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Clinical Lipidology Roundtable Discussion

PCSK9 inhibitors for prevention of atherosclerotic cardiovascular disease

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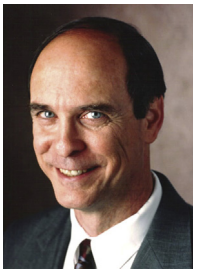
Abstract: The discovery of proprotein convertase subtilisin kexin-type 9 (PCSK9) and the development of inhibitors of PCSK9 function appear to mark an epochal advance in clinical lipidology. PCSK9 is a circulating protein that binds to low-density lipoprotein (LDL) receptors and facilitates their lysosomal degradation following internalization in cells. Blocking PCSK9 thus increases the recycling of LDL receptors and results in more receptors on the cell surface, particularly in the liver, thereby lowering LDL levels. In this Roundtable, we discuss the recent large cardiovascular outcomes trials in which evolocumab and alirocumab, monoclonal antibodies directed against PCSK9, successfully reduced major cardiovascular events. We discuss the safety of these drugs as well as the safety of maintaining very low LDL cholesterol levels. Finally, we address pragmatic considerations affecting the use of PCSK9 inhibitors in clinical practice.



Dr Guyton

Dr Guyton: This Roundtable discussion will examine the role of proprotein convertase subtilisin kexin-type 9 (PCSK9) inhibition in clinical lipid practice today. I am joined by 2 clinical investigators who have led the evaluation of PCSK9 inhibitors—Robert Giugliano of Brigham and Women's Hospital in Boston, Massachusetts and Vera Bittner of the University of Alabama at Birmingham and by JCL Associate Editor Eliot Brinton of the Utah Lipid Center in Salt Lake City.

Near the beginning of the 20th century, Anitschow in Russia discovered that feeding cholesterol to rabbits would produce atherosclerosis. Around 1950, the connection between cholesterol and coronary heart disease was confirmed in the clinical setting by the Framingham Heart Study. With the advent of ultracentrifugation, lipoproteins came into the picture, and for the next 30 or 40 years, most of the effort in this field was devoted to understanding the science of lipoproteins. A clinical breakthrough occurred in 1987 with the launch of lovastatin, the first statin, followed by clinical trials showing the efficacy of statins for ameliorating the morbidity and mortality of atherosclerotic disease.

I have highlighted these epochal discoveries in lipidology because I think that the discovery of PCSK9 in recent years and the clinical trials showing that PCSK9 inhibition can reduce cardiovascular events also mark an epochal advance in lipidology. PCSK9 inhibition may take its place on par with the events I have mentioned.

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Let us begin with a question for Dr Giugliano. What is PCSK9? Can you give us a 1-minute summary?


Dr Giugliano

Dr Giugliano: No problem. PCSK9 stands for proprotein convertase subtilisin kexin-type 9. Those words just describe the molecular domains of the protein. It's a protein that regulates cholesterol metabolism. Basically, it's responsible for escorting the low-density lipoprotein (LDL) receptor on the hepatocyte to its degradation internally within the cell. Occasionally, individuals are born with a gain-of-function mutation in PCSK9, and then there's lots of destruction of LDL receptors going on. Those patients have very high LDL concentrations.

On the other hand, if you have a loss-of-function mutation in PCSK9 or if you give them medication that blocks the function of PCSK9, then there's less degradation of the LDL receptor, so more of the LDL receptors are available and can recycle and sit on the cell membrane, where they can remove more of the circulating LDL from the blood and have lower LDL level.

Dr Guyton: Dr Bittner, how long have we known about PCSK9 and how was it discovered?


Dr Bittner

Dr Bittner: It's actually an amazingly short time frame. There was a group of investigators in France led by Dr Abifadel, who were working on the genetics of familial hypercholesterolemia (FH) and found several people that had FH-type phenotypes, but who didn't have mutations in either the LDL receptor or the apolipoprotein B gene. In 2002, this group found gain-of-function mutations in the PCSK9 gene that mimicked the FH phenotype. The PCSK9 protein was first characterized in 2003. Loss of function mutations associated with hypocholesterolemia was subsequently described by Dr Helen Hobbs, Dr Jonathan Cohen, and colleagues in 2005. Epidemiologic studies then showed that individuals with the loss of function variants had a lower incidence of coronary heart disease, thus generating interest in PCSK9 as a treatment target.

Dr Guyton: If I remember correctly, they had surprisingly low cardiovascular risk, much lower cardiovascular risk than expected. Do you have an idea of how that came about?

Dr Giugliano: I have two comments about that observation. First, this is a lifelong issue if you have a loss-of-function mutation, or a gain-of-function mutation, and our treatments are not administered from birth. The second thing is, look carefully at the number of events in the group with a loss of function. I believe the estimated relative reduction was around 88%. There was one person out of the 85 who had an event in the loss of function group.

Dr Guyton: A statistical quirk might have contributed.

Dr Giugliano: Yes, the confidence interval about that estimate is extremely broad.

Dr Guyton: Now, we have monoclonal antibodies that block PCSK9 action by tying up the circulating PCSK9 in the body. What are the lipoprotein changes that occur with PCSK9 inhibition? I'll direct this to Dr Bittner.

Dr Bittner: PCSK9 inhibitors basically lower all the apoB lipoproteins, so you see reductions in LDL cholesterol, in apoB, and in non–high-density lipoprotein (HDL) cholesterol. Depending on the dose of the agent, the reductions are in the 50-60% range. In addition, PCSK9 inhibitors also lower lipoprotein(a) by around 25%.

Dr Guyton: Dr Giugliano, you led the FOURIER study with evolocumab. Could you summarize the kind of patients that were included in that study, and give us an idea of the main results?

Dr Giugliano: Sure. I was very fortunate to be a member of the executive committee in the FOURIER trial, and there we targeted patients with stable atherosclerotic cardiovascular disease, including prior MI, prior ischemic stroke, and patients who had symptomatic peripheral arterial disease or prior peripheral arterial revascularization. They had to have LDL cholesterol on a stable dose of statin (preferred high intensity but accepted moderate-intensity statins) that was at least 70 mg/dL, or they could have a non-HDL cholesterol at least 100 mg/dL. Those are the important entry criteria. There were 3 main findings. One was that evolocumab reduced the LDL compared to placebo by 59% on average. The achieved LDL in the evolocumab arm was 30 mg/dL. Second point was that the clinical cardiovascular events were significantly reduced.

The broad composite for events was reduced by 15% after a median follow-up of 2.2 years, and a more narrow triple end point of cardiovascular death, myocardial infarction, or stroke was reduced by 20%. The third key finding was that there was no excess in safety events, and the drug was well tolerated. There was an excess in minor injection site reactions with evolocumab.

Dr Guyton: Great. We're going to come back and expand on that, but we just now have had the results of the ODYSSEY Outcomes trial presented, and Dr Bittner, could you describe that patient population and the main results?

Dr Bittner: I had the opportunity of being on the Steering Committee for ODYSSEY Outcomes. Our population is distinct from the FOURIER population in that we focused on a population of people who had a recent acute coronary syndrome. Participants had to be within 1-12 months of an acute coronary syndrome to qualify for the ODYSSEY Outcomes trial.

The lipid/lipoprotein criteria were very similar to what FOURIER had: LDL-C of 70 mg/dL or higher, non–HDL-C of 100 mg/dL or higher, or as a third entry criterion, an apoB of 80 mg/dL or greater. These lipid/lipoprotein criteria had to be met on a background of stable high-intensity statin therapy or at least maximal tolerated statin therapy.