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Internal Medicine Section

Novel Lipid Indices and Lipoprotein(a) in Cardiovascular Risk Stratification for Chronic Kidney Disease: A Narrative Review

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ABSTRACT

Chronic Kidney Disease (CKD) is a major and growing global health challenge affecting millions of individuals worldwide. Cardiovascular Disease (CVD) remains the leading cause of morbidity and mortality in patients with CKD, with atherosclerotic CVD contributing substantially to adverse outcomes. Traditional lipid parameters often fail to adequately capture the complex dyslipidaemia associated with CKD, resulting in underestimation of cardiovascular risk. In addition to elevated Triglycerides (TG) and reduced High-Density Lipoprotein Cholesterol (HDL-C), patients with CKD frequently exhibit increased levels of Lipoprotein(a) {Lp(a)}, an established independent risk factor for atherosclerosis and thrombosis. In recent years, several novel lipid indices derived from conventional lipid parameters and Lp(a) have emerged as potentially superior markers of atherogenic risk. These include the Atherogenic Index of Plasma (AIP), Castelli Risk Indices (CRI), Atherogenic Coefficient (AC), and Lipid Tetrad Index (LTI). Unlike isolated lipid measurements, these composite indices provide a more comprehensive assessment of the balance between atherogenic and protective lipoproteins and may better reflect the unique lipid abnormalities seen in CKD. Although growing evidence suggests that these indices are associated with cardiovascular risk and disease progression in CKD, the available literature remains fragmented, and their clinical utility has not been comprehensively synthesised. The novelty of the present review lies in its integrated evaluation of both Lp(a) and emerging lipid indices as cardiovascular risk assessment tools in CKD. By consolidating current evidence, highlighting pathophysiological links, and identifying existing research gaps, the present review aimed to provide a contemporary perspective on their potential role in improving cardiovascular risk stratification and guiding future research in CKD populations.

Keywords: Atherogenic coefficient, Biomarkers, Dyslipidaemias, Risk assessment

INTRODUCTION

The CKD affects a substantial and growing fraction of the global population. Recent study showed CKD affects nearly 10% of global population [1]. CKD has rapidly risen in rank as a cause of death: in 2023 it was the 9th leading global cause of mortality, with roughly 1.5 million deaths [2]. India alone contributes the second-highest global burden of CKD, with an estimated ~138 million cases (urban and rural combined) and CKD was already among India's top 10 causes of death by 2019 [3]. Much of the CKD burden is driven by diabetes and hypertension, now endemic in South Asia.

Importantly, CVD is the primary cause of death in CKD patients. Even early-stage CKD dramatically magnifies CV risk: CKD is considered by many experts a "risk equivalent" for atherosclerotic disease [4]. Impaired kidney function appears to contribute roughly 10-12% of global cardiovascular deaths [5]. In CKD the cardiovascular mortality rate far exceeds that of progression to End-Stage Renal Disease (ESRD) [6]. Thus, identifying modifiable risk factors for atherosclerosis in CKD is a clinical priority.

Dyslipidaemia is a well-recognised, modifiable CVD risk factor, and CKD patients exhibit characteristic lipid abnormalities [7]. However, CKD dyslipidaemia differs from the typical hypercholesterolaemia of the general population. Whereas "traditional" risk factors like diabetes, hypertension, and smoking are prevalent in CKD, CKD itself induces a unique pro-atherogenic lipid profile. Serum TG tend to be elevated, HDL-C low, and Low-Density Lipoprotein Cholesterol (LDL-C) often normal or even low. Moreover, CKD alters lipoprotein particle composition and function in ways not captured by standard lipid panels [8]. Contributing mechanisms include reduced activity of lipoprotein lipase and hepatic lipase, decreased LDL receptor function, increased TG-rich lipoprotein remnants, and dysfunctional HDL (due to low lecithin-cholesterol acyltransferase activity and high Cholesteryl Ester Transfer Protein (CETP) activity) [8]. Uraemia-associated inflammation and oxidative stress further exacerbate endothelial dysfunction and atherogenesis.

The Lp(a), is another critical lipid-related factor. Lp(a) consists of an LDL-like particle covalently linked to Apolipoprotein(a) {Apo(a)}. It has both pro-atherogenic and pro-thrombotic properties due to its structural homology with plasminogen and tendency to carry oxidised phospholipids. In the general population, elevated Lp(a) is an independent genetic risk factor for coronary and cerebrovascular disease. CKD patients often have increased Lp(a) levels: the kidney plays a role in Lp(a) clearance, so impaired renal function or heavy proteinuria (e.g., nephrotic syndrome) leads to Lp(a) accumulation [8,9]. High Lp(a) in CKD correlates with accelerated atherosclerosis.

Recognising the limitations of isolated lipid measurements, recent studies have focused on composite lipid indices such as the AIP, CRI-I and CRI-II, AC, and LTI, which integrate multiple lipid parameters and may better reflect the overall atherogenic milieu and cardiovascular risk in patients with CKD.

Pathophysiology of Dyslipidaemia in CKD

Through a variety of processes, CKD causes intricate changes in lipoprotein metabolism. Low HDL-C and hypertriglyceridaemia are common even in the mild to moderate phases of CKD [10]. These abnormalities worsen as CKD advances; in stages 4-5, more than two-thirds of patients satisfy the criteria for dyslipidaemia [10]. Most haemodialysis patients have significant dyslipidaemia.

Hepatic LDL receptor downregulation increased hepatic Very-Low-Density Lipoprotein (VLDL) production, and decreased activity of lipoprotein lipase and hepatic TG lipase (caused by uraemic toxins) are among the underlying reasons. In particular, TG-rich lipoproteins accumulate and are removed more slowly. HDL particles become smaller and dysfunctional due to alterations in enzymes {low Lecithin-Cholesterol Acyltransferase (LCAT) and high CETP activity} and the loss of antioxidant proteins. Additionally, smaller, denser LDL particles-which are very atherogenic-are becoming more prevalent in CKD [10].

Beyond these lipid abnormalities, CKD creates a pro-inflammatory and pro-oxidative environment that accelerates atherosclerosis. Chronic inflammation, characterised by elevated circulating cytokines and impaired nitric oxide bioavailability, together with oxidative stress, contributes to endothelial dysfunction, vascular injury, and plaque formation [11,12]. The accumulation of uraemic toxins such as indoxyl sulphate, p-cresyl sulphate, and advanced glycation end products further exacerbates oxidative stress, promotes vascular inflammation, and impairs endothelial function. Additionally, disturbances in mineral metabolism and persistent uraemia enhance vascular calcification and atherogenesis. In advanced CKD, particularly among dialysis patients, the cardiovascular benefits of statin therapy are often attenuated, possibly because non lipid factors-including chronic inflammation, oxidative stress, uraemic toxin accumulation, and advanced glycation of lipoproteins-play a dominant role in disease progression [10].

While the cardiovascular consequences of CKD-associated dyslipidaemia are well recognised, accumulating evidence suggests that lipid abnormalities also contribute directly to the progression of kidney disease itself [7,10]. Thus, dyslipidaemia in CKD should be viewed not only as a cardiovascular risk factor but also as a potential mediator of ongoing renal injury.

The CKD-related dyslipidaemia may accelerate kidney disease progression through lipid-mediated cellular damage. Lipid overload within the kidney can induce podocyte injury and tubular dysfunction. Excess lipid droplets accumulate in glomerular and tubular epithelial cells, activating inflammatory and profibrotic pathways involving Tumour Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Transforming Growth Factor-beta (TGF-β), thereby promoting glomerulosclerosis and tubulointerstitial fibrosis. Furthermore, oxidised LDL and modified lipoproteins, particularly carbamylated apolipoprotein B-containing particles, can directly injure renal endothelial cells and exacerbate oxidative stress and inflammation. These processes establish a vicious cycle in which declining kidney function worsens dyslipidaemia, while dyslipidaemia further accelerates renal damage, linking cardiovascular and renal pathology in CKD [7,13].

Overall, CKD-associated dyslipidaemia is characterised by [10]: (1) hypertriglyceridaemia resulting from impaired clearance of TG-rich lipoproteins; (2) reduced HDL-C levels due to defective HDL maturation and impaired reverse cholesterol transport; (3) normal or reduced LDL-C concentrations despite an increased predominance of small, dense, and oxidised LDL particles; and (4) elevated Lp(a) levels, particularly in patients with nephrotic-range proteinuria and impaired renal clearance. In addition, CKD promotes carbamylation of apolipoprotein B-containing lipoproteins through exposure to elevated urea-derived cyanate. Carbamylated LDL exhibits enhanced atherogenicity, increased vascular retention, impaired receptor-mediated clearance, and greater propensity to induce endothelial dysfunction and inflammation [14]. This relatively novel mechanism may contribute substantially to the excess cardiovascular risk observed in CKD despite apparently normal LDL-C levels. Together, inflammation, oxidative stress, and lipoprotein modifications such as oxidation and carbamylation further accelerate atherosclerosis in patients with CKD.

Lipoprotein(a) in CKD

The Lp(a) is an LDL-like lipoprotein distinguished by its unique protein component, apo(a), which is covalently bound to apoB. Apo(a) contains multiple Kringle IV repeats, conferring structural similarity to plasminogen. High Lp(a) levels are strongly genetically determined and are an established causal risk factor for atherosclerotic CVD and calcific aortic valve disease. Lp(a) promotes atherosclerosis via several mechanisms: it carries oxidised phospholipids, stimulates vascular inflammation, impairs fibrinolysis (through apo(a)'s plasminogen mimicry), and may accelerate thrombosis [14].

In CKD, Lp(a) dynamics are altered. The kidney appears to participate in Lp(a) catabolism, so impaired renal function tends to raise circulating Lp(a) levels [9]. Literature has revealed that patients with untreated CKD have markedly higher median Lp(a) than controls [9,10,14], and that dialysis modality influences levels (peritoneal dialysis often results in higher Lp(a) than haemodialysis) [8,14,15]. In addition, heavy proteinuria (as in nephrotic syndrome or peritoneal dialysis) leads to an "acute-phase" type hepatic overproduction of Lp(a), regardless of Apo(a) isoform size [9]. Notably, successful kidney transplantation or remission of proteinuria typically reduces Lp(a) levels, underscoring the kidney's role [9].

Clinically, elevated Lp(a) in CKD is concerning because it may partly explain the high CVD burden. Although large prospective CKD trials are lacking, observational data link high Lp(a) in kidney patients with more atherosclerosis. Elevated Lp(a) concentrations have been associated with markers of subclinical atherosclerosis, including increased carotid intima-media thickness and greater cardiovascular event risk in patients with CKD, although the strength of evidence varies across studies [16]. The excess atherogenicity of Lp(a) is thought to be independent of traditional lipids, so CKD patients with high-normal LDL-C but elevated Lp(a) may be under-recognised as high-risk. Recent reviews note that CKD patients with large apo(a) isoforms are particularly prone to Lp(a) accumulation [9].

Novel Lipid Indices

Several composite lipid indices have been introduced to quantify atherogenic dyslipidaemia beyond single lipid values. These indices combine standard lipid measures (and in one case, Lp(a)) into ratios or formulae believed to better correlate with atherogenic particle burden. Each is described below:

1. Atherogenic Index of Plasma (AIP)

Definition: AIP is defined as the logarithm of the ratio of serum TGs to HDL-C {log(TG/HDL-C)} [17,18].

Clinical significance: AIP is intended to reflect the balance between atherogenic lipoproteins, including TG-rich VLDL and small dense LDL, and protective HDL-C. Elevated AIP corresponds to high TG and low HDL-C levels, characteristic of an atherogenic lipoprotein phenotype. Previous studies have demonstrated that AIP correlates with the prevalence of small dense LDL particles and insulin resistance [19]. Furthermore, meta-analyses conducted in metabolic syndrome and general population cohorts have reported that AIP possesses good predictive ability for cardiometabolic risk [18]. However, these findings originate largely from non CKD populations and therefore cannot be directly extrapolated to patients with CKD. Although preliminary studies suggest that AIP may be elevated in CKD and could reflect the characteristic dyslipidemic profile of this population, robust CKD-specific prospective data validating its predictive performance for cardiovascular outcomes remain limited [20].

AIP is gaining acceptance as a simple prognostic index: for example, systematic reviews find significantly higher AIP in patients with metabolic syndrome and an acceptable predictive accuracy (AUC ~0.86) for that syndrome [18]. In routine practice, AIP can be calculated from a standard fasting lipid profile without extra cost.

Data on AIP in CKD are limited but suggest it may be a useful risk marker. Mannangi NB et al., found that pre-dialysis CKD patients had a significantly higher mean AIP than healthy controls, and that AIP correlated strongly with Lp(a) levels. In their study, AIP emerged as one of the best predictors of atherogenic status in CKD, on par with LTI [17].

2. Castelli Risk Indices I and II (CRI-I, CRI-II)

Definition: CRI-I is the ratio of Total Cholesterol (TC) to HDL-C, while CRI-II is LDL-C/HDL-C [15].

Clinical significance: These ratios are conventional indicators of atherogenic risk and are also referred to as the cardiac risk ratios. A greater ratio of "bad" cholesterol (LDL or total minus HDL) to protective HDL is indicated by a higher CRI-I or CRI-II. They have been used to measure risk in epidemiologic research and clinical practice. For instance, CRI-I is correlated with coronary stenosis and the presence of carotid plaque in general populations. The convenience of employing common lipids is appealing [15].

In CKD cohorts, CRI values tend to be elevated relative to healthy controls. For instance, Mannangi NB et al., reported significantly higher CRI-II (but not CRI-I) in CKD patients versus controls [17]. The AC (below) captures similar information. Overall, while CRI ratios do track with general lipid derangements, they may not add much beyond non HDL or other indices in CKD. Still, some guidelines note them as risk markers, and they may aid risk stratification in resource-limited settings. Their main advantage is they require no additional tests beyond LDL and HDL measurements.

3. Atherogenic Coefficient (AC)

Definition: The AC is defined as (TC-HDL-C)/HDL-C, i.e., the ratio of non HDL cholesterol to HDL-C [21]. It effectively combines all atherogenic cholesterol (LDL+VLDL+IDL remnants) relative to HDL

Clinical significance: AC is another marker of overall atherogenic lipid burden. A higher AC means a larger proportion of cholesterol is carried by non protective particles. It is conceptually similar to non HDL-C measures. Numerous studies have linked elevated AC to metabolic syndrome and cardiovascular risk, sometimes outperforming CRI indices.

There is little information about AC that is unique to CKD. When Mannangi NB et al., (2015) calculated AC, they discovered that there was no significant difference between CKD patients and controls [17]. This might be as a result of AC's mathematical proximity to CRI-I (simply scaled by HDL). AC may not provide independent information beyond AIP and CRI since, in reality, it will track with TG/HDL and LDL/HDL. AC has not been shown to be a reliable predictor of CKD in any long-term research. Its clinical incremental value is yet unknown due to its resemblance to current ratios.

4. Lipid Tetrad Index (LTI)

Definition: The LTI was defined by Enas EA et al., as (TC×TG×Lp(a))÷ HDL-C [22]. This index multiplies three atherogenic factors (TC, TGs, and Lp(a)) and divides by the protective HDL level, yielding a single composite.

Clinical significance: The goal of LTI is to combine many lipid abnormalities into a single measurement. It acknowledges the independent atherogenic effect of Lp(a) in addition to traditional lipids by specifically mentioning it. Theoretically, a "worst-case" lipid profile-higher LTI-reflects concurrent increase of TG, Lp(a), and TC in relation to HDL. LTI may stratify risk beyond simple ratios, according to early research in non CKD populations [17].

The LTI had one of the greatest relationships with Lp and was considerably greater in patients than controls in Mannangi NB et al., CKD study (a) [17]. Given that LTI includes measured Lp(a), this makes sense. LTI will increase if a CKD patient has low HDL and increased TG and Lp(a). Although LTI has not been evaluated prospectively in any big trials, its conceptual significance comes in its ability to capture many dyslipidaemias at once. LTI may identify those with really harmful profiles in CKD, where mixed dyslipidaemia is prevalent. However, its immediate usefulness in ordinary practice is limited since it is more difficult to compute (needs Lp(a) measurement), particularly in situations where Lp(a) is not often measured. However, LTI emphasises how crucial it is to take non LDL lipoproteins into account when assessing CKD risk [23,24].

Comparison with Conventional Lipid Profile

In cardiovascular risk assessment, traditional lipid parameters, including TC, LDL-C, HDL-C, and TG, remain fundamental. However, these measures have important limitations in CKD. Despite markedly elevated cardiovascular risk, many patients with CKD exhibit normal or only mildly elevated LDL-C and TC concentrations [10]. Consequently, alternative markers such as non HDL cholesterol and Apolipoprotein B (ApoB) have been proposed to better capture residual atherogenic risk. Non HDL cholesterol reflects the cholesterol content of all atherogenic lipoproteins, including LDL, VLDLs, intermediate-density lipoproteins, and remnant particles, whereas ApoB directly quantifies the total number of circulating atherogenic lipoprotein particles [25]. Several studies have demonstrated that ApoB and non HDL cholesterol may predict cardiovascular risk more accurately than LDL-C alone, particularly in individuals with hypertriglyceridaemia and mixed dyslipidaemia [20,21]. In CKD, where TG-rich lipoproteins, remnant particles, and small dense LDL particles accumulate despite relatively normal LDL-C levels, ApoB and non HDL cholesterol may provide a more comprehensive assessment of atherogenic burden [25].

Evidence regarding lipid-lowering therapy in CKD further highlights the complexity of cardiovascular risk assessment in this population. The SHARP trial [20] demonstrated that lipid-lowering therapy with simvastatin plus ezetimibe significantly reduced major atherosclerotic events in patients with non-dialysis-dependent CKD and selected dialysis patients, supporting the benefit of lipid lowering in earlier stages of CKD. In contrast, the Four-Dimensional (4D) [26], and An Assessment of Survival and Cardiovascular Events (AURORA) trials [27], failed to demonstrate significant cardiovascular benefit from statin therapy among patients receiving maintenance haemodialysis. These findings suggest that traditional lipid-mediated mechanisms may be more relevant in earlier CKD stages, whereas non traditional risk factors such as inflammation, oxidative stress, vascular calcification, and uraemic toxins may play a larger role in advanced kidney failure. Therefore, conventional lipid targets, such as LDL-C <70 mg/dL, may not fully capture cardiovascular risk in CKD and remain less well established than in the general population [10].

By contrast, lipid ratios and indices can uncover hidden risk. AIP, CRIs, AC and LTI synthesise information from multiple lipids, reflecting the atherogenic environment more holistically. For example, two patients with identical LDL-C could have very different AIP if one has high TG and low HDL; in CKD this scenario is common. Indices may therefore better differentiate those who need aggressive intervention. Importantly, indices usually use the same inputs as the standard panel (TG, HDL, LDL, TC), so they are cost-neutral. This makes them attractive in resource-limited settings: several authors point out that simple indices "may prove a boon" for patient management where advanced tests are unaffordable [17]. In such contexts, indices could help prioritise patients for therapy or referral.

On the other hand, novel indices are not without drawbacks. There are no universally accepted cut-off values for AIP or LTI; suggested thresholds (e.g., AIP >0.1 or >0.24 for moderate/high-risk) come mainly from non-CKD populations [18]. Heterogeneity in patient populations makes it difficult to apply one standard. Also, indices like LTI require Lp(a) measurement, which is not routinely done. Finally, guidelines currently do not incorporate these indices: major CKD guidelines (KDIGO, AHA/ACC) still focus on LDL and traditional risk factors. Thus, while indices have conceptual advantages, their clinical utility awaits further validation. Important studies are discussed in [Table/Fig-1] [13,17,21,28-34].

Author and year	Population	Design	Indices assessed	Main finding relevant to manuscript
Mannangi NB et al., 2015 [17]	India; 30 CKD patients and 30 controls	Case-control	AIP, LTI, CRI-I, CRI-II, AC	AIP, LTI, and CRI-II were significantly higher in CKD than controls; AIP and LTI showed the strongest correlation with Lp(a).
Adejumo OA et al., 2016 [28]	Southern Nigeria; 105 pre-dialysis CKD patients and 105 matched controls	Case-control	AIP with routine lipid profile	Median AIP, LDL-C, and TG were higher and HDL-C lower in CKD; supports AIP elevation in predialysis CKD but without hard outcome validation.
Lee MJ et al., 2017 [33]	Korea; 1,174 incident dialysis patients	Nationwide prospective cohort	AIP	Both the lowest and highest AIP quintiles were associated with higher all-cause mortality; the highest AIP quintile also predicted cardiovascular mortality, indicating a U-shaped rather than purely linear relationship.
Raju DS and Kedari GS, 2022 [13]	India; 45 controls and 135 CKD stage 3-5 patients	Case-control/stage-stratified	AIP	AIP rose progressively with CKD severity, from 0.07 in controls to 0.17 in stage 3, 0.27 in stage 4, and 0.33 in stage 5; LDL-C did not differ significantly across stages.
Kalaivani R et al., 2023 [30]	India; 70 non-dialysis CKD subjects and 70 controls	Analytical case-control	AIP, LTI, AC, CRI-I, CRI-II	AIP and LTI were significantly higher in CKD, while AC and Castelli indices were less discriminatory; authors concluded AIP and LTI were the most suitable indices, with AIP favored because it is cost-neutral and routine-lab based.
Omole OR et al., 2024 [31]	Nigeria; 150 CKD stage 3-5 patients and 50 controls	Cross-sectional case-control	Atherogenic index and LDL/HDL ratio	CKD patients had more atherogenic lipid profiles than controls, and the atherogenic index rose significantly with advancing CKD stage.
Ma L et al., 2024 [21]	China; 350 maintenance haemodialysis patients (451 screened)	Observational cohort	AIP, non HDL-C, non HDL-C/HDL-C, LCI	Higher AIP and other lipid-derived indices predicted Acute Ischemic Stroke (AIS) occurrence and worse stroke outcome in haemodialysis; among the tested lipid-derived markers, AIP had the strongest correlation with AIS risk.
Peng Y et al., 2024 [32]	China; 1,946 adult haemodialysis patients from 20 dialysis centers	Multicentre cross-sectional	AIP	Each 1-unit increase in AIP was associated with a 21% higher odds of intradialytic hypotension; higher AIP quartiles also had progressively higher odds of IDH.
Hu Y et al., 2025 [29]	China; 869 peritoneal dialysis patients from 5 hospitals	Multicentre cohort	AIP	AIP showed a non-linear association with all-cause mortality, with an inflection point around 0.63; this supports threshold/reverse-epidemiology effects rather than a simple monotonic relationship in PD.
Li L et al., 2025 [34]	United States; 4,403 adults with CKD from NHANES	National cohort with mortality follow-up	AIP	Higher AIP independently predicted all-cause mortality (adjusted HR 2.03) and cardiovascular mortality (adjusted SHR 1.60) in established CKD.

[Table/Fig-1]: Review of current literature [13,17,21,28-34].

Clinical Implications

The potential clinical benefits of novel lipid indices in CKD include improved risk stratification and earlier intervention. If AIP or LTI reliably identify patients at highest risk of cardiovascular events, clinicians could target these individuals for intensive management, including aggressive lipid-lowering therapy, lifestyle modification, and closer monitoring. For example, a patient with CKD who has borderline LDL-C but a markedly elevated AIP may warrant more comprehensive cardiovascular evaluation despite apparently normal conventional lipid parameters.

The utility of these indices may be particularly relevant in specific CKD subgroups. In patients with early-stage CKD (stages 1-3), where traditional lipid abnormalities may be less pronounced but cardiovascular risk is already elevated, indices such as AIP and CRI may help identify individuals with residual atherogenic risk who might otherwise be overlooked. Similarly, patients with diabetic CKD, who commonly exhibit hypertriglyceridaemia, low HDL-C, and increased small dense LDL particles, may derive greater benefit from index-based risk assessment than non diabetic CKD patients. In contrast, in advanced CKD and dialysis-dependent populations, where non traditional cardiovascular risk factors such as inflammation, oxidative stress, vascular calcification, and uraemic toxins play a dominant role, the incremental value of lipid indices remains less certain and requires further investigation.

In resource-limited settings such as many parts of India, calculating indices from existing lipid data is practical and inexpensive [17]. This may assist primary care physicians in identifying CKD patients who require referral to nephrology or cardiology services and may facilitate earlier preventive interventions.

Monitoring indices over time may also be useful. AIP and CRIs could potentially track response to lipid-lowering therapy, dietary modification, and lifestyle interventions. Because these indices often improve with reductions in TG levels and increase in HDL-C, they may serve as simple markers of treatment response.

From a guideline perspective, there is currently insufficient evidence to recommend routine index calculation. Nevertheless, KDIGO 2024 recognises CKD as a high cardiovascular risk condition and recommends statin therapy for appropriate patient groups [35]. In the future, incorporation of validated lipid indices into CKD-specific risk prediction models, alongside established parameters such as estimated Glomerular Filtration Rate (eGFR) and albuminuria, may improve cardiovascular risk prediction and help individualise treatment decisions.

An important advantage of these indices is their cost-effectiveness. Unlike ApoB or Lp(a), which require additional laboratory testing and may not be universally available, indices such as AIP and CRI can be derived from routine lipid profiles without extra expense. Consequently, they may represent practical tools for cardiovascular risk assessment in regions with limited healthcare resources and restricted access to advanced cardiovascular imaging.

Future Direction

Future studies must fill these critical gaps. Recent trials of lipoprotein(a)-lowering therapies, including pelacarsen (Lp(a) HORIZON) and olpasiran (OCEAN(a)-DOSE), have demonstrated substantial reductions in circulating Lp(a) levels and may provide new opportunities for cardiovascular risk modification in CKD populations. Further prospective studies are needed to determine whether incorporation of AIP, CRI, AC, LTI, ApoB, and Lp(a) improves prediction of cardiovascular and renal outcomes in CKD [36,37].

Independent of conventional risk variables, longitudinal cohort studies of patients with CKD should evaluate whether lipid indices predict cardiovascular events, progression to ESRD, or death. Clinically, significant cut-offs might be determined by such investigations. Changes in indices should be assessed as intermediate outcomes in randomised trials of lipid-modifying medications (statins, fibrates, PCSK9 inhibitors) in CKD in order to confirm their applicability.

One interesting approach is to include indices into risk prediction algorithms. For instance, AIP or non HDL ratios may be included

in risk algorithms for CKD patients in future iterations of the Kidney Disease: Improving Global Outcomes (KDIGO) recommendations. Similarly, lipid ratios or Lp(a) might be included to cardiovascular risk scores (e.g., Atherosclerotic Cardiovascular Disease (ASCVD) risk calculators) to improve them for CKD patients.

Personalised treatment is another option; CKD patients who are likely to have increased Lp(a) might be identified by genetic testing for apo(a) size variations. Trials of novel Lp(a)-lowering therapies (antisense oligonucleotides or Small interfering RNA (siRNA) are underway in the general population; CKD patients with very high Lp(a) may eventually be candidates for such treatments if safety is established.

Finally, more data are needed in diverse populations. The majority of evidence to date comes from small or homogeneous cohorts. Large-scale epidemiologic studies in India and other South Asian populations which have unique risk profiles would inform locally relevant risk stratification.

Limitation(s)

A formal Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) based systematic review methodology was not employed, and the literature search was narrative rather than systematic. The available CKD-specific evidence is limited and relies heavily on a small number of observational studies, particularly the study by Mannangi NB et al., [17]. Furthermore, heterogeneity in study populations, lipid measurements, and outcome definitions limits direct comparison across studies. Consequently, conclusions should be interpreted as hypothesis-generating rather than definitive.

Current knowledge is limited by heterogeneity and scarcity of data. Most studies on lipid indices in CKD are cross-sectional and observational, often with small sample sizes. There is no consensus on index thresholds; even the best-studied cut-offs (e.g., AIP 0.1, 0.24 for low/moderate/high-risk) derive from non-CKD groups and may not apply to CKD populations. Many studies lack external validation. Additionally, CKD itself is heterogeneous: lipid patterns differ between diabetic vs. non diabetic CKD, nephrotic vs. non nephrotic, dialysis vs. pre-dialysis. This heterogeneity complicates generalisation.

Confounding is another drawback: it might be difficult to separate the influence of lipids in CKD patients since they often have additional CVD risk factors (such as inflammation and hypertension). Additionally, cholesterol levels may act as confounders or effect modifiers when interpreting study results. Lastly, there is a dearth of data particular to India. Due to the high prevalence of CKD in India, limited studies or extrapolation from Western data are necessary due to the unavailability of large Indian cohorts. This review identifies indices that seem promising, but the findings must be taken carefully until large prospective studies in CKD (and particularly in Indian CKD populations) are carried out.

CONCLUSION(S)

Cardiovascular risk is significantly increased by the unique dyslipidemic milieu that CKD produces, which includes high TGs, low HDL-C, tiny dense LDL, and often raised Lp(a). This risk may be underestimated by standard lipid panels. To provide a more complete assessment of atherogenicity, novel lipid indices including the AIP, CRIs, AC, and LTI include many lipid parameters (including Lp(a) in the case of LTI). According to preliminary data, CKD patients had significantly higher levels of AIP and LTI, which are correlated with other risk factors. These indices are easy to compute and might be particularly helpful in environments with limited resources when more complex testing is not feasible. By including these new indicators, early CV risk diagnosis in CKD may be improved, allowing for more focused therapies. However, more excellent research is required before they can be widely used, including longitudinal validation of indices, the creation of cut-offs unique to CKD, and their incorporation into clinical practice recommendations. However, given the severe CV load associated with CKD, focusing on lipid indices and Lp(a) is a viable route to improved results.

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