

# The Cholesterol Hypothesis to the Cholesterol Principle

Genetic, Epidemiologic, and Clinical Trials Proving Causality

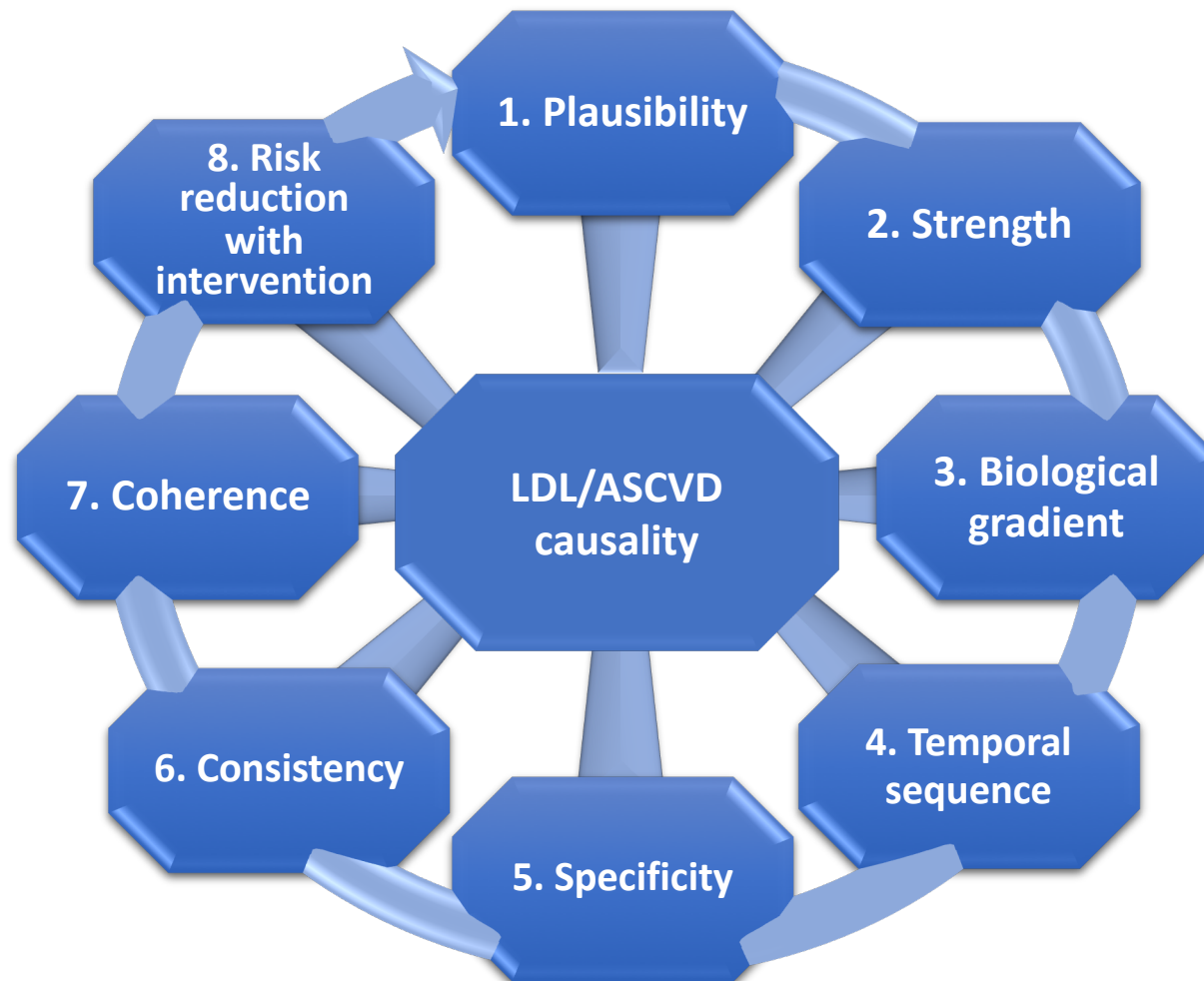
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# Introduction

- The Cholesterol Hypothesis, also known as the Lipid Hypothesis, postulates a direct link between blood cholesterol levels and CHD.
  - Studies show a higher and earlier occurrence of heart disease in patients with higher blood lipid levels.
  - Strategies to decrease plasma lipid levels (primarily LDL-C) reduces CHD risk at the patient and population level.
- Although other CHD risk factors exist, the causal role of lipid accumulation in CHD pathogenesis has been shown in clinical, epidemiologic, and genetic analyses.
- Based on the strength of available evidence, is it time to rename the “Cholesterol Hypothesis” the “Cholesterol Principle”?

CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol.

# The Cholesterol Hypothesis: Criteria for LDL-C and ASCVD Causality

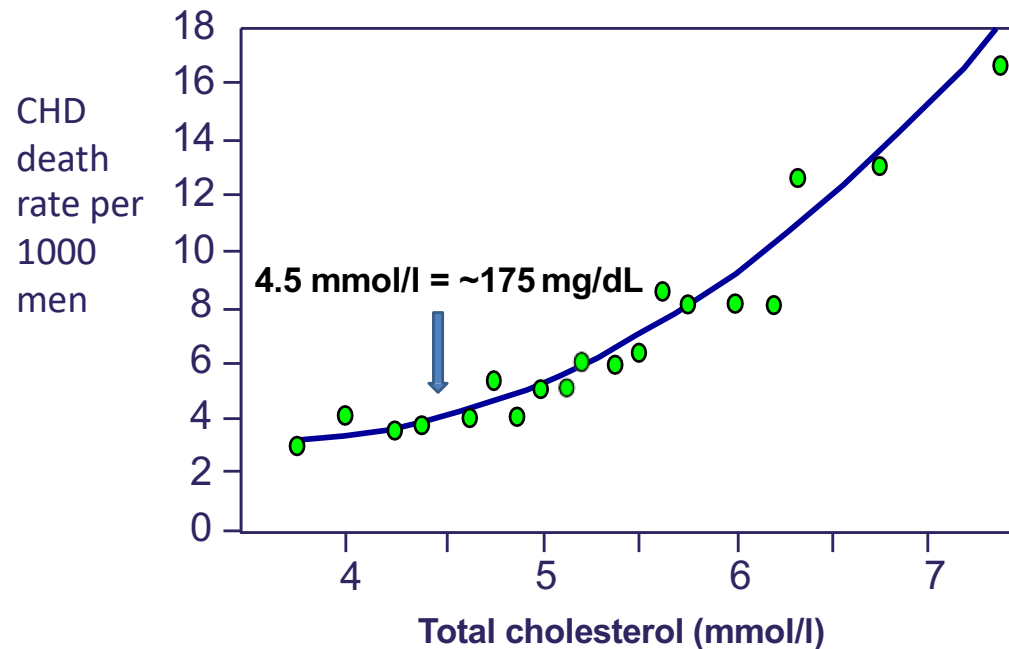


ASCVD=atherosclerotic cardiovascular disease; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol.

Ference BA, et al. *Eur Heart J*. 2017;38(32):2459-2472.

# MRFIT (1986): Established Epidemiologic Association Between Cholesterol and Cardiovascular Mortality

MRFIT: Age-adjusted 6-year CHD death rate and total serum cholesterol in 361,662 U.S. men (age 35-57 years)



CHD=coronary heart disease; MRFIT=Multiple Risk Factor Intervention Trial.

Martin MJ, et al. *Lancet*. 1986;2:933-936.

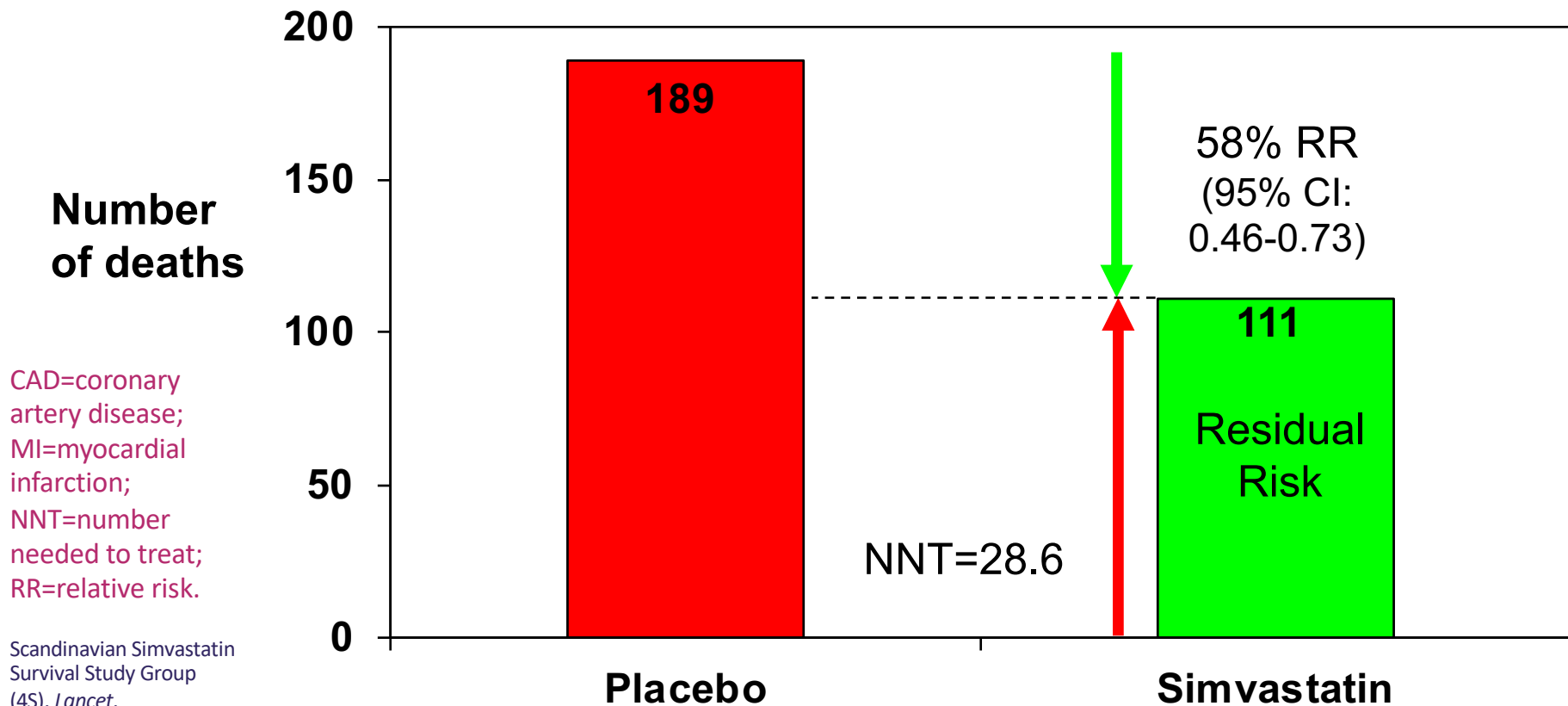
# Residual Risk

- Cholesterol reduction provides a powerful tool to reduce CHD risk, but elevated lipid levels are not the only CHD risk factor.
- A substantial proportion of statin-treated patients experience residual risk due to unaddressed inflammatory risk.
- A number of biologic processes may drive this residual risk.

CHD=coronary heart disease.

# Scandinavian Simvastatin Survival Study (4S) Group: Primary Endpoint—Coronary Mortality

Randomized controlled trial of cholesterol-lowering in 4444 patients with CAD (post-MI and/or angina) and total cholesterol 212-309 mg/dL, to investigate whether long-term simvastatin 20-40 mg/day reduced total mortality and coronary events

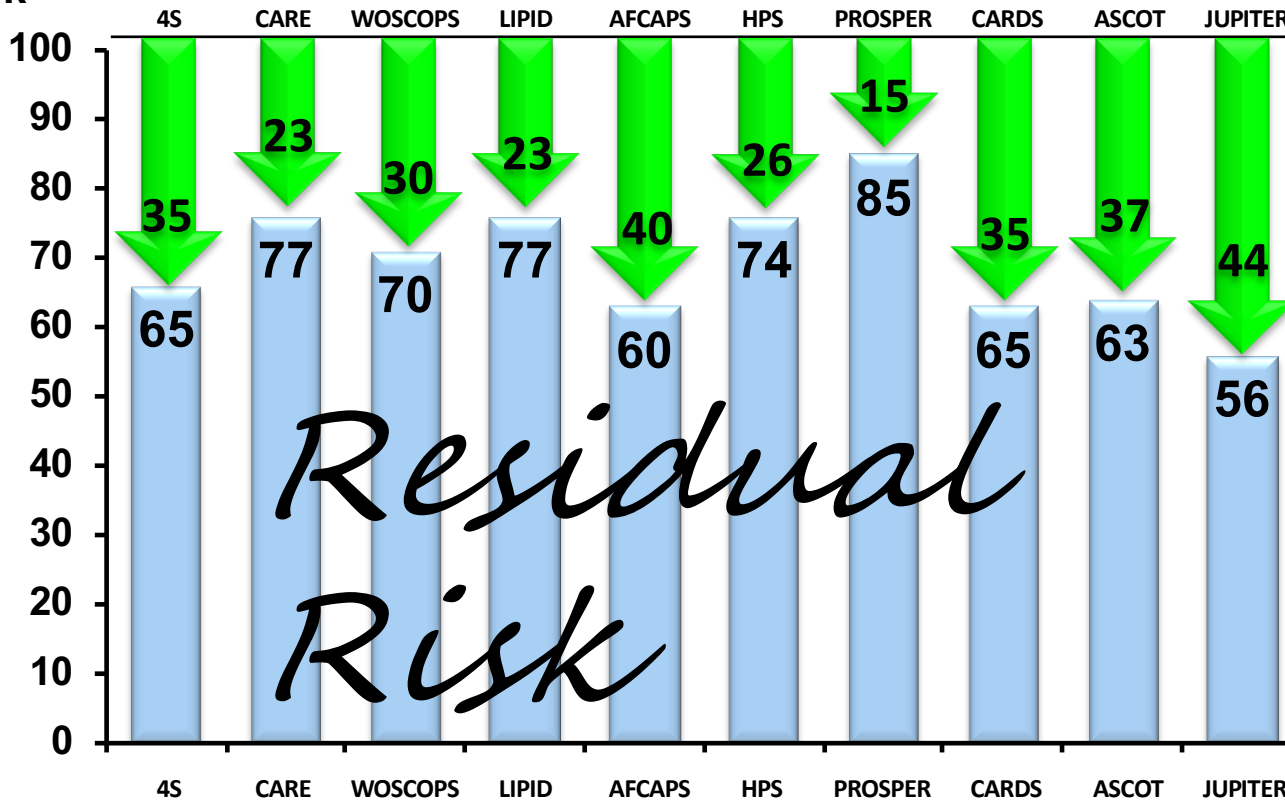


CAD=coronary artery disease;  
MI=myocardial infarction;  
NNT=number needed to treat;  
RR=relative risk.

Scandinavian Simvastatin Survival Study Group (4S). *Lancet*. 1994;344:1383-1389.

# Despite Benefits of LDL-C Lowering with Statins, Treated Patients have Substantial Residual Risk for CAD Events

Relative Risk



4S=Scandinavian Simvastatin Survival Study; AFCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA= Anglo-Scandinavian Cardiac Outcomes Trial; CAD=coronary artery disease; CARDS=Collaborative Atorvastatin Diabetes Study; CARE=Cholesterol and Recurrent Events; HPS=Heart-Protection Study; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C=low-density lipoprotein cholesterol; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; PROSPER=Prospective Study of Pravastatin in Elderly at RISK; WOSCOPS=West of Scotland Coronary Prevention Study.

Jellinger P, et al. *Endocr Pract.* 2017;23(4):479-497. CTT Collaborators. *Lancet.* 2005;366:1267-1278.

# Conclusion

- Elevated cholesterol is an established CHD risk factor
  - CHD risk is amplified in patients with elevated lipid levels, particularly LDL-C
  - Strategies to decrease LDL-C have been shown to successfully reduce CHD events
  - Also known as the “Cholesterol Principle”
- Inflammation also contributes to atherosclerosis development; it is an independent treatment target and research is ongoing.

CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol.