Low-density lipoproteins cause atherosclerotic cardiovascular disease (ASCVD)
1. Evidence from genetic, epidemiologic and clinical studies

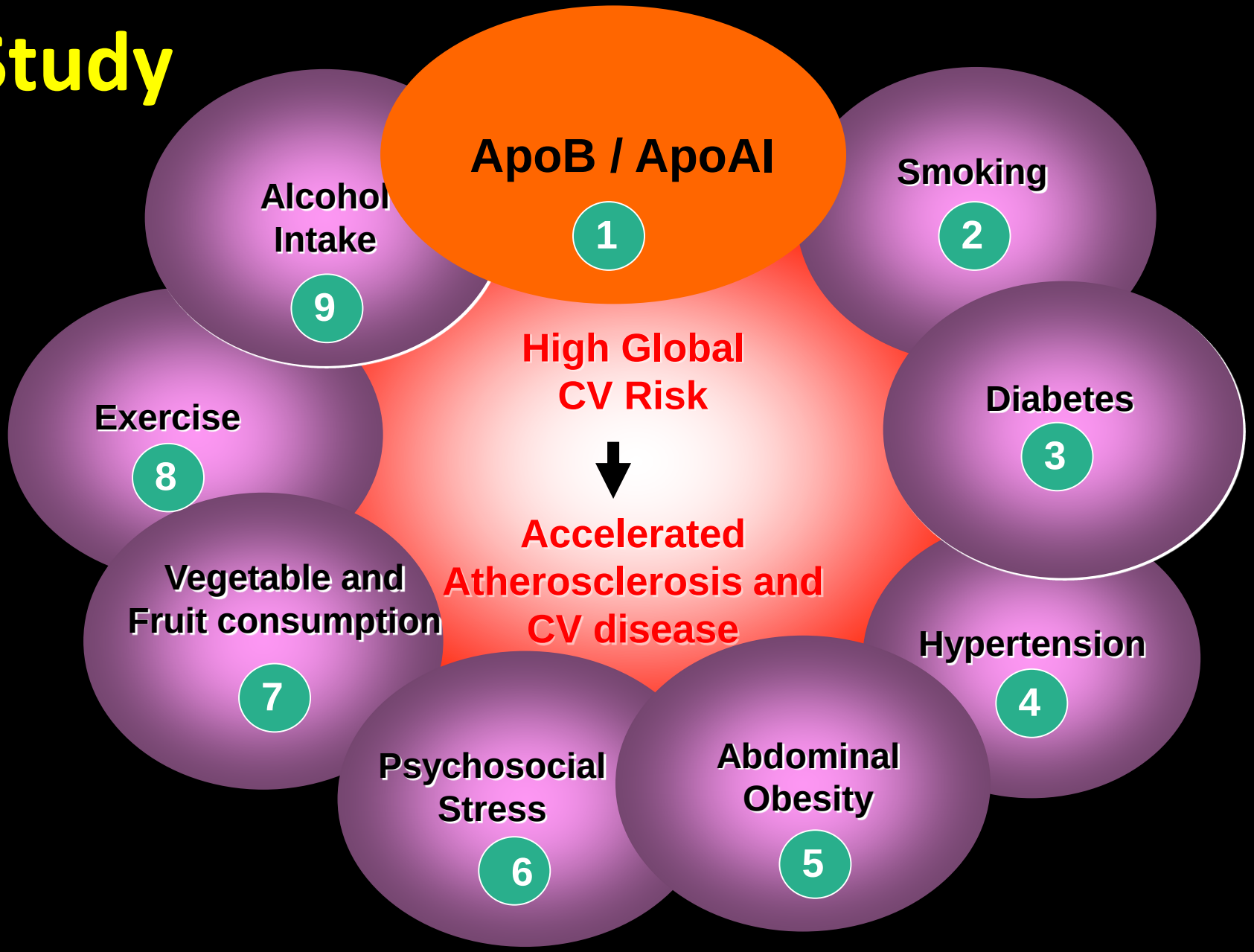
A Consensus Statement from the

European Atherosclerosis Society Consensus Panel

Rationale

INTERHEART Study

LDL accounted for ~50% of the Population Attributable Risk



Slide courtesy of MJ Chapman
S. Yusuf et al. Lancet 2004; 364:937-52

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

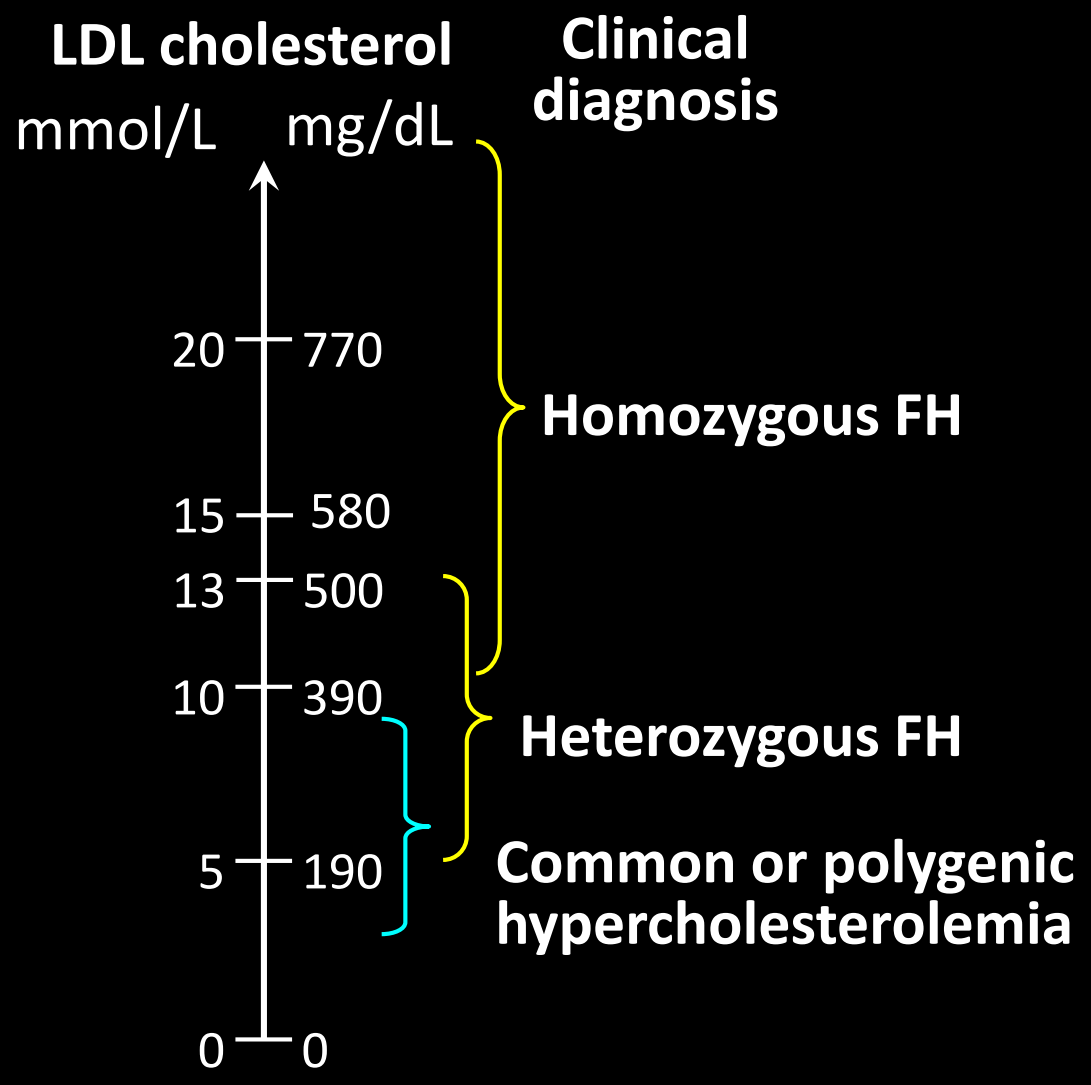
LDL-C is the total amount of cholesterol contained in LDL particles, and is usually calculated

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

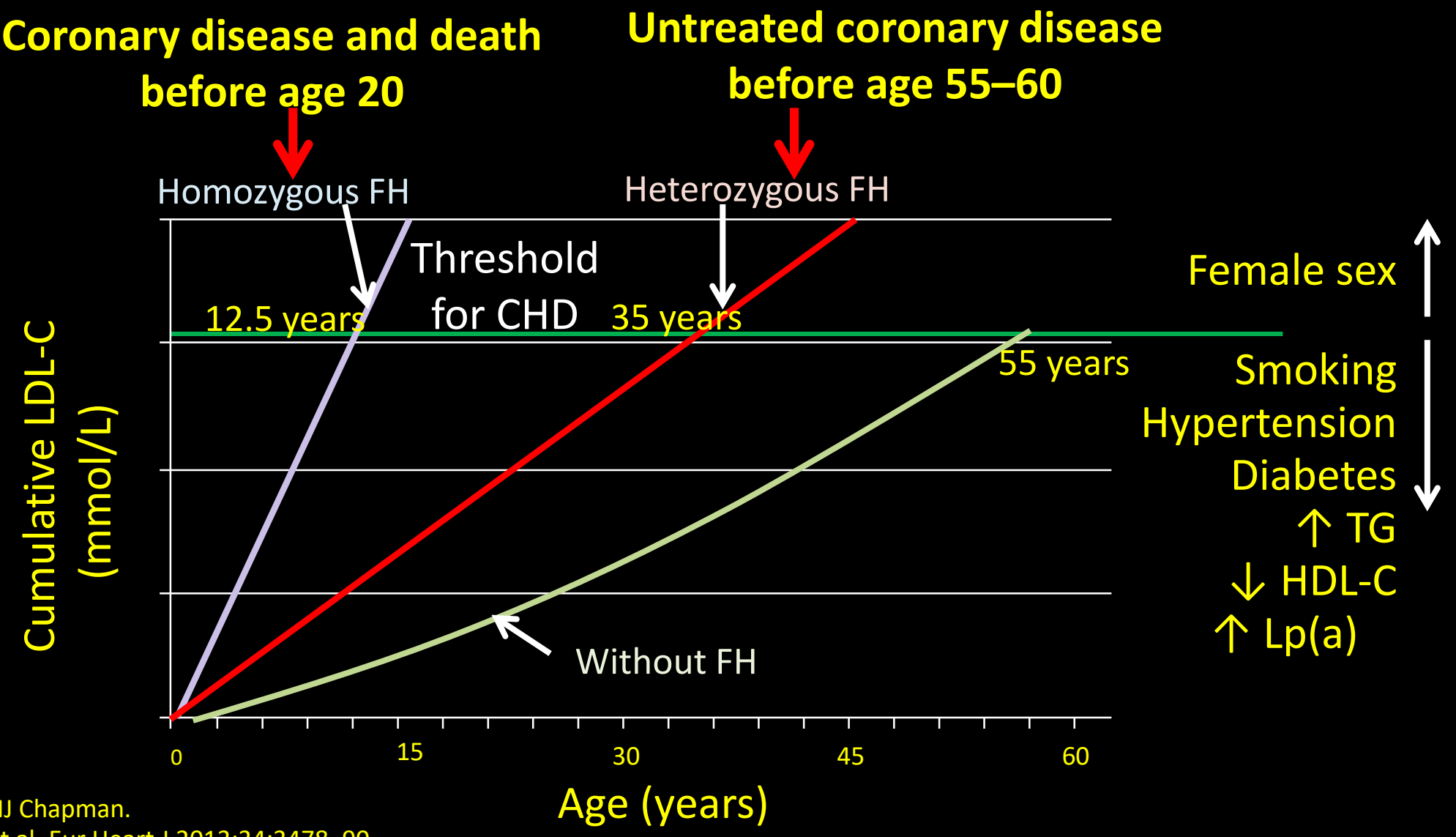
Familial Hypercholesterolaemia (FH)



The most frequently mutated gene in FH is the LDL receptor gene

Adapted from Cuchel M, Eur Heart J 2014;35:2146-57

LDL-C Burden With or Without FH as a Function of Age

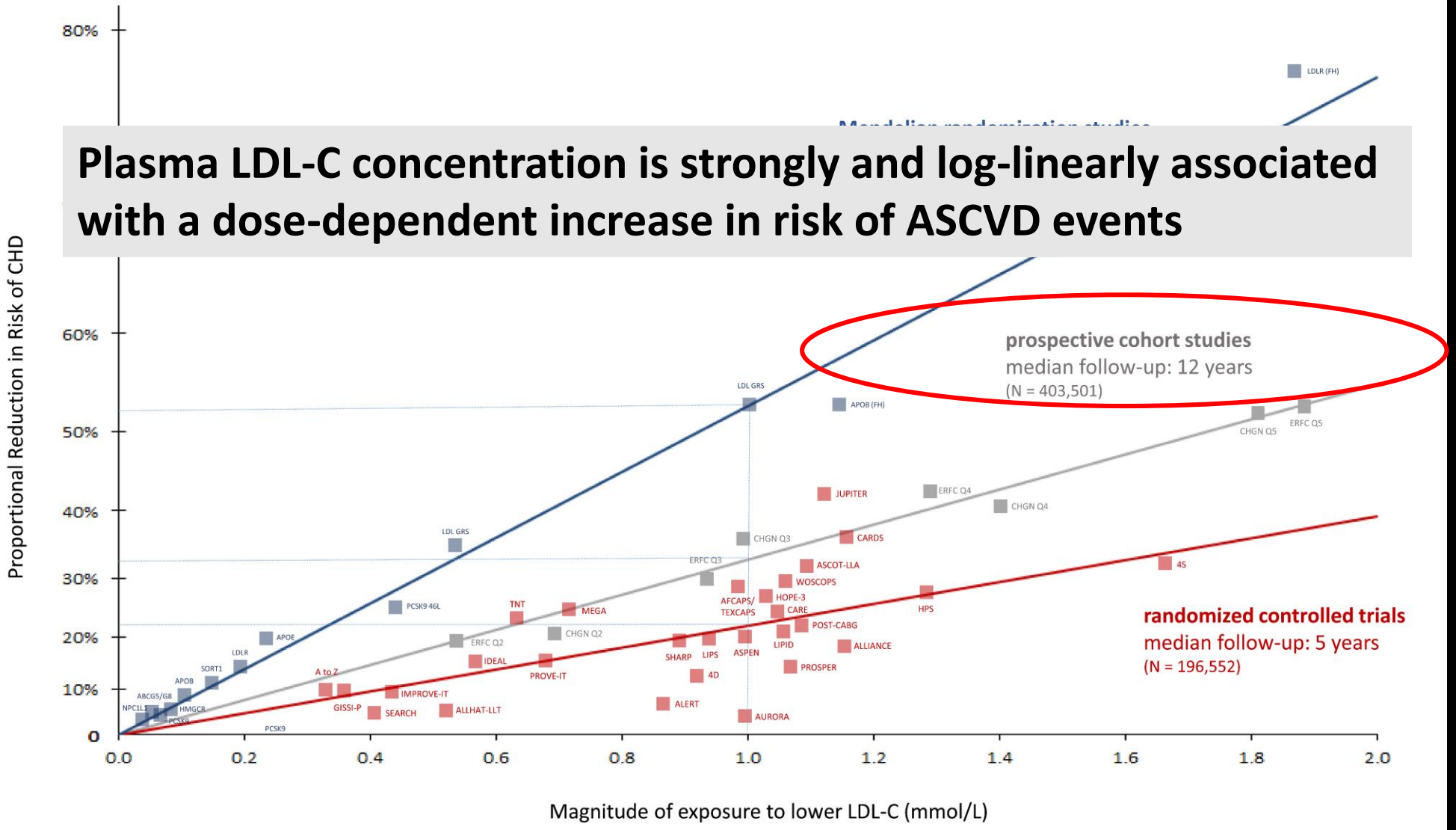


Slide courtesy of MJ Chapman.
Nordestgaard BG et al. Eur Heart J 2013;34:3478–90.

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

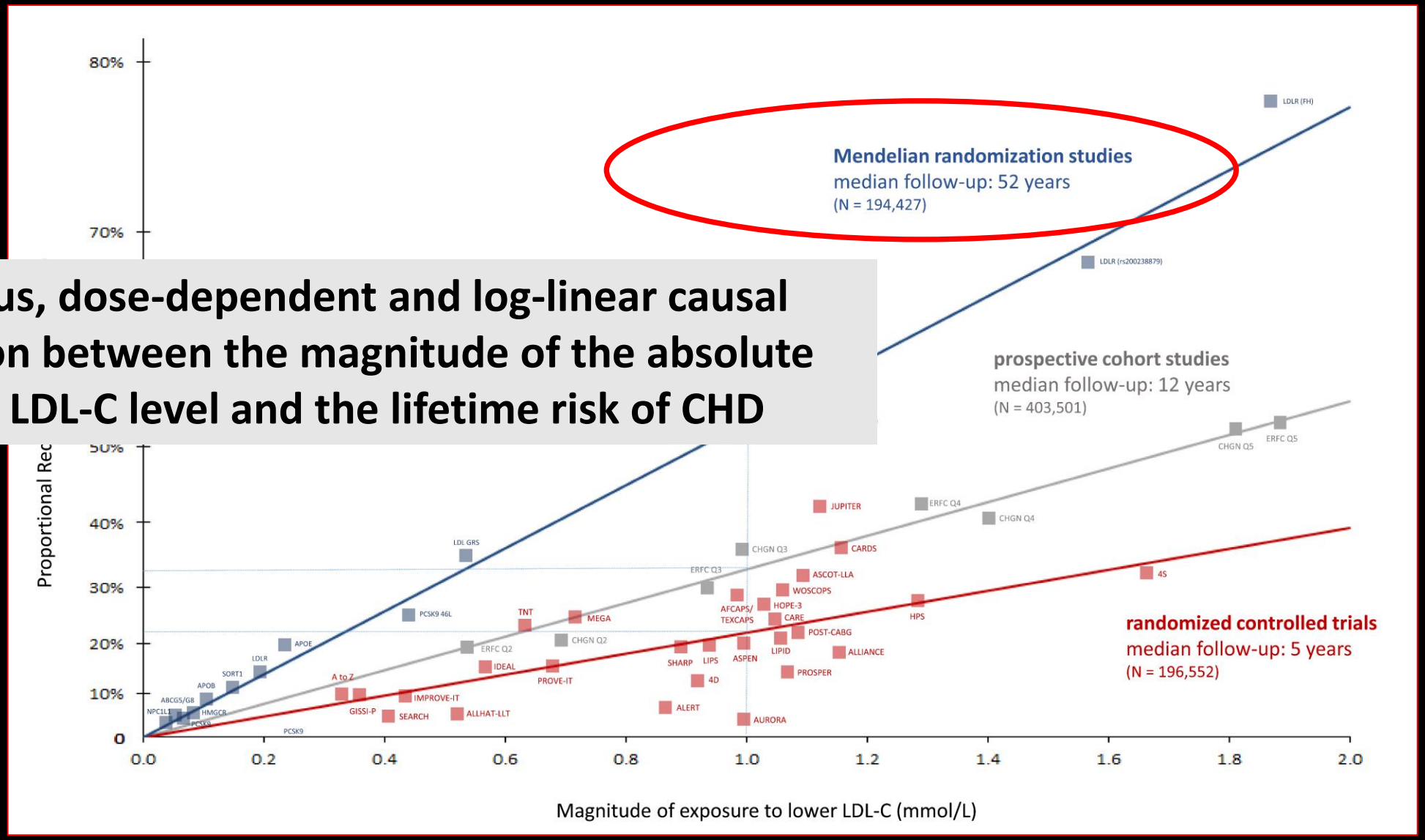


European Heart Journal. doi:10.1093/eurheartj/ehx144

Mendelian Randomization

A naturally randomized trial which largely avoids confounding by other factors

Mendelian Randomization Studies

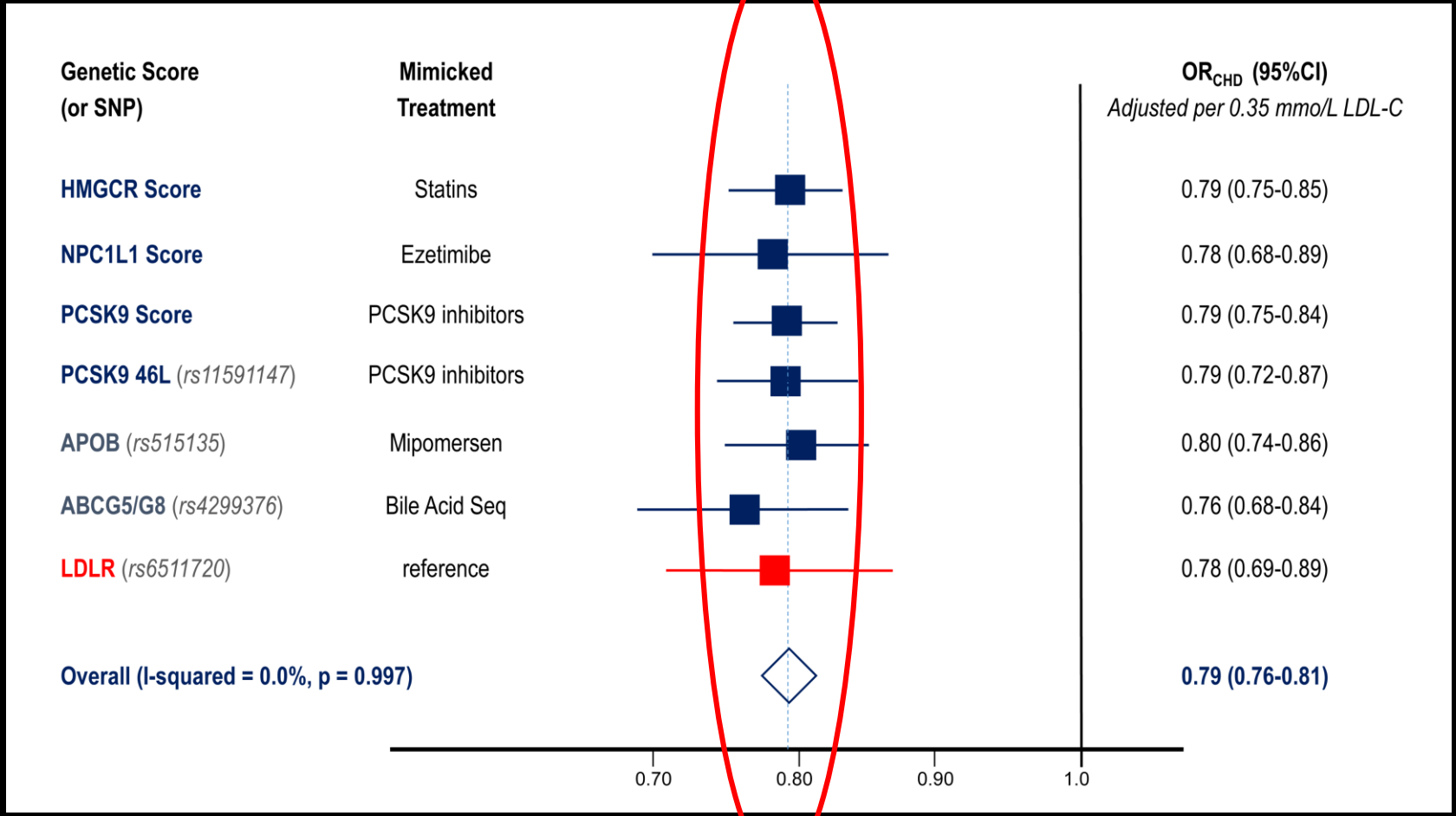


Continuous, dose-dependent and log-linear causal association between the magnitude of the absolute change in LDL-C level and the lifetime risk of CHD

European Heart Journal. doi:10.1093/eurheartj/ehx144

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***



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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'

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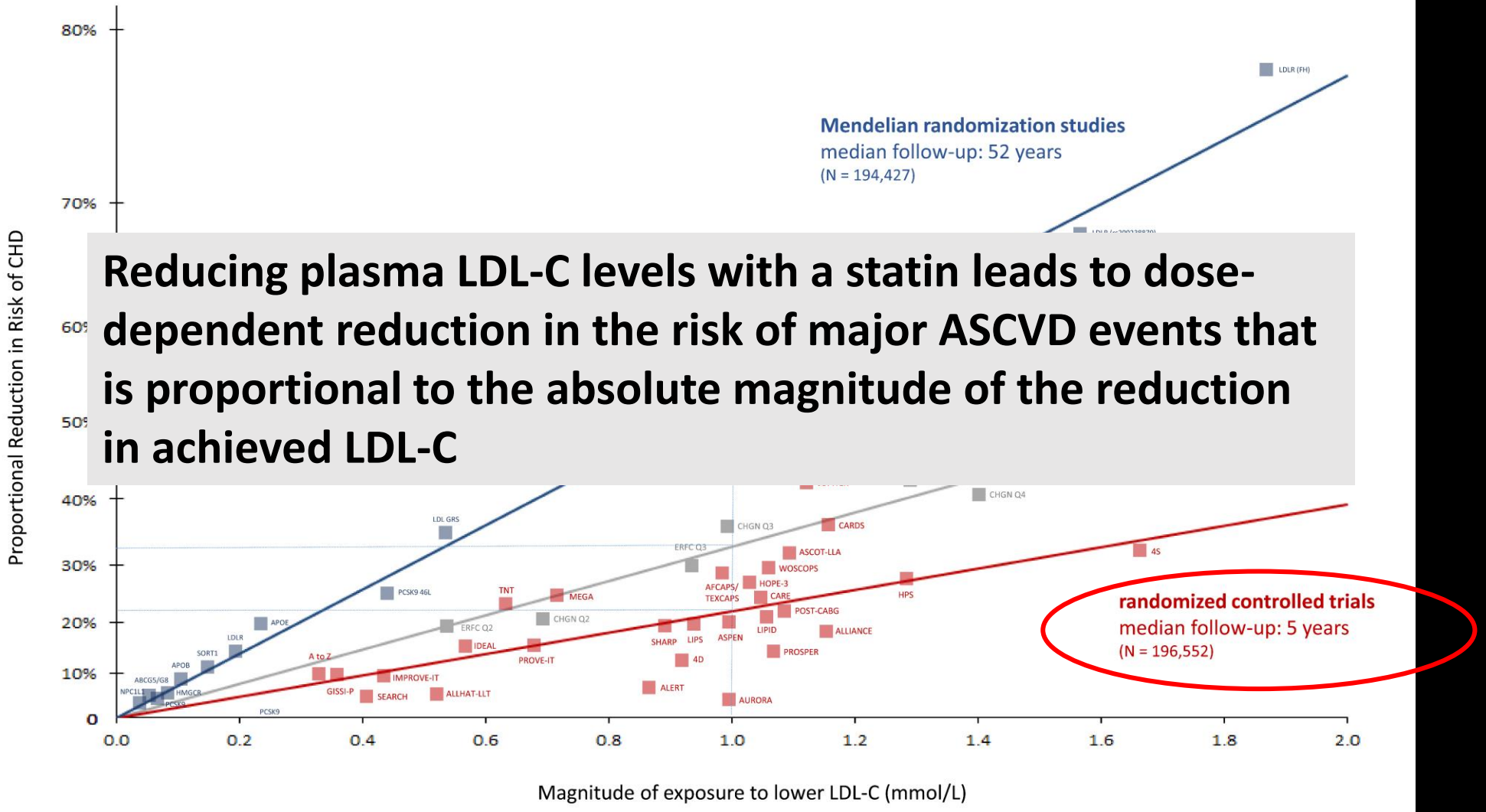
Evidence from Randomized Controlled Trials

Randomized Controlled Trials

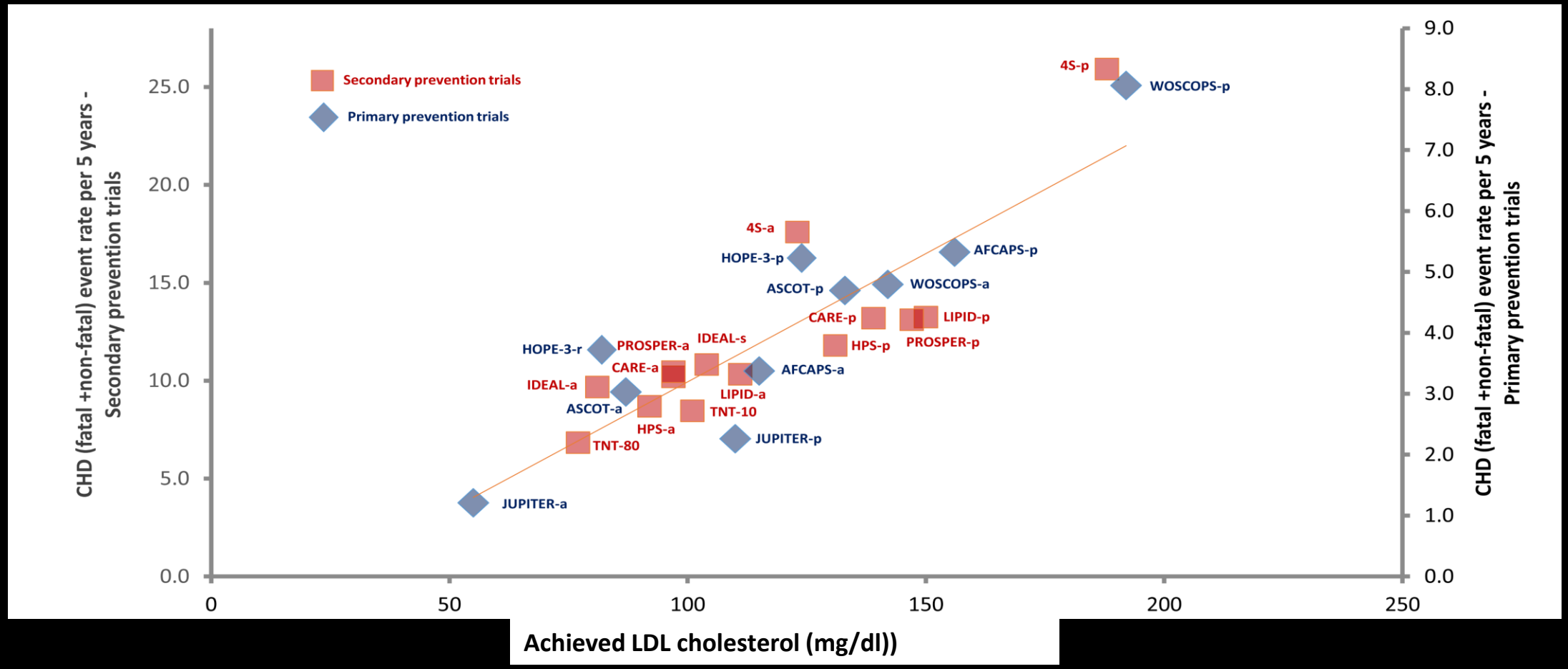


Reducing plasma LDL-C levels with a statin leads to dose-dependent reduction in the risk of major ASCVD events that is proportional to the absolute magnitude of the reduction in achieved LDL-C

European Heart Journal. doi:10.1093/eurheartj/ehx144.

Randomized Controlled Trials

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



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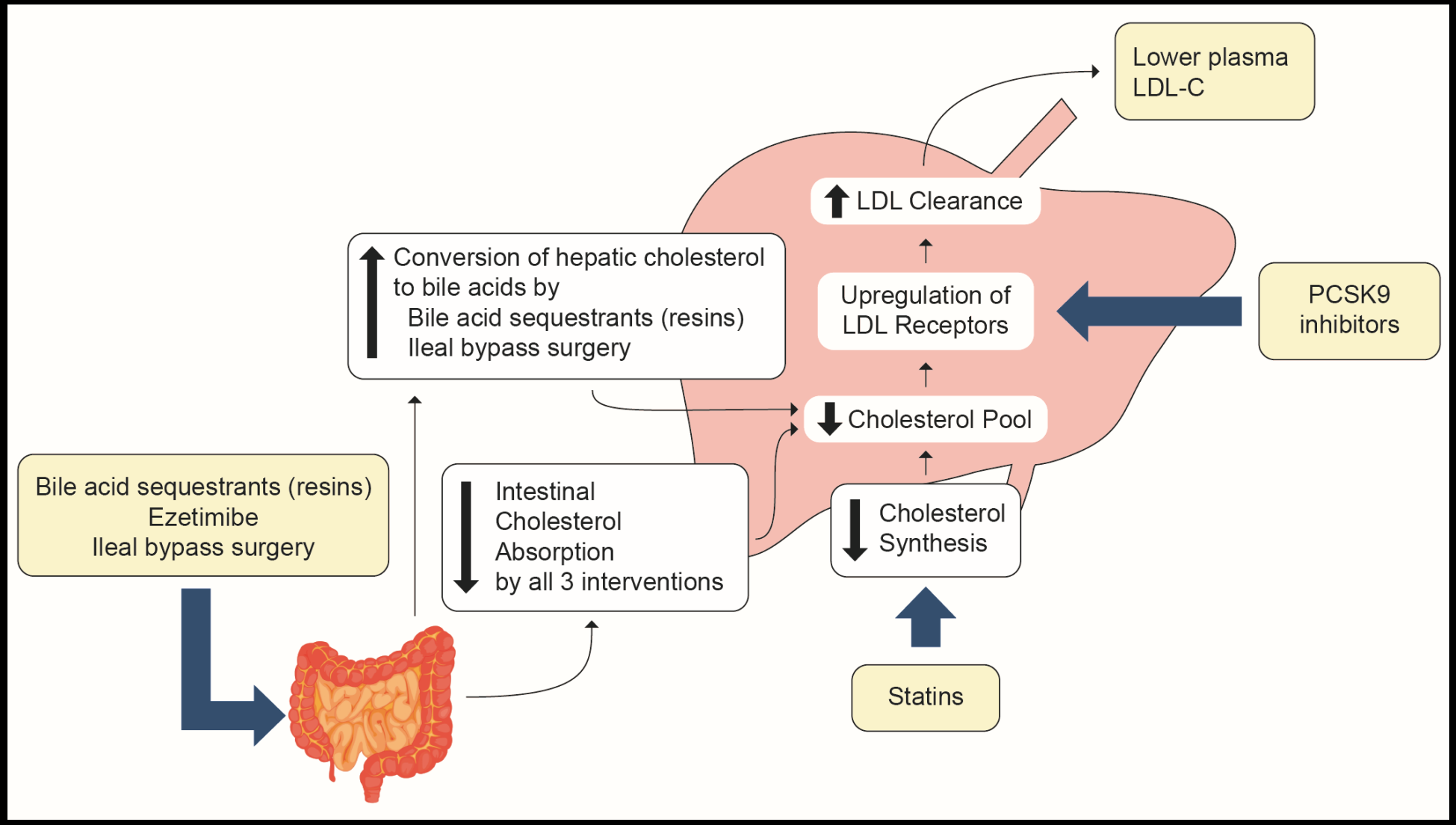
Evidence from Randomized Controlled Trials

These trials are with pharmacological agents that involve the LDL receptor

Site of Action of LDL-lowering Therapies



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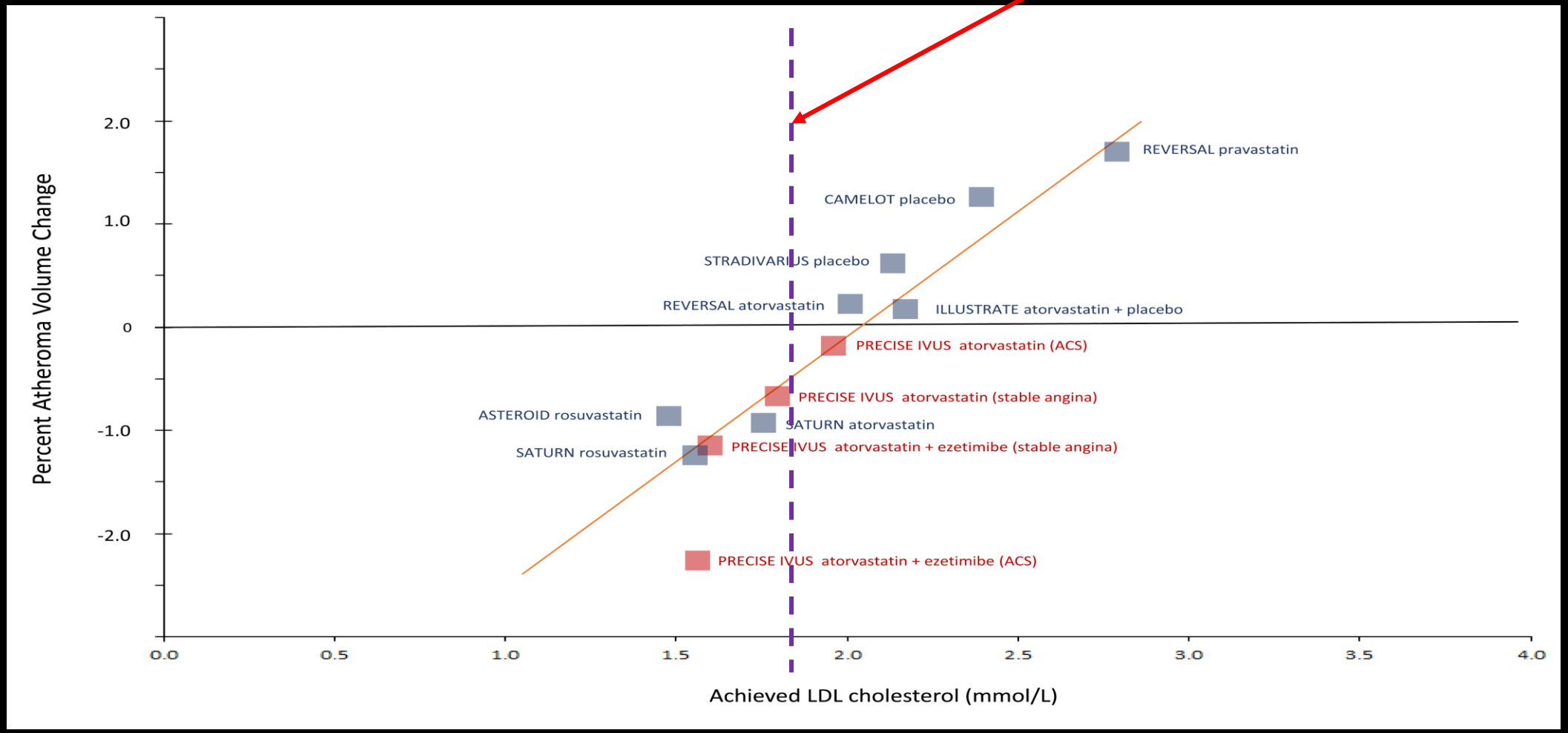
Evidence from IVUS Studies

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



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Summary of the Causality Evidence

Criteria for Causality: LDL and ASCVD

Criterion	Evidence Grade*	Summary of Evidence for LDL
Plausibility	1	• LDL and other apo B-containing lipoproteins (VLDL, IDL and Lp(a)) are directly implicated in the **initiation and progression of ASCVD** • Experimentally induced elevations in plasma LDL and other apoB-containing lipoproteins **lead to atherosclerosis** in all mammalian species studied.
Strength	1	• Monogenic and polygenic-mediated **lifelong elevations in LDL** lead to markedly **higher lifetime risk**
Biological gradient	1	• Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials uniformly demonstrate **a dose-dependent, log-linear association** between the **absolute magnitude of exposure to LDL and risk of ASCVD**
Temporal sequence	1	• Monogenic lipid disorders and Mendelian randomization studies demonstrate that **exposure to elevated LDL precedes the onset of ASCVD**
Specificity	1	• Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that **LDL is associated with ASCVD independent of other risk factors**

Criteria for Causality: LDL and ASCVD, contd

Criterion	Evidence Grade*	Summary of Evidence for LDL
Consistency	1	• More than 200 studies involving >2 million participants with >20 million person-years of follow-up and >150,000 cardiovascular events consistently demonstrate a **dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD**
Coherence	1	• Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a **dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD**
Reduction in risk with intervention	1	• More than 30 randomized trials involving >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

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.

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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

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CURRENT OPINION

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