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Role of Lipoprotein(a) in Familial Hypercholesterolaemia and Atherosclerotic Cardiovascular Disease

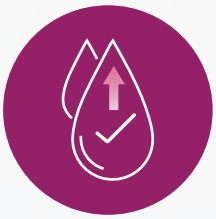
Genetic factors, pathology, and treatment approaches

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide

Dyslipidaemia (an abnormally high level of one or more lipids in the blood) is a well-known risk factor for CVD

Dyslipidaemia can cause blockages in major blood vessels by forming plaques, resulting in **atherosclerotic CVD (ASCVD)**

Lipids such as cholesterol are transported across the bloodstream by lipid carrier proteins known as **lipoproteins**



- High density lipoproteins (HDL) transport cholesterol to the liver for clearance
  - "Good" cholesterol

- Low density lipoproteins (LDL) transport cholesterol to other tissues
- Accumulation of LDL-bound cholesterol (LDL-C) in the blood can lead to clogging of arteries
  - "Bad" cholesterol

Serum LDL-C levels are an important indicator of CVD risk and severity

While conventional treatments are targeted towards decreasing LDL-C levels, these alone are not fully preventive or curative for ASCVD

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Lipoprotein(a): An emerging marker of ASCVD

Apolipoproteins

- Protein component of lipoproteins
- Help solubilise hydrophobic lipids in the bloodstream

Apolipoprotein B (ApoB)

- Main apolipoprotein found in LDL-C
- Associated with increased ASCVD risk at higher levels

Emerging evidence suggests the independent causal role of **lipoprotein(a) [Lp(a)]**, an LDL variant, in ASCVD

Structure and function of Lp(a)

Lp(a) is composed of apolipoprotein(a) [Apo(a)] covalently bound to ApoB

LPA (the gene encoding ApoA) has evolved from the duplication of the plasminogen gene and comprises kringle domains, which confer protease and fibrinolytic activity

***LPA* lacks some of these kringle sequences**

Evolution of Lp(a) as an ASCVD risk factor

1963

Identification and characterisation of Lp(a)

1974–80

Genetic control of Lp(a) recognised

Lp(a) levels found to be linked to coronary heart disease (CHD)

2009

Large-scale studies reporting Lp(a) as a potentially causal risk factor in ASCVD

While LDL-C and ApoB levels are important biomarkers of lipid metabolism, Lp(a) is now emerging as a potential driver of ASCVD

Yet, Lp(a) levels are rarely measured in routine clinical practice

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Genetics and pathology of Lp(a) in ASCVD and therapeutic strategies

Genetic influence on Lp(a)

70% to ≥90%

Lp(a) levels are determined genetically, suggesting significant genetic control on the risk of ASCVD

Findings from genetic and epidemiological studies

- *LPA* genotypes and corresponding high Lp(a) levels are associated with an increased risk of CHD and calcific aortic valvular disease
- Single nucleotide polymorphisms in the *LPA* genetic loci have been found to be strongly associated with Lp(a) levels
- Potential associations of Lp(a) with cerebrovascular disease and risk of stroke

Pathological mechanisms of Lp(a)-mediated ASCVD

Atherosclerosis

Oxidised phospholipids bound to Apo(a) trigger:

- Inflammation
- Calcification
- Fat deposition in arteries

Lp(a) binds to the extracellular matrix of endothelial cells and interacts with fibrinogen on the arterial wall, thereby:

- Activating monocyte migration
- Releasing pro-inflammatory cytokines

Atherothrombosis

Apo(a) is structurally similar to plasminogen and inhibits its activation by competitively binding its interacting partners, causing:

- Inhibition of fibrinolysis
- Promotion of thrombosis

Challenges in adopting Lp(a) as an ASCVD risk factor

- Large distribution of Lp(a) in serum lipid fraction
- Variability in level of Lp(a)
- Differences in measurement thresholds across assays
- Heterogeneous size of Lp(a) particles
- Differences in methods of measurement, assay calibrations, and sensitivity

Existing therapies

- Statins
- Lipoprotein apheresis
- Monoclonal antibodies against proprotein subtilisin kexin type 9 (PCSK9), which controls LDL receptor (LDLR) levels

Therapies under investigation

- Anti-sense oligonucleotide (pelacarsen)
- siRNAs targeting Apo(a)

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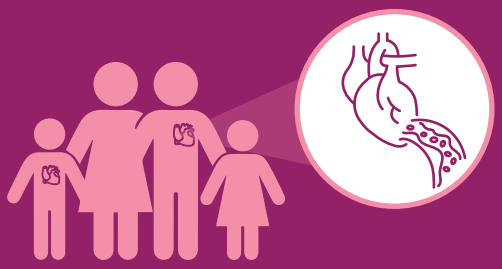
Lp(a) as a risk predictor of ASCVD in familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a genetic condition in which affected individuals have significantly elevated levels of LDL-C since birth



FH affects roughly **1/250** individuals

The most common cause of FH are **mutant alleles**

- ***LDLR* (90% of cases)**
- ***APOB***
- ***PCSK9***

- These mutations result in dysfunction of proteins involved in LDL-C clearance
- This has also been shown to affect plasma levels of Lp(a) through a gene dosage effect of LDLR mutations on plasma Lp(a) level

As conventional therapies focus on decreasing the level of LDL-C and ApoB, elevated Lp(a) levels pose a continuous residual risk to patients with FH receiving treatment

Monitoring Lp(a) levels can help in better risk stratification of patients with FH

Current treatments for FH

- Statins are started early in children with heterozygous FH to control LDL-C levels
- A PCSK9 inhibitor is used in addition to statins in very high-risk adult patients with heterozygous FH and ASCVD
- PCSK9 inhibition using the monoclonal antibody evocumbam has been shown to moderately lower Lp(a) levels

Lp(a) lowering strategies

- Cholesteryl ester transfer protein inhibitors
- Hormonal therapy using thyromimetics (eprotirome) and oestrogen
- Mipomersen
- Lipoprotein apheresis
- RNA-based drugs
- Inhibitors targeting lipoprotein receptors

- **There is a strong dose-dependent effect of the level of Lp(a) on the risk of ASCVD**
- **The genetic influence on the level of Lp(a) is significantly higher than dietary and environmental influences**
- **Robust and universally applicable screening strategies are needed for measurement of Lp(a) and risk stratification of various populations at risk of ASCVD**
- **A combinatorial treatment approach is warranted for effective management of patients with FH, given the synergistic effect of elevated LDL-C and Lp(a)**

References

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