# Prevalence of Elevated Lipoprotein(a) among Atherosclerotic Cardiovascular Disease Patients with Lipoprotein(a) Measurements: Evidence from a Systematic Literature Review


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## Background

- Lipoprotein(a) [Lp(a)] is an inherited, independent and causative risk factor for atherosclerotic cardiovascular disease (ASCVD).[1-4] Elevated Lp(a) is associated with an estimated 2-fold increased ASCVD risk.[1,5-6]
- Approximately 1.43 billion people have elevated Lp(a) (≥50 mg/dL) globally with highest proportion in African region and lowest in Asia.[6-7]
- Despite resurgence in publications on Lp(a) in recent years, there has not been a systematic review of prevalence of elevated Lp(a) in patients with ASCVD.

## Objective

- The objective of this systematic literature review (SLR) was to study the prevalence of elevated Lp(a) levels among patients with ASCVD across geographies.
- Other objectives were to understand the treatment patterns and burden of elevated Lp(a) in patients with ASCVD across geographies.

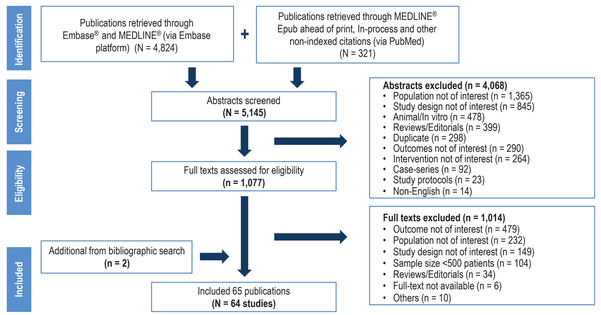
## Methodology

- The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[8]
- Embase®, MEDLINE®, and MEDLINE®-In Process databases were searched to identify the data on patients with ASCVD from studies published from 2010 to September 2020.
- Studies with patients with at least one Lp(a) measurement and ≥500 overall study participants were included. Full-text articles published in English language were selected for inclusion.
- The SLR included observational studies, randomised controlled trials (RCTs) and meta-analyses.
- The Newcastle–Ottawa Scale (NOS) was used to assess the quality of observational studies.[9]

## Results

Of the 5,145 records identified from the literature databases, 64 studies were included in this SLR **(Figure 1)**.

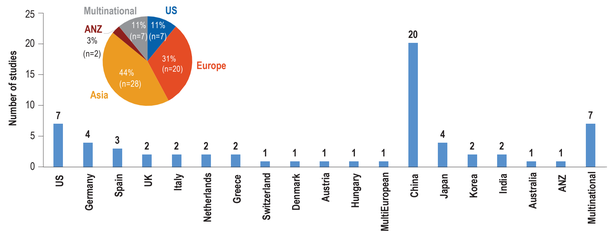
**Figure 1: Study selection flow chart**




## Overview of studies

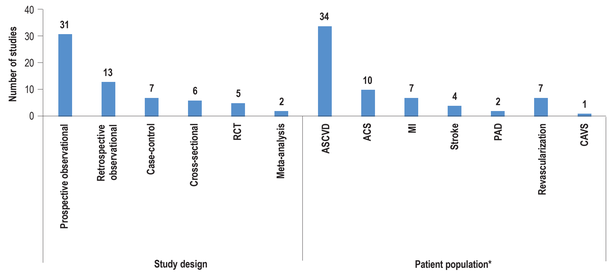
- A large majority of the studies were from Asia (n=28, 44%) or Europe (n=20, 31%). Seven studies (11%) were from the USA **(Figure 2)**. Nearly half of the studies were of prospective observational design (n=31) **(Figure 3)**.
- A total of 34 studies (53%) included a mix of patients with any ASCVD condition while other studies focused on specific ASCVD subgroups including those with acute coronary syndromes (ACS), myocardial infarction (MI), stroke, prior revascularization procedures, peripheral artery disease (PAD) and calcific aortic valve stenosis (CAVS) **(Figure 3)**.
- For observational studies, the quality score ranged from 3 to 8 stars, with the majority of studies scoring 5 or more stars.

**Figure 2: Distribution of studies by region**




**ANZ**: Australia and New Zealand; **UK**: United Kingdom; **US**: United States.

**Figure 3: Study design and population types**

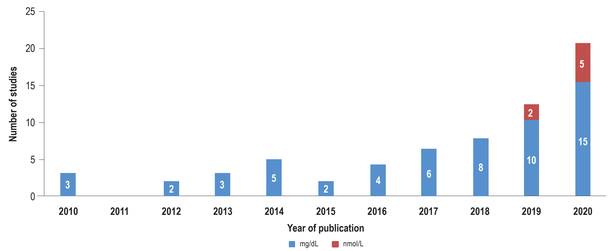



*One study reported separate data for MI and stroke, therefore counted under both categories.
**ACS**: Acute coronary syndrome; **ASCVD**: Atherosclerotic cardiovascular disease; **CAVS**: Calcific aortic valve stenosis; **MI**: Myocardial infarction; **PAD**: Peripheral artery disease; **RCT**: Randomised controlled trial.

## Lp(a) units and thresholds reported

- Lp(a) was reported in mg/dL unit in 55 studies and in nmol/L in 6 studies. These include one study that measured Lp(a) in mg/dL and also reported the converted values to nmol/L units.
- 39 studies (61%) were published in the last three years (between 2018 and 2020) denoting the growing evidence on Lp(a) in ASCVD **(Figure 4)**. Interestingly, we observed that only recently studies started reporting Lp(a) in nmol/L units - published between 2019-2020.

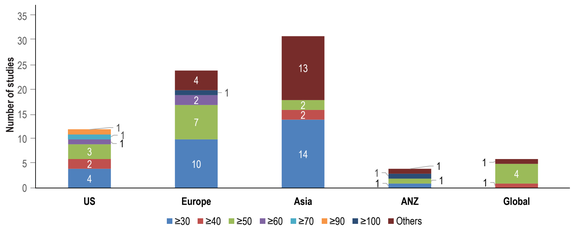
**Figure 4: Number of studies by publication year and Lp(a) units**




One study provided data in both units and counted in each unit type.

- The Lp(a) thresholds adopted in the included studies varied across geographies with 29 studies (45%) reporting the threshold of ≥30 mg/dL and 17 studies (27%) reporting the threshold of ≥50 mg/dL **(Figure 5)**.
- All studies from China, except one, reported the threshold of ≥30 mg/dL.
- 19 studies (30%) reported the prevalence of elevated Lp(a) based on the statistical distribution of the Lp(a) levels within that cohort (e.g. upper tertile, quartile, quintile, or > median).

**Figure 5: Thresholds considered for high/elevated Lp(a) (in mg/dL) across geographies**

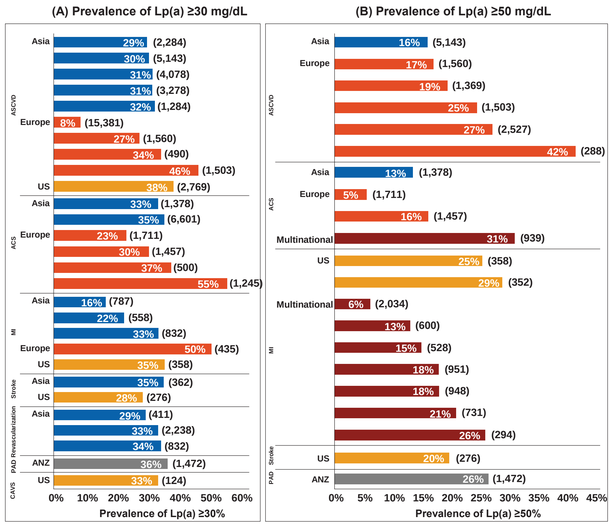



**ANZ**: Australia and New Zealand; **US**: United States.
Number of studies are overlapping; a study may report more than 1 threshold.
*'Others' include studies which divided the cohort according to the Lp(a) distribution (e.g. tertiles, quartiles, quintiles, or median).

## Prevalence of elevated Lp(a)

- The crude average prevalence of elevated Lp(a) defined as ≥30 mg/dL was 32% across 27 studies (range, 8% to 55%) while it was 20% across 14 studies when defined as ≥50 mg/dL (range, 5% to 42%).
- The worldwide prevalence of elevated Lp(a) defined as ≥30 mg/dL or ≥50 mg/dL varied greatly across geographies and population types **(Figure 6)**.

**Figure 6: Prevalence of elevated Lp(a) levels among the ASCVD population types**




NOTE: Numbers in brackets represent the number of patients in the study with Lp(a) measurement.
Some studies included ≥500 overall subjects, however Lp(a) measurement was reported for lesser number of patients.

- In China, the prevalence of Lp(a) ≥30 mg/dL ranged from 22-35% while it was 16% for Lp(a) ≥50 mg/dL.
- Studies conducted in Spain and Austria reported the highest prevalence of elevated Lp(a) (≥30 mg/dL: 46% - 55%; ≥50 mg/dL: 42%).
- Studies from Germany and Switzerland reported the lowest prevalence of elevated Lp(a) (≥30 mg/dL: 8%; ≥50 mg/dL: 5%).
- Studies from European countries reported the highest variability in prevalence estimates of elevated Lp(a) (≥30 mg/dL: 8-55%; ≥50 mg/dL: 5-42%) while the studies from Asia reported relatively consistent prevalence estimates especially for population with a mix of ASCVD conditions (~30% with elevated Lp(a) defined as ≥30 mg/dL).
- No specific trend in elevated Lp(a) prevalence was noted in terms of ASCVD population types suggesting that the Lp(a) levels are independent of the type of ASCVD condition.
- Two studies based on the UK Biobank participants reported that the prevalence of Lp(a) ≥150 nmol/L and ≥175 nmol/L among ASCVD patients was 20% and 16%, respectively (N = 17,326), while in patients with either ASCVD or statin use, the prevalence of Lp(a) ≥150 nmol/L and ≥175 nmol/L was 18% and 14%, respectively (N = 73,391).
- In RCTs the prevalence of elevated Lp(a) was reported as ≥49 mg/dL in 20% (N = 3395); ≥50 mg/dL in 26% (N = 915); ≥60 mg/dL in 25% (N = 18,924); >74 mg/dL in 10% (N = 7863); and >165 nmol/L in 25% of patients (N = 25,096), respectively.

## Conclusion

- No specific trend in Lp(a) prevalence was noted in terms of ASCVD population types suggesting that the Lp(a) levels are independent of the type of ASCVD condition.
- Highest number of studies were identified from China where the prevalence of Lp(a) ≥30 mg/dL was 22-35%.
- On average the prevalence across the included studies is consistent with the findings of the previously published multi-geography publications (≥30 mg/dL: 32%; ≥50 mg/dL: 20%).[6,10]
- The crude prevalence of elevated Lp(a) of ≥30 mg/dL and ≥50 mg/dL was 16-35% and 13-16% in Asia, 8-55% and 5-42% in Europe, 28-38% and 20-29% in the US, and 36% and 26% in ANZ, respectively.
- The thresholds considered to define elevated Lp(a) vary widely across regions with ≥50 mg/dL commonly used in the US and Europe, ≥30 mg/dL commonly used in Asia, and many studies adopting a statistical distribution approach within the study cohort.
- Geographies/ethnicity, patient selection and time and method of Lp(a) measurement might contribute to the variations observed in the Lp(a) prevalence across studies and need to be explored in future studies.
- Large, well-designed epidemiology studies are required to further confirm the prevalence of elevated Lp(a) in ASCVD patients and examine the drivers behind different prevalence between countries. Further consolidation of existing evidence would benefit from a meta-analysis approach to identify an average prevalence per region.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## Conflict of interest

NK, GM and AFF are employees of Novartis. RG was an employee of Novartis at the time of conduct of this study.

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