HDL-cholesterol myth:

Higher HDL-cholesterol level means lower cardiovascular disease risk.

HDL-cholesterol truth:

HDL-cholesterol level is only a part of the HDL story; it doesn't give an indication if the HDL particle is functioning properly.

How did this myth start?

The concept that high-density lipoprotein cholesterol (HDL-C) is beneficial dates back to research from nearly 70 years ago.[1]

And in 1977, the prominent Framingham cohort study demonstrated that low HDL-cholesterol concentrations were associated with increased risks of coronary heart disease.[2]

In 1986, the second HDL measurement from the Framingham cohort became available for long-term analysis:[3] Individuals in the lowest 20% of HDL-cholesterol levels had twice the risk of coronary heart disease compared to those in the highest 20% of HDL-cholesterol levels.[3]

This inverse association between HDL-cholesterol level and disease risk has been replicated in multiple, large-scale observational studies such as the Münster Heart Study, the Atherosclerosis Risk in Communities (ARIC), and the Emerging Risk Factors Collaboration (ERFC) combined analysis.[4-6]

Low HDL-cholesterol level was thus believed to be a risk factor for heart health.

1951
Study found HDL-cholesterol level was reduced in patients with coronary heart disease

1977
The Framingham Study 4-year data

1986
The Framingham Study 12-year data

1997
The Münster Heart Study

2001
The ARIC study

2009
ERFC combined analysis

HDL assumption called into question by multiple studies

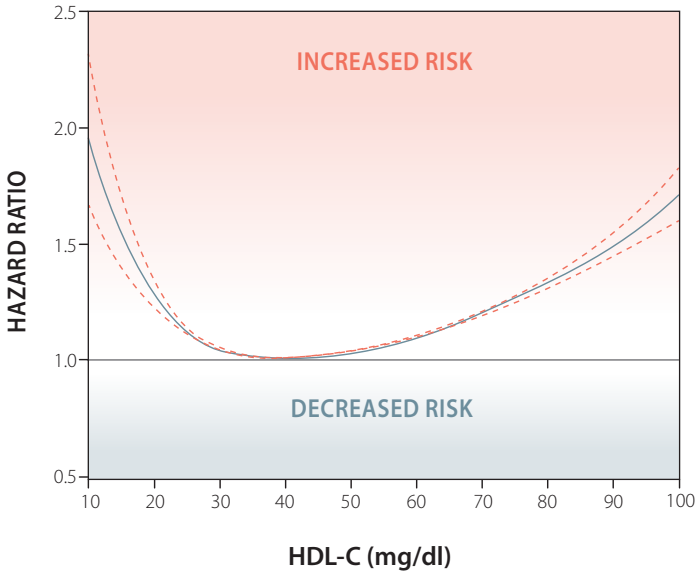
However, recent large-scale genetic studies have raised doubt about the accuracy of that assumption.

Multiple studies involving tens of thousands of individuals have found that genetically higher or lower HDL-cholesterol concentrations do not change risks of cardiovascular disease or type 2 diabetes.[7-10]

These data indicate HDL-cholesterol level itself isn't likely to be protective against these diseases.

In fact, higher HDL-cholesterol level itself is not always better. Data from the more recent cohort studies found a U-shaped association.[11-12]

Figure 1: U-Shaped Curve with HDL-C and All-Cause Mortality
(figure adapted from Bowe B et al. *Clin J Am Soc Nephrol.* 2016;11(10):1784-1793.[21]



In a cohort of 1,764,986 men in the US followed for ~10 years, very-low and high HDL-C concentrations were associated with increased risk of all-cause mortality.

Having very low or very high HDL-cholesterol levels is linked to increased mortality.

2012

Genetically low HDL-cholesterol levels were not associated with increased risk of myocardial infarction.

Genetically high HDL-cholesterol levels did not lower risk of myocardial infarction.

2015

Genetically low HDL-cholesterol levels were not associated with increased risk of type 2 diabetes.

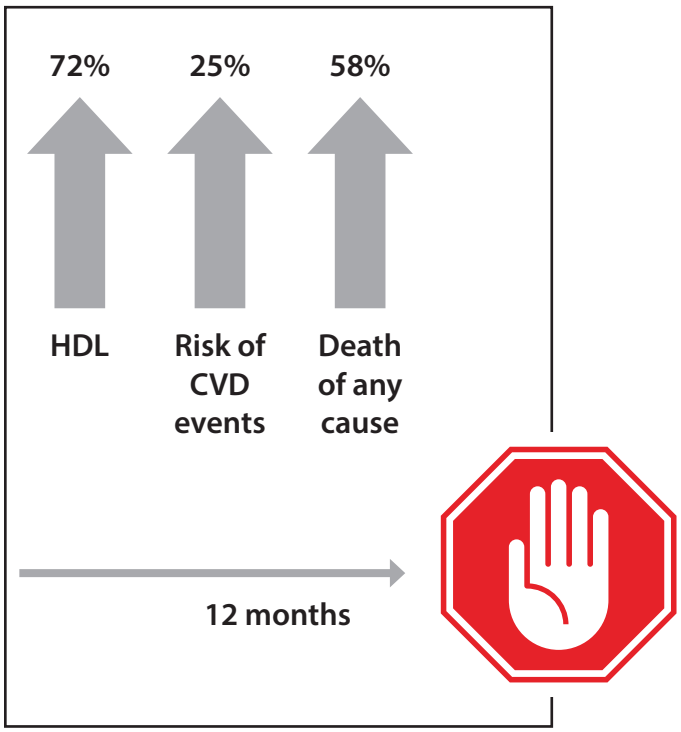
2017

Review of multiple studies: HDL-cholesterol level itself is unlikely to be causally protective against coronary heart disease.

Trials raising HDL-cholesterol did not reduce risks

When drug trials tested the assumption that increasing HDL-cholesterol concentration would translate into clinical benefits, the results were disappointing.

For example, in the ILLUMINATE Study that involved patients at high cardiovascular risk, the HDL-raising drug increased HDL cholesterol levels by 72% at 12 months, but the trial was terminated early because the risk of death and cardiac events increased.[13]



Raising HDL-cholesterol levels via different drugs failed to reduce the risk of cardiovascular events, including when combined with statins.[13-18]

2005
The FIELD Study
Fenofibrate

2007
The ILLUMINATE Study
CETP inhibitor torcetrapib + statin

2011
The AIM-HIGH Study
Pharmaceutical niacin + statin

2012
The dal-OUTCOMES Study
CETP inhibitor dalcetrapib

2014
The HPS2-THRIVE Study
Pharmaceutical niacin + laropiprant

2017
The ACCELERATE Study
CETP inhibitor evacetrapib

The FIELD Study: The Fenofibrate Intervention and Event Lowering in Diabetes Study; **The ILLUMINATE Study:** The Ibrutinib plus Obinutuzumab versus Chlorambucil plus Obinutuzumab in First-line Treatment of Chronic Lymphocytic Leukaemia Study; **The AIM-HIGH Study:** The Atherothrombosis Intervention in Metabolic Syndrome with low HDL/HIGH Triglycerides Study; **The dal-OUTCOMES Study:** The Dalcetrapib in Patients Hospitalized for an Acute Coronary Syndrome Study; **The ACCELERATE Study:** Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes Study

HDL-cholesterol truth:

HDL-cholesterol level is only a part of the HDL story; it doesn't give an indication if the HDL particle is functioning properly.

Quantity does not reflect quality

HDL-cholesterol levels measure the amount of cholesterol carried in the HDL particles but don't give information about HDL particle function. Only functioning particles effectively reduce cardiovascular risk.[19]

HDL function can be assessed through:[20]

- The number of HDL particle (HDL-P)
- The various sizes of HDL particles
- The integrity of HDL particle components
- Myeloperoxidase (MPO) and oxidized low-density lipoprotein (oxLDL)

Summary

Focusing only on HDL-cholesterol level (i.e., the amount of cholesterol transported by HDL particles) is no longer sufficient for determining risk. HDL cholesterol is a static measurement that poorly reflects the dynamic HDL function.[20] Assessing HDL particle function is vital to fully appreciate cardiovascular risk!

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