identified by the ACC/AHA cholesterol guidelines [1].

In this chapter, we review the evidence in patterns of dyslipidemia and management in the elderly, women and pregnancy, CKD, ESRD, HIV, and different racial/ethnic groups.
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2. Dyslipidemia in the elderly

2.1 Epidemiology

According to census projections, the population age 65 and older is expected to double between 2012 and 2060, from 43.1 to 92.0 million [2]. CVD is the main cause of mortality in this age group. Lipid-lowering pharmacological intervention is one of the most successful cardiovascular preventative interventions. Concerns about its safety and efficacy in this age group have led different countries to adopt different strategies concerning the use of lipid-lowering drugs in the elderly [3]. In US population as reported in the National Health and Nutrition Examination Survey (NHANES) publications, across all age groups, triglyceride levels increase with age and reach a peak in men aged 50–59 years and in women aged 60–69 years. Apolipoprotein B (Apo B) and small dense LDLc also increase with age, while HDL-c does not seem to vary with age [4].

2.2 Management

Lifestyle modification including adhering to a heart healthy diet, regular exercise, avoidance of tobacco products, and maintenance of a healthy weight remains a critical component of ASCVD risk reduction.

2.2.1 Secondary prevention statin trials in elderly

In general, the elderly are usually underrepresented in published clinical trials. The only large randomized statin trials that focused on older patients are the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and the Study Assessing Goals in the Elderly (SAGE) trial.

PROSPER is a randomized controlled trial in which 5804 patients aged 70–82 years with a history of, or risk factors for, vascular disease were randomized to receive pravastatin (40 mg/day; n = 2891) or placebo (n = 2913). Follow-up was 3.2 years. Pravastatin was found to reduce the incidence of coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke. Suggesting pravastatin may be utilized to manage dyslipidemia in the elderly and be prescribed to [5]. Later, the Study Assessing Goals in the Elderly (SAGE) compared the effect of intensive (atorvastatin 80 mg/day) with moderate (pravastatin 40 mg/day) cholesterol lowering with statins in a cohort of 893 patients, 65–85 years of age with coronary artery disease (CAD), and follow-up for 12 months. Atorvastatin-treated patients experienced greater LDL-C reductions than did pravastatin-treated patients, a trend toward fewer major acute cardiovascular events and a significantly greater reduction (77%) in all-cause death [6].

British Heart Foundation Heart Protection Study evaluated the role of simvastatin 40 mg/day versus placebo in 20,536 patients with coronary atherosclerosis and diabetics with coronary heart disease (CHD) risk equivalence. About 28% of randomized patients were ≥70 years of age. Among the 1263 individuals with 75–80 years of age at study entry, the rate of major coronary events in the simvastatin group was significantly lower than placebo group [7]. The long-term intervention with pravastatin in ischemic disease (LIPID) trial randomized patients with prior myocardial infarction or unstable angina to receive pravastatin 40 mg/day versus placebo, of which 39% (3514) were of age 65–75 years. Here, pravastatin reduced the risk for all CVD events, and similar adverse effects were observed in older and younger patients [8].
Other major secondary prevention trials, which included large numbers of elderly patients, are cholesterol and recurrent events (CARE) and Scandinavian simvastatin survival study (4S). In subgroup analyses of both studies, the absolute benefit of treatment was significantly greater in older patients as compared to younger patients for cardiovascular events [5, 10]. The 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommended high-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical atherosclerotic cardiovascular disease (ASCVD), unless contraindicated. A larger amount of data supports the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD who are >75 years of age. However, the limited information available did not clearly support initiation of high-intensity statin therapy for secondary prevention in individuals >75 years of age [1]. Statin therapy to higher risk elderly patients is appropriate. In individuals with clinical ASCVD >75 years of age, practitioners should evaluate the potential for ASCVD risk-reduction benefits, adverse effects, drug-drug interactions and consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it [1, 11]. Physicians treating the elderly must also consider the functional age of the patient and the impact of long-term drug therapy on safety and quality of life. Caution is recommended when statins are used in frail elderly patients, who may be more susceptible to drug-related myopathy and other side effects [12].

2.2.2 Primary prevention and statin trials

The Anglo-Scandinavian Cardiac Outcomes trial randomized 19,342 hypertensive patients (aged 40–79 years with at least three other cardiovascular risk factors) to be assigned to atorvastatin 10 mg or placebo. Nonfatal myocardial infarction and fatal cardiovascular disease were significantly lower in the statin group [13]. In a post hoc analysis, efficacy and safety of atorvastatin in 1129 patients aged 65–75 years at randomization was compared with 1709 younger patients in the Collaborative Atorvastatin Diabetes Study (CARDS). Primary end point of time to first occurrence of acute coronary heart disease events, coronary revascularizations, or stroke was similar in both groups. The overall safety profile of atorvastatin was similar between age groups [14]. Justification for the Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) is a randomized, double-blind, placebo-controlled trial with 17,802 participants of which 5695 were 70 years or older with LDL-C levels <130 mg/dl and high-sensitivity C-reactive protein levels of 2.0 mg/L or more without cardiovascular disease and were randomly assigned in a 1:1 ratio to receive 20 mg of rosuvastatin daily or placebo. In secondary analysis of this trial, no significant heterogeneity was found in treatment effects by age, absolute reductions in event rates associated with rosuvastatin were greater in elderly. The relative rate of any serious adverse event among older patients in the rosuvastatin versus placebo group was 1.05 (CI, 0.93–1.17) [15, 16].

As per 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults; four statin benefit groups are individuals with ASCVD, individuals with primary elevations of LDL-C ≥190 mg/day, individuals 40–75 years of age with diabetes and LDL-C 70 to 189 mg/dl without clinical ASCVD, and individuals without clinical ASCVD or diabetes who are 40–75 years of age and have LDL-C 70–189 mg/dl and an estimated 10-year ASCVD risk of ≥7.5%. This requires a clinician-patient discussion. Few data are available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD. Therefore, initiation of
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Statins for primary prevention of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care. The Pooled Cohort Equations can also provide information on expected 10-year ASCVD risk for those 76–79 years of age that may inform the treatment decision. A discussion of the potential ASCVD risk-reduction benefits, risk of adverse effects, drug-drug interactions, and consideration of patient preferences should precede the initiation of statin therapy for primary prevention in older individuals [1].

2.2.3 Statin and side effects

In the PROSPER study, no rhabdomyolysis or serum CK concentration > 10 times the upper limit of normal was reported. There was no statistically significant difference in the incidence of reported myalgia between the pravastatin and placebo groups (1.2 and 1.1%, respectively). In the SAGE study, incidence of myalgia was also not different between the atorvastatin and pravastatin treatment groups (3.1% versus 2.7%) with only one individual found to have CK level > 10 times the upper limit of normal in the pravastatin treatment group but none in the atorvastatin group [5, 6]. In a retrospective study, Graham et al. reported rhabdomyolysis risk was similar and low for monotherapy with atorvastatin, pravastatin, and simvastatin. Combined statin-fibrate use was associated with increased risk, especially in older patients with diabetes mellitus [17].

All of the available statins, with the exception of pravastatin and rosuvastatin, are metabolized by the cytochrome P450 (CYP) system. Serum concentrations of these statins can potentially be increased when other medications competing for the CYP system or CYP isoenzyme inhibitors are prescribed and can lead to increased risk of myositis and rhabdomyolysis. There is an age-related decrease in glomerular filtration rate, decrease in hepatic blood flow, decrease in drug clearance, and increased expression of P-glycoproteins resulting in alterations in the rate of drug transport across cellular membranes [18–20].

2.3 Other medications

2.3.1 Ezetimibe

Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of ezetimibe combined with simvastatin, as compared to simvastatin alone in 18,144 patients with acute coronary syndrome. Subgroup analysis showed a benefit of ezetimibe in the 7971 patients’ over 65 years and 2798 patients’ over 75 years of age [21].

2.3.2 Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The first large cardiovascular outcome study using PCSK9 inhibitor therapy (FOURIER) was a randomized, double-blind placebo-controlled trial of 27,564 subjects with 12,254 patients over the age 65 years with ASCVD and LDL-C levels ≥70 mg/dl while on maximally tolerated statin therapy, randomly assigned to receive evolocumab or placebo. In these patients, there was a significant decrease in composite outcome of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization. However, cost is prohibitive for generalized use [22].
2.3.3. Fibrates

No data are available for fibrates in patients over 75 years of age. World Health Organization Clofibrate Study, Helsinki Heart Study (HHS), Bezafibrate Infarction Prevention (BIP), and Veterans Affairs Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed reduction in the risk of myocardial infarction. Fenofibrate is considered the preferred agent, due to once-daily dosing and a favorable adverse reactions profile. Caution is needed in elderly patients with reduced renal function [23–26].

In conclusion, cardiovascular prevention clinical trial evidence for the patients over age 75 years is very limited. Management of dyslipidemia in the elderly requires consideration of comorbidities, safety considerations, polypharmacy, and priorities of care.

3. Dyslipidemia in women

3.1 Gender and cardiovascular risk

CVD is a major cause of death in women. While the risk of CVD in men increases after age 40 years, risk develops 7–10 years later in women. Incidence of CAD in premenopausal women is 3–4 times lower than in men [27, 28]. After menopause due to loss of vasodilating property of estrogen and increased sympathetic activity, the risk of CAD is increased and is similar to men [29–31]. Risk factors unique to women are use of oral contraceptives, menopause, hormone replacement therapy, gestational hypertension, and diabetes. Obesity and metabolic syndrome are also more prevalent in women [32].

Plasma cholesterol levels and LDL-C levels are similar in both sexes during the infancy and adolescence. LDL levels increase progressively in both men and women after the age of 20, but more rapidly in men. Size of the LDL particles reduces as men age, while it remains stable in women until menopause then becomes smaller [33].

3.2 Management of dyslipidemia

In 1999, American heart association (AHA) developed the first women-specific clinical report regarding recommendations for CVD prevention [34]. In the 2011 AHA update, effectiveness-based guidelines for the prevention of CVD in women recommended lifestyle approaches for LDL-C < 100 mg/dl, HDL-C > 50 mg/dl, triglycerides <150 mg/dl, and non-HDL-C (total cholesterol minus HDL) <130 mg/dl (class I recommendation; level of evidence B). LDL-C-lowering drug therapy with lifestyle therapy in women with coronary heart disease (CHD) to achieve an LDL-C < 100 mg/dl (class I; level of evidence A) and is also indicated in women with other atherosclerotic CHD or diabetes mellitus or 10-year absolute risk 20% (class I; level of evidence B). A reduction to <70 mg/dl is reasonable in very-high-risk women like those with recent acute coronary syndrome (ACS) or multiple cardiovascular risk factors with CHD and may require an LDL-lowering drug combination (class IIa; level of evidence B) and is also indicated in women with other atherosclerotic CHD or diabetes mellitus or 10-year absolute risk 20% (class I; level of evidence B). A reduction to <70 mg/dl is reasonable in very-high-risk women like those with recent acute coronary syndrome (ACS) or multiple cardiovascular risk factors with CHD and may require an LDL-lowering drug combination (class IIa; level of evidence B). In women >60 years of age and with an estimated CHD risk >10%, statins could be considered if hsCRP is >2 mg/dl after lifestyle modification and no acute inflammatory process is present (class IIb; level of evidence B). Niacin or fibrate therapy can be useful when HDL-C is low (<50 mg/dl) or non-HDL-C is elevated (>130 mg/dl) in high-risk women after LDL-C goal is reached (class IIb; level of evidence B) [35].
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In 2013 ACC/AHA guidelines added, treatment decisions for women should be based on the level of ASCVD risk. Statin treatment based on estimated 10-year ASCVD risk avoids the overtreatment of lower risk groups, such as younger, non-Hispanic white women who, despite moderate elevations in LDL-C, are typically not at significantly increased risk for ASCVD in the absence of other substantial risk factors [1]. The European Atherosclerosis Society (ESC/EAS) recommends that assessment of CV risk should be gender specific and recommended statin therapy be initiated as primary and secondary prevention for women at high risk [36].

3.3 Women in hyperlipidemia clinical trials

Women have been underrepresented in many primary and secondary prevention trials. In major primary prevention trials, the number of women varied from 15 to 49%. In AFCAPS (15%), HPS (30%), ALLHAT-LLT (49%), and in ASCOT-LLA trial (19%) were women [37, 38]. In a prospective, randomized, open-labeled, blinded Japanese primary prevention trial of patients with hypercholesterolemia, 5547 (68%) were women randomly assigned to diet alone or diet with pravastatin daily. Treatment with a low dose of pravastatin reduced the risk of CHD but subgroup analysis of CHD risk in women was not statistically significant [39]. JUPITER trial participants included 6801 women ≥60 years of age and 11,001 men ≥50 years of age with high-sensitivity C-reactive protein ≥2 mg/L and LDL-C < 130 mg/dl, randomized to rosuvastatin versus placebo. JUPITER demonstrated that for primary prevention, rosuvastatin reduced CVD events in women with a relative risk reduction similar to that in men, a finding supported by meta-analysis of primary prevention statin trials [40].

In major secondary prevention trials, 4S included 827 (19% woman), CARE 576 (14%), LIPID 1516 (17%), TNT 1902 (19%), and SEARCH trial included 2052 (17%) women [41–44]. Cholesterol lowering with simvastatin produced similar reductions in relative risk for major coronary events in women compared with men. There were too few female deaths to assess the effects on mortality in women [41]. A meta-analysis of 13 large trials for a total of 11,435 women in primary prevention and 8272 in secondary prevention concluded that lipid lowering does not affect CHD mortality in women for primary prevention, but it is effective for secondary prevention [27].

3.4 Gender differences in statin use

Women are more likely to have poor lipid control. There have been conflicting results regarding gender differences in benefit of statins in women with CVD. However, in a meta-analysis performed on data from 22 trials of statin therapy versus control (n = 134,537) and five trials of more intensive versus less intensive statin therapy, 27% of 174,149 randomized participants were women. In men and women at an equivalent risk of cardiovascular disease, statin therapy was equally effective for the prevention of major vascular events. Kostis et al. performed a meta-analysis consisting of 18 randomized clinical trials of statins with gender-specific outcomes and found statin therapy was associated with significant decreases in cardiovascular events and in all-cause mortality in women and men [45].

There is a gender-specific impact of transporter polymorphisms on statin pharmacokinetics. Estrogen-induced water and sodium retention, increased volume for lipophilic drugs, higher protein-binding globulins, higher CYP3A4 activity, lower body mass index, and lower renal clearance in women may affect absorption of different statins. Women seem to be at greater risk of statin-induced rhabdomyolysis. In a US case-control study of 252,460 users of lipid-lowering therapy, there was
trend for increased risk of rhabdomyolysis [46]. In the JUPITER study, the occurrence of serious adverse events was similar in both men and women [40].

3.5 Pregnancy

3.5.1 Normal changes in pregnancy

Metabolic adaptations during pregnancy are essential to meet the physiological demands of pregnancy as well as development of the fetus. An increase in insulin resistance results in increases in maternal glucose and free fatty acid concentrations, allowing for greater substrate availability for fetal growth. Production of progesterone leads to lipogenesis, lipids are transported across the placenta and metabolized; this signifies the essential role of lipids to normal fetal development [47, 48]. Within 6 weeks of gestation, lipid levels drop slightly followed by rise in both total cholesterol and marked increase in triglycerides (TG). HDL-C levels and apolipoprotein A-I levels also increase during normal gestation, with peak levels during the second trimester. As TG levels rise, there is a decrease in low-density lipoprotein (LDL) size with an increased proportion of atherogenic small-dense LDL. Both cholesterol and triglyceride concentrations decrease significantly within 24 h of delivery. However, while TG levels continued to decrease rapidly returning to nonpregnant levels during the puerperium, LDL-C remained elevated for at least 6–7 weeks postpartum [49, 50]. During pregnancy, lipoprotein Lp(a) levels increase with gestational age and fall to prepregnancy levels within 6 months postpartum [51, 52].

3.5.2 Lipids and complications in pregnancy

Preeclamptic women exhibit higher mean serum TG levels, elevated LDL-C fractions, increased levels of Lp(a), and lower HDL cholesterol levels compared with healthy pregnant women [49]. Amsterdam Born Children and Their Development (ABCD) cohort study showed that every unit increase in TG was linearly associated with an increased risk of preeclampsia, pregnancy-induced hypertension, and preterm delivery. Total cholesterol was not associated with any of the outcome measures [53]. Women who have higher concentrations of small-dense LDL fractions during pregnancy tend to have increased risk of cardiovascular disease later in life [53, 54].

In the multicenter, prospective Coronary Artery Risk Development in Young Adults study, 1010 women of which 49% identified as black with at least one singleton birth with 20 years of follow-up were evaluated. There was a U-shaped relationship between prepregnancy cholesterol concentrations and preterm birth risk with both low (<156 mg/dl) and high cholesterol (>195 mg/dl) related to preterm birth risk [55]. Observational and experimental evidence increasingly supports a relation between growth and development during fetal and infant life and health in later years. Additionally, preterm newborns have been found to be at an increased risk of CVD later in life [56].

3.5.2.1 Antihyperlipidemia therapy

Pregnant women are generally excluded from clinic trials, thus the data are limited. HMG-CoA reductase inhibitors have been associated with teratogenicity and congenital malformation and are not recommended. Fibrates and nicotinic acid have not been well studied and are not recommended. Omega fatty acids, on the other hand, can be safely used as monotherapy to decrease TG levels.
4. Dyslipidemia in CKD and ESRD

4.1 Epidemiology and pathogenesis

Patients with CKD and ESRD are at an increased risk of CVD, and are more likely to die because of adverse cardiovascular events [57]. In addition to traditional risk factors like hypertension, diabetes mellitus, dyslipidemia, and a family history of CAD, patients with CKD are plagued by nontraditional risk factors like homocysteinemia, mineral bone disease, carbamylation, and chronic inflammation [58, 59]. As CKD progresses, an unstable vascular environment ensues which threatens endothelial function and lipoprotein integrity and thus potentiating adverse cardiovascular outcomes. Figure 1 shows mechanism of dyslipidemia in this population.

Dyslipidemia in these patients is undoubtedly one of the strongest risk factors for these adverse cardiovascular outcomes. Despite these data, however, CVD remains underdiagnosed and undertreated in patients with CKD. Dyslipidemia has been found to be distinctly different from the general population and variable depending on the stage of CKD [60]. The lipid profile of patients with nondialysis-dependent CKD is usually composed of low HDL-C and high triglycerides with normal to low total cholesterol and low-density lipoprotein cholesterol [61]. In fact, plasma triglycerides start to increase in early stages of CKD and show the highest concentrations in nephrotic syndrome and in dialysis patients, especially those who are treated with peritoneal dialysis [60]. In patients with nondialysis-dependent CKD, the hypertriglyceridemia has been attributed to delayed catabolism and increased hepatic production of triglyceride-rich lipoproteins, and to a smaller extent by the presence of lipase inhibitors [62]. This altered catabolism in turn results in the accumulation of triglyceride-rich lipoproteins, like IDL and small-dense LDL (sdLDL) which are highly atherogenic [63, 64].

Though elevated LDL-C is not a typical feature of these patients, sdLDL, an LDL subtype, is increased and carries the ability to penetrate the vessel wall, becomes oxidized, and triggers the atherosclerotic process. The subfractions of HDL in CKD and ESRD are also different than that of the general population. In uremia [65], LDL and HDL, their subfractions, lipidomes, and proteomes, gradually become more susceptible to structural modifications such as carbamylation, oxidation, glycation, nitration, and homocysteinylatation [66, 67]. Most of these effectors are irreversible and amplify the uptake by the scavenger receptors on the surface of macrophages [60]. HDL’s vital components like ApoA-I, PON-1, and LCAT are altered, ultimately attenuating HDL’s cyto- and vascular-protective properties [68]. The reduced

Figure 1. Mechanism of dyslipidemia in chronic kidney disease (CKD), end stage renal disease (ESRD), and human immunodeficiency virus (HIV) patients.
PON-1 activity further predisposes LDL and HDL to more oxidation and, in turn, dysfunction and enhanced atherogenic potential [69]. In fact, it has been found that increasing serum HDL-C over time is paradoxically associated with significantly higher all-cause and cardiovascular mortality [70].

4.2 Management

Recent studies show that statin therapy can decrease cardiovascular mortality in CKD population. Heart Protection Study and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated that CKD patients treated with simvastatin exhibited a reduction of cardiovascular morbidity and mortality [71, 13]. Results from the Pravastatin Pooling Project showed similar cardioprotective effects [72]. Atorvastatin and rosuvastatin also reduced the relative risk of cardiovascular events in CKD patients and improved outcomes were found with higher atorvastatin doses [73–75]. Study of Heart and Renal Protection (SHARP) trial randomized 9270 patients with CKD with no prior history of CAD and found that simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in CKD patients [76].

KDIGO panel provides recommendations for dyslipidemia in patients at all stages of CKD based on a few large, randomized controlled trials and post hoc analyses of the subgroup of CKD patients from statin trials in the general population [76, 77]. In adult CKD patients ≥50 years age, statin therapy alone is recommended for those with GFR ≥ 60 ml/min and statin or statin/ezetimibe therapy is recommended for GFR < 60 ml/min. In adults aged 18–49 years with CKD, statin treatment is recommended in patients with known coronary disease, diabetes mellitus, prior ischemic stroke or estimated 10-year incidence of coronary death or nonfatal myocardial infarction >10%. Neither ACC/AHA nor KDIGO guidelines recommend initiation of statin therapy or combination treatment with statin and ezetimibe in dialysis-dependent patients on the basis of results from the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) and Deutsche Diabetes Dialyse Studie (4-D) trials. However, patients already on lipid-lowering therapy at the time of progression to dialysis may continue treatment [76, 78–80].

Novel and innovative therapies are needed to address the multiple lipid/lipoprotein abnormalities that facilitate high cardiovascular risk and mortality in patients with dialysis-dependent CKD.

5. Dyslipidemia in renal transplant recipients

5.1 Epidemiology

Risk of cardiovascular events in kidney transplant recipients is markedly elevated as compared to people without CKD. Prevalence of hyperlipidemia ranges from 16 to 78% in kidney transplant recipients. Hypercholesterolemia has peak incidence at 12 months posttransplant and correlates with excessive body weight. After transplantation, increases in total cholesterol, LDL-C, very-low-density lipoprotein (VLDL)-cholesterol, and TG have been noted. In addition, LDL-C may be more susceptible to oxidation, making the particle more atherogenic. HDL-C levels may be normal or even high although the composition of HDL may not be normal [81].
Dyslipidemia

5.2 Mechanisms of dyslipidemia

Immunosuppressive agents contribute significantly to hyperlipidemia in renal transplant recipients. Corticosteroids induce insulin resistance. Hyperinsulinemia leads to increased hepatic uptake of free fatty acids (FFA) which constitute the main substrate for VLDL cholesterol synthesis. There is increased conversion of VLDL to LDL cholesterol, leading to a rise in LDL cholesterol levels and downregulation of LDL receptors [81–83]. Calcineurin inhibitors interfere with binding of LDL-to-LDL receptor leading to increase in LDL-C, interfere with bile acid synthesis and lead to LDL receptor downregulation. Cyclosporine is highly lipophilic. Tacrolimus is associated with less hyperlipidemia [84]. Rapamycin inhibits lipoprotein lipase, associated with decrease in apolipoprotein-B 100 catabolism, and increases secretion of VLDL cholesterol [85]. Other secondary causes include nephrotic syndrome, hypothyroidism, diabetes mellitus, excessive alcohol intake, obesity, chronic liver disease, and genetic predisposition.

5.3 Management

Lipid profile evaluation including total cholesterol, LDL, HDL, and triglyceride levels is recommended. Kidney Disease Improving Global Outcomes (KDIGO) suggest treatment with statins in adult kidney transplant recipients [77]. Assessment of Lescol in Renal Transplantation (ALERT) trial is the only multicenter, randomized, double-blind, placebo-controlled trial in renal transplant recipients. In this study, 2102 renal transplant recipients with total cholesterol 4·0–9 mmol/l were randomized to receive fluvastatin (n = 1050) or placebo (n = 1052). After a mean follow-up of 5 years, fluvastatin lowered LDL cholesterol concentrations by 32%. Although cardiac deaths and nonfatal myocardial infarction seemed to be reduced, fluvastatin did not reduce rates of coronary intervention procedures or mortality [86]. Of 1787 patients who completed ALERT, 1652 (92%) were followed in the extension trial with mean follow-up of 6.7 years which showed 29% reduction in cardiac death or definite nonfatal myocardial infarction in the fluvastatin arm [87]. Due to the known interaction of calcineurin inhibitors through CYP3A isoenzyme system, lower doses of statins are generally used as compared to general population. Among fibrates, fenofibrate is less myotoxic than gemfibrozil when combined with statin but fenofibrate should be avoided in advanced CKD. Bile acid sequestrants are not widely used due to gastrointestinal side effects and can also interfere with absorption of immunosuppressants. Ezetimibe is considered safe in renal transplant recipients.

6. Dyslipidemia in HIV

Antiretroviral therapy (ART) has prolonged the survival of HIV-infected individuals, which, in effect, has increased the prevalence of comorbidities, like coronary heart disease. Studies have shown that HIV-infected individuals have higher cardiovascular disease (CVD) risk than uninfected persons in the United States [88–90]. Paisible et al. reported a 1.5–2-fold increased risk of incident myocardial infarction compared with uninfected subjects [91]. Among HIV patients, women have been found to have higher CVD risk than men [92]. Risk, however, cannot be attributed to HIV alone as traditional CVD risk factors like smoking [93], dyslipidemia, diabetes mellitus, and hypertension [92] have been found to be more common among those infected. Table 1 summarizes the traditional and nontraditional risk factors for cardiovascular disease in special populations.
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Their lipid profile is comprised of hypertriglyceridemia, increased sdLDL, and low HDL-C levels [94, 95]. Atheromas have been found to have larger lipid pools with dystrophic calcifications [96]. Consequently, the coronary arteries have a higher burden of coronary plaque and prevalence of detectable calcium [97–99]. These plaques are rupture-prone and associated with inflammation [100] and monocyte activation [101]. As a result, patients tend to have higher rates of subclinical vascular disease [102, 103]. ART-associated lipodystrophy has been linked with these cardiac and metabolic complications [104]. However, newer ART medications have had less effect on dyslipidemia and related myocardial events [105]. Still, CD4 cell depletion and immune dysfunction perpetuates HIV-related atherosclerosis, irrespective of ART [106]. Silverberg et al. reported that CD4 counts <200 cells/mm$^3$ were significantly associated with increased risk of MI [105]. While viral load and prior ART use were not associated with MI, unsuppressed HIV viremia was associated with MI [89] and stroke [107]. Dyslipidemia and its effects on the cardiovascular system in HIV are dynamic and multimodal. In these states of chronic inflammation, it is difficult to associate quantities of cholesterol types with outcomes. That is, in these special populations, there may not be a “good” or “bad” cholesterol, but rather dysfunctional lipoprotein atherosclerosis.

Studies have shown that statins are safe and beneficial in those infected with HIV; however, the use of statins remains relatively low [89, 108, 109]. Reasons include (1) the low prevalence of elevated LDL-C, (2) their uncertain efficacy for CVD prevention, and (3) the potential to adverse side effects and negative drug-drug interactions [80]. National Lipid Association (NLA) recommends that all HIV-infected patients be first assessed for cardiovascular risk and counseled about lifestyle interventions like diet, exercise, and smoking for the prevention of atherosclerotic cardiovascular disease. In addition, a fasting lipid panel should be obtained in all newly identified HIV-infected patients before and after starting antiretroviral therapy. TG >500 mg/dl that are refractory to lifestyle modification or changes in ART (if an option) should be treated with either a fibrate (fenofibrate preferred) or prescription omega-3 fatty acids to lower TG to <500 mg/dl. Non-HDL-C and

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CKD, chronic kidney disease; HIV, human immunodeficiency virus.

Table 1. Traditional and nontraditional risk factors for cardiovascular disease in special populations.
Dyslipidemia

LDL-C should be reassessed for appropriate management with statin therapy with caution of drug-drug interactions and side effects. To this end, the NLA Expert Panel recommends clinicians to prescribe pitavastatin as the generally preferred agent in HIV-infected patients [80].

7. Racial differences in dyslipidemia

7.1 Epidemiology

National Health and Nutrition Examination Survey (NHANES) is the primary data source for national prevalence rates of dyslipidemia in the US with data on Whites, black/African Americans, and Hispanics/Latinos but is limited in data on Asian subgroups [110]. NHANES data in 2013 showed that the prevalence rate of high LDL-C was highest among Mexican men (40%) and women (30%), followed by non-Hispanic black men (33%) and women (31%). Non-Hispanic white men (30%) and women (29%) had the lowest prevalence of high LDL-C. The prevalence rates of low HDL were 20% in black men and 10% in black women as compared to prevalence rates among non-Hispanic white men (33%) and women (12%) and Hispanic American men (34%) and women (15%). NHANES data in 2008 reported prevalence of high TG in 35% of Hispanic Americans, 33% among non-Hispanic whites, and 16% among non-Hispanic blacks compared to prevalence rates among non-Hispanic white men (33%) and women (12%). American Heart Association (AHA), in conjunction with the Centers for Disease Control and Prevention, and the National Institutes of Health reported prevalence of hyperlipidemia in non-Hispanic black men (32.6%) and non-Hispanic black women (36.1%), Hispanic men (43.1%), Hispanic women (41.2%), non-Hispanic white men (37%) and women (43.4%) and for non-Hispanic Asian, prevalence was 39.9% in men and 40.5% in women [111]. Data from outpatient cohort of adults 35 years or older from 2008 to 2011 in northern California found that compared with non-Hispanic whites, every minority subgroup had an increased prevalence of high triglycerides except blacks. Most minority groups had an increased prevalence of low HDL-C, except for Japanese and blacks. The prevalence of HDL-C was increased among Asian Indians, Filipinos, Japanese, and Vietnamese compared with non-Hispanic whites [113]. Table 2 shows cholesterol levels in minority populations compared to non-Hispanic Whites in the United States.

The Study of Health Assessment and Risk in Ethnic groups (SHARE), a prospective Canadian trial, showed that South Asians including Asian Indians had an increased prevalence of total cholesterol, high LDL-C, low HDL-C, and high TG compared to European and Chinese cohort [114]. The Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter cohort study of 6814 adults aged 45 to 84 years who were free of clinical CVD at baseline were evaluated for CVD risk and self-reported use of lipid-lowering therapy. Black and Hispanic Americans had prevalence of dyslipidemia that was comparable to that of non-Hispanic whites but were less likely to be treated and controlled. Ethnic disparities were attenuated substantially by adjustment for health-care access variables [115]. Data from the Hispanic Community Health Study (HCHS)/Study of Latinos (SOL), an observational study, showed high prevalence of dyslipidemia among Central American men and Puerto Rican women [116].

7.2 Dyslipidemia and cardiovascular outcomes

In the US, cardiovascular mortality rates are highest in blacks as compared to Hispanics [117]. An early study of CHD among Japanese migrants compared with
Japanese living in Japan showed higher rates of CAD in Japanese immigrants in America [118]. In a study of immigrant Asian Indian men in US, Enas et al. reported high prevalence of CAD, low HDL-C levels, and hypertriglyceridemia. Authors suggested “insulin resistance” as a common pathogenetic mechanism [119]. Increased risk of CAD in south Asian community was seen in data from other studies as well [114, 120, 121].

The 2013 ACC-AHA guidelines for the treatment of cholesterol expand the indications for statin therapy for the prevention of CVD. Ten-year ASCVD risk assessment calculator has been added to determine statin use [122]. ASCVD risk calculator is derived from cohorts that included African-American or white participants with at least 12 years of follow-up. Data from other racial/ethnic groups were insufficient, precluding their inclusion in the final analyses. The equations were also assessed in external validation studies with data from other available cohorts [123]. For other ethnic groups, ACC/AHA recommends use of the equations for non-Hispanic whites, though it acknowledges that estimates may underestimate the risk for American Indians, some Asian Americans (e.g., of south Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of east Asian ancestry) and some Hispanics (e.g., Mexican Americans) [124].

### 7.3 Statin metabolism

There are several genetic variants associated with altered statin metabolism. Single-nucleotide polymorphisms in the genes that encode the organic anion-transporting polypeptide (OATP) 1B1 (521 T > C), which regulates hepatic uptake of statins, and the adenosine triphosphate-binding cassette G2 (ABCG2) transporter (421C > A), which regulates hepatic efflux, have been reported [125–127]. Plasma exposure to rosuvastatin and its metabolites was significantly higher in Chinese, Malay, and Asian-Indian subjects compared with white subjects living in Singapore [128]. Rosuvastatin, a HMG-CoA reductase inhibitor, is excreted into bile mediated by breast cancer resistance protein (BCRP). BCRP 421C > A polymorphism may play an important role in the pharmacokinetics of rosuvastatin in healthy Chinese males [129]. In a Japanese study, single-nucleotide polymorphisms in OATP-C, such as T521C (Val174Ala), has
been reported to be associated with altered pharmacokinetics of pravastatin [125]. In a US-based study cohort of 69 European-Americans and 38 African-Americans, SLCO1B1 genotype, in particular, the 521C allele, had a significant effect on the pharmacokinetics of pravastatin. European-Americans demonstrated significantly higher pravastatin levels as compared to African-Americans [130]. There is less information on statin metabolism in other racial/ethnic minority groups. In a randomized placebo-controlled trial of 25,673 patients, the absolute risk of myopathy with adding niacin-laropiprant to statin-based LDL cholesterol-lowering therapy was more than 10 times as great among Chinese as compared to their European counterparts [131]. The relative risk of myopathy with niacin-laropiprant versus placebo was also higher in Chinese patients [132].

Lifestyle risk factors include unhealthy diet, obesity, and physical inactivity. Racial/ethnic disparities also exist in these lifestyle risk factors. According to the National Health Interview Survey (NHIS) 2008–2010, Asian adults were less likely to be current smokers or to be obese. Black adults were more likely to be physically inactive, to be obese, and to get insufficient sleep. Hispanics were less likely than non-Hispanic adults to smoke cigarettes, get insufficient sleep, but were more likely to be inactive in terms of aerobic and muscle-strengthening leisure time. Immigration and acculturation have a profound impact on lifestyle in both Hispanics and Asians in the US [133]. Asian Indian, Filipino, Vietnamese women, and Asian Indian men have increased risk dyslipidemias as compared to non-Hispanic whites. Further research is needed to determine the role of dyslipidemia subtypes and other risk factors in explaining the higher risk of CVD in minority subgroups. By understanding these differences, clinicians will be able to provide more culturally competent recommendations on prevention and management of dyslipidemia.

8. Conclusion

In conclusion, differences in dyslipidemia patterns, risk factors, and management exist in the elderly, women and pregnancy, CKD, ESRD, HIV, and different racial ethnic groups. Nevertheless, they are frequently underrepresented in clinical trials, which calls for more inclusive research that will develop stronger recommendations of daily practice.

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