

The AIM-HIGH Study

How it Impacted Our Understanding of HDL Cholesterol in Cardiovascular Health

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Cholesterol is an essential compound that contributes to a variety of physiological functions integral to human life. Obtained from dietary sources and synthesized within organs such as the liver, cholesterol serves as a precursor to both fat-soluble vitamins and steroid hormones. In addition, cholesterol is needed for the proper functioning of every cell within our body—it ensures that cell membranes are built with appropriate fluidity, and it is involved in intracellular transport and signaling. Interestingly, despite all of its functions within the body, high levels of cholesterol can lead to pathology. The most well known pathology, atherosclerosis, involves an accumulation of cholesterol as fatty deposits in arteries. Eventually, the thickening of arterial walls and the aggregation of plaque cause the narrowing of arteries. Atherosclerosis becomes a dangerous condition with the rupture of atherosclerotic plaque & activated platelets that lead to thrombosis and heart attacks, as shown in Fig. 1. It is important for both doctors and patients to better understand cholesterol, especially because it is a contributing factor to these deadly events (1).

Cholesterol has been classified into different categories based on the lipoprotein that carries it through the blood. The three primary types of cholesterol are low-density lipoprotein (LDL), very-low density lipoprotein (VLDL), and high-density lipoprotein (HDL). LDL cholesterol, commonly referred to as “bad cholesterol,” carries cholesterol throughout the body; as Fig. 2 shows, the LDL cholesterol can

dangerously accumulate into plaque if LDL levels are too high. VLDL cholesterol is mostly comprised of triglycerides and can actually strengthen LDL aggregates, which makes it another risky form of cholesterol if levels are not within a normal physiological range. On the other hand, HDL or “good” cholesterol removes excess cholesterol from the blood and transports it back to the liver. This reverse cholesterol transport process helps keep blood cholesterol levels under control (1).

With such functionally different types of cholesterol, various medications have been developed to manipulate levels of each type as needed in order to decrease the risk of pathology. Because of the strong scientific support and evidence of the dangers of high levels of LDL cholesterol, LDL is a primary target of many forms of medication. The most potent of these medications are statins, which impede the production of cholesterol by the liver and help with the reabsorption of cholesterol into the liver. These two means of reducing blood levels of LDL

cholesterol directly stabilize plaque progression. As shown by trials such as the Heart Protection Study (HPS) and the ASCOT trials, statins have been found to have a huge impact on atherosclerotic development by lowering LDL levels up to 60 percent, and also mildly increasing HDL levels (1-3).

While lowering LDL cholesterol levels is indeed a crucial aspect of fighting atherosclerosis, physicians also seek to raise HDL cholesterol in an effort to further control atherosclerotic progression. The scientific community has accepted the benefit of high HDL levels in reducing cardiovascular events particularly due to the Framingham Study of the 1980s. Comprised of 2815 elderly men and women, the Framingham Study demonstrated that HDL cholesterol had a significant “inverse association with the incidence of coronary heart disease ($p < 0.001$) in either men or women” (4). As shown in Fig. 3, the study concluded that “low HDL-cholesterol levels are associated with a higher risk of coronary heart disease irrespective of the level of LDL-cholesterol” (5).

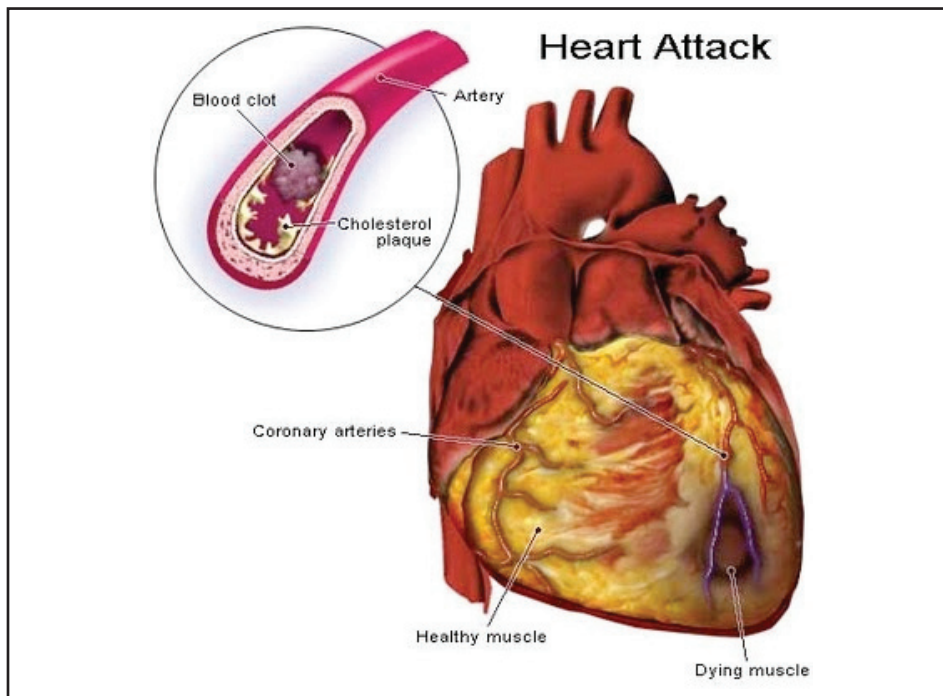


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Fig. 1: Myocardial infarction, or heart attack.

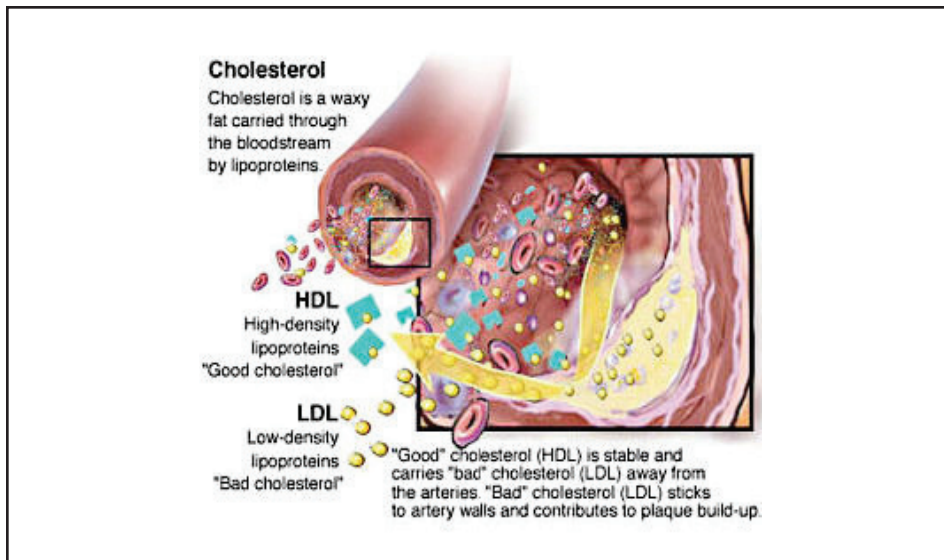


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Fig. 2: HDL and LDL cholesterol.

With the strong evidence provided by the Framingham Study, medications were developed to raise HDL cholesterol levels in patients with low HDL levels, who comprise “up to 29% of patients with [coronary heart disease]” (6). The two most potent medications that raise HDL levels are fibrates and niacin, also known as vitamin B₃ and nicotinic acid. Both have raised HDL levels significantly, with niacin raising HDL levels “by up to 30%” (6). However, fibrates have the additional benefit of lowering triglyceride levels greatly, while niacin primarily focuses on raising HDL levels with some effects on triglycerides (5). Niacin, produced by Abbott Pharmaceuticals in the form of the extended-release drug Niaspan, is a main drug that focuses on raising HDL levels for cardiovascular benefit. It has been widely prescribed, and Abbott made \$1 billion off the drug in 2010 alone (7). Such wide usage has been encouraged under the pretense that raising HDL levels will benefit patient health and combat the incidence of cardiovascular events, as demonstrated by the Framingham Study. However, this long-held belief has now been called under question by the Atherosclerosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health outcomes (AIM-HIGH) trial. The AIM-HIGH trial surprised the medical and scientific community by demonstrating that Niaspan provides no benefit in combating the incidence of cardiovascular events, despite rais-

ing HDL levels. A look into past trials and the AIM-HIGH trial can provide insight into how the public should interpret the implications of such shocking changes to the scientific understanding of Niaspan and HDL cholesterol in terms of cardiovascular health.

Before AIM-HIGH

Before the AIM-HIGH trial, the medical community believed that high HDL levels were associated with a decreased rate of cardiovascular events in high-risk patients. In 1999, The HDL Atherosclerosis Treatment Study (HATS) analyzed 160 patients with coronary heart disease and low HDL cholesterol levels. The study assessed the effects of Niaspan + statin on patients compared to placebo groups with no Niaspan + statin treatment. The HATS trial demonstrated that “combining nicotinic acid with a statin improved HDL-cholesterol and LDL-cholesterol, inhibited the progression of atherosclerosis, and reduced cardiovascular event rates in a high-risk population with established coronary heart disease” (5). With these findings, HATS demonstrated the strong superiority of dual Niaspan and statin treatment to patients at risk of atherosclerosis and heart disease. However, statins have been accepted as an effective treatment for people at such risk, at all costs. Thus, there was a blatant need for trials comparing statin treatment to statin + Niaspan treatment, showing the specific benefits of Niaspan alone.

In 2004, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2) trial studied 167 high-risk patients with low HDL levels and normal LDL levels. The researchers compared the effects of Niaspan + statin to statin alone on carotid artery intima-media thickness (CIMT), a measurement representative of atherosclerotic levels. The results showed that Niaspan + statin significantly increased HDL levels and significantly reduced triglyceride levels compared to the statin group alone, with insignificant changes in LDL in both groups. There was a significant increase in CIMT in the statin group, whereas the Niaspan + statin group showed no change in CIMT, indicating Niaspan’s role in combating atherosclerotic development. ARBITER-2, however, was not monitoring the magnitude of cardiovascular events as an endpoint, since researchers used CIMT as an indicator of event occurrence to reach the conclusion that Niaspan + statin decreases cardiovascular event occurrence. Therefore, a trial was needed specifically to observe the effect of Niaspan + statin on cardiovascular event rates; this need was finally fulfilled with the AIM-HIGH trial (5).

The AIM-HIGH Trial

The AIM-HIGH trial enrolled 3,414 participants, all of whom were at risk for cardiovascular events, had controlled LDL levels, and had a history of low HDL, high triglycerides, and heart disease. The trial was funded by the National Institutes of Health (NIH), as well as by Abbott Pharmaceuticals, who covered around \$25 million of the costs. The trial was also monitored by an independent group of physicians and scientists to ensure proper oversight. The patients were divided into groups of statin + placebo and statin + Niaspan for analysis of the rate of cardiovascular events. Physicians and patients eagerly awaited the trial’s outcome to influence their decisions regarding treatment combating heart disease and atherosclerosis (7).

Unexpectedly, the trial had to be stopped 18 months early due to the lack of clear benefit from Niaspan treatment. While data showed that Niaspan increased HDL levels and reduced

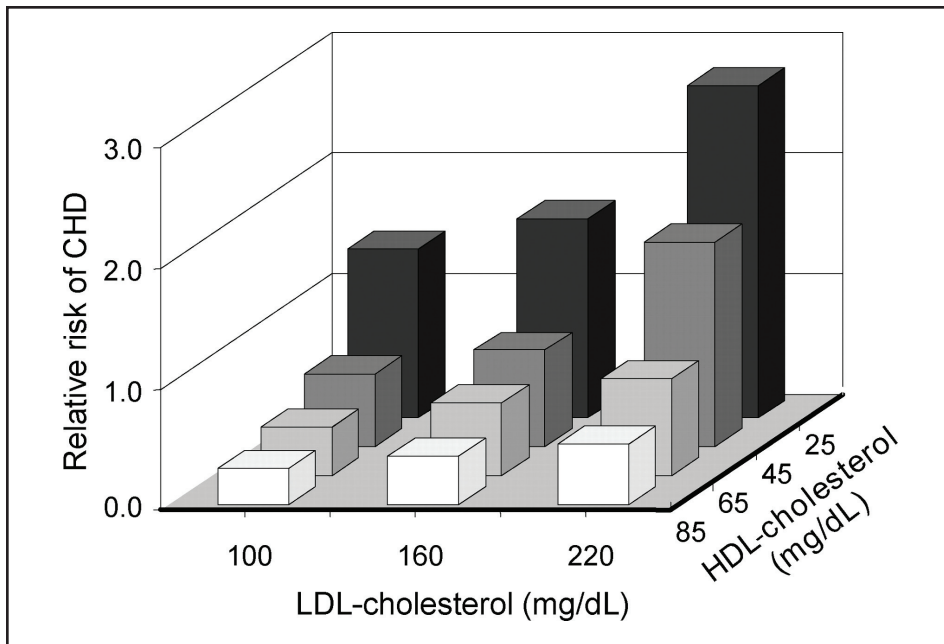


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Fig. 3: Coronary heart disease risk in Framingham Study based off of HDL and LDL levels.

triglyceride levels significantly, there was no significant reduction in “fatal or non-fatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures to improve blood flow in the arteries of the heart and brain” (8). In fact, the trial actually found more strokes in the Niaspan group than the control; however, due to analysis of past trials, these strokes have been deemed as anomalies due to chance rather than as any significant danger. Nevertheless, the researchers concluded that “adding high dose, extended-release niacin to statin treatment in people with heart and vascular disease, did not reduce the risk of cardiovascular events, including heart attacks and stroke” (8). Such a conclusion has raised a number of concerns considering the changes these findings might make on the long-established approach to reducing heart risk; furthermore, simply the number of individuals currently prescribing for Niaspan warrants a thorough investigation into the validity of these claims.

Implications

The AIM-HIGH trial has directly challenged a widely accepted medical consensus: raising HDL cholesterol with medications such as Niaspan can save lives. The results of the Framingham Study have clearly shown that high HDL levels can prevent cardiovas-

cular events. However, the AIM-HIGH study has negated the conclusion that raising HDL levels by medication benefits cardiovascular health. AIM-HIGH has shown that there is a distinct difference between high HDL levels due to genetics or cardiovascular exercise and high HDL levels due to medication. The results of AIM-HIGH contradict the conclusions of the ARBITER-2 study, which asserted that Niaspan+statin treatment reduced incidence of cardiovascular events based off CIMT measurements. Physicians and scientists are now pushing for more trials to further investigate Niaspan and raising HDL cholesterol levels. Perhaps the use of different kinds of statins other than the simvastatin used in AIM-HIGH will be enlightening in a future trial. Furthermore, differences in cholesterol particle size among HDL cholesterol may also be an area of interest for future studies.

The results of AIM-HIGH have already led to sharp declines in the prescription of Niaspan for at-risk patients. Despite the fact that the NIH has explicitly stated that patients already on the drug should remain on it until further studies are conducted, those with unwanted side effects associated with Niaspan can safely consider dropping the drug. Nonetheless, the need for more insight into why raising HDL levels with medication fails to prevent life-threatening cardiovascular events remains an issue.

Conclusion

The AIM-HIGH trial has made a huge impact on the medical community, as well as on the lives of those at risk of cardiovascular disease. Not only has it helped advance the world’s understanding of cholesterol and heart disease, but it has also served as an example of how clinical trials should be conducted. Abbott’s role in funding a study that has shaken their profits shows a degree of integrity that serves as a model for all pharmaceutical companies. Furthermore, the direct comparison of two realistic treatment choices such as statin with or without Niaspan was very helpful for physicians and patients and should be incorporated more in trials for other drugs. Thus, while the world may not fully understand the mysteries of cholesterol yet, the AIM-HIGH trial has taken us a step closer to the truth, and, for such a deadly disease such as heart disease, that is truly a remarkable step.

References

1. High Cholesterol Prevention (2011). Available at <http://www.mayoclinic.com/health/high-blood-cholesterol/DS00178/DSECTION=prevention> (October 2011).
2. Heart Protection Study Collaborative Group, *Lancet* **360**, 7-22 (2002).
3. P. Sever *et al.*, *Lancet* **361**, 1140-1158 (2003).
4. T. Gordon *et al.*, *Am. J. Med.* **62**, 707-714 (1977).
5. A. Taylor, *Eur. Heart J. Suppl.* **8**, F74-F80 (2006).
6. A. Wierzbicki, *Curr. Med. Res. Opin.* **18**, 36-44 (2002).
7. H. Krumholz, Five Lessons From Niaspan’s Disappointing Study (2011). Available at <http://www.forbes.com/sites/harlanrumholz/2011/05/31/five-lessons-from-niaspans-disappointing-study/> (October 2011).
8. NIH stops clinical trial on combination cholesterol treatment (2011). Available at <http://www.nih.gov/news/health/may2011/nhlbi-26.htm> (October 2011).
9. The AIM-HIGH Investigators, *Am. Heart J.* **161**, 471-477 (2011).
10. J. Shepherd, *Eur. Heart J. Suppl.* **7**, F15-F22 (2005).

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