In 2003, mutations in the gene encoding the enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) were identified as genetic causes for familial hypercholesterolemia (1). Investigations soon showed that PCSK9 was a key regulator of low-density lipoprotein (LDL) cholesterol metabolism that promoted the hepatic degradation of LDL receptors and reduced the liver’s ability to remove circulating LDL cholesterol. The subsequent characterization of loss-of-function mutations in PCSK9 that result in markedly reduced LDL cholesterol plasma levels set the stage for a new class of lipid-lowering therapies that might prevent cardiovascular disease (CVD) (2).

Drug development progressed rapidly. Within the past 5 years, many monoclonal antibodies, including evolocumab, alirocumab, and bococizumab, were developed as PCSK9 inhibitors that disrupt the interaction between PCSK9 and the LDL receptor. These inhibitors, which are administered subcutaneously in monthly or semimonthly injections, produced striking reductions in LDL cholesterol when compared with placebo or ezetimibe in randomized, controlled trials (3, 4).

In this issue, Navarese and colleagues (5) report the results of a meta-analysis of study-level data from 24 randomized trials that evaluated the effects of PCSK9 antibodies in 10,159 adults with hypercholesterolemia. Most trials involved patients treated with statins who had not met target LDL cholesterol goals, although some focused only on patients who did not tolerate statins. Summary trial data showed that, compared with placebo or ezetimibe control groups, PCSK9 inhibition led to a 47% reduction in LDL cholesterol and a 26% reduction in lipoprotein(a) levels. Data also showed reductions in all-cause mortality rates, cardiovascular mortality rates, and myocardial infarctions, all of which were statistically significant except the cardiovascular mortality outcome (P = 0.084). These results were robust in sensitivity analyses that were stratified by intensity of background statin therapy or by comparator (placebo or ezetimibe). Serious adverse events occurred in approximately 9% and 8% of PCSK9 and comparator groups, respectively. The summary estimates did not include recent results of the Open-Label Study of Long-Term Evaluation Against LDL Cholesterol (OSLER) trials 1 and 2, which studied evolocumab; composite findings of those 2 trials showed a statistically significant reduction in a combined cardiovascular end point with evolocumab (6).

Navarese and colleagues found that the relative reduction of LDL cholesterol levels with PCSK9 inhibitors was similar to or even slightly greater in participants receiving statin treatment than in patients not receiving statin treatment—a finding that highlights the potential value of PCSK9 inhibition as an adjunct to standard therapy. Statins (and ezetimibe) may induce up-regulation of PCSK9, partially attenuating their LDL cholesterol-lowering effect (7, 8). Therefore, PCSK9 inhibitors may be particularly helpful in patients who do not achieve the expected LDL cholesterol reduction with maximally tolerated statins, have very high baseline LDL cholesterol levels (that is, patients with familial hypercholesterolemia, particularly those needing LDL cholesterol apheresis), or have confirmed statin intolerance.

The meta-analysis also found that the comparative LDL cholesterol reduction was smaller when control groups were treated with ezetimibe rather than placebo. A recent large trial, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), showed that adding ezetimibe to simvastatin is a safe and effective treatment strategy in high-risk patients over a median of 6 years (9). In addition, compared with the costly injection of monoclonal antibodies, most statins are already available in generic, relatively inexpensive forms, and ezetimibe will go off patent in the near future.

The most remarkable finding of the meta-analysis is the reduction in all-cause mortality rates, cardiovascular mortality rates, and myocardial infarctions with PCSK9 inhibitors. These results, although they are very encouraging, warrant cautious interpretation. Included trials were of small or moderate size and mostly had short follow-up periods. The total number of events was small (for example, the results for all-cause mortality were based on only 40 events), several studies did not report any events at all, and quantitative pooling of rare events remains a challenging task. Moreover, the trials that were summarized were not specifically designed or powered to assess and detect differences in clinical outcomes or rare adverse events. Summaries based on such limited information are tentative at best.

Little is known about the long-term adverse effects of sustained PCSK9 inhibition, including neurocognitive outcomes and diabetes. Basic studies in animal models have suggested that PCSK9 inhibition could impair glucose metabolism (10). Ultimately, trials with long follow-up periods together with real-world experience will be necessary to better characterize the safety profile of PCSK9 inhibition, as well as the patient’s tolerance of long-term subcutaneous injections.

Are we entering a new era in lipid-lowering treatment? The current 2013 American College of Cardiology/American Heart Association cholesterol guideline focuses largely on statin therapy and does not establish specific treatment goals. If the efficacy and safety profile of PCSK9 inhibitors is confirmed in long-term trials with a larger number of clinical events and if costs are not prohibitive, clinicians will be able to add PCSK9 inhibitors or ezetimibe to statin therapy and achieve additional LDL cholesterol reductions. Furthermore, with multiple evidence-based safe therapeutic options, it will be critical to establish the optimal sequence and
combination of drugs as well as the LDL cholesterol goals that minimize long-term risk in different patient populations. Studies assessing CVD outcomes and cost-effectiveness of different lipid-lowering strategies in populations at different risks for CVD will provide answers to these questions.

The initial clinical trial experience with PCSK9 inhibitors fuels cautious enthusiasm. The meta-analysis by Navarese and colleagues provides important preliminary information on clinical outcomes as the U.S. Food and Drug Administration considers approval of PCSK9 inhibitors for clinical use. Confirmation of these findings in long-term, ongoing, pivotal trials with prespecified primary CVD end points and monitoring of a broad range of adverse events will help establish the role of these novel agents in CVD risk management.

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Financial Support: Dr. Cainzos-Achirica is supported by a research grant from the Spanish Society of Cardiology. Dr. Martin is supported by the Pollin Cardiovascular Prevention Fellowship, the Marie-Josée and Henry R. Kravis endowed fellowship, and a National Institutes of Health training grant (T32 HL007024).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0920.

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