Target cardiovascular risk rather than cholesterol concentration
New American guidelines are a brave and wise departure from current practice

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The recent American “Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults” heralds a new era in the prevention of atherosclerotic cardiovascular disease and stroke by focusing on reducing risk and abandoning cholesterol concentrations as targets. The new guidelines indicate that once lifestyle interventions have been exhausted drugs should be started on the basis of patient risk, that only those drugs known to reduce risk should be used, and that a singular focus on cholesterol concentrations should be abandoned.

This tectonic shift in prevention breaks with decades of recommendations stretching back to 1988, when the National Heart, Lung, and Blood Institute released the first US guidelines, which established clear thresholds for starting lipid lowering drugs and goals for treatment. Moreover, it is a marked departure from the European Society of Cardiology guidelines, published two years ago, which strongly endorse low density lipoprotein cholesterol (LDL-C) concentrations as targets for drug treatment.

Clinicians and the public may find the new recommendations jarring. Doctors are taught about targets, tested in examinations about them, and may be evaluated and even paid according to their patients’ lipid concentrations. Academics make careers that are founded on studies to investigate how best to help patients reach salutary lipid concentrations, often with the newest lipid lowering drug. Professional societies and public health organizations raise money to promote target related initiatives directed at patients and the profession, and governments have launched public health campaigns. Regulatory agencies approve drugs on the basis of their ability to lower LDL-C concentrations, without evidence about their effect on patient outcomes. The assumption that drugs that lower LDL-C concentrations also lower risk was unquestioned until recently.

A spate of studies over the past few years contributed to an insight that had previously eluded the field. Cholesterol plays a key role in atherosclerosis, but its modification by drugs does not always produce the expected result. Drugs have thousands of effects and their influence on cholesterol concentrations does not convey their net effect on patient risk. Trials showed that lowering LDL-C and raising high density lipoprotein cholesterol did not necessarily lower risk. Slowly, doubt emerged about the assumption that lipid levels on drug therapy were a surrogate for outcomes. Moreover, it became clear that the drug target recommendation was not based directly on trial evidence. The large lipid lowering trials tested the hypothesis that a drug at a fixed dose would reduce risk in a specific population. Drugs—not strategies—were tested and the drugs were not titrated to achieve target concentrations. It is worth noting that previous guidelines from the American College of Cardiology and the American Heart Association moved away from treatment targets when faced with this evolving evidence. However, because these guidelines were not cholesterol guidelines, their recommendations pertaining to prevention and lipids were not widely reported or appreciated.

The focus on targets led to treatment strategies that had not been shown to reduce patient risk. Blockbuster drugs generated billions of dollars in sales on the basis of their ability to help patients reach cholesterol targets, even though they had uncertain effects on patient risk.

In the American College of Cardiology and the American Heart Association guidelines, statins can be largely understood as drugs that reduce risk rather than cholesterol. Statins reduce risk regardless of initial LDL-C concentrations, so the guidelines frame the question in terms of whether the patient’s risk is high enough to merit treatment with statins rather than whether LDL-C is high enough to justify treatment. The new guidelines draw attention to absolute risk and the size of the potential benefit, an important point given that statins have tended to be used preferentially in lower risk patients. Also, a singular focus on lipid concentrations could mean that low risk patients with modestly raised LDL-C concentrations are treated but high risk patients with lower concentrations are not.

The latest guidelines’ method of calculating risk and the treatment thresholds recommended drew criticism almost immediately. At least one prominent team has already published concerns about the calculator’s accuracy. This criticism may persist as experts study the new calculator, determine its accuracy in various populations, and refine it over time.
the risk thresholds for treatment should be understood as recommendations and not dictums. For any individual, the decision about the worth of a drug treatment depends on how that person feels about potential benefits, burdens, and harms—something that no writing group can determine. Ultimately, the decision depends on our ability to provide patients with the knowledge and guidance needed to make high quality decisions about their treatment.

The new guidelines are also a cautionary tale about the premature translation of medical guidelines into performance measures. They highlight that the push to chase targets was based on speculation, not on direct trial evidence, and opened the door to the use of drugs that had not been fully tested. I hope that the European Society of Cardiology will consider the principles of these guidelines closely and agree that it is time to abandon the focus on LDL-C concentrations. Disagreements about methods of calculating risk should not divert attention from this central conceptual aspect of the new guidelines. Finally, I hope that some of the controversy will renew enthusiasm for incorporating shared decision making into recommendations.

In the end, the new guidelines are worthy of admiration. It is remarkable that an expert writing group, steeped in the dogma of cholesterol treatment targets, could dispassionately evaluate the evidence and reach a conclusion that was such a brave and wise departure from current practice. We still need to resolve how best to calculate risk and in which populations. We also need to move past the idea that patients and doctors should defer to thresholds for treatment and develop tools that will facilitate shared decisions about prevention strategies. Nevertheless, the advances in this guideline should be acknowledged. It will probably take some time before these new concepts can be fully understood and incorporated into practice. But at least in the United States the approach to preventing atherosclerotic heart disease and stroke is on a more evidence based course. Patients will be the beneficiaries when we translate these concepts into proper new practices.

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