Low-density lipoproteins cause atherosclerotic cardiovascular disease (ASCVD)

1. Evidence from genetic, epidemiologic and clinical studies

A Consensus Statement from the European Atherosclerosis Society Consensus Panel
Rationale
INTERHEART Study

LDL accounted for ~50% of the Population Attributable Risk

Slide courtesy of MJ Chapman
Why We Need This Statement?

LDL cholesterol has long been implicated as a major modifiable cardiovascular risk factor
BUT
Some have queried whether it is simply a biomarker
The Evidence Reviewed:

- To avoid selection bias we evaluated the *totality of evidence* from separate meta-analyses of prospective epidemiologic studies, Mendelian randomization and other genetic studies, together with randomized clinical trials for causality of LDL in ASCVD.

- The database included *more than 200 studies involving over 2 million participants with over 20 million person-years of follow-up and more than 150,000 cardiovascular events*.
**LDL vs. LDL Cholesterol**

LDL is the main apolipoprotein B-containing lipoprotein

LDL-C is the total amount of cholesterol contained in LDL particles, and is usually calculated

Under most conditions, LDL-C concentration and LDL particle number are highly correlated

**LDL particles comprise ~ 90% of circulating apoB-containing lipoproteins**
Evidence from Inherited Disorders of Lipid Metabolism
Familial Hypercholesterolaemia (FH)

The most frequently mutated gene in FH is the LDL receptor gene.
LDL-C Burden With or Without FH as a Function of Age

Coronary disease and death before age 20

Homozygous FH

Threshold for CHD

12.5 years

Heterozygous FH

35 years

Untreated coronary disease before age 55–60

Female sex

Smoking

Hypertension

Diabetes

↑ TG

↓ HDL-C

↑ Lp(a)

Cumulative LDL-C (mmol/L)

Without FH

Age (years)

0 15 30 45 60

55 years

Evidence from Prospective Epidemiologic Studies
Prospective Epidemiologic Studies

Plasma LDL-C concentration is strongly and log-linearly associated with a dose-dependent increase in risk of ASCVD events.

European Heart Journal. doi:10.1093/eurheartj/ehx144
Mendelian Randomization
A naturally randomized trial which largely avoids confounding by other factors
Continuous, dose-dependent and log-linear causal association between the magnitude of the absolute change in LDL-C level and the lifetime risk of CHD.
Mendelian Randomization Studies

Each of the genetic variants associated with LDL-C has a similar effect on the risk of CHD per unit lower LDL-C.

European Heart Journal. doi:10.1093/eurheartj/ehx144
Mendelian Randomization Studies

- Meta-analyses of Mendelian randomization studies involving >300,000 participants and 80,000 CHD cases provide compelling evidence that LDL is causally associated with the risk of ASCVD.

- The causal effect of LDL on ASCVD is *largely independent* of the mechanism by which LDL is ‘lowered’.
Evidence from Randomized Controlled Trials
Reducing plasma LDL-C levels with a statin leads to dose-dependent reduction in the risk of major ASCVD events that is proportional to the absolute magnitude of the reduction in achieved LDL-C.
Randomized Controlled Trials

Absolute yearly event rate on LDL-lowering treatment was strongly and linearly associated with the absolute achieved LDL-C level.

Evidence from Randomized Controlled Trials

These trials are with pharmacological agents that involve the LDL receptor.
Evidence from IVUS Studies

Progression of coronary atherosclerotic plaque volume can be arrested at achieved LDL-C levels of ~1.8 mmol/L (70 mg/dL)

Summary of the Causality Evidence
## Criteria for Causality: LDL and ASCVD

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Evidence Grade*</th>
<th>Summary of Evidence for LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plausibility</td>
<td>1</td>
<td>• LDL and other apo B-containing lipoproteins (VLDL, IDL and Lp(a)) are directly implicated in the <strong>initiation and progression of ASCVD</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Experimentally induced elevations in plasma LDL and other apoB-containing lipoproteins <strong>lead to atherosclerosis</strong> in all mammalian species studied.</td>
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<tr>
<td>Strength</td>
<td>1</td>
<td>• Monogenic and polygenic-mediated <strong>lifelong elevations in LDL</strong> lead to markedly higher lifetime risk</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>1</td>
<td>• Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials uniformly demonstrate a <strong>dose-dependent, log-linear association</strong> between the <strong>absolute magnitude of exposure to LDL</strong> and risk of ASCVD</td>
</tr>
<tr>
<td>Temporal sequence</td>
<td>1</td>
<td>• Monogenic lipid disorders and Mendelian randomization studies demonstrate that <strong>exposure to elevated LDL precedes the onset of ASCVD</strong></td>
</tr>
<tr>
<td>Specificity</td>
<td>1</td>
<td>• Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that <strong>LDL is associated with ASCVD independent of other risk factors</strong></td>
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<td>Consistency</td>
<td>1</td>
<td>• More than 200 studies involving &gt;2 million participants with &gt;20 million person-years of follow-up and &gt;150,000 cardiovascular events consistently demonstrate a <strong>dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD</strong></td>
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<td>Coherence</td>
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<td>• Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a <strong>dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD</strong></td>
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<td>Reduction in risk with intervention</td>
<td>1</td>
<td>• More than 30 randomized trials involving &gt;200,000 subjects and 30,000 ASCVD events evaluating therapies specifically designed to lower LDL consistently demonstrate that reducing LDL-C reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C</td>
</tr>
</tbody>
</table>

Criteria graded according to quality criteria adopted by the ESC; Class 1: Evidence and/or general agreement that the criterion for causality is fulfilled. Class 2: Conflicting evidence and/or a divergence of opinion about whether the criterion indicated causality European Heart Journal. doi:10.1093/eurheartj/ehx144.
LDL and ASCVD: Key Findings

- Cumulative LDL burden determines the initiation and progression of ASCVD.
- There is a dose-dependent, log-linear association between absolute LDL-C level and cardiovascular risk. This association is independent of other cardiovascular risk factors and consistent across the multiple lines of evidence.
- Evidence accrued from >30 randomized trials involving >200,000 individuals and 30,000 cardiovascular events evaluating treatments specifically designed to lower LDL consistently show that reducing LDL-C reduces the risk of cardiovascular events. This benefit is proportional to the absolute reduction in LDL-C.
Implications

• Cumulative LDL arterial burden is a central determinant of the initiation and progression of ASCVD

• The lower the LDL-C level attained by agents which primarily target LDL receptors, the greater the clinical benefit accrued.

• Both proportional (relative) risk reduction and absolute risk reduction relate to the magnitude of LDL-C reduction.

• Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable, especially in those with familial hypercholesterolaemia.