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REVIEW

Alteration of lipid metabolism in chronic kidney disease, the role of novel antihyperlipidemic agents, and future directions

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The role of anti-hyperlipidemic therapy remains of key importance in the treatment of atherosclerotic disease. Moreover, given an already exaggerated predisposition for vascular disease at baseline, there is a preponderance of data that show management of hyperlipidemia is especially important in patients with chronic kidney disease. This is a concise, up-to-date review of lipid physiology, alterations in lipid concentrations with progressive renal failure, and currently available and emerging hyperlipidemic treatment options. Specifically, the roles of these therapies in patients with chronic kidney disease are reviewed.

Keywords

hyperlipidemia; chronic kidney disease (CKD); PCSK9; lipid physiology; hyperlipidemia in CKD; hyperlipidemia management

1. Introduction

The incidence of chronic kidney disease (CKD) is growing rapidly and remains a major cause of morbidity and mortality in the United States. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define CKD as kidney damage or impaired kidney function, present for greater than three months, regardless of cause. Multiple biomarkers or tests can be used to indicate kidney damage, including albuminuria, glomerular filtration rate (GFR), urine sediment analysis, renal imaging, and microscopic pathological changes. GFR and albuminuria are generally the most commonly used tools for assessment of renal function. Per KDIGO guidelines, CKD is defined as a urine albumin to creatinine ratio (ACR) 30 $\geq$ mg/g or estimated GFR (eGFR) less than 60 mL/min per 1.73 m^2. Patients with these results are at increased risk of acute kidney injury (AKI) and end-stage renal disease (ESRD) compared to patients with a lower ACR and eGFR (Levey et al., 2011).

CKD patients experience more severe and frequent cardiovascular disease (CVD) compared to the general population, and their CVD remains under-recognized and undertreated. Increased cardiovascular risk in CKD is multifaceted, in part due to pathophysiology specific to CKD (Gansevoort et al., 2013). Cardiovascular morbidity and mortality in the setting of CKD was studied in two major general population cohorts completed in Canada and Taiwan. In the Canadian study, patients with stage 3B and 4 kidney disease experienced reductions in life expectancy of approximately 17 and 25 years, respectively (Hemmelgarn et al., 2009). Similar results were obtained in the Taiwanese study, with both analyses clearly delineating reduction in life expectancy associated with declining renal function (Wen et al., 2008).

As discussed above, there is clear evidence of increased cardiovascular morbidity and mortality in CKD patients due to an amalgamation of complex disease processes. Traditional risk factors for CKD such as diabetes and hypertension certainly contribute to increased cardiovascular risk. However, more complex mechanisms mediated by CKD include inappropriately active sympathetic nervous system response, heightened renin-angiotensin system activity (Schiffrin et al, 2007) and increased concentration of asymmetric dimethylarginine – an inhibitor of nitric oxide production (Zoccali et al., 2002). Cumulatively, these physiological changes manifest as hypertension, increased systemic vascular resistance, reduced cardiac output, concentric left ventricular (LV) hypertrophy, and LV dysfunction (Gansevoort et al., 2013; Schiffrin et al, 2007; Zoccali et al., 2002). Dyslipidemia with an concomitant predisposition for atherogenesis has also been well characterized in CKD patients (Bakris, 2012). This review will focus on alterations of lipid metabolism due to pathophysiology from CKD, as

well as a discussion of the mechanism and efficacy of various treatment options.

2. Lipoprotein metabolism and changes in normal homeostasis caused by CKD

To understand changes in lipoprotein metabolism due to CKD, a basic understanding of normal metabolism with key players is required. Structurally, cholesterol is hydrophobic and thus insoluble in water – as such lipids must be bound and transported with proteins in a lipoprotein complex. Lipoproteins are composed of a surrounding hydrophilic layer of phospholipids and apolipoproteins, which aid in lipoprotein formation and function, with a hydrophobic cholesterol ester core. Based on various characteristics such as particle density, molecular size/weight, and associated apolipoproteins (apoproteins, Apo), lipoproteins can be classified into one of seven categories: chylomicrons, chylomicron remnants, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), high density lipoproteins (HDL), and lipoprotein (a) (Lp[a]).

The major apoproteins (Apo A-I, Apo A-II, Apo A-IV, Apo-V, Apo B-48, Apo B-100, Apo C-I, Apo C-II, Apo C-III, Apo E, and Apo(a)) are generated in the liver and intestines. Broadly, apoproteins assist with structure/formation of lipoproteins, serve as active binding ligands for various lipoprotein receptors, and are activators/inhibitors of specific enzymes critical in lipid processing (Feingold and Grunfeld, 2000). Apoproteins are catabolized as part of the life cycle of lipid particles. Importantly, multiple apoproteins undergo filtration in the glomerulus, and are catabolized by proximal tubular cells in the nephron. Studies measuring apoprotein levels in CKD patients suggest Apo A-IV and Apo B are renally excreted, as serum levels tend to increase with decline in GFR (Mikolasevic et al., 2017). The most important clinical use for serum apoprotein quantification is assessment of cardiovascular risk (Dominiczak and Caslake, 2011), in fact serum Apo B and A-I (and their calculated ratio) may be better markers of cardiovascular risk than traditional tests such as total and LDL cholesterol (Andrikoula and McDowell, 2008; Thompson and Danesh, 2006).

Chylomicrons (identified by Apo B-48) are large triglyceride-rich particles formed by the intestines and serve to shuttle cholesterol and triglycerides to the liver via chylous fluid. Chylomicron size is largely dependent on the amount of dietary fat consumed, as increased lipid consumption leads to greater mobilization of triglycerides into a chylomicron molecule. Of note, microsomal transport protein (MTP) is a critical transport protein in intestinal epithelial cells required for movement of lipid from the endoplasmic reticulum to apoproteins. Absence of MTP leads to an inability to produce chylomicrons, a condition known as abetalipoproteinemia. Inhibition of MTP offers another potential therapeutic target in dyslipidemia, and will be discussed further below. Subsequent extraction of the triglycerides in muscle and adipose tissue produces a cholesterol enriched byproduct called a chylomicron remnant. VLDL particles are generated by the liver, also utilizing MTP for uptake of both cholesterol and triglycerides. Each VLDL molecule contains one Apo B-100 core structural apolipoprotein along with other important apoproteins including Apo E, Apo C-II, and Apo C-III. Similar to chylomicrons, VLDL transports triglycerides (albeit from the liver versus the intestine) and their size is also contingent upon triglyceride concentration. VLDL particles are transformed to IDL remnants after removal of triglycerides from peripheral tissue. IDL particles are then transformed to smaller, further cholesterol enriched LDL particles that carry the vast majority of circulating cholesterol. Small, cholesterol dense LDL molecules tend to remain in circulation longer (due to poor receptor affinity) and more easily bind to and enter the arterial wall, forming a strong predisposition for atherogenesis (Feingold and Grunfeld, 2000).

With a basic understanding of the major participants, one can better understand the overarching process of lipid metabolism. The process starts with the exogenous lipoprotein pathway. Ingested dietary lipids are recast as triglyceride rich chylomicrons, which are subsequently metabolized in muscle and adipose tissue by lipoprotein lipase. Free fatty acids released by lipoprotein lipase are also metabolized by peripheral tissue. The remaining byproduct of the chylomicron–aptly termed a chylomicron remnant–is taken up by the liver, completing the exogenous pathway. From here, the endogenous pathway is initiated with VLDL formulation in the liver. Triglyceride rich VLDL molecules are processed by lipoprotein lipase in peripheral tissue in iterative fashion, forming IDL and eventually LDL, while simultaneously releasing free fatty acids with each round of catabolism. LDL is absorbed systemically (including the arterial walls), via the LDL receptor, but is resorbed most predominantly in the liver. The opposing process of cholesterol removal from peripheral cells is termed reverse cholesterol transport. This process begins with formation of Apo A-I, the core structural protein of nascent HDL (also referred to as pre-beta HDL). Lipid and cholesterol from hepatocytes, enterocytes, and macrophages are deposited into Apo A-I via ATP-binding cassette 1 (ABCA1), ultimately forming mature HDL. Mature HDL molecules deposit cholesterol back to the liver either through direct interaction with hepatic receptors or transfer through VLDL/LDL. Selective reuptake of HDL by the liver is mediated by the transport protein scavenger receptor B1 (SR-BI). HDL binds to SR-BI, and cholesterol from the mature HDL is transported into the liver without resorption of the HDL particle (Feingold and Grunfeld, 2000). Of note, the ability of macrophages to efficiently eliminate cholesterol to HDL may play an important role in combating atherosclerosis. As such, the ABCA1 transport protein remains of great clinical interest, as mouse models have demonstrated macrophages lacking ABCA1 show a reduction in macrophage reverse cholesterol transport (Wang et al., 2007).

There are numerous changes to normal lipid metabolism that result as a consequence of declining renal function; the entire plasma lipidome changes with CKD disease severity (Duranton et al., 2018). Patients with CKD exhibit a secondary form of dyslipidemia similar to that of patients with insulin resistance. HDL is decreased in both insulin resistant and CKD patients, primarily due to an increase in the catabolic rate of Apo A-1 (Okubo et al., 2004). Catabolism of Apo A-1 is inversely related to HDL particle size (Ooi et al., 2005). Moreover, as evidenced by Kronenberg et al., atherogenic molecules such as Lp(a) become elevated with decreasing GFR and increased proteinuria (Kronenberg, 2014). Mul-

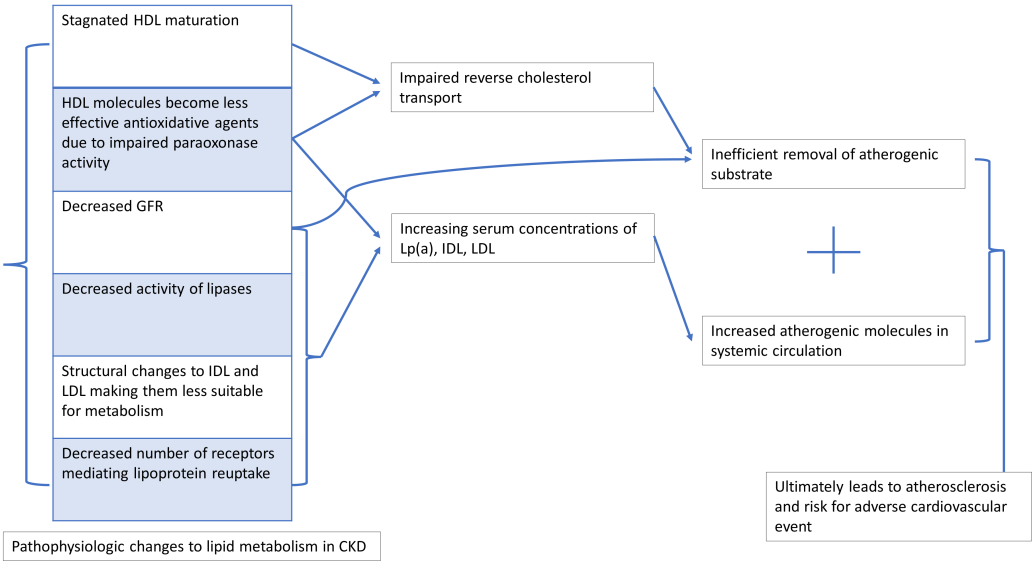

Figure 1. Mechanism of Atherosclerosis Due to Pathophysiologic Changes in Lipid Metabolism Associated with CKD

tiple factors contribute to decreased clearance and metabolism of IDL and LDL in CKD. Progressive kidney disease has been associated with decreased production of lipoprotein lipase, endothelial cell dysfunction, structural changes to IDL and LDL making them less suitable for metabolism, and a decrease in receptors mediating lipoprotein reuptake (Kaysen, 2009; Zhang et al., 2017). In terms of reverse cholesterol transport, HDL molecules do not mature appropriately with advancing renal failure, leaving triglyceride rich nascent HDL molecules in systemic circulation. Moreover, HDL molecules in CKD patients are also less effective antioxidative agents when compared to normal patients due to a decrease in paraoxonase activity (Kaysen, 2009). (Paraoxonase is a hydrolytic enzyme that acts on a wide range of substrates; its protective role against lipid oxidation has been well characterized (Litvinov et al., 2012)). A schematic detailing how pathophysiologic changes in lipid metabolism from CKD manifest in atherosclerosis is outlined in Fig. 1.

The role of the pro-atherogenic Lp(a) molecule in CKD has been of escalating clinical interest. Lp(a) is produced primarily by the liver, and is composed of an Apo(a) molecule covalently bound to the Apo B-100 core of LDL. The Apo(a) component of Lp(a) contains multiple "kringle" repeats, and as such its molecular weight can vary widely (250-800 kilodaltons). Individuals with high molecular weight Apo(a) proteins tend to have lower levels of circulating Lp(a); this may be due in part to impaired hepatic secretion of high molecular weight Apo(a) molecules (Feingold and Grunfeld, 2000). The teleologic role of Lp(a) role in normal lipid physiology has not been well described, however there is clear evidence that Lp(a) is pro-atherogenic (Kolski and Tsimikas, 2012). Lp(a) remains of interest in the nephrology community, as Lp(a) clearance has been associated with renal function. In the early 1990s, an Austrian study showed an increase in endogenous Lp(a) levels with decreasing GFR. In fact, Lp(a) levels were four times higher in patients with nephrotic range proteinuria compared to normal controls (Kronenberg, 2014). *In-vivo* studies suggest this may be due to excess Lp(a) production in nephrotic patients. Interestingly, excess production of Lp(a) appears to be completely resolved in transplanted patients and moderately reduced in hemodialysis patients (Kronenberg, 2014). Also of note, the relationship between GFR and Lp(a) level may not be linear (Kovesdy et al., 2002; Uhlig et al., 2005) and changes in serum Lp(a) levels may occur predominately in the early stages of CKD (Kronenberg et al., 2000). 2013 KDIGO guidelines do not recommend routine measurement of Lp(a), however monitoring these values is an area of further research interest within the nephrology community (KDIGO, 2013). Moreover, the usual method to calculate LDL cholesterol does not distinguish between cholesterol derived from LDL and Lp(a), and in fact is the net total of cholesterol levels from both lipoproteins. In nephrotic syndrome, LDL cholesterol levels corrected for Lp(a)-derived cholesterol were 27 mg/dL lower than uncorrected concentrations (compared to only 9 mg/dL in non-nephrotic patients). Essentially, this "pseudo-pharmacogenetic effect" results in inaccurate determination of LDL cholesterol in patients with nephrotic syndrome (Kronenberg, 2014). A boxplot showing Lp(a) levels across CKD is shown in Fig. 2 (Morena et al., 2017), and a table reviewing published studies that have measured Lp(a) across stages of CKD is provided in Table. 1 (Kronenberg et al., 2000; Lin et al., 2015; Parsons et al., 2002; Rahman et al., 2014; Sechi et al., 1999; Uhlig et al., 2005).

As an interesting aside, along with increased atherosclerotic risk, increase in Lp(a) levels may also pose greater predisposition for aortic stenosis. This is most likely mediated by intensified calcification of aortic valve leaflets from greater serum concentrations of Lp(a) (Rogers and Aikawa, 2015). More specifically, the proposed mechanism suggests that Lp(a) and valve interstitial cell (VIC)–derived autotaxin may induce valve calcification by upregulating inflammation-induced bone morphogenetic protein (BMP) (Bouchareb et al, 2015). Moreover, studies have shown large scale confirmation of the association between two Lp(a) variants and aortic stenosis – and in fact, risk of aortic stenosis may be pro-

portional to one's specific lipoprotein allelic profile (Chen et al, 2018). Further characterization of the role and mechanism of Lp(a) in aortic stenosis is needed, particularly in CKD patients, especially given new data that suggest there is an increase incidence of aortic stenosis with declining renal function (Vavilis et al., 2019).

3. Current and Novel Anti-Hyperlipidemic Therapies and their Role in CKD

3.1 HMG-CoA Reductase Inhibitors

Statins are efficient lipid lowering agents that have proven mortality benefit in patients with cardiovascular disease. Their mechanism of action is complex, but most notably revolves around inhibition of HMG-CoA reductase. HMG-CoA reductase converts HMG-CoA into mevalonic acid, a cholesterol precursor, in hepatocytes. Statins not only competitively inhibit the HMG-CoA reductase molecule – they alter the entire protein configuration upon binding (Corsini et al, 1999). Inhibition of HMG-CoA reductase causes a subsequent decrease in mevalonic acid and total intracellular cholesterol. The reduction of cholesterol in hepatocytes causes an increase in LDL receptor production, which allows for greater evulsion of circulating LDL and its precursors (Sehayek et al., 1994).

Several major studies have demonstrated positive cardiovascular outcomes in CKD patients on statin therapy. Published in 2011, the Study of Heart and Renal Protection (SHARP) trial included over 9438 patients across stages of CKD (approximately 3000 of whom were ESRD on dialysis) and followed LDL levels in patients randomized to placebo versus simvastatin plus ezetimibe. Treatment in the ezetimibe plus simvastatin group was associated with reduced LDL cholesterol by an average of 33 mg/dL over about 5 years, with a 17% reduction in major atherosclerotic events (myocardial infarction, coronary death, coronary revascularization, and ischemic stroke) compared to placebo. SHARP did not have sufficient power to assess specific effects on major atherosclerotic events between dialysis and non-dialysis CKD patients (Sharp, 2010). The Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis (4D) trial was a prospective study of 1255 type 2 diabetic patients on dialysis, and revealed that atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction, or stroke (Wanner et al., 2005). Similarly, the Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis (AURORA) trial showed that initiation of rosuvastatin in dialysis patients lowered LDL cholesterol, but did not have a statistically significant effect on the composite primary end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (Fellstrom et al., 2009). Overall, the data for statin use in CKD patients – especially ESRD – remain contentious. A meta-analysis of nearly 50 studies of statin use in CKD demonstrated that patients with CKD (pre-dialysis, dialysis, and transplant) on statin therapy experienced reduced cardiovascular events and mortality (Strippoli et al., 2008), and the magnitude of cardiovascular benefit approximates that of statin treatment in other populations (Pedersen et al, 1994; Strippoli et al., 2008). Additional high powered randomized control studies are required to definitively elucidate the role of anti-hyperlipidemic therapy in CKD.

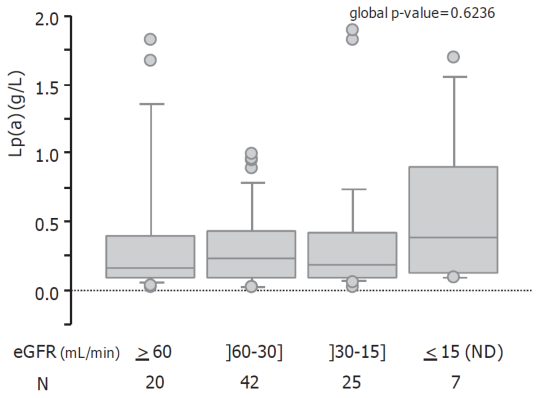

Figure 2. Lp(a) Levels Across CKD

Various studies have explored the progression of albuminuria and GFR with statin therapy in CKD patients. The Effects of Add-on Fluvastatin Therapy in Patients with Chronic Proteinuric Nephropathy on Dual Renin-Angiotensin System Blockade (ESPLANADE) trial showed that in patients with residual proteinuria ($\geq$ 500 mg/day) on appropriate angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blockade (ARB) therapy, addition of fluvastatin did not reduce proteinuria (Ruggenenti et al., 2010). Similarly, the Effects of Fosinopril and Pravastatin on Cardiovascular Events in Subjects With Microalbuminuria (PREVEND-IT) trial determined that in baseline microalbuminuric (between 15-300 mg/day) patients, treatment with pravastatin had no significant reduction in albuminuria at four-year follow up (Asselbergs et al., 2004). Both of these large scale, randomized control trials showed no significant improvement in albuminuria in CKD patients on appropriate medical treatment (ACE-inhibitors, ARB) and optimized blood pressure control. The role of statins in preservation of GFR has also been studied. A secondary analysis of PREVEND-IT found no change in GFR in placebo versus pravastatin treated arm (Atthobari et al., 2006). A post hoc analysis of SHARP also revealed no significant difference in doubling of serum creatinine or risk of ESRD in the statin/ezetimibe treatment group versus placebo (Haynes et al., 2014). The Japanese Assessment of Clinical Usefulness in CKD Patients with Atorvastatin (ASUCA) trial showed no difference in the rate of progression of CKD between patients randomized to atorvastatin or non-statin lipid-lowering treatment (Kimura, 2017). Overarchingly, the bulk of evidence suggests that statins do not significantly decrease the rate of progression of renal dysfunction (Atthobari et al., 2006; Haynes et al., 2014; Navaneethan et al., 2009; Rahman et al., 2008). However, this is not to say statins have no role in renal protection; multiple observational and randomized trials have found that statin therapy may protect against contrast induced nephropathy (Ball and McCullough, 2014; McCullough et al., 2016).

Per KDIGO guidelines, the primary rationale for statin therapy is to reduce mortality from atherosclerosis (KDIGO, 2013), as most recent trials show no evidence that treatment of dyslipidemia improves renal outcomes (Baigent et al., 2011). KDIGO recommendations for statin initiation in adults 18-49 years old with CKD (not on hemodialysis or post transplantation status) are pri-

marily aimed at patients with cardiovascular risk factors including: known coronary disease (myocardial infarction or coronary revascularization), diabetes mellitus, prior ischemic stroke, or estimated 10-year incidence of coronary death/nonfatal MI of $\geq$ 10% based on the Framingham risk score (KDIGO, 2013). The risks and benefits of statins should be addressed prior to initiation, as statins are not without side effects. Side effects include statin-associated muscle symptoms (SAMS), diabetes mellitus (DM), central nervous system complaints, rhabdomyolysis, and rarely statin-induced necrotizing autoimmune myopathy (SINAM) (Thompson et al., 2016). Moreover, statin therapy should not be initiated in chronic hemodialysis patients (Fellstrom et al., 2009; KDIGO, 2013; Wanner et al., 2005), however it can be continued in patients already on therapy at time of dialysis initiation (KDIGO, 2013). Ultimately, initiation of statins in CKD patients should be contingent upon atherosclerotic disease risk factors, as there is insufficient evidence to recommend statin therapy for renal protection alone (Verdoodt et al., 2018).

3.2 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

PCSK9 is a serine protease, coded on chromosome one, that reduces both hepatic and extra-hepatic LDL receptor levels (Schmidt et al., 2008). Upon binding PCSK9, LDL receptors on the cell membrane are targeted for lysosomal degradation. The loss of LDL receptors from the hepatocyte surface prevents extraction of systemic LDL. At present, there are two approved human monoclonal antibodies against PCSK9– alirocumab and evolocumab – that bind to PCSK in 1:1 fashion. Upon binding to PCSK9, the molecule is degraded and unable to bind to LDL receptors. The net result is an increase in LDL receptors, most remarkably on the hepatocyte surface, allowing for more efficient removal of circulating LDL molecules (Rosenson et al., 2018). Moreover, serum levels of atherogenic Lp(a) particles are reduced up to 30% (in a dose dependent fashion) in patients treated with PCSK9 inhibitors (Sahebkar and Watts, 2013). The mechanism of Lp(a) reduction seen in patients on PCSK9 inhibitor treatment described above remains unclear (Hoover-Plow and Huang, 2013; Kotani and Banach, 2017), but may be mediated by the LDL receptor (Soutar and Naoumova, 2007). (Though contentious, there is evidence that LDL receptors may have a role in Lp(a) catabolism (Kolski and Tsimikas, 2012)).

Most trials thus far involving PCSK9 inhibitors have revolved around exploration of cardiovascular outcomes. The Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome (ODYSSEY OUTCOMES) multicenter control trial randomized more than 18,000 patients to use of alirocumab, versus a placebo control group taking maximum tolerated statin, after an acute coronary syndrome (ACS) event. The composite endpoint of nonfatal MI, ischemic stroke, unstable angina and cardiovascular disease-specific mortality occurred in 9.5% of the patients on alirocumab and 11.1% of those on placebo (p = 0.0003), after a median follow up of 34 months (Szarek et al., 2018). The Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events (ODYSSEY LONG TERM) trial revealed, over a period of 78 weeks, a 62% drop in LDL levels when alirocumab was added to maximum tolerated levels of statin therapy – with no significant increase in adverse events (Robinson et al., 2015). The Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial demonstrated that addition of evolocumab to statin therapy produced lower LDL levels and induced coronary atheroma regression (Nicholls et al., 2016). Finally, the Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease (FOURIER) trial studied evolocumab use in 27,564 patients with known prior atherosclerotic cardiovascular disease (ASCVD), who had LDL level >70mg/dL (or any non-HDL >100) on maximally tolerated statin therapy. Patients on evolocumab in addition to statin experienced a 59% drop in LDL level (to a median 30 mg/dL) compared to placebo. After a median follow up time of 26 months, there was a 1.5% reduction in cardiovascular death, MI, stroke, hospitalization for unstable angina, or revascularization in the evolocumab treated group. Moreover, aside from injection-site reactions seen in 2% of participants, PCSK9 inhibitor therapy was generally well tolerated, with no major increase in adverse events including neurocognitive events, creatinine kinase/aminotransferase elevation, allergic reaction, rhabdomyolysis, or new-onset diabetes (Sabatine et al., 2017).

At present, the cardiovascular literature is the only source that offers guidelines for PCSK9 inhibitor use, as major trials of PCSK9 inhibitors have targeted the high risk cardiovascular population (McCullough et al., 2018). In brief, the American College of Cardiology (ACC) recommends consideration of PCSK9 inhibitor addition (to maximally tolerated statin and ezetimibe) in high-risk ASCVD patients whose LDL level remains $\geq$ 70 mg/dl. The ACC also recommends consideration of PCSK9 inhibitors for patients with severe primary hypercholesterolemia (LDL level $\geq$ 190 mg/dl), if LDL level remains greater than 100 mg/dL on maximally tolerated statin and ezetimibe (Grundy et al., 2018). PCSK9 physiology in CKD requires further exploration, and there is evidence that PCSK9 plasma concentrations do not correlate with GFR (Morena et al., 2017; Rogacev et al., 2016), but are elevated in protein wasting conditions (such as nephrotic syndrome or peritoneal dialysis) (Jin et al., 2014). However, a preliminary abstract generated from a post hoc analysis of FOURIER suggests that PCSK9 inhibitors may in fact offer cardiovascular benefit across CKD stages. The analysis reviewed cardiovascular outcomes in relation to baseline calculated GFR using the CKD-EPI equation. 8077 patients had GFR $\geq$ 90 mL/min/1.73 m^2, 15,034 stage 2 CKD, and 4443 $\geq$ stage 3 CKD, with age and comorbidity prevalence increasing with worsening CKD. Analysis revealed that LDL reduction at 48 weeks was similar between placebo vs. evolocumab across CKD groups. However, in the placebo arm, rates of the primary endpoint (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) were higher with worsening CKD (Charytan et al, 2018). While these are promising results, the exact role of PCSK9 and its pharmacologic inhibitor in the CKD population remains unclear (Mafham and Haynes, 2018); rigorous study will be required before its importance in cardiac and renal physiology is understood.

Table 1. Published Studies Measuring Lp(a) Levels Across Stages of CKD

Source	Patient Population	Number of Patients	Lp(a) levels vs GFR Findings		Association between Lp(a) levels and GFR observed
Lin et al. (2015)	Type 2 diabetic patients without clinical CV disease or pre-existing CKD	400 (196 men, 204 women)	Each two-fold higher plasma Lp(a) level was associated with an additional decline in eGFR by 0.50 mL/min/year when adjusting for Age, gender, race, baseline SCr, BMI, hypertension, lipid-lowering medications, smoking, alcohol use, hemoglobin A1c, and urinary ACR ($p < 0.001$)		Yes
Rahman et al. (2014)	CKD patients 21 to 74 years old	3939	GFR in mL/min/1.73 m^2 < 30 30 - < 40 40 - < 50 50 - < 60 > 60	Lp(a) in mg/dL - median (range) 31.3 (12-69) 26.45 (9-63) 23.35 (8-64) 23 (8-53) 18.3 (7-46)	Yes
Uhlig et al. (2005)	CKD patients who participated in the Modification of Diet in Renal Disease (MDRD) study.	804 (485 men, 319 women)	GFR in mL/min/1.73 m^2 13-19 19-26 26-32 32-39 39-46 46-55	Lp(a) in nmol/L* (mean 95% CI interval) 26.4 (23.3-29.9) 24.7 (21.7-28.1) 26.7 (23.5-30.3) 24.7 (21.8-28.0) 27.7 (24.4-31.5) 25.9 (22.9-29.3)	No *adjusted for age, sex, race, molecular weight of smaller apo(a) isoform, proteinuria, CRP level, triglyceride level.
Parsons et al. (2002)	Pre-existing CKD (plasma Cr level, 1.08 to 11.68 mg/dL) not on dialysis	197 (144 men, 53 women)	GFR in mL/min/1.73 m^2 < 10 10-20 20-30 30-45 45-75 Controls	Lp(a) in mg/dL - median (range) 38.6 (0.6-156.0) 30.3 (2.6-163.7) 26.1 (0.0-163.7) 20.8 (0.0-99.8) 16.8 (2.1-81) 12.5 (0.0-88.7)	Yes
Kronenberg (2014)	CKD patients (serum Cr 2.02 +/− 1.16)	227 (154 men, 73 women)	GFR in ml/min per 1.73 m^2 < 45 45-90 > 90	Lp(a) in mg/dL - mean +/− SD [median] 35.7 +/− 33.6 [24.3] 29.3 +/− 30.4 [17.4] 22.8 +/− 30.8 [9.7]	Yes
Sechi et al. (1999)	Patients with established hypertension	250 (122 men, 118 women)	Lp (a) 15.6 +/− 16.4 mg/dL ($N = 153$) in patients with CrCl $\geq$ 90 ml/min/1.73m^2 Lp (a) 21.7 +/− 23.9 mg/dL ($N = 97$) in patients with CrCl between 30-89 ml/min/1.73 m^2		Yes (confirmed by frequency distribution graph in Fig 1 or original manuscript)

Table 2. Summary of Hyperlipidemic Treatment Options

Drug Class	Medications	Mechanism of Action	Indication	Recommended in CKD for prevention of ASCVD
ASO against Apo(a)	ISIS-APO(a)RX (not commercially available)	ASO against Apo(a), major structural apoprotein of Lp(a). Causes downstream decrease in circulating Lp(a) levels. In clinical trials, regardless of baseline Lp(A) levels, a dose dependent mean Lp(a) reduction of 78% with maximal reduction of 92% at highest doses was noted.	Currently being investigated in humans, no clear indications at present	Novel agent, limited studies in CKD patients
ASO against Apo B	mipomersen	ASO to coding region for Apo B. Causes substantial decrease in circulating LDL levels.	Homozygous familial hypercholesterolemia: adjunct option after optimizing medical therapy (these include maximal tolerated dose of statin, niacin, bile acid sequestrants, ezetimibe, and PCSK9 inhibitors)	For use in homozygous familial hypercholesterolemia, not approved for primary prevention -- limited data in CKD patients
ATP citrate lyase inhibitor	bempendoic acid	Lowers LDL cholesterol level by inhibiting ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway that acts upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (target for statins)	No recommendation per 2018 ACC/AHA guidelines. However, recent study suggests bempendoic acid added to maximally tolerated statin therapy led to significantly lower LDL cholesterol levels (without higher incidence of overall adverse events compared to placebo)	Novel agent, currently under study in CKD patients
Bile Acid Sequestrant	cholestyramine, colestipol, colesevelam	Interrupts enterohepatic circulation of bile acids, causing increased synthesis of bile acids. Increased metabolism of cholesterol to bile acids causes an enhanced demand for cholesterol, as reflected by increased expression of LDL receptors. Increase in LDL receptors allows for greater extraction of circulating LDL. (Tsimikas, 2017)	Adjunct therapy: in patients with very severe hypercholesterolemia, adding sequestrants to otherwise maximal cholesterol-lowering therapy in patients who are not eligible for a PCSK9 inhibitor can be considered.	No recommendations per 2013 KDIGO guidelines
Cholesterol absorption inhibitors	ezetimibe	Limits intestinal cholesterol absorption	2^{nd} line agent to be used with maximum tolerated statin to achieve target LDL goal	Yes, recommended to be used with statin therapy if necessary to achieve target LDL
Eicosapentaenoic acid	icosapent ethyl	Omega-3 fatty acid with a 96% pure ethyl ester of eicosapentaenoic acid. Mechanism similar to Omega-3 fatty acids, namely increased triglyceride metabolism through increase in lipoprotein lipase.	No recommendation per 2018 ACC/AHA guidelines	Novel agent, limited studies in CKD patients

Table 2. Summary of Hyperlipidemic Treatment Options (cont.)

Drug Class	Medications	Mechanism of Action	Indication	Recommended in CKD for prevention of ASCVD
Fibric acid derivatives	fenofibrate, gemfibrozil	PPAR-α agonist, PPAR-α activation initiates a cellular cascade eventually upregulating lipoprotein lipase, ultimately allowing for more efficient catabolism of VLDL and triglycerides	Adjunct therapy: may mildly lower LDL levels in patients with normal triglycerides. May be useful in some patients with severe hypertriglyceridemia.	Fibrates are not recommended to prevent or reduce cardiovascular risk in adults with CKD and hypertriglyceridemia
MTP inhibitor	lomitapide	Inhibitor of MTP, a critical transport protein required for movement of lipid from the endoplasmic reticulum to apoproteins. Stagnates formation of chylomicrons and VLDL by the liver.	Homozygous familial hypercholesterolemia: adjunct option after optimizing medical therapy (these include maximal tolerated dose of statin, niacin, bile acid sequestrants, ezetimibe, and PCSK9 inhibitors)	For use in homozygous familial hypercholesterolemia, not approved for primary prevention -- limited data in CKD patients
Nicotinic Acid	niacin	Inhibits triglyceride synthesis resulting in accelerated intracellular hepatic apo B degradation and decreased secretion of VLDL/LDL particles. (Tsimikas, 2016)	Adjunct therapy: may mildly lower LDL levels in patients with normal triglycerides. May be useful in some patients with severe hypertriglyceridemia.	Nicotinic acid has not been well studied in advanced CKD and therefore is not recommended for treatment of severe hypertriglyceridemia
Omega-3 Fatty Acids	fish oil, dietary supplements	Complex mechanism involving multiple intracellular pathways. One of the mechanisms for triglyceride reduction includes increased lipolysis by lipoprotein lipase.	Recommended for use in patients with severe hypertriglyceridemia (along with lifestyle changes, avoidance of alcohol/carbohydrates, etc.)	No recommendations per 2013 KDIGO guidelines
PCSK9 Inhibitors	alirocumab, evolocumab	Prevents hepatocyte LDL receptor recycling through inhibition of PCSK9, optimizing removal of circulating LDL	3rd line agent to be used as adjunct therapy in high risk ASCVD patients who have not achieved target LDL level on maximum tolerated statin and ezetimibe	Role of PCSK9 in CKD is area of heavy interest and is being evaluated
Statins	atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	HMG CoA reductase inhibition allows for increased production of hepatocyte LDL receptors, optimizing removal of circulating LDL	1st line therapy for LDL lowering, used for primary and secondary prevention of ASCVD	Yes, in select patient groups. Recommended not to initiate statin therapy for patients on hemodialysis

3.3 Antisense apo(a) targeted therapy and other lipid lowering agents

Lp(a) offers a promising therapeutic target for dyslipidemia and atherosclerosis, especially in CKD patients. There are numerous agents clinically available that have been shown to decrease Lp(a) levels including LDL apheresis (acutely 60–80%, time-averaged 30–35%), niacin (20-30%), mipomersen (20-40%), IL-6 antagonists (30%), and PCSK9 inhibitors (20-40%) (Tsimikas, 2016). Of special interest is a specific antisense oligonucleotide (ASO) directed against Apo(a), the major structural apoprotein of Lp(a). Early studies using ASO against Apo(a) in Lp(a)-transgenic mice revealed that ASO significantly lowered Lp(a) levels (Merki et al., 2011). This led to the formation of the human ASO, ISIS-APO(a)RX, which binds to the exon 24–25 splice site of the mature human Apo(a) transcript (Merki et al., 2011). ISIS-APO(a)Rx was evaluated in humans and revealed a dose dependent mean Lp(a) reduction of 78% with a maximal reduction of 92% at highest doses, regardless of baseline Lp(A) levels (Fig. 3) (Tsimikas, 2017; Tsimikas et al, 2015). While still under investigation, ASO present a powerful therapeutic strategy for patients with dyslipidemia, but their role in the CKD population has yet to be defined.

There are several other noteworthy anti-hyperlipidemic therapies that should be mentioned. Lomitapide is an inhibitor of MTP, which as discussed above is a critical transport protein required for movement of lipid from the endoplasmic reticulum to apoproteins. By inhibiting MTP, formulation of chylomicrons and VLDL by the liver is stagnated. The most common side effect is gastrointestinal symptoms, namely diarrhea. Lomitapide was approved in 2012 by the United States Food and Drug Administration for treatment of homozygous familial hypercholesterolemia (FH) (Perry, 2013). Mipomersen, an ASO complementary to the coding region for Apo B, has also been approved for treatment of homozygous FH. The use of lomitapide and mipomersen is generally aimed at homozygous FH patients whose LDL levels did not respond to optimal medical therapy (Raal et al, 2010). While these agents have offered major benefit in LDL reduction, for now, their treatment role is limited to patients with homozygous FH. There is limited evidence supporting their use as a primary prevention tool for cardiovascular events, and even less data on their usage in CKD patients. The use of ezetimibe, an intestinal cholesterol absorption inhibitor, is recommended by the ACC as an adjunct therapy in patients with clinical ASCVD who are already taking statins for secondary prevention and have an LDL of 70–189 mg/dL (Grundy et al., 2018). Ezetimibe can safely be given to patients with CKD, and as shown in the SHARP trial, when taken with a statin clearly has cardiovascular risk lowering benefit (Baigent et al., 2011). Fibrates are activators of peroxisome proliferator-activated receptor alpha (PPAR-α), and through catabolism of triglyceride-rich particles and reduced secretion of VLDL they decrease serum triglyceride levels (Staels et al., 1998). Fibrates have been shown to improve cardiovascular outcomes, as well as reduce albuminuria and protect GFR in CKD patients (Jun, et al, 2014). Omega-3 fatty acids have well known triglyceride lowering effects, regardless of baseline levels (Phillipson et al., 1985); the mechanism of this decrease remains elusive, but involves increased lipolysis through lipoprotein lipase (Shearer et al., 2012). Multiple studies in hemodialysis patients have shown Omega-3 supplementation dramatically reduced triglycerides but had mixed effects on other lipoproteins (Friedman and Moe, 2006). Cholesteryl ester transfer protein (CETP) mediates bidirectional transfer of cholesterol esters and triglycerides between plasma lipoproteins. Inhibition of CETP increases serum concentration of HDL cholesterol and decreases the concentration of VLDL and LDL cholesterol. As such, CETP inhibition via monoclonal antibodies, vaccines, and antisense oligonucleotides remains of major clinical interest (Shrestha et al., 2018). There are numerous emerging therapies including icosapent-etyhl (Bhatt et al, 2017), bempedoic acid (Pinkosky et al., 2016; Ray et al, 2019), Apo C-III (a key regulator in hypertriglyceridemia) inhibition (Rocha et al., 2017) and novel cellular binding proteins (Maqbool et al., 2015), that are being studied as tailored tools to combat dyslipidemia–their effect in the CKD population has yet to be determined. A brief summary of hyperlipidemic treatment options (including a few therapies not mentioned above) is provided in Table. 2 (Einarsson et al., 1991; Fares et al., 2014; Grundy et al., 2018; Kamanna and Kashyap, 2008; KDIGO, 2013; Ray et al, 2019; Shearer et al., 2012).

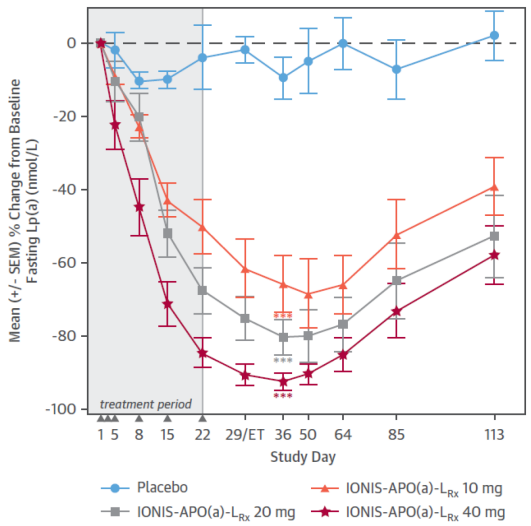

Figure 3. Dose Dependent Mean Lp(a) Reduction with ISIS-APO(a)Rx

4. Summary and future directions

Increased cardiovascular morbidity and mortality in CKD patients have been well described in the literature. Pathophysiological changes associated with lipid metabolism due to CKD have been well characterized and are discussed broadly above. Overarchingly, CKD causes 1) formation of more lipid dense cholesterol molecules, 2) increased circulating atherogenic lipoproteins (including Lp(a)) through reduced clearance), 3) decreased lipoprotein lipase activity, and 4) impaired reverse cholesterol transport. Statins are able to reduce cholesterol synthesis and as a result, increase LDL receptor expression in the hepatocyte, optimizing extraction of circulating LDL. Their role in conjunction with ezetimibe in non-hemodialysis dependent CKD patients is supported by clinical trials and meta-analyses. There is evidence that statins may reduce the risk of contrast induced nephropathy, yet this does

not appear to attenuate the progression of CKD.

There are numerous areas of future interest in terms of dyslipidemia in the CKD population. Further characterization of the role and function of Lp(a), as well as its mechanism of increase in CKD patients is critical. Will PCSK9 inhibitors and anti-sense oligonucleotides directed against Lp(a) mRNA have the same or greater cardiovascular benefits in CKD patients, and is this mediated by a reduction in Lp(a) concentrations? While it is clear that statins do not have a role in renal protection, are PCSK9 inhibitors able to avert progression of renal failure through an alternate mechanism? Through better understanding the process of dyslipidemia and atherogenesis in the CKD population – as well as our various hyperlipidemic treatment options – we may more effectively optimize our patients' cardiovascular and perhaps even renal dysfunction risk.

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Conflict of interest

The authors declare that there is no conflict of interest.

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