

ABSTRACT

A recent change in the paradigm of lipids management relates to the use of low-density-lipoprotein cholesterol (LDL-C) goals to direct the dose and type of statin prescribed. In place of LDL-C goals, the intensity of statin therapy (based on the ability of a particular dose of a drug to lower LDL-C) is now recommended by the American College of Cardiology and the American Heart Association to be calibrated to the level of cardiovascular risk. The role of niacin and fenofibrate has largely declined, although an emerging role for fenofibrate in the treatment and prevention of microvascular complications in patients with diabetes mellitus is emerging and presents interesting potential to extend the benefits of this class of drugs. Finally, the benefits of lipid lowering in patients with chronic kidney disease has now been demonstrated in randomised controlled trials and could probably be represented in the algorithms for risk stratification in future.

Keywords:

Lipids; Statin; Cardiovascular risk

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INTRODUCTION

Blood lipids are amongst the most important modifiable risk factors for cardiovascular disease. Of the lipids routinely measured in the blood, randomised controlled trials have demonstrated repeatedly that treatments which lower the levels of low-density-lipoprotein cholesterol (LDL-C) in the blood reduce the risk of cardiovascular disease. Statins remain the most extensively used therapies in clinical trials.

Over the last decade, several clinical trials have been carried out that have impacted on the way that lipid lowering is practised. These are gradually being incorporated into clinical practise guidelines.

Changes to Lipids Management Guidelines

The most dramatic recent change in the way blood lipids are treated relates to the use of LDL goals to direct the dose and type of statin prescribed. In treating patients to lower blood lipids, the intensity of treatment should be calibrated to the degree of risk, so that the most intensive treatments are reserved for those at the highest risk. This maximises benefits of treatments while minimising risk and cost, since the risk of adverse events and cost increases with the higher doses of statins required to deliver more intensive therapy. For several decades now, the intensity of treatment was based on setting LDL-C targets, which were generally lower for patients with higher risk of cardiovascular disease. In 2013, the American

College of Cardiology and the American Heart Association released guidelines for the treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults which changed that paradigm.¹ In place of LDL-C targets, the intensity of statin therapy (based on the ability of a particular dose of a drug to lower LDL-C) was calibrated to the level of risk. In addition, the guidelines identified four groups of individuals who would benefit from statin therapy: 1) those with clinical atherosclerotic cardiovascular disease; 2) those with LDL-C >190 mg/dl; 3) those with diabetes; and 4) those with estimated risk of atherosclerotic cardiovascular disease >7.5% based on a new pooled risk equation developed specifically for this guideline that took into account the differences in risk between men and women, and the different ethnic groups in the United States. Despite early objections, many countries have begun to adopt the practise of using the risk level to determine the statin type/dose, rather than LDL-C goals.

The basis of these recommendations is that clinical trials have all (without exception) used fixed doses of statins and none adopted a treat-to-goal strategy. This is a valid approach. Fundamental to the choice of approaches (treat-to-target vs fixed-dose statins) relates to our view of the LDL-C hypothesis. For proponents of the LDL-C hypothesis, the belief is that LDL is directly involved in the pathogenesis of atherosclerotic cardiovascular disease and, therefore, that the level of LDL-C achieved after treatment is the main arbiter of the degree of risk reduction achieved by said treatment. On the other hand, critics point to the fact that statins may have pleotropic effects beyond lowering LDL-C and that LDL-C lowering may not be the relevant biological pathway through which these drugs act. Both these approaches have their merits. With the use of LDL-C goals, some patients at high risk but who have relatively low levels of LDL-C even before treatment would receive doses of trial drugs that may be lower than those used in the trial. The new ACC/AHA guidelines avoid this. At the same time, there is a body of evidence that treatments working through other pathways (including diet, intestinal bypass, cholestyramine, niacin and ezetimibe) have the same predicted effect as if the LDL-C lowering was carried out with a statin. Since different treatments with the same LDL-C lowering have similar efficacy in reducing atherosclerotic cardiovascular disease, it may not be too much of a reach to believe that LDL-C lowering is central to the process of prescribing lipid-lowering agents to reduce atherosclerotic cardiovascular disease. This was most recently demonstrated through the IMPROVE-IT study, which showed that the combination of statin and ezetimibe reduced LDL-C more than that for a statin alone, and that there was a significant reduction in atherosclerotic cardiovascular disease in those who received the more intensive therapies and achieved lower LDL-C levels².

As such, if we discard LDL-C targets, it has been suggested that individuals at the highest risk in our population who require intensification of therapy to achieve even lower LDL-C than

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that achieved by the maximally tolerated statin, may not benefit from these additional therapies. Finally, I have a concern that the advent of new, powerful LDL-C lowering medications (such as the PCSK9 inhibitors which lower LDL-C below that of the maximum statin)³, may render these guidelines irrelevant, as we switch back to treating patients to goal once again. Time will tell.

Additional Findings from Trials on Niacin and Fibrate

Several other studies conducted in the last decade will have an impact on the guidelines.

Firstly, two trials of niacin added to optimal therapy with statins to LDL-C provided negative findings.^{4,5} In fact, the heart protection study² resulted in some adverse effects from either niacin or the accompanying laropirant which were higher in the treatment than in the control group.⁴ My sense is that the role of niacin in lipid lowering is relegated to those patients who remain hyperlipidaemic despite maximal tolerated statin levels.

Secondly, the ACCORD study showed us that there is no difference in event rates between patients with T2D randomly assigned to fibrate therapy or placebo.⁶ Only a subgroup analysis (in both the ACCORD⁶ study and the FIELD⁷ study) showed that fibrate therapy might be beneficial only to those with elevated triglycerides and low levels of high-density-lipoprotein cholesterol (HDL-C). Both ACCORD and FIELD provided intriguing data suggesting the fenofibrate may be helpful in reducing the risk or progression of microvascular complications including retinopathy, kidney disease and lower extremity amputations.⁷ The reasons for these effects are unclear at this time. However, fenofibrate now has an indication for the prevention of retinopathy in some countries.

Lipid Lowering in Chronic Kidney Disease

Finally, after decades of recognising that chronic kidney disease is an important risk factor for atherosclerotic cardiovascular disease, we finally have data from a randomised controlled clinical trial that showed that adding ezetimibe to a statin will further remove the LDL-C and reduce the risk of atherosclerotic disease.⁹ To my mind, the demonstration that chronic kidney disease is not only a risk factor for atherosclerotic cardiovascular disease, but that treatment with LDL-C-lowering therapy (in this instance the combination of simvastatin and ezetimibe) could lower this risk is a key reason for including chronic kidney disease in the assessment of risk in our patients.

CONCLUSION

In summary, the strategy for lipid lowering has shifted. Therapy based on LDL-C goals has been discarded by some, in preference for fixed doses of statins used in clinical trials. This may not be accepted by all health systems and may be rendered

irrelevant by the advent of novel, powerful lipid-lowering agents. The role of niacin and fenofibrate has largely declined, with the latter benefiting a sub-set of the population with diabetes and the metabolic syndrome. However, an emerging role for fenofibrate in the treatment and prevention of microvascular complications in patients with diabetes mellitus is emerging and presents interesting potential to extend the benefits of this class of drugs. Finally, the benefits of lipid lowering in patients with chronic kidney disease has now been demonstrated in randomised controlled trials and chronic kidney disease should probably be represented in the algorithms for risk stratification to determine whether patients require lipid-lowering therapy.

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LEARNING POINTS

- A recent change in the paradigm of lipids management relates to the recommendations by the American College of Cardiology and the American Heart Association to direct the dose and type of statin prescribed to the level of cardiovascular risk in place of LDL-C targets.
- The benefits of lipid lowering in patients with chronic kidney disease have been demonstrated in randomised controlled trials and could be represented in future algorithms to risk-stratify patients for lipid-lowering therapy.
- The role of niacin in lipid lowering is limited to patients who remain hyperlipidaemic despite maximal tolerated statin levels.

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