



# Relationship between lipoprotein(a) levels, cardiovascular outcomes and death in patients with chronic kidney disease: a systematic review of prospective studies

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## Abstract

**Introduction and aim** In the general population, high levels of lipoprotein(a) (Lp(a)) are an independent risk factor for atherosclerotic cardiovascular diseases. However, the information available in patients with chronic kidney disease (CKD) is less robust. The main objective of this updated systematic review of prospective studies was to analyze the association between elevated Lp(a) levels and cardiovascular outcomes or death in patients with CKD.

**Methods** The PRISMA guidelines were used to carry out this systematic review. Randomized clinical trials or prospective observational studies that evaluated the association between Lp(a) levels and cardiovascular outcomes or death in CKD patients were searched in the current literature.

**Results** Fifteen studies including 12,260 individuals were identified and considered eligible for this systematic review. In total, 14 prospective cohorts and one post-hoc analysis of a randomized clinical trial were analyzed. Eight studies evaluated hemodialysis patients, one study analyzed patients on peritoneal dialysis, while six studies evaluated subjects with different stages of CKD. Median follow-up duration ranged from 1 to 8.6 years. Our findings showed that elevated Lp(a) values were associated with a higher risk of cardiovascular events or death in most studies, despite adjusting for traditional risk factors.

**Conclusion** The findings of this systematic review show that there is a positive association between Lp(a) levels and fatal and non-fatal cardiovascular events in patients with CKD.

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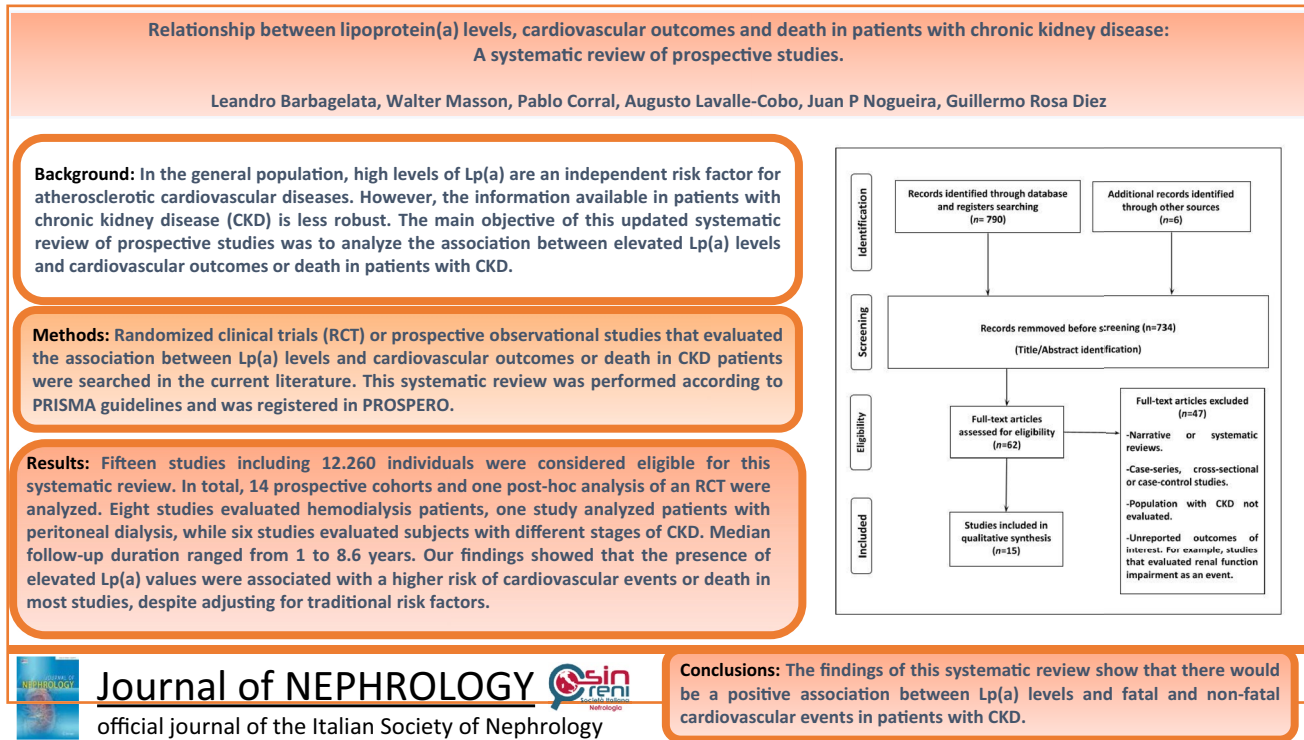
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## Graphical abstract



**Keywords** Lipoprotein(a) · Chronic kidney disease · Systematic review · Dyslipidemia

## Introduction

Chronic kidney disease (CKD) is a major health problem worldwide. In addition, cardiovascular disease is the leading cause of mortality and morbidity in CKD patients [1]. Therefore, identifying and managing cardiovascular risk factors associated with CKD is a good strategy to prevent and delay fatal and non-fatal atherosclerotic events. Abnormalities in cholesterol metabolism have been described in patients at all stages of CKD [2]. Renal dysfunction is also associated with many disorders in lipoprotein metabolism leading to atherogenic dyslipidemia and formation of atherosclerotic plaques in the vascular wall [3]. Traditionally, dyslipidemia associated with CKD shows hypertriglyceridemia, normal or elevated low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B levels, and decreased high-density lipoprotein cholesterol (HDL-C) values [4]. Additionally, the role of new lipid markers such as lipoprotein (a) [Lp(a)] have been evaluated in patients with CKD [5].

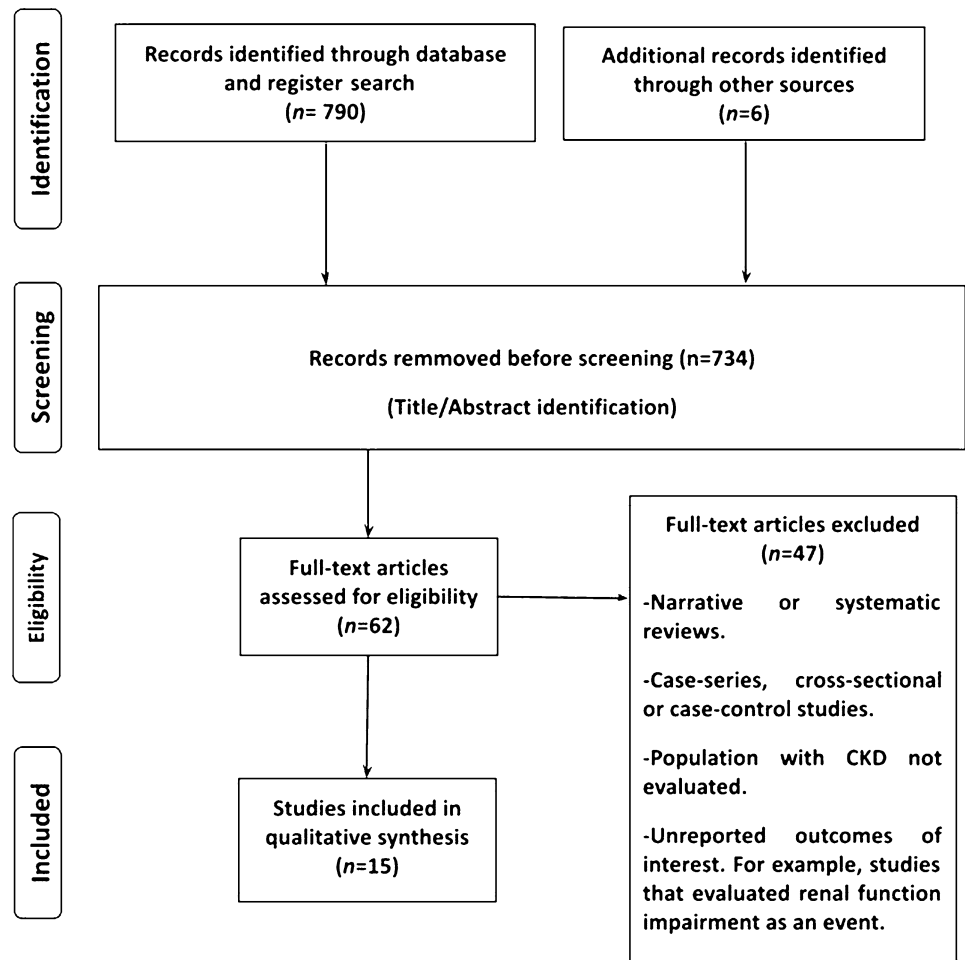
Lp(a) consists of an LDL-like core lipoprotein particle bound by a single disulfide bond to a glycoprotein of variable molecular weight, known as apolipoprotein(a) [apo(a)] [6]. In the general population, high levels of Lp(a) are an

independent risk factor for atherosclerotic cardiovascular diseases through mechanisms associated with increased atherogenesis, inflammation, and thrombosis [7].

In the context of normal renal function, Lp(a) levels are mainly genetically determined and inversely related to the molecular weight of apo(a) isoforms [8]. However, the impaired kidney function results in increased Lp(a) levels, regardless of genetic predisposition [9].

Many prospective observational studies have evaluated the association between Lp(a) levels and mortality or cardiovascular outcomes in CKD patients [10–24]. However, the populations included, the cut-off points for Lp(a) analyzed, the follow-up times and the outcomes evaluated were heterogeneous in published studies. A previous review analyzed some studies that evaluated the association between Lp(a) values and cardiovascular events in patients with CKD [25]. However, this review includes both cross-sectional and case-control studies, and only patients with end-stage renal disease were evaluated. Furthermore, it did not consider some recently published studies.

Therefore, the main objective of the present updated systematic review of prospective studies was to analyze the association between elevated Lp(a) levels and cardiovascular outcomes or death in patients with CKD.

**Fig. 1** Flow diagram of the study screening process

## Materials and methods

**Data extraction and quality assessment:** This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. This systematic review was registered in PROSPERO (CRD42022353307).

A literature search was performed to detect studies that evaluated the association between Lp(a) levels and events of interest. Two independent reviewers searched the electronic PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane Controlled Trials databases using “lipoprotein (a)” AND “chronic kidney disease” terms, alone or combined with the following terms: “cardiovascular disease”, “major adverse cardiovascular events”, “all-cause mortality”, “stroke”, “myocardial infarction”, “cardiovascular mortality” and “coronary artery disease”. The final article search ended on 31 July, 2022.

The following inclusion criteria were used to select eligible studies: (1) Randomized clinical trials or observational studies with a cohort design (prospective or retrospective);

(2) Studies evaluating patients with CKD; (3) Studies evaluating two groups of patients: with elevated Lp(a) levels or not. In this case, we did not set a specific cut-off point for Lp(a); (4) Studies that evaluated the relationship between Lp(a) levels and the risk of cardiovascular events or death; (5) Studies with a follow-up > 6 months.

There were no linguistic, geographic or publication restrictions, while expert opinions, reviews, case-series, and cross-sectional and case-control studies were excluded.

The primary endpoints of the study were mortality and incidence of cardiovascular events. The outcomes were defined according to the reported events within the selected studies.

Data were extracted on the baseline population and effect sizes for the relationship between Lp(a) and outcomes. Effect sizes and 95% confidence intervals (CI) for Lp(a) were reported as odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) according to the reports of the original publications.

The quality of the included studies was assessed by two independent review authors using the criteria of the Quality

**Table 1** Sample size, characteristics of the populations and follow-up

Study (year)	<i>n</i>	Population	Follow-up (year)
Cressman (1992)* [10]	129	Hemodialysis patients aged 23–86 years Mean age, 58 ± 14 years. Male gender, 48.8% Most common causes: hypertension 23%, chronic glomerulonephritis 21%, diabetes 18%, polycystic kidney disease 12%	4
Cressman (1994)* [11]	129	Hemodialysis patients. Mean age, 61 years. Pre-existing cardiovascular disease, 27.9%	4
Koda (1999) [12]	390	Hemodialysis patients. Mean age, 56.6 ± 14 years, Male gender, 61.8%. Diabetes, 14.6%	2.3
Kronenberg (1999) [13]	440	Hemodialysis patients Mean age, 57 ± 15 years. Male gender, 57.5%	5
Ohashi (1999) [14]	268	Hemodialysis patients (79% chronic glomerulonephritis and 21% diabetic nephropathy). Male gender, 57%. Mean age, 57.6 ± 14 years	5
Illescu (2002) [15]	54	Peritoneal dialysis patients. Mean age, 58.1 ± 15.9 years. Male gender, 44.4%. Most common causes: diabetic nephropathy (50%) and glomerulonephritis (22.2%)	2
Longenecker (2002)* [16]	864	Hemodialysis patients Most common causes: diabetes (48%), hypertension (17%) and glomerulonephritis (15%). Median age, 59 years. Female gender, 47%	2.8
Longenecker (2005)* [17]	833	Hemodialysis patients Median age, 59.2 years. Female gender, 46.9%	2.3
Shlipak (2005) [18]	1249	Patients with CKD (eGFR < 60 mL/min/1.73 m <sup>2</sup> ) > 65 years. Mean eGFR, 50 mL/min/1.73 m <sup>2</sup> . Mean age, 75 ± 6 years. Male gender, 47%	8.6
Konishi (2015) [19]	904	Patients with CKD (eGFR < 60 mL/min/1.73 m <sup>2</sup> not on hemodialysis) who underwent a first PCI	4.7
Kollerits (2016) [20]	1255	Hemodialysis patients with type 2 diabetes mellitus, aged 18–80 years	4
Bajaj (2017) [21]	3744	Patients between 21–74 years with CKD (eGFR 20–70 mL/min/1.73 m <sup>2</sup> for persons aged 21–44 years, 20–60 mL/min/1.73 m <sup>2</sup> for persons aged 45–64 years, and 20–50 mL/min/1.73 m <sup>2</sup> for persons aged 65–74 years) Mean age, 58 years. Male gender, 54.7%	7.5
Li (2022) [22]	452	Patients hospitalized for ACS with CKD (eGFR < 60 mL/min/1.73 m <sup>2</sup> ) and not on hemodialysis. Mean age, 73 ± 11 years. Male gender, 60.2%	3.9
Viad (2022) [23]	110	Patients with CKD stages 2 to 4 and dyslipidemia Most common causes: glomerulonephritis (33.6%), hypertension (14.5%) and polycystic disease (13.6%). Mean age, 55.6 ± 10.9 years. Male gender, 55.5%	1
Poudel (2022) [24]	1439	Patients with CKD (eGFR 20–70 mL/min/1.73 m <sup>2</sup> ) and ASCVD Mean age, 61.6 years. Female gender, 41%	6.8

ACS acute coronary syndrome; ASCVD atherosclerotic cardiovascular disease; CKD chronic kidney disease; eGFR estimated glomerular filtration rate; MACE major clinical adverse events; MI myocardial infarction; PCI percutaneous coronary intervention

\*Two differently published analyses originating from the same population

in Prognostic Studies (QUIPS) tool [27]. Any discrepancy between the two reviewers was resolved through discussion and by involving a third reviewer.

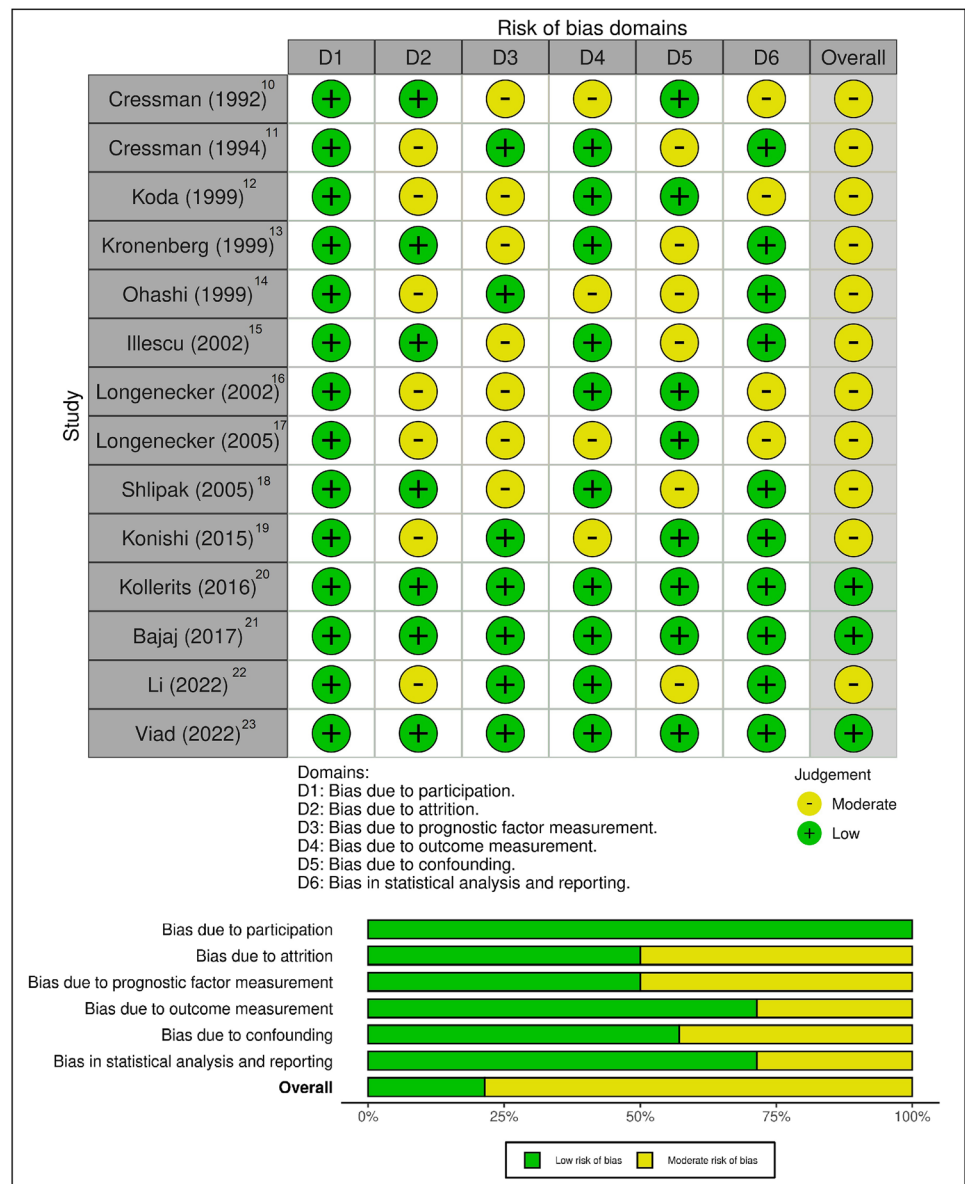
Meta-analysis was not possible due to heterogeneity of the populations included, the different cut-off points and measurements of Lp(a) used, and the type of outcomes reported.

## Results

In total, fifteen studies including 12,260 individuals were identified and considered eligible for this systematic review. A flow diagram of the screening process is shown in Fig. 1.

Altogether, 14 prospective cohorts [10–15, 17–24] and one post-hoc analysis of a Randomized Clinical Trial [16] were analyzed. Eight studies evaluated hemodialysis patients, one study analyzed patients on peritoneal dialysis, while six studies evaluated subjects with different stages of CKD. Median follow-up duration ranged from 1 to 8.6 years. Sample sizes, characteristics of the populations and follow-ups of the studies included in this review are shown in Table 1.

Bias assessment using the QUIPS tool was performed in 14 studies. The study developed by Poudel et al. [24] was not analyzed because at the time of this review, only their abstract had been published. Based on this evaluation, twelve studies were assessed as being at moderate risk of bias and three studies as being at low risk of bias. The quality of the studies evaluated can be seen in Fig. 2.

**Fig. 2** Bias assessment of included studies

## Association between Lp(a) levels and outcomes in hemodialysis patients

Two different analyses originating from the same population were reported by Cressman et al. in two old publications [10, 11]. The former demonstrated that serum Lp(a) concentration (per 1 unit log increase) was associated with a higher risk of atherosclerotic events (OR 1.02) during the follow-up period. In addition, patients with values of Lp(a) > 38.4 mg/dl compared to subjects with values ≤ 38.4 mg/dl showed different survival curves ( $p = 0.021$ ). The latter analysis showed that serum Lp(a) concentration (per 1 unit log increase) was associated with a higher risk of cardiovascular death (RR 1.60). Koda et al. reported that Japanese patients with Lp(a) values ≥ 30 mg/

dl receiving chronic dialysis therapy had higher cardiovascular mortality (RR 3.93) but not higher all-cause mortality, after an average follow-up of 2.3 years [12]. Similarly, another study evaluating the same cut-off point showed that a lower value of Lp(a) was an independent predictor of future fatal cardiovascular outcomes (RR 0.71) [14].

Longenecker et al. published two different analyses based on the same population [16, 17]. Although the authors did not find a significant association between Lp(a) values and mortality, one of the analyses showed that patients with Lp(a) levels > 52.5 nmol/l and > 206 nmol/l have a higher risk of non fatal and fatal atherosclerotic events (HR 1.37 and 1.88, respectively). More recently, a post hoc analysis of the prospective 4D Study (German Diabetes Dialysis Study) showed that a high Lp(a)

**Table 2** Methodology, endpoints and effect measures used in the included studies

Study (year)	Methodology used	Cut-off point of Lp(a)	Endpoint evaluated and measure effect reported
<b>Hemodialysis patients</b>			
Cressman (1992) <sup>a</sup> [10]	Lp(a) assay: radioimmunoassay Cox regression analyses Model adjusted for cardiovascular risk factors and time on hemodialysis	Per 1 unit increase of log Lp(a) > 38.4 mg/dl vs. ≤ 38.4 mg/dl (median)	Fatal or nonfatal ASCVD OR 1.02 (95% CI 1.01–1.04) Kaplan–Meier survival curves (log-rank test) were different in these groups ( $p = 0.021$ )
Cressman (1994) <sup>a</sup> [11]	Lp(a) assay: radioimmunoassay Cox regression analyses Multivariate analysis of baseline clinical and laboratory variables	Per 1 unit increase of log Lp(a)	Cardiovascular death RR 1.60 (95% CI 1.08–2.4)
Koda (1999) [12]	Lp(a) assay: latex-enhanced turbidimetric assay Cox regression analyses Model adjusted for age, gender, diabetes and albumin,	≥ 30 mg/dl vs. < 30 mg/dl	Cardiovascular death RR 3.93 ( $p < 0.01$ , 95% CI not reported) All-cause mortality No independent association observed (measures not reported)
Kronenberg (1999) [13]	Lp(a) assay: antibody enzyme-linked immunosorbent assay Cox regression analyses Model adjusted for age, history of coronary disease, apo(a) phenotype, diabetes, HDL-C and apolipoprotein B	Per 1 unit increase of log Lp(a)	CAD events No association was shown. P values between 0.15 and 0.50 were reported (measure not described)
Ohashi (1999) [14]	Lp(a) assay: enzyme-linked immunosorbent assay Cox regression analyses Model adjusted for demographic conditions and cardiovascular risk factors	< 30 mg/dl vs. ≥ 30 mg/dl	CAD mortality RR 0.71 ( $p < 0.05$ , 95% CI not reported)
Longenecker (2002) <sup>b</sup> [16]	Lp(a) assay: ELISA Cox regression analyses Model adjusted for demographic conditions, ASCVD risk factors, cause of CKD, albumin, and congestive heart failure	≥ 52.1 nmol/l vs. < 52.1 nmol/l (median)	Lp(a) level was not associated with mortality (measure effect not reported)
Longenecker (2005) <sup>b</sup> [17]	Lp(a) assay: ELISA Cox regression analyses Model adjusted for demographic and comorbid conditions, ASCVD risk factors, albumin, and C-reactive protein	≥ 52.5 nmol/l vs. < 52.5 nmol/l (median) ≥ 206 nmol/l vs. < 206 nmol/l (90th percentile)	Nonfatal and fatal ASCVD HR 1.37 (CI 95% 1.03–1.82) HR 1.88 (95% CI 1.25–2.81)

Table 2 (continued)

Study (year)	Methodology used	Cut-off point of Lp(a)	Endpoint evaluated and measure effect reported
Kollerits (2016) [20]	Lp(a) assay: ELISA Cox regression analyses Model adjusted for age, gender, medication allocation (placebo or atorvastatin) and history of coronary heart disease	Per 1 unit increase of log Lp(a)	All-cause mortality HR 1.09 (95% CI 1.03–1.16) Cardiovascular death HR 1.04 (95% IC 0.95–1.14) MI HR 0.96 (95% CI 0.87–1.07) Fatal and non-fatal cardiac outcomes HR 1.01 (95% CI 0.94–1.08) Fatal and non-fatal cerebrovascular outcomes HR 0.99 (95% CI 0.88–1.13) MACE HR 1.04 (95% CI 0.97–1.11)
CKD patients			
Shlipak (2005) [18]	Lp(a) assay: ELISA Cox regression analyses Model adjusted for age, sex, race, education, prevalent cardiovascular disease, and cardiovascular risk factors	Upper quartile compared with the lower 3 quartiles	Cardiovascular death HR 1.20 (95% CI 0.93–1.54)
Konishi (2015) [19]	Lp(a) assay: latex agglutination immunoassays Cox regression analyses Model adjusted for age, sex, race/ethnicity, education level, cardiovascular risk factors and history of cardiovascular disease	High vs. low Lp(a) according to median levels	All-cause death or ACS HR 1.35 (95% CI 1.01–1.82)
Bajaj (2017) [21]	Lp(a) assay: ELISA Cox regression analyses Model adjusted for age, sex, race/ethnicity, education level, cardiovascular risk factors and history of cardiovascular disease	Quartile 4 (> 61.3 mg/dl) vs. quartile 2 (9.8–26.0 mg/dl)	MI HR 1.49 (95% CI 1.05–2.11) Death HR 1.28 (95% CI 1.05–1.57) MI or death HR 1.29 (95% CI 1.07–1.56) MACE HR 2.86 (95% CI 1.85–4.42)
Li (2022) [22]	Lp(a) assay: latex turbidimetric Cox regression analyses Model adjusted for cardiovascular risk factors, medications, history of cardiovascular disease and LVEF	Lp(a) $\geq$ 50 mg/dl vs. Lp(a) < 30 mg/dl	
Viad (2022) [23]	Lp(a) assay: ELISA Cox regression analyses Multivariate analysis (variables included not reported)	Per 1 unit increase of log Lp(a) Lp(a) $\geq$ 10 mg/dl vs. Lp(a) < 10 mg/dl	ASCVD OR 1.22 (95% CI 0.99– 1.51) OR 0.03 (95% CI 0.001– 2.99)

Table 2 (continued)

Study (year)	Methodology used	Cut-off point of Lp(a)	Endpoint evaluated and measure effect reported
Poudel (2022) [24]	Lp(a) assay: latex-enhanced immunoturbidimetric assay Cox regression analyses Model adjusted for age, sex, race, education level, income, cardiovascular risk factors, eGFR and drug therapy	Per 1 SD increase of log Lp(a)	ASCVD HR 1.05 (95% CI 0.96–1.15) CHD HR 0.99 (CI 95% 0.89–1.11) Ischemic stroke HR 1.10 (95% CI 0.87–1.40) PAD HR 1.06 (95% CI 0.88–1.28)
Peritoneal dialysis patients Illescu (2002) [15]	Lp(a) assay: ELISA Cox regression analyses Model adjusted for age, diabetes, diastolic blood pressure and albumin	≥ 65 nmol/l vs. < 65 nmol/l Per 1 unit increase of log Lp(a)	Death from any cause RR 3.09 ( $p = 0.03$ , 95% CI not reported) RR 1.004 (95% CI 1.002–1.007)

ACS acute coronary syndrome; ASCVD atherosclerotic cardiovascular disease; CAD coronary artery disease; CI confidence interval; CKD chronic kidney disease; ELISA enzyme-linked immunosorbent assay; HR hazard ratio; HDL-C high density lipoprotein cholesterol; LVEF left ventricular ejection fraction; log: logarithm; MACE major adverse cardiovascular events; MI myocardial infarction; OR odds ratio; PAD peripheral arterial disease; RR relative risk; RCT randomized clinical trial; SD standard deviation

<sup>a</sup>Two differently published analyses based on the same population

concentration was a risk predictor for all-cause mortality in hemodialysis patients with diabetes mellitus [20]. However, the study did not show significant associations with the other endpoints evaluated.

Unlike previous reports, a small study that included 440 hemodialysis patients did not find a significant association between Lp(a) levels and coronary artery disease outcomes [13]. However, this study showed that the genetically determined apo(a) phenotype was a strong and independent predictor for coronary events.

### Association between Lp(a) levels and outcomes in CKD patients

Shlipak et al. reported that patients with CKD and high Lp(a) values (upper quartile compared with the lower 3 quartiles) had more cardiovascular death (HR 1.20) after an average follow-up of close to 9 years [18]. Similarly, another study showed that CKD patients (not on hemodialysis) with high Lp(a) values undergoing percutaneous coronary intervention had a poor prognosis [19]. Patients with an Lp(a) level above the median showed a higher incidence of the combined endpoint of all-cause death or acute coronary syndrome as compared with subjects with a level below the median (HR 1.35). Bajaj et al. reported that after adjusting for potential confounders, the highest quartile of Lp(a) was associated with increased risk of myocardial infarction (HR 1.49), death (HR 1.28) and the composite outcome of myocardial infarction or death (HR 1.29) compared with the second quartile of Lp(a) in patients with CKD (estimated glomerular filtration rate [eGFR] > 20 mL/min/1.73 m<sup>2</sup>) [21]. Another study evaluated patients (not on hemodialysis) hospitalized for acute coronary syndrome with CKD [22]. During a median follow-up of 3.9 years, an elevated Lp(a) value (≥ 50 mg/dl vs. < 30 mg/dl) was found to be an independent predictor for major adverse cardiovascular events (HR 2.86).

On the other hand, a small study that evaluated patients with CKD stages 2 to 4 and dyslipidemia did not show a significant association between Lp(a) values and atherosclerotic events, although a clear trend was observed when Lp(a) was analyzed as a continuous variable [23]. Similarly, Poudel et al. did not find a statistically significant association between Lp(a) levels and atherosclerotic events when evaluating patients with CKD and atherosclerotic cardiovascular disease [24]. Nevertheless, Lp(a) was a marker of increased risk for atherosclerotic outcomes in white subjects, patients without diabetes, or with an eGFR between 45 and 70 ml/min/1.73 m<sup>2</sup>.



## Association between Lp(a) levels and outcomes in peritoneal dialysis patients

Only one study evaluated patients on peritoneal dialysis [15]. The results of this study suggest that Lp(a) levels were associated with all-cause mortality. In this sense, the reported HRs were 3.09 and 1.004 when the Lp(a) values were analyzed dichotomously ( $\geq 65$  nmol/l vs.  $< 65$  nmol/l) or continuously (per 1 unit log increase), respectively.

The methodology, endpoints and effect measures used in the included studies can be seen in Table 2.

## Discussion

This systematic review includes a full body of evidence-based prospective studies that examined the relationship between Lp(a) levels and cardiovascular outcomes or death in patients with CKD.

The dyslipidemia observed in patients with CKD acquires some particular characteristics. CKD patients usually present normal plasma levels of LDL-C, reduced plasma levels of HDL-C, and high plasma levels of triglycerides and Lp(a) [4]. This usual pattern should be distinguished from dyslipidemia occurring in patients with nephrotic syndrome, which is characterized by high levels of LDL-C and triglycerides, and normal plasma levels of HDL-C [28].

Previous data suggest that the kidney is directly involved in the catabolism of Lp(a). The interaction between different variables, such as Lp(a) genotype, eGFR or presence of proteinuria, modulate the levels of Lp(a) observed in patients with CKD [29]. Furthermore, CKD patients undergoing hemodialysis have been shown to have increased Lp(a) levels compared to healthy controls. Additionally, Lp(a) levels decrease following renal transplantation [30]. However, as occurs in the general population, Lp(a) levels are inversely correlated with the genetically determined apo(a) isoform size, with higher levels of plasma Lp(a) being associated with smaller apo(a) isoform sizes [31].

The relationship between Lp(a) and cardiovascular outcomes or death was addressed in numerous studies developed in the general population, but despite this, only a limited number of studies evaluated this association in patients with CKD. It is still controversial whether Lp(a) increases the risk of atherosclerotic cardiovascular disease or death in CKD because of the discrepant results and the rather small size of the various studies.

This systematic review analyzed studies in three clinical scenarios related to kidney disease. On the one hand, six studies that included patients with CKD were analyzed, five of which excluded hemodialysis patients [19, 21–24]. One study did not exclude patients with advanced kidney disease, although the mean eGFR was 50 mL/min/1.73 m<sup>2</sup>

(proportion of patients on dialysis not reported) [18]. The association between elevated Lp(a) values and increased risk of cardiovascular events was demonstrated in four of these studies [18, 19, 21, 22]. In contrast, two studies did not show a significant association. In one of them, the low number of patients enrolled could explain the findings, since the authors reported a statistically non-significant trend for this association [23]. The other study reported a significant association between Lp(a) and cardiovascular outcomes only in certain subgroups, such as white patients or subjects with mild-moderate CKD. Characteristics of the population evaluated or simply due to chance-related issues could explain the neutral results in the global analysis in this case.

On the other hand, eight studies analyzed hemodialysis patients. Three studies showed a significant association between elevated Lp(a) values and cardiovascular events [10, 14, 17] and two other studies with cardiovascular mortality [11, 12]. In addition, one study associated this lipid marker with excess all-cause mortality [20], while two other studies did not [12, 16]. Likewise, two studies found no relationship between cardiovascular events and Lp(a) levels [13, 20].

One of the main reasons why conflicting results can be observed is the difference in CKD etiologies of studied patients. For example, unlike previous findings in dialysis patients, Kollerits et al. did not find an association between Lp(a) levels and atherosclerosis-related endpoints [20]. Interestingly, this study was the only one that included all patients with diabetes. Thus, it might be argued that hemodialysis patients with diabetes die more frequently from events caused by other cardiovascular causes, such as congestive heart failure or sudden cardiac death unrelated to acute myocardial infarction. In addition, the neutral finding reported by Kronenberg et al. [13] could have been influenced by the definition of coronary events used in this study (the authors considered the presence of coronary artery stenosis  $> 50\%$ ). The inclusion of events defined by angiographically-confirmed stenosis is problematic in case not all patients undergo coronary angiography. This could have caused a selection bias in defining the event group since it is likely that some individuals in the event-free group had an asymptomatic stenosis. Moreover, the reasons for the discrepancies between the studies with hemodialysis patients might also be due to different prevalence rates of comorbidities, ethnic differences, genetic issues [apo (a) isoforms], the assay used for Lp(a) measurement and/or the sample size.

Finally, a single study evaluated patients on peritoneal dialysis, showing a positive association between the lipid marker and the increased risk of mortality [15]. However, this study only included 54 patients. Therefore, we need more information to clarify the prognostic value of Lp(a) in this particular clinical setting.

The positioning of Lp(a) as a risk factor in patients with CKD could be relevant in the future. It has been established

that Lp(a) is a risk factor for cardiovascular disease, but final proof of causality awaits a randomized trial of Lp(a) lowering. Currently, there are no approved medications to specifically lower Lp(a). As is well known, statins are inefficient or may even increase Lp(a) serum levels [32]. Niacin reduces Lp(a) between 20 and 25%. However, clinical trials with these agents did not show a reduction of major cardiovascular events, and currently their use is not recommended [33]. In contrast, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have been demonstrated to decrease Lp(a) levels and reduce cardiovascular events, but are less effective in subjects with Lp(a) > 50 mg/dl [34]. Promising therapies for Lp(a) include antisense oligonucleotides that selectively bind messenger RNA coding for apo(a) [35]. For example, subcutaneous administration of Pelacarsen in a phase 2 trial decreased Lp(a) levels by 35–80% [36]. Unfortunately, CKD patients were underrepresented in phase 2 trials and are probably also underrepresented in ongoing phase 3 studies [37].

This systematic review has several limitations. Firstly, there was clinical heterogeneity due to the different populations included. Indeed, the follow-up times were different as well. Secondly, the cardiovascular endpoints evaluated were different among the studies evaluated. Thirdly, our study included different Lp(a) measurements. Fourthly, given the observational nature of the studies included, the presence of biases and confounders was highly expected. Finally, we were unable to perform a quantitative analysis (meta-analysis) mainly due to the heterogeneity of the populations included, the different measures of Lp(a) used, and the type of events reported. However, the best available evidence to date has been analyzed in this review.

## Conclusion

In this systematic review we demonstrated that high Lp(a) levels in patients with CKD were associated with an increased risk of cardiovascular events and death in most of the prospective studies evaluated. The cardiovascular benefits of the new Lp(a)-lowering molecules should be demonstrated in future research that includes patients in different stages of CKD.

**Author contributions:** W.M and L.B participated in the conception and design of the research. W.M. and L.B participated in the data collection. The interpretation and final selection of the data was done by W.M, L.B and G.RD. W.M, P.C, A.LC and J.P.N. drafted the manuscript. All authors performed a critical review of the final document. All authors have read and agreed to the published version of the manuscript.

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**Data availability** All data generated or analysed during this study are included in this published article.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical statement** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## References

1. Reiss AB, Miyawaki N, Moon J, Kasselmann LJ, Voloshyna I, D'Avino R Jr et al (2018) CKD, arterial calcification, atherosclerosis and bone health: inter-relationships and controversies. *Atherosclerosis* 278:49–59. <https://doi.org/10.1016/j.atherosclerosis.2018.08.046>
2. Pan X (2022) Cholesterol metabolism in chronic kidney disease: physiology, pathologic mechanisms, and treatment. *Adv Exp Med Biol* 1372:119–143. [https://doi.org/10.1007/978-981-19-0394-6\\_9](https://doi.org/10.1007/978-981-19-0394-6_9)
3. Bulbul MC, Dage T, Afsar B, Uluşu NN, Kuwabara M, Covic A et al (2018) Disorders of lipid metabolism in chronic kidney disease. *Blood Purif* 46(2):144–152. <https://doi.org/10.1159/000488816>
4. Theofilis P, Vordoni A, Koukoulaki M, Vlachopoulos G, Kalaitzidis RG (2021) Dyslipidemia in chronic kidney disease: contemporary concepts and future therapeutic perspectives. *Am J Nephrol* 52(9):693–701. <https://doi.org/10.1159/000518456>
5. Hohenstein B (2017) Lipoprotein(a) in nephrological patients. *Clin Res Cardiol Suppl* 12(Suppl 1):27–30. <https://doi.org/10.1007/s11789-017-0086-z>
6. Jawi MM, Frohlich J, Chan SY (2020) Lipoprotein(a) the insurgent: a new insight into the structure, function, metabolism, pathogenicity, and medications affecting lipoprotein(a) molecule. *J Lipids* 1(2020):3491764. <https://doi.org/10.1155/2020/3491764>
7. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR et al (2021) Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. <https://doi.org/10.1161/ATV.000000000000147>
8. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH (1992) Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest* 90(1):52–60. <https://doi.org/10.1172/JCI115855>
9. Auguet T, Senti M, Rubies-Prat J, Pelegri A, Pedro-Botet J, Nogues X et al (1993) Serum lipoprotein(a) concentration in patients with chronic renal failure receiving haemodialysis: Influence of apolipoprotein (a) genetic polymorphism. *Nephrol Dial Transpl* 8:1099–1103
10. Cressman MD, Heyka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF (1992) Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. *Circulation* 86(2):475–482. <https://doi.org/10.1161/01.cir.86.2.475>
11. Cressman MD, Abood D, O'Neil J, Hoff HF (1994) Lp(a) and premature mortality during chronic hemodialysis treatment.

- Chem Phys Lipids 67–68:419–427. [https://doi.org/10.1016/0009-3084\(94\)90165-1](https://doi.org/10.1016/0009-3084(94)90165-1)
12. Koda Y, Nishi S, Suzuki M, Hirasawa Y (1999) Lipoprotein(a) is a predictor for cardiovascular mortality of hemodialysis patients. *Kidney Int Suppl* 71:S251–S253. <https://doi.org/10.1046/j.1523-1755.1999.07167.x>
  13. Kronenberg F, Neyer U, Lhotta K, Trenkwalder E, Auinger M, Pribasnig S et al (1999) The low molecular weight apo(a) phenotype is an independent predictor for coronary artery disease in hemodialysis patients: a prospective follow-up. *J Am Soc Nephrol* 10(5):1027–1036. <https://doi.org/10.1681/ASN.V1051027>
  14. Ohashi H, Oda H, Ohno M, Watanabe S, Sakata S (1999) Lipoprotein(a) as a risk factor for coronary artery disease in hemodialysis patients. *Kidney Int Suppl* 71:S242–S244. <https://doi.org/10.1046/j.1523-1755.1999.07164.x>
  15. Iliescu E, Marcovina S, Morton A, Lam M, Koschinsky M (2002) Apolipoprotein(a) phenotype and lipoprotein(a) level predict peritoneal dialysis patient mortality. *Perit Dial Int* 22(4):492–499
  16. Longenecker J, Klag M, Marcovina S, Powe N, Fink N et al (2002) Small apolipoprotein(a) size predicts mortality in end-stage renal disease: the CHOICE study. *Circulation* 106(22):2812–2818. <https://doi.org/10.1161/01.cir.0000038946.91899.bb>
  17. Longenecker J, Klag M, Marcovina S, Liu YM, Jaar B, Powe N et al (2005) High lipoprotein(a) levels and small apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. *J Am Soc Nephrol* 16(6):1794–1802. <https://doi.org/10.1681/ASN.2004110922>
  18. Shlipak M, Fried L, Cushman M, Manolio T, Peterson D, Stehman-Breen C et al (2005) Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 293(14):1737–1745. <https://doi.org/10.1001/jama.293.14.1737>
  19. Konishi H, Miyauchi K, Tsuboi S, Ogita M, Naito R, Dohi T et al (2016) Plasma lipoprotein(a) predicts major cardiovascular events in patients with chronic kidney disease who undergo percutaneous coronary intervention. *Int J Cardiol* 205:50–53. <https://doi.org/10.1016/j.ijcard.2015.12.007>
  20. Kollerits B, Drechsler C, Krane V, Lamina C, März W, Dieplinger H et al (2016) Lipoprotein(a) concentrations, apolipoprotein(a) isoforms and clinical endpoints in haemodialysis patients with type 2 diabetes mellitus: results from the 4D Study. *Nephrol Dial Transpl* 31(11):1901–1908. <https://doi.org/10.1093/ndt/gfv428>
  21. Bajaj A, Damrauer S, Anderson A, Xie D, Budoff M, Go A et al (2017) Lipoprotein(a) and risk of myocardial infarction and death in chronic kidney disease: findings from the CRIC study (chronic renal insufficiency cohort). *Arterioscler Thromb Vasc Biol* 37(10):1971–1978. <https://doi.org/10.1161/ATVBAHA.117.309920>
  22. Li Q, Chen Y, Yu L, Zhu L, Wang Z, Jiao S et al (2022) The relationship between lipoprotein(a) and cardiovascular events in acute coronary syndrome patients with and without chronic kidney disease. *Atherosclerosis* 349:204–210. <https://doi.org/10.1016/j.atherosclerosis.2022.04.007>
  23. Vlad CE, Foia L, Pavel-Tanasa M, Toma V, Florea L, Voroneanu L et al (2022) Evaluation of cardiovascular events and progression to end-stage renal disease in patients with dyslipidemia and chronic kidney disease from the North-Eastern area of Romania. *Int Urol Nephrol* 54(3):647–659. <https://doi.org/10.1007/s11255-021-02919-2>
  24. Poudel B, Rosenson RS, Kent S, Bittner V, Gutierrez O et al (2022) Lipoprotein (a) and the risk for atherosclerotic cardiovascular events among adults with chronic kidney disease and a history of atherosclerotic cardiovascular disease. *J Am Coll Cardiol* 79(9):1–3489
  25. Vlad C, Burlacu A, Florea L, Artene B, Badarau S, Covic A et al (2019) A comprehensive review on apolipoproteins as nontraditional cardiovascular risk factors in end-stage renal disease: current evidence and perspectives. *Int Urol Nephrol* 51(7):1173–1189. <https://doi.org/10.1007/s11255-019-02170-w>
  26. Arya S, Kaji AH, Boermeester MA (2021) PRISMA reporting guidelines for meta-analyses and systematic reviews. *JAMA Surg* 156(8):789–790. <https://doi.org/10.1001/jamasurg.2021.0546>
  27. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C (2013) Assessing bias in studies of prognostic factors. *Ann Intern Med* 158(4):280–286. <https://doi.org/10.7326/0003-4819-158-4-201302190-00009>
  28. Speer T, Ridker PM, von Eckardstein A, Schunk SJ, Fliser D (2021) Lipoproteins in chronic kidney disease: from bench to bedside. *Eur Heart J* 42(22):2170–2185. <https://doi.org/10.1093/eurheartj/ehaa1050>
  29. Hopewell JC, Haynes R, Baigent C (2018) The role of lipoprotein (a) in chronic kidney disease. *J Lipid Res* 59(4):577–585. <https://doi.org/10.1194/jlr.R083626>
  30. Kerschdorfer L, König P, Neyer U, Bösmüller C, Lhotta K, Auinger M, Hohenegger M et al (1999) Lipoprotein(a) plasma concentrations after renal transplantation: a prospective evaluation after 4 years of follow-up. *Atherosclerosis* 144(2):381–391. [https://doi.org/10.1016/s0021-9150\(99\)00014-3](https://doi.org/10.1016/s0021-9150(99)00014-3)
  31. Boffa MB, Koschinsky ML (2022) Understanding the ins and outs of lipoprotein (a) metabolism. *Curr Opin Lipidol* 33(3):185–192. <https://doi.org/10.1097/MOL.0000000000000823>
  32. Wang X, Li J, Ju J, Fan Y, Xu H (2021) Effect of different types and dosages of statins on plasma lipoprotein(a) levels: a network meta-analysis. *Pharmacol Res* 163:105275. <https://doi.org/10.1016/j.phrs.2020.105275>
  33. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J et al (2014) Effects of extended release niacin with laropiprant in high-risk patients. *N Engl J Med* 371:203–212. <https://doi.org/10.1056/NEJMoa1300955>
  34. Stiekema LCA, Stroes ESG, Verweij SL, Kassahun H, Chen L, Wasserman SM et al (2019) Persistent arterial wall inflammation in patients with elevated lipoprotein(a) despite strong low density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment. *Eur Heart J* 40(33):2775–2781. <https://doi.org/10.1093/eurheartj/ehy862>
  35. Lippi G, Favaloro EJ, Sanchis-Gomar F (2020) Antisense lipoprotein [a] therapy: state-of-the-art and future perspectives. *Eur J Intern Med* 76:8–13. <https://doi.org/10.1016/j.ejim.2020.04.036>
  36. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E et al (2020) Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med* 382(3):244–255. <https://doi.org/10.1056/NEJMoa1905239>
  37. Fernández-Prado R, Perez-Gomez MV, Ortiz A (2020) Pelacarsen for lowering lipoprotein(a): implications for patients with chronic kidney disease. *Clin Kidney J* 13(5):753–757. <https://doi.org/10.1093/ckj/sfaa001>

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