TOPIC: Health Technology Assessment - **DISEASE:** Cardiovascular Disorders (including MI, Stroke, Circulatory)

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Clinical Burden of Elevated Levels of Lipoprotein(a) for Patients with Atherosclerotic Cardiovascular Disease in the Real Clinical Practice in Italy

Chiara Biancotto[1], Diletta Valsecchi[1], Claudia Cristofani[1], Simone Poli[1], Chiara Veronesi[2], Valentina Perrone[2], Luca Degli Esposti[2]

[1]Novartis Farma S.p.A., Milan, Italy; [2]CliCon S.r.l. Società Benefit Health, Economics & Outcomes Research, Bologna, Italy

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BACKGROUND AND OBJECTIVES

- **Elevated Lp(a)** is independently and causally associated with an increased risk of atherosclerotic cardiovascular disease (**ASCVD**) [1,2].
- The 2022 EAS Lp(a) consensus paper, in line with the ESC/EAS dyslipidemia guidelines [3], recommends measuring Lp(a) at least once in an adult's lifetime [4].
- However, evidence has shown that Lp(a) is currently measured in a small minority of subjects, including those at high and very high cardiovascular risk [5].

Objectives. This real-world analysis is aimed at comparing the characteristics of ASCVD patients with elevated (≥50 mg/dL) vs normal (<30 mg/dL) Lp(a) levels, and to assess the impact of elevated Lp(a) on the risk of future ASCVD events and the related economic burden for the Italian National Health Service (INHS).

PATIENTS AND METHODS

Data source, study population and design

- This retrospective cohort study investigated patients with **available Lp(a) measurement and established ASCVD** found between 2012 and March 2023 in laboratory and administrative databases of a pool of healthcare entities geographically distributed across Italy and corresponding to approximately 5.5 million health-assisted citizens (**Figure 1**).

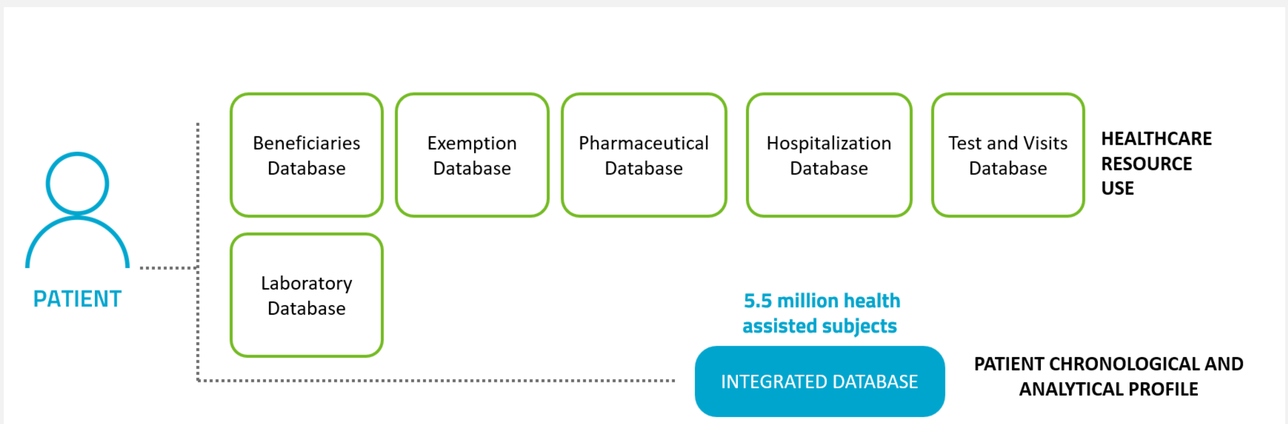

Figure 1. Administrative databases used for the analysis.

- The index-date was that of the first detected ASCVD hospitalization during the observation period.
- After stratification of the included ASCVD patients by elevated and normal Lp(a) levels, demographics, clinical characteristics, presence of comorbidities and most commonly prescribed medications were compared between the groups at baseline, while the occurrence of cardiovascular events and direct healthcare costs were compared **during the first 3 years of follow-up**.

Healthcare direct costs

Healthcare direct costs, calculated per patient per year (PPPY) **during the first 3 years of follow-up** were compared between ASCVD patients with elevated vs normal Lp(a) levels, considering total direct costs and single items, namely drug prescriptions, outpatient specialist services (OSS) and hospitalizations.

Outliers (patients with costs exceeding the mean cost plus 3-fold standard deviation) were excluded.

A Generalized Linear Model (GLM) adjusted for baseline variables was run to identify the potential predictors of cost increase during the first 3 years of follow-up.

Clinical outcomes

The rate of ASCVD events per 100 people/year **during the first 3 years of follow-up** was compared between the groups with elevated vs normal Lp(a) levels.

A Cox model was developed to identify the potential predictors of the increased risk of ASCVD **during the first 3 years of follow-up**.

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PATIENTS AND METHODS

Demographic, clinical and laboratory variables in ASCVD patients with elevated Lp(a) levels vs normal levels

At index-date, ASCVD patients with elevated Lp(a) levels (N=719) vs those with normal levels (N=2585) were younger (67.5 ± 12.9 vs 69.2 ± 13.4 years, p<0.010), had similar gender distribution (nearly 70% males) and higher likelihood of ischemic heart disease as index ASCVD hospitalization (73.9%, vs 68.5% p<0.010).

Moreover, patients with elevated Lp(a) levels showed a larger utilization of lipid-lowering therapies and antihypertensives, and slightly higher values of LDL-cholesterol compared with those with normal levels (107.1 ± 42.0 vs 99.5 ± 39.4 mg/dL, p<0.001).

Healthcare costs in ASCVD patients with elevated Lp(a) levels vs normal levels during the first 3 years of follow-up

As shown in **Table 1**, during the first 3 years of follow-up, ASCVD patients with elevated Lp(a) levels had significantly (p<0.05) higher total healthcare mean costs (PPPY) compared to those with normal levels, mainly driven by hospitalizations.

Table 1. Direct healthcare costs during the first 3 years of follow-up in patients with elevated Lp(a) levels vs normal levels. Costs are given as mean PPPY (€). Significant p values are in bold.

	ASCVD patients		
	Lp(a) <30 mg/dL N=1,842	Lp(a) ≥50 mg/dL N=487	p
Drugs prescriptions (€)	1,238.99 ± 1,302.51	1,261.95 ± 1,216.22	0.726
Hospitalizations (€)	3,357.73 ± 3,034.69	3,666.54 ± 3,034.44	**<0.05**
OSS provisions (€)	208.58 ± 454.07	286.86 ± 720.82	**<0.001**
Total costs (€)	**4,805.30 ± 3,559.64**	**5,215.36 ± 3,526.67**	**<0.05**

The GLM confirmed that during the first 3 years of follow-up, elevated Lp(a) levels resulted to a significant (p<0.05) increase (+€ 401.13) of total annual direct costs (**Table 2**).

Table 2. GLM for potential predictors of cost increase during the first 3 years of follow-up. Significant p values are in bold.

	€	95% CI		p
Age	21.13	10.93	31.32	**<0.001**
Male	595.31	309.40	881.23	**<0.001**
Statins	167.07	-121.45	455.60	0.256
Diabetes	1337.94	988.75	1687.12	**<0.001**
Lp(a) <30 mg/dL (Ref.)				
Lp(a) ≥50 mg/dL	**401.13**	**44.67**	**757.58**	**<0.05**

Cardiovascular outcomes in ASCVD patients during the first 3 years of follow-up

During the first 3 years of follow-up, ASCVD patients with elevated Lp(a) levels had significantly higher rates of ASCVD events vs those with normal levels (respectively, 19.9 vs 17.9 per 100 people/year, p<0.001). The Cox model revealed that diabetes and male gender increased the risk of incurring a second ASCVD event during the first 3 years of follow-up respectively by 22% (p<0.05) and by 23% (p<0.05).

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CONCLUSIONS

The present real-world analysis showed that **patients with a previous ASCVD event and elevated Lp(a) levels are at higher risk of incurring a successive ASCVD** event, and their management implies increased healthcare costs for the INHS, mainly due to hospitalization expenses.

These findings corroborate the **importance of Lp(a) testing** to implement more effective cardiovascular risk assessment and to prevent future events in high-risk patients, which in turn might alleviate the economic burden sustained by the healthcare systems for ASCVD patients [6].