

Talking Statins with Antonio Gotto

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For over four decades, Antonio Gotto Jr, MD, DPhil, has pioneered atherosclerosis and cholesterol research, playing a leading role in landmark clinical trials demonstrating that lowering cholesterol can reduce the risk for cardiovascular disease (CVD). Gotto is currently dean emeritus of Weill Cornell Medical College and provost for Medical Affairs Emeritus of Cornell University and a member of the Cholesterol Trialists' Treatment Group.

In 1973, at Baylor College of Medicine and the Methodist Hospital in Houston, Texas, he helped launch the Coronary Primary Prevention Trial, "the first test of the cholesterol hypothesis." The trial examined CVD outcomes when using cholestyramine to treat men with no previous CVD but high levels of LDL cholesterol.

"We participated in the study for over seven years, and at the end, there was a 12% reduction in LDL and 19% reduction in fatal and nonfatal heart attacks. This was the first definitive proof that if you had high LDL cholesterol and you reduced it over a period of time with a drug, you could decrease your risk of having a cardiovascular event," said Gotto.

Gotto later served as Chairman of Medicine at Baylor College of Medicine and The Methodist Hospital from 1977 to 1997.

In the 1990s, Gotto chaired the Steering Committee of the Air Force/Texas Coronary Artery Study (AFCAPS/TEXCAPS) testing lovastatin. This landmark trial demonstrated the benefit of statins for individuals without CVD who had average LDL-C and low HDL-C, with a 37% decrease in cardiovascular events over five years.

This year, Gotto, along with Henry Pownall, Ph.D., lent his expertise as guest editor of the Methodist DeBakey Cardiovascular Journal for an issue on lipids and lipoproteins in CVD. In March 2019, Gotto joined me for an interview on the latest updates in cholesterol research, statin myths and controversies, and more. Excerpts of the conversation are printed below, edited for clarity and length.

... on the "cholesterol hypothesis"

AG: As far as I'm concerned, the "cholesterol hypothesis" is not a hypothesis because it has been proven and re-proven. Lipids are not the only thing that contribute to cardiovascular disease, but they certainly are one of the major risk factors, and LDL cholesterol and apoB are considered to be causal with respect to atherosclerosis and blocking of the arteries.

... on optimal LDL levels

AG: For LDL, the lower the better, although we don't know yet know the ideal number. Some of the recent studies with PCSK9 inhibitors have gotten LDL down very low, into the teens. We are born with an LDL in cord blood of around 40, so that's where my own target would be. We have evidence that lowering LDL from the high 60s into the low 50s will reduce cardiovascular events, and the



Antonio M Gotto Jr, MD, DPhil

FOURIER and ODYSSEY trials both showed that, when using PCSK9 inhibitors on top of statins, you would continue to see benefit lowering LDL as low as 20 mg/dL.

But there is a diminishing return because the reduction in cardiovascular events is proportional to the absolute reduction of LDL. A 39 mg/dL reduction in LDL will give a 20% to 22% reduction in cardiovascular events over a five-year period. So if you're starting with an LDL over 100, the absolute benefit will be greater than it would be starting with an LDL under 100. You'll still get benefit at those lower starting values, but the magnitude will not be as great.

... on research into the clinical effects of raising HDL

AG: You just have to combat the misinformation with valid information. I mean, doctors are convinced that statins are beneficial. If you go to a dinner with doctors, with cardiologists, and you ask how many take statins, probably 90% of them will raise their hand.

There is some very encouraging data from NHANES showing that, over the last 20 years, statin use has increased and LDL levels have decreased. But while there is progress being made with millions of people taking cholesterol-lowering drugs and baseline levels of LDL and triglycerides coming down, HDL hasn't changed very much.

... on cholesterol conspiracies and being labeled as part of the "Cholesterol Mafia"

AG: There were about five of us grouped into the so-called "Cholesterol Mafia." It was based on a book written by Thomas Moore called Heart Failure. Moore was on the talk shows, and in 1989 he was featured in The Atlantic magazine. The cover said, "The Cholesterol Myth: Lowering cholesterol is next to impossible with diet, and often dangerous with drugs—and it won't make you live any longer." We now know that each one of those statements is wrong and each one of them has been disproven by now.

Moore also came up with a hypothesis that the whole "cholesterol myth" was put together as a giant conspiracy between the doctors; the American College of Cardiology, which wanted to get more members; the American Heart Association, which wanted to raise more money from the public; the Government, which wanted more money for heart research; and the pharmaceutical company, which wanted to sell more drugs. According to him, it was all masterminded by a group that he called the Cholesterol Mafia, and with a name like Antonio Gotto, I wasn't too surprised to be included.

... on addressing misinformation about statins

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... on making sense of conflicting results in cholesterol research

AG: I would look at the results of the meta-analysis carried out by the Cholesterol Trialists' Treatment Group—a group of scientists and doctors, researchers worldwide—and coordinated by the Oxford University Clinical Trials Group. It provides overwhelming evidence in hundreds of thousands of patients for the benefit of statins in reducing cardiovascular disease and total mortality across males, females, old, young, diabetics, and nondiabetics in a variety of different settings. It also shows excellent safety. If you look at the accumulated evidence, there's never been a class of drugs that's been more thoroughly studied or understood or tested than statins, and they certainly have stood the test of time.

... on public perception and media coverage

AG: I think, overall, public perception is positive. But it took 20 years and millions of patients taking statins to show the association between high-intensity statins and new-onset diabetes. Nonetheless, the benefit in reducing cardiovascular risk with statins greatly outweighs the risk for developing diabetes. Moreover, guidelines recommend that individuals with established diabetes be treated by statins, which has been shown to greatly reduce the risk of cardiovascular events. And a double-blind study found that many of the people who are so-called "statin intolerant" with muscle symptoms were able to tolerate a different or lower-dose statin. In terms of overall safety, statins are one of the safest classes of drugs that have ever been introduced. That's not to say that there aren't some side effects, but the benefits greatly outweigh the risk.

Jane Brody wrote an article last month for New York Times discussing statins and her own personal experience with them, and it's very positive. I think she was a skeptic for a while, but the article talked about the benefits of the statins. Articles like

this, written by respected individuals who don't really have any connection with the research or the industry, will help convince the public that people who need statins should take them.

... on addressing patient concerns

AG: At the physician level, we need to talk one-on-one with our patients about the importance of controlling and lowering cholesterol. This needs to be enforced by a team effort—the nurse, the dietician, the nutritionist, the physician all need to give the same message. Follow-up is also important: making sure the patient understands the diet, the medication, and how to take it, and measures to make sure that the patient is being compliant.

... on statins and heart-healthy lifestyles

AG: Statins don't replace a healthy lifestyle. In the AFCAPS/TexCAPS study, the patients were very vigorous about their exercise programs and diligent about their diet. The statins do a lot more good and you get a lot more benefit from them if it's used in conjunction with a healthy lifestyle.

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Laura Gerik is Assistant Managing Editor of the *Methodist DeBakey Cardiovascular Journal*.

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