# A Brief History of Cholesterol: From Guidelines to Statins

#### By Robert Ferguson

Cholesterol is a vital substance in the body, necessary for many critical functions, yet it has long been associated with heart disease. Over the years, medical guidelines for cholesterol management have evolved, leading to the widespread use of statins to lower cholesterol levels. However, as understanding of cholesterol's role in the body has deepened, concerns have grown regarding both the benefits and risks of cholesterol-lowering treatments, including statins. Additionally, the historical connection between cholesterol and heart disease is rooted in controversial research, notably the work of **Ancel Keys**, which has shaped decades of public health policy.

## The Importance of Cholesterol in the Body

Cholesterol is required for producing hormones like **testosterone**, **estrogen**, and **cortisol**, which regulate metabolism, reproduction, and immune response. It is also a fundamental component of cell membranes and is crucial for brain function. The brain contains about 25% of the body's cholesterol, which is essential for forming synapses, maintaining neuronal communication, and supporting cognitive functions.

While cholesterol is necessary for life, it has been largely demonized due to its association with heart disease. However, it's important to recognize that the body thrives on an optimal balance of cholesterol, and it is essential for numerous bodily functions.

#### The Role of Ancel Keys and the Heart-Diet Hypothesis

The connection between cholesterol and heart disease was not "solidified" in the 1940s as much as it was popularized by the work of **Ancel Keys**, an American physiologist who was instrumental in promoting what became known as the **diet-heart hypothesis**. In the 1950s, Keys proposed that dietary saturated fat raised blood cholesterol levels, which, in turn, increased the risk of heart disease. His famous **Seven Countries Study**, published in **1970**, suggested a correlation between saturated fat intake, cholesterol levels, and heart disease rates across various populations.

However, Keys' research has been widely criticized for its selective use of data, as his study excluded countries where saturated fat consumption was high but heart disease rates were low, such as France. This selective analysis led to the **diet-heart hypothesis** becoming accepted without robust evidence, laying the foundation for decades of dietary advice that linked cholesterol and fat intake to heart disease. As a result, cholesterol became the prime target for heart disease prevention strategies, leading to the development of cholesterol-lowering drugs, including statins.

## Early Cholesterol Guidelines and the Shift to Lower Thresholds

The **National Cholesterol Education Program (NCEP)** was established in 1985 by the National Institutes of Health (NIH) to develop guidelines for cholesterol management. In **1987**, the NCEP issued its first set of guidelines, which classified cholesterol levels as follows:

- Normal: Below 200 mg/dL
- Borderline high: 200-239 mg/dL

• High: Above 240 mg/dL

At the time, these guidelines were based on research that linked high cholesterol to heart disease, much of it influenced by Keys' earlier work. However, these guidelines did not consider the body's critical need for cholesterol or its role in other vital processes beyond heart health.

In **1993**, the NCEP revised its guidelines, **lowering the threshold for high cholesterol from 240 mg/dL to 200 mg/dL**, a significant change that greatly expanded the number of people classified as having high cholesterol. This shift made millions of Americans eligible for treatment with cholesterol-lowering drugs, primarily statins, further entrenching the focus on cholesterol as a primary risk factor for heart disease.

## **Statins: How They Work and Growing Concerns**

Statins became the treatment of choice for high cholesterol following the approval of **lovastatin** (Mevacor) by Merck in 1987, the first statin on the market. Statins work by inhibiting the enzyme HMG-CoA reductase, which is responsible for cholesterol production in the liver. By blocking this enzyme, statins effectively reduce levels of **low-density lipoprotein (LDL)** cholesterol, commonly referred to as "bad" cholesterol.

However, statins' mechanism of lowering cholesterol has raised concerns. While they are effective at reducing LDL cholesterol and cardiovascular risk, they also block the production of cholesterol that the body requires for other vital functions, such as brain health and hormone production.

## **Growing Concerns About Statin Side Effects**

Over the years, concerns have emerged about the potential side effects of long-term statin use, including increased risks of:

- 1. **Dementia and Alzheimer's Disease:** Cholesterol is critical for brain function, and some studies suggest that lowering cholesterol too much may impair cognitive functions and increase the risk of **dementia** and **Alzheimer's disease**. The brain needs cholesterol to form synapses and depriving it of adequate cholesterol could negatively impact brain health over time.
- 2. **Type 2 Diabetes:** Research has linked statin use to an increased risk of **Type 2 diabetes**, particularly in individuals already predisposed to metabolic disorders. Statins may impair **insulin sensitivity** and increase blood sugar levels, which can exacerbate the risk of developing diabetes.
- 3. High Blood Pressure and Myopathy: Statin use has also been associated with side effects like muscle pain and weakness (myopathy), high blood pressure, and in rare cases, a severe condition called rhabdomyolysis, which can cause muscle breakdown and kidney damage.
- 4. Other Health Risks: Some studies have reported that low cholesterol levels are linked to an increased risk of all-cause mortality, as suggested by data from the Framingham Heart Study. Very low cholesterol levels have been associated with higher rates of cancer, respiratory diseases, and infections.

## The Framingham Study's Warning: The Risks of Low Cholesterol

While the Framingham Heart Study is often cited for establishing the link between high cholesterol and heart disease, it also revealed an important finding that is often overlooked: **low cholesterol levels** were associated with an **increased risk of all-cause mortality**. People with cholesterol levels below 160

mg/dL had higher mortality rates from conditions unrelated to heart disease, such as **cancer** and **respiratory diseases**.

This finding highlights the importance of maintaining a balance in cholesterol levels rather than focusing solely on reducing them to avoid heart disease. Cholesterol is essential for many bodily functions, and extremely low levels can pose risks.

## **Conflict of Interest Concerns**

The lowering of cholesterol thresholds and the widespread promotion of statin use have also raised questions about **conflicts of interest**. Several members of the **Cholesterol Guidelines Committee** had financial ties to pharmaceutical companies that manufactured statins, such as **Merck** and **Pfizer**. **Pfizer's Lipitor (atorvastatin)**, approved in **1996**, became the best-selling drug in the world, further fueling concerns that cholesterol guidelines were influenced by the pharmaceutical industry.

## The Introduction of Risk Calculators

In the early 2000s, the NCEP introduced **risk calculators** to evaluate a person's overall cardiovascular risk by considering factors beyond cholesterol levels, such as **age**, **gender**, **blood pressure**, and **comorbidities** like **Type 2 diabetes**. These tools expanded the scope of statin therapy, making even those with cholesterol levels under 200 mg/dL eligible for statins if they had additional risk factors.

## Conclusion

Cholesterol has played a central role in public health discussions for decades, largely due to the controversial work of Ancel Keys and the promotion of the **diet-heart hypothesis**. While statins have proven effective in reducing cholesterol levels and **barely** lowering the risk of heart disease, they have also sparked concerns about overprescription and potential side effects, including increased risks of **dementia**, **Type 2 diabetes**, **muscle weakness**, and **all-cause mortality**.

The history of cholesterol management reminds us that while lowering cholesterol may barely reduce cardiovascular risks, the body requires a balanced amount of cholesterol for overall health. Data from the **Framingham Heart Study** and the growing body of research on statins' side effects suggest that a more nuanced approach to cholesterol management is needed, one that considers the benefits of cholesterol alongside the risks of reducing it too much.

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