

Clinical Significance of Lipoprotein(a) in Cardiovascular Risk Stratification Among Patients with Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Background: Lipoprotein(a) [Lp(a)] is an established atherogenic lipoprotein, but its clinical significance for cardiovascular risk stratification in patients with type 2 diabetes mellitus (T2DM) remains incompletely characterized. This systematic review evaluated the association between Lp(a) concentrations and cardiovascular outcomes in adults with T2DM.

Methods: A literature search was conducted in PubMed, Embase, Scopus, Cochrane Library, and ClinicalTrials.gov from database inception through August 2026. Eligible observational cohort studies involving adults with T2DM assessed circulating Lp(a) concentrations and reported cardiovascular outcomes. Data on study characteristics, Lp(a) measurement, outcomes, follow-up, and adjusted effect estimates were extracted. Methodological quality was assessed using the Newcastle–Ottawa Scale. Findings were synthesized narratively because of substantial heterogeneity.

Results: Four cohort studies involving 7,220 patients from South Korea, Japan, China, and Slovenia were included. Higher Lp(a) concentrations were consistently associated with increased cardiovascular risk. Elevated Lp(a) was associated with incident cardiovascular disease, cardiac death or acute coronary syndrome, recurrent cardiovascular events, myocardial infarction, and cardiovascular mortality. Adjusted hazard ratios ranged from 1.20 to 3.02 across different comparisons and outcomes. Associations were particularly evident among patients with markedly elevated Lp(a) concentrations and, in one study, among women for myocardial infarction.

Conclusion: Elevated Lp(a) concentrations were consistently associated with adverse cardiovascular outcomes in patients with T2DM. Lp(a) measurement may provide additional information for cardiovascular risk stratification beyond conventional risk factors. Prospective multicenter studies using standardized assays and consistent thresholds are warranted.

Keywords: Lipoprotein(a); Type 2 diabetes mellitus; cardiovascular disease; Cardiovascular risk; Cardiovascular mortality; Myocardial infarction; Stroke; Systematic review.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global metabolic disorder associated with a substantially increased burden of cardiovascular disease (CVD). A systematic review of international evidence has demonstrated that CVD is highly prevalent among individuals with T2DM and represents a major contributor to morbidity and mortality in this population.¹ The

cardiovascular burden of diabetes is multifactorial and is influenced by hyperglycemia, insulin resistance, hypertension, dyslipidemia, endothelial dysfunction, chronic inflammation, and accelerated atherosclerosis.² The diagnosis and classification of diabetes further recognize T2DM as a complex metabolic condition associated with multiple long-term vascular complications.³ Consequently, cardiovascular risk assessment and prevention remain fundamental components of diabetes



management.

Lipoprotein(a) [Lp(a)] has emerged as an important additional determinant of cardiovascular risk. Lp(a) is a structurally distinctive, cholesterol-rich lipoprotein composed of an apolipoprotein B-100-containing LDL-like particle covalently linked to apolipoprotein(a) [apo(a)]. Its circulating concentration is predominantly genetically determined by variation in the LPA gene and remains relatively stable throughout life.⁴ Unlike conventional lipid parameters, Lp(a) is therefore relatively less influenced by lifestyle and environmental factors.⁵ Increasing Lp(a) concentrations have been consistently associated with a higher risk of atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction and ischemic stroke.^{4,6} The biological effects of Lp(a) extend beyond cholesterol transport, with proatherogenic, proinflammatory, and potentially prothrombotic properties mediated in part through oxidized phospholipids, vascular inflammation, endothelial dysfunction, and effects on fibrinolysis.^{6,7}

The relevance of Lp(a) may be particularly important in individuals with T2DM, who already have an elevated baseline risk of ASCVD. Evidence suggests that the relationship between Lp(a) and diabetes is complex, with elevated Lp(a) contributing to cardiovascular risk while epidemiological studies have also reported associations between lower Lp(a) concentrations and the development of T2DM.⁸ This bidirectional relationship highlights the need to evaluate Lp(a) specifically within diabetic populations rather than relying solely on evidence derived from the general population. The potential contribution of Lp(a) to residual cardiovascular risk is especially relevant because conventional risk-factor management may not fully eliminate the excess vascular risk associated with diabetes.

Several observational studies have directly evaluated the prognostic significance of Lp(a) in patients with T2DM. In a 10-year prospective cohort study involving patients with T2DM without previous CVD, Lim et al. reported that individuals with higher Lp(a) concentrations had a significantly greater risk of subsequent cardiovascular events, with the highest Lp(a) quartile associated with an adjusted hazard ratio of 1.92 (95% CI, 1.26–2.92) compared with the lowest quartile.⁹ Similarly, elevated Lp(a) concentrations have been associated with both the presence and angiographic severity of coronary artery disease in patients with T2DM, suggesting that Lp(a) may provide information beyond conventional lipid measurements.¹⁰

Evidence has also extended to patients with established cardiovascular disease. Among patients with diabetes who underwent percutaneous coronary intervention, Lp(a) was associated with long-term clinical outcomes, indicating that its prognostic relevance may persist even after coronary revascularization.¹¹ In patients with T2DM and previous cardiovascular events, elevated Lp(a) has likewise been associated with recurrent adverse outcomes, further supporting its potential role in identifying individuals at particularly high residual cardiovascular risk.¹² These findings are consistent with more recent evidence demonstrating associations between elevated Lp(a) and myocardial infarction, cardiovascular mortality, and all-cause mortality among patients with T2DM.¹³ The relationship between circulating Lp(a) and mortality has also been examined beyond diabetic populations. A systematic review and dose-response meta-analysis reported associations between circulating Lp(a) concentrations and both all-cause and cause-specific mortality, supporting the broader prognostic relevance of Lp(a) across cardiovascular and non-cardiovascular outcomes.¹⁴ In addition, a recent systematic review and meta-analysis specifically examining individuals across prediabetes and diabetes found that elevated Lp(a) was associated with cardiovascular outcomes, providing further evidence that Lp(a)

may contribute to cardiovascular risk across different stages of abnormal glucose metabolism.¹⁵

Growing evidence has consequently led to increasing recognition of Lp(a) in contemporary cardiovascular prevention strategies. The 2026 ACC/AHA multisociety guideline on dyslipidemia recommends measuring Lp(a) at least once to identify individuals who may have increased ASCVD risk, with concentrations ≥ 125 nmol/L (50 mg/dL) considered elevated.¹⁶ Contemporary clinical approaches to elevated Lp(a) emphasize its role in risk assessment and the importance of interpreting Lp(a) concentrations within the broader context of an individual's cardiovascular risk profile.¹⁷ The American Heart Association has similarly characterized Lp(a) as a genetically determined, causal, and prevalent risk factor for ASCVD, reinforcing its clinical importance as a risk-enhancing biomarker.¹⁸

Despite this expanding evidence base, uncertainty remains regarding the magnitude and consistency of the association between elevated Lp(a) and cardiovascular outcomes specifically among patients with T2DM. Differences in study populations, Lp(a) measurement techniques, genetic determinants, outcome definitions, adjustment for conventional cardiovascular risk factors, and clinically relevant concentration thresholds may contribute to variation between studies. Furthermore, emerging therapeutic strategies targeting Lp(a) have increased the importance of accurately identifying patients who may derive clinical benefit from improved Lp(a)-based risk stratification.¹⁹ Therefore, this systematic review aims to synthesize the available evidence regarding the association between elevated Lp(a) concentrations and cardiovascular outcomes in patients with T2DM and to evaluate the potential role of Lp(a) as an additional marker for cardiovascular risk stratification in this high-risk population.

METHODOLOGY

A Study Design and Reporting

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review examined the association between circulating lipoprotein(a) [Lp(a)] concentrations and cardiovascular outcomes among adults with type 2 diabetes mellitus (T2DM). The outcomes of interest included incident cardiovascular disease (CVD), cardiac death, acute coronary syndrome (ACS), recurrent cardiovascular events (CVEs), myocardial infarction (MI), cardiovascular mortality, and stroke.

Literature Search

A comprehensive literature search was performed in PubMed, Embase, Scopus, Cochrane Library, and ClinicalTrials.gov from database inception through August 2026. Search terms and controlled vocabulary combined concepts relating to "lipoprotein(a)," "Lp(a)," "type 2 diabetes mellitus," "cardiovascular disease," "myocardial infarction," "cardiovascular mortality," "stroke," "acute coronary syndrome," and "recurrent cardiovascular events," using the Boolean operators "AND" and "OR." Reference lists of relevant articles were also screened manually to identify additional eligible studies. The electronic searches identified 1,442 records: PubMed (n=624), Embase (n=412), Scopus (n=356), Cochrane Library (n=38), and ClinicalTrials.gov (n=12).

Eligibility Criteria

Studies were eligible if they (1) included adults with T2DM; (2) measured or categorized circulating Lp(a) concentrations; (3) evaluated cardiovascular outcomes; and (4) reported an association between Lp(a) and at least one prespecified outcome.

Observational cohort studies, including prospective and retrospective cohorts, were eligible. Studies were excluded if they involved populations other than patients with T2DM, did not assess Lp(a), did not report relevant cardiovascular outcomes, or lacked sufficient information for eligibility assessment. Conference abstracts and reports without adequate full-text data were excluded.

Study Selection

After removal of 386 duplicate records, 1,056 unique records underwent title and abstract screening. Full texts were sought for 160 potentially relevant reports; six could not be retrieved. The remaining 154 reports underwent full-text assessment. Of these, 150 were excluded because of an ineligible population (n=58), exposure (n=32), outcome (n=28), study design (n=21), or publication type (n=11). Four cohort studies were ultimately included, comprising 7,220 participants.

Data Extraction

Data were extracted using a standardized approach, including author, publication year, country, study design, setting, sample size, participant characteristics, baseline cardiovascular status, Lp(a) assay and units, exposure categories or thresholds, follow-up duration, outcome definitions, number of events, adjusted effect estimates, confidence intervals, and covariates included in multivariable models. Hazard ratios (HRs) with 95% confidence intervals (CIs) were preferentially extracted when reported.

Quality Assessment and Data Synthesis

Methodological quality of the four cohort studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates selection, comparability, and outcome ascertainment in cohort studies. Because the included studies differed substantially in participant characteristics, baseline cardiovascular status, Lp(a) thresholds, laboratory assays, follow-up duration, and outcome definitions, quantitative meta-analysis was not considered appropriate. Findings were therefore synthesized narratively, with effect estimates compared according to cardiovascular outcome and Lp(a) category. No causal inference was made from the observational evidence.

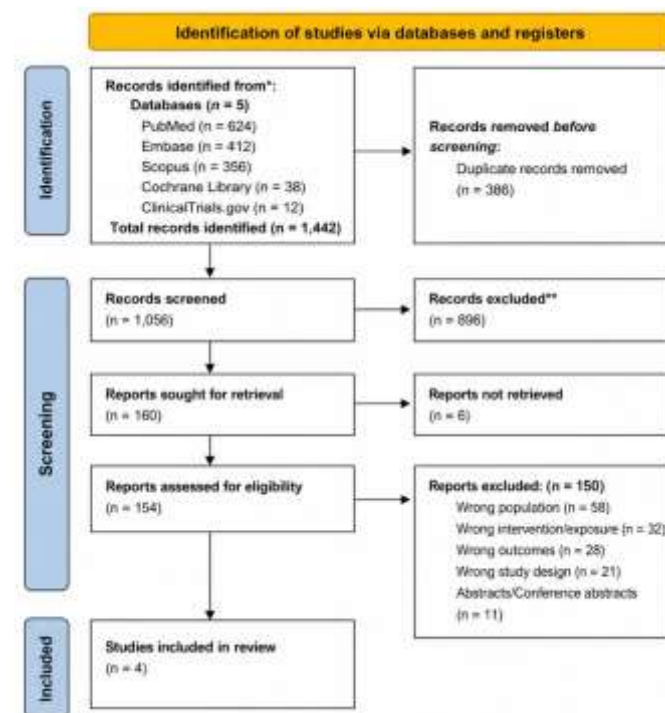
RESULTS

A Study Selection Process:

Database and registry searches identified 1,442 records in total from PubMed (n = 624), Embase (n = 412), Scopus (n = 356), Cochrane Library (n = 38), and ClinicalTrials.gov (n = 12). After removing 386 duplicate records, 1,056 records remained for title and abstract screening. Following screening, 160 reports were sought for retrieval, of which 6 reports could not be retrieved. Subsequently, 154 full-text reports were assessed for eligibility. Of these, 150 reports were excluded due to wrong population (n = 58), wrong intervention/exposure (n = 32), wrong outcomes (n = 28), wrong study design (n = 21), and abstracts/conference abstracts (n = 11). Finally, 4 studies were included in the

systematic review as they met the predetermined inclusion criteria. The PRISMA 2020 flow diagram provides an overview of the study selection process (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram of the Study Selection Process



Baseline Characteristics and Patient's Demography

Four studies comprising 7,220 patients with type 2 diabetes mellitus (T2DM) were included. The studies were conducted in South Korea, Japan, China, and Slovenia, with participants ranging from approximately 58.5 to 67.9 years in age. Male participants represented approximately 62.5%–83.5% of the study populations. The clinical characteristics varied across studies, with some enrolling patients without previous cardiovascular disease (CVD), while others included patients with established coronary artery disease or previous cardiovascular events. Lp(a) was measured in mg/dL using different laboratory assays and was categorized using quartiles, median-based groups, or predefined cutoffs. The cardiovascular outcomes assessed included CVD, myocardial infarction, cardiovascular death, acute coronary syndrome, stroke, and recurrent cardiovascular events. Detailed demographic and baseline characteristics are summarized in Table 1.

Table 1. Characteristics of Studies Included in the Systematic Review

Variable	Lim et al., 2016	Konishi et al., 2016	Zhang et al., 2020	Čuješ et al., 2026
Country	South Korea	Japan	China	Slovenia
Study design	Prospective cohort	Single-center observational cohort	Prospective observational cohort	Retrospective observational cohort
Setting	University-Affiliated Diabetes Center, St. Vincent's Hospital	Juntendo University Hospital	3 medical centers	University Medical Center Maribor
Sample size	833	1,136	2,284	2,967
T2DM patients	833	1,136	2,284	2,967
Age	55.2 ± 9.9 years	65.3 ± ~9.8 years*	58.54 ± 10.47 years	67.9 (60.2–74.7) years
Sex (% male)	39.6%	83.5%	73.3%	62.5%
Diabetes duration	7.8 ± 6.3 years	NR	NR	NR

Baseline CVD	No prior CVD	CAD patients undergoing PCI	Prior CVE + stable CAD	No prior MI
Lp(a) measurement	One-step sandwich ELISA (TintElize Lp[a])	Latex agglutination immunoassay	Immunoturbidimetry (LASAY Lp[a] auto)	Particle-enhanced immunonephelometric assay (Siemens ProSpec)
Lp(a) unit	mg/dL	mg/dL	mg/dL	mg/dL
Lp(a) categorization/cutoff	Quartiles	Median split	<10, 10–<30, ≥30 mg/dL	≤50, 51–90, >90 mg/dL
Follow-up	11.1 years	4.7 years	7,613 patient-years	MI: 15.1 y; CV mortality: 12.7 y; all-cause mortality: 9.1 y
Primary CV outcome	New-onset CVD	Cardiac death + ACS	Recurrent CVEs	First MI; CV mortality; all-cause mortality
Outcome definition	CAD or ischemic stroke	Cardiac death or incident ACS	CV death, nonfatal MI, stroke	MI/CV death according to ICD-10
CV events	202 CVD events	NR	153 recurrent CVEs	372 MI; 1,081 CV deaths
Effect measure	HR	HR	HR	HR
Main effect estimate	HR 1.92 (1.26–2.92), Q4 vs Q1	HR 1.20 (1.00–1.42), high vs low	HR 2.049 (1.308–3.212), ≥30 vs <10 mg/dL	MI: HR 1.83 (1.10–3.06) for 51–90; HR 2.80 (1.74–4.51) for >90 mg/dL†
CV mortality estimate	NR	NR	HR 2.708 (1.340–5.475), ≥30 vs <10 mg/dL	HR 1.42 (1.07–1.89) for 51–90; HR 1.38 (1.01–1.91) for >90
Adjusted model	Multivariable Cox	Multivariable Cox	Adjusted Cox	Multivariable Cox
Adjustment variables	Age, sex, diabetes duration, hypertension, smoking, BMI, HbA1c, diabetic nephropathy, eGFR, Lp(a)-corrected LDL-C, insulin, ACEi/ARB, statin, aspirin	Age, BMI, eGFR, LVEF, multivessel disease, insulin, statins	Age, sex, BMI, smoking, hypertension, dyslipidemia, family history of CAD, diseased vessels, LDL-C, FBG, statins, antidiabetic drugs	LDL-C, hypertension, eGFR <60; age used as time scale
Key findings	Highest Lp(a) quartile independently predicted CVD	High Lp(a) predicted cardiac death/ACS after PCI	High Lp(a) independently predicted recurrent CVEs	Elevated Lp(a) associated with first MI particularly in women and higher CV mortality
Main limitation	Single-center, one ethnic group; quartile-based Lp(a) classification	Single-center Japanese population; residual/unknown confounding	Observational design; baseline Lp(a) only; assay potentially affected by apo(a) size	Retrospective hospitalized cohort; incomplete covariates; competing risk of death for MI

* Konishi et al.: overall age is approximately 65.3 years, derived from the reported group means.

† Čuješ et al.: the reported MI HRs in the interaction model correspond to women; interaction terms indicate attenuation in men.

Table 2. Newcastle–Ottawa Scale (NOS) Quality Assessment of Included Cohort Studies

Study	Representativeness of exposed cohort (1)	Selection of non-exposed cohort (1)	Ascertainment of exposure (1)	Outcome absent at baseline (1)	Comparability: age/sex (1)	Comparability: other factors (1)	Assessment of outcome (1)	Follow-up long enough (1)	Adequacy of follow-up (1)	Total /9
Lim et al., 2016	★	★	★	★	★	★	★	★	–	8/9
Konishi et al., 2016	★	★	★	★	★	★	★	★	–	8/9
Zhang et	★	★	★	★	★	★	★	★	★	9/9

al, 2020										
Čuješ et al., 2026	★	★	★	★	★	★	★	★	★	8/9

Risk of Bias Assessment (ROBINS-I)

The four observational cohort studies were evaluated for risk of bias using the ROBINS-I tool (Figures 2 and 3). Overall, three studies (Lim et al., 2016; Konishi et al., 2016; and Zhang et al., 2020) were rated as having a moderate overall risk of bias,^{9,11,12} while Čuješ et al. (2026) was rated as having a serious overall risk of bias.¹³ Moderate risk in the three studies was primarily related to potential residual confounding, whereas the Čuješ et al. study had serious concerns mainly due to confounding and missing data.¹³ For all included studies, the classification of Lp(a) exposure (D3) was assessed as low risk, and the domain relating to deviations from intended exposure (D4) was considered not applicable.

For bias due to confounding (D1), three studies (75%) were rated as moderate risk and one study (25%) as serious risk. Selection of participants (D2) was rated as low risk in three studies (75%) and moderate risk in one study (25%). Classification of Lp(a) exposure (D3) was rated as low risk in all four studies (100%). Missing data (D5) was rated as low risk in two studies (50%), moderate risk in one study (25%), and serious risk in one study (25%). Measurement of outcomes (D6) was rated as low risk in three studies (75%) and moderate risk in one study (25%). Selection of the reported result (D7) was rated as moderate risk in all four studies (100%). Overall, 75% (3/4) of the included studies were rated as having a moderate overall risk of bias, whereas 25% (1/4) were rated as having a serious overall risk of bias. As shown in Figure X and Figure X, the ROBINS-I assessment summarizes the domain-level and overall risk of bias across the included studies.

Figure 2: Traffic Light Plot of Domains Showing Risk of Bias for Included Studies Using ROBINS-I



Figure 3: Traffic Light Plot Summary for Included Studies Using ROBINS-I

Systematic Review of Outcomes

The four included studies evaluated the association between lipoprotein(a) [Lp(a)] levels and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM). The outcomes assessed included incident cardiovascular disease (CVD), cardiac death, acute coronary syndrome (ACS), recurrent cardiovascular events (CVEs), myocardial infarction (MI), cardiovascular mortality, and stroke. Overall, the findings demonstrated a consistent relationship between elevated Lp(a) concentrations and a greater cardiovascular risk among patients with T2DM. However, the specific outcomes and patient populations varied across the included studies. (Table 3)

Incident Cardiovascular Disease

One study evaluated the development of incident CVD among

patients with T2DM who had no previous cardiovascular disease. Lim et al. (2016) followed 833 participants for approximately 11.1 years and reported 202 cardiovascular events during follow-up. Patients in the highest Lp(a) quartile had a significantly greater risk of developing CVD compared with those in the lowest quartile (HR 1.92, 95% CI 1.26–2.92). These findings indicate that elevated Lp(a) may independently contribute to the development of cardiovascular disease even in patients with T2DM without established CVD at baseline.

Cardiac Death and Acute Coronary Syndrome

Konishi et al. investigated cardiovascular outcomes in diabetic patients undergoing percutaneous coronary intervention (PCI).¹¹ Over a median follow-up of 4.7 years, higher Lp(a) levels were associated with an increased risk of the composite outcome of cardiac death or acute coronary syndrome. After multivariable adjustment, the association remained modest but significant (HR 1.20, 95% CI 1.00–1.42). This suggests that Lp(a) may provide additional prognostic information in diabetic patients with established coronary artery disease undergoing PCI.

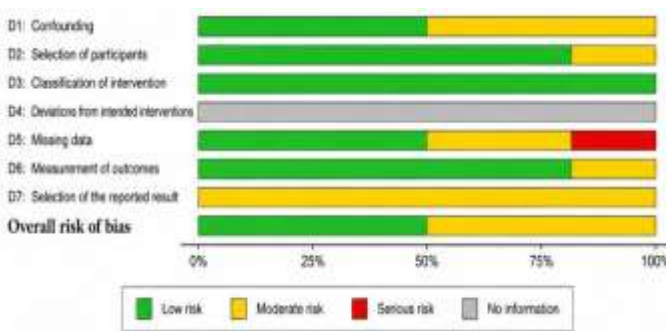
Recurrent Cardiovascular Events

The association between Lp(a) and recurrent cardiovascular events was assessed by Zhang et al. in 2,284 patients with T2DM and previous cardiovascular events.¹² During 7,613 patient-years of follow-up, 153 recurrent CVEs occurred, including 68 cardiovascular deaths, 30 nonfatal myocardial infarctions, and 55 strokes. The incidence of recurrent CVEs increased progressively across Lp(a) categories, from 4.4% in the low-Lp(a) group (<10 mg/dL) to 8.5% in the high-Lp(a) group (≥30 mg/dL). Compared with the low-Lp(a) group, patients with Lp(a) ≥30 mg/dL had a significantly higher risk of recurrent CVEs (HR 2.049, 95% CI 1.308–3.212).¹²

Myocardial Infarction

Čuješ et al. (2026) evaluated the association between Lp(a) levels and myocardial infarction among 2,967 patients with T2DM. Higher Lp(a) concentrations were associated with an increased risk of MI, with the strongest association observed at levels >90 mg/dL. Compared with patients with Lp(a) ≤50 mg/dL, the reported hazard ratios were 1.83 (95% CI 1.10–3.06) for 51–90 mg/dL and 2.80 (95% CI 1.74–4.51) for >90 mg/dL. The association was particularly evident among women, suggesting a possible sex-related difference in the cardiovascular impact of elevated Lp(a).

Cardiovascular Mortality



Evidence for the relationship between Lp(a) and cardiovascular mortality has been reported among patients with established cardiovascular disease. In the cohort studied by Zhang et al., 68 of

the 153 recurrent cardiovascular events recorded during follow-up were cardiovascular deaths.¹² Cardiovascular mortality was significantly higher among patients with Lp(a) concentrations ≥ 30 mg/dL than among those with concentrations < 10 mg/dL, with an adjusted hazard ratio of 2.708 (95% CI, 1.340–5.475).¹² These findings indicate that elevated Lp(a) may identify patients with T2DM and previous cardiovascular events who remain at increased risk of cardiovascular death. Consistent with this observation, Čuješ et al. reported an association between higher Lp(a) concentrations and cardiovascular mortality, further supporting the prognostic relevance of Lp(a) in long-term

cardiovascular risk assessment.¹³

Stroke was also identified among the recurrent cardiovascular outcomes reported by Zhang et al. in patients with T2DM and a history of cardiovascular disease.¹² Of the 153 recurrent cardiovascular events documented during follow-up, 55 were strokes.¹² The progressive increase in recurrent cardiovascular events across increasing Lp(a) categories suggests that elevated Lp(a) may contribute to a broader pattern of adverse cardiovascular outcomes, including cerebrovascular events, in patients with T2DM and established cardiovascular disease.¹²

Table 3: Summary of Cardiovascular Outcomes of Lipoprotein(a) in Patients with Type 2 Diabetes Mellitus

Study	Incident CVD	Cardiac Death / ACS	Recurrent CVEs	Myocardial Infarction	CV Mortality	Stroke
Lim et al., 2016	202/833 (24.2%); higher Lp(a) associated with CVD. Q4 vs Q1: HR 1.92 (95% CI 1.26–2.92); $p < 0.001$.	Not assessed	Not assessed	Not separately assessed	Not separately assessed	Not separately assessed
Konishi et al., 2016	Not assessed	Higher Lp(a) associated with cardiac death/ACS after PCI; adjusted HR 1.20 (95% CI 1.00–1.42).	Not separately assessed	Not separately assessed	Not separately assessed	Not separately assessed
Zhang et al., 2020	Not assessed	Not separately assessed	153/2284 recurrent CVEs; 4.4%, 7.7%, and 8.5% across low, medium, and high Lp(a). High vs low: HR 2.049 (95% CI 1.308–3.212); $p = 0.002$.	30 events; high vs low Lp(a): HR 3.016 (95% CI 1.144–7.949); $p = 0.026$.	68 events; high vs low Lp(a): HR 2.708 (95% CI 1.340–5.475); $p = 0.006$.	55 events; high vs low: HR 1.118 (95% CI 0.518–2.413); $p = 0.777$.
Čuješ et al., 2026	Not assessed	Not assessed	Not assessed	12.5% experienced MI. In women, 51–90 mg/dL: HR 1.79 (95% CI 1.07–2.99); > 90 mg/dL: HR 2.67 (95% CI 1.66–4.32).	36.4% died from CV causes; 51–90 mg/dL: HR 1.42 (95% CI 1.07–1.89); > 90 mg/dL: HR 1.38 (95% CI 1.01–1.91).	Not assessed

Note: NR/not assessed indicates that the outcome was not reported or was not evaluated separately in the respective study. For Zhang et al., recurrent CVEs comprised cardiovascular death, non-fatal MI, and stroke. For Čuješ et al., the MI estimates shown are from sex-specific analyses in women.

DISCUSSION

This systematic review synthesized evidence from four observational studies involving 7,220 patients with type 2 diabetes mellitus (T2DM) to examine the relationship between circulating lipoprotein(a) [Lp(a)] concentrations and cardiovascular outcomes. Overall, the findings indicate that higher Lp(a) levels are associated with an unfavorable cardiovascular profile in patients with T2DM, although the magnitude of this association differed according to the population studied and the specific outcome evaluated. The reported endpoints included incident cardiovascular disease (CVD), recurrent cardiovascular events, myocardial infarction (MI), cardiovascular mortality, cardiac death, acute coronary syndrome

(ACS), and stroke.

Evidence concerning the development of incident CVD was provided by Lim et al., who prospectively followed 833 patients with T2DM without pre-existing CVD for a median of 11.1 years.⁹ During follow-up, 202 participants developed CVD. Individuals in the highest Lp(a) quartile had a significantly greater risk of CVD than those in the lowest quartile (HR 1.92, 95% CI 1.26–2.92; $p < 0.001$).¹² These findings suggest that Lp(a) may contribute to cardiovascular risk before clinically apparent CVD develops. This observation is particularly relevant in T2DM, in which chronic metabolic disturbances and other vascular risk factors may already promote accelerated atherosclerotic disease.

The prognostic relevance of Lp(a) was also evident in patients with established coronary artery disease. Konishi et al. evaluated 1,136 patients with diabetes who underwent percutaneous coronary intervention (PCI) and found that higher Lp(a) concentrations were associated with the composite endpoint of cardiac death or ACS over a median follow-up of 4.7 years.¹¹ Following multivariable adjustment, the association remained

statistically significant (HR 1.20, 95% CI 1.00–1.42).¹¹ Although the effect estimate was less pronounced than that observed for incident CVD in the study by Lim et al., these results indicate that Lp(a) may retain prognostic value even after coronary revascularization in patients with established coronary artery disease.^{9,11}

Further evidence was obtained from patients with T2DM who had already experienced cardiovascular disease. Zhang et al. followed 2,284 such patients for 7,613 patient-years and documented 153 recurrent cardiovascular events.¹² The event rate increased from 4.4% among patients with Lp(a) concentrations <10 mg/dL to 8.5% among those with concentrations ≥30 mg/dL.¹² Compared with the lowest Lp(a) category, the high-Lp(a) group had approximately twice the risk of recurrent cardiovascular events (HR 2.049, 95% CI 1.308–3.212).¹² These findings extend the evidence beyond first cardiovascular events and suggest that elevated Lp(a) may also identify patients with T2DM who remain vulnerable to subsequent cardiovascular complications.

The association with MI was further demonstrated by Čuješ et al. among 2,967 patients with T2DM who had no previous history of MI.¹³ Increasing Lp(a) concentrations were associated with progressively greater risk of first MI. Compared with concentrations ≤50 mg/dL, the risk was higher at 51–90 mg/dL (HR 1.83, 95% CI 1.10–3.06) and >90 mg/dL (HR 2.80, 95% CI 1.74–4.51).¹³ Notably, the association was more apparent among women, whereas a statistically significant relationship was not demonstrated in men.¹³ This finding raises the possibility that sex may modify the cardiovascular effects of Lp(a), although such an observation requires confirmation in larger and more diverse populations.

Cardiovascular mortality showed a similar pattern. In the cohort reported by Zhang et al., 68 of the 153 recurrent cardiovascular events were cardiovascular deaths, and patients with Lp(a) concentrations ≥30 mg/dL had a substantially higher risk of cardiovascular death than those with concentrations <10 mg/dL (HR 2.708, 95% CI 1.340–5.475).¹² Čuješ et al. likewise observed higher cardiovascular mortality among patients with elevated Lp(a), with HRs of 1.42 (95% CI 1.07–1.89) for concentrations of 51–90 mg/dL and 1.38 (95% CI 1.01–1.91) for concentrations >90 mg/dL, compared with ≤50 mg/dL.¹³ Collectively, these findings suggest that Lp(a) may have prognostic relevance not only for nonfatal cardiovascular events but also for cardiovascular mortality in T2DM.

The evidence for stroke was less consistent. Zhang et al. reported 55 strokes among the 153 recurrent cardiovascular events recorded during follow-up.¹² However, the association between elevated Lp(a) and stroke did not reach statistical significance (HR 1.118, 95% CI 0.518–2.413; $p = 0.777$).¹² Thus, although higher Lp(a) was associated with an overall increase in recurrent cardiovascular events, its relationship with individual cerebrovascular outcomes appeared weaker. This discrepancy may reflect differences in the biological mechanisms underlying specific cardiovascular endpoints, limited statistical power for individual outcomes, or variation in patient characteristics and Lp(a) distributions.

Interpretation and Comparison With Previous Evidence

The findings of this review are broadly consistent with the established evidence describing Lp(a) as an important, predominantly genetically determined cardiovascular risk factor. Lp(a) may promote atherosclerotic disease through multiple biological pathways, including pro-atherogenic and pro-inflammatory effects, while its structural and biological characteristics may also contribute to thrombotic processes.^{7,18} These mechanisms provide a plausible explanation for the associations observed across several cardiovascular endpoints in patients with T2DM.

The clinical importance of Lp(a) is further related to the possibility of residual cardiovascular risk despite management of conventional lipid parameters. Because Lp(a) concentrations are substantially determined by genetic factors and are relatively stable over the life course, an elevated level may identify cardiovascular susceptibility that is not fully captured by routine lipid measurements.^{7,8} This may be particularly relevant in T2DM, where multiple conventional risk factors are already present and the residual risk after standard risk-factor management can remain substantial.

The present findings are also supported by broader evidence in populations with abnormal glucose metabolism. A recent systematic review and meta-analysis reported that elevated Lp(a) was associated with cardiovascular outcomes across individuals with prediabetes and diabetes, with higher concentrations generally corresponding to greater cardiovascular risk.¹⁵ In addition, a dose-response meta-analysis found associations between circulating Lp(a) concentrations and both all-cause and cause-specific mortality, supporting the prognostic relevance of Lp(a) beyond individual cardiovascular events.¹⁴ The current review adds to this literature by focusing specifically on patients with T2DM and demonstrating associations across incident disease, recurrent events, MI, cardiovascular mortality, and other clinically relevant outcomes.

Differences between individual studies should nevertheless be interpreted carefully. Variability in Lp(a) measurement methods, concentration thresholds, patient selection, baseline cardiovascular status, outcome definitions, and adjustment for confounding factors may influence the magnitude of observed associations. Furthermore, the observational design of all included studies means that residual confounding cannot be excluded. These methodological considerations are important when interpreting Lp(a) as a prognostic marker and when considering whether associations observed in epidemiological studies translate into treatment benefits.

Clinical Implications

The findings have potential implications for cardiovascular risk assessment in patients with T2DM. Contemporary dyslipidemia guidance recognizes Lp(a) as a clinically relevant risk-enhancing biomarker and recommends measurement to identify individuals who may have additional ASCVD risk.¹⁶ Current clinical approaches emphasize incorporating Lp(a) into the overall assessment of cardiovascular risk rather than interpreting its concentration in isolation.¹⁷

Because Lp(a) is largely genetically determined and remains comparatively stable, measurement may provide information that is not readily obtained from conventional modifiable risk factors.^{7,8} Patients with markedly elevated Lp(a), particularly those with established cardiovascular disease or multiple additional risk factors, may therefore warrant closer cardiovascular risk assessment and optimization of established preventive strategies. The American Heart Association has characterized Lp(a) as a causal and prevalent risk factor for ASCVD, further supporting its consideration in contemporary cardiovascular prevention.¹⁸

At the same time, elevated Lp(a) should not be interpreted as an indication for a specific Lp(a)-lowering intervention on the basis of observational evidence alone. The clinical significance of Lp(a) measurement currently lies primarily in improved risk stratification and intensification of appropriate management of established cardiovascular risk factors. Emerging therapeutic approaches directed specifically at Lp(a) may further alter this landscape as evidence from clinical trials becomes available.¹⁹

Strengths and Limitations

A strength of this review is the inclusion of clinically relevant cardiovascular outcomes across different stages of cardiovascular

disease, ranging from incident CVD to recurrent events, MI, and cardiovascular mortality. However, interpretation should consider several limitations. The number of included studies was small, and all were observational, limiting the ability to establish causality. Considerable variation was also present in Lp(a) categorization, measurement methods, study populations, and follow-up duration, which may affect comparability between studies. In addition, some studies included patients with established or previous cardiovascular disease, whereas others evaluated patients without prior CVD.

Future Directions

Further large-scale prospective studies are needed to determine whether Lp(a) provides additional prognostic value beyond established cardiovascular risk factors in T2DM. Future research should use standardized Lp(a) measurement and clinically comparable thresholds and should investigate potential differences according to sex and baseline cardiovascular risk. Long-term studies evaluating whether targeted reduction of Lp(a) translates into fewer cardiovascular events in patients with T2DM are also warranted.

CONCLUSION

Elevated lipoprotein(a) [Lp(a)] concentrations were consistently associated with increased cardiovascular risk among patients with type 2 diabetes mellitus across the included observational cohorts. Higher Lp(a) levels were linked to incident cardiovascular disease, acute coronary syndrome, cardiac death, recurrent cardiovascular events, myocardial infarction, and cardiovascular mortality. These findings support Lp(a) as a potentially useful additional biomarker for cardiovascular risk assessment in patients with type 2 diabetes, particularly those with established or elevated cardiovascular risk. However, differences in Lp(a) assays, concentration thresholds, outcome definitions, follow-up duration, and study populations limit direct comparison across studies. Larger prospective multicenter studies using standardized Lp(a) measurement and clinically consistent thresholds are needed to establish its incremental prognostic value and inform its integration into routine cardiovascular risk stratification.

Ethical Approval

Ethical approval was not required for this systematic review because it involved the synthesis and analysis of previously published literature and did not involve human participants, animals, or the collection of primary data.

Data Availability

No new datasets were generated or analyzed during this systematic review. The review was based on previously published literature and publicly available information.

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Informed Consent

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Conflict of Interest

The authors declare that they have no competing interests.

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Declaration of AI-Assisted Language Editing

Grammarly was used to correct language.

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