

The Role of Non-statin Therapy to Improve Cardiovascular Outcomes

Abdulhalim Jamal Kinsara¹, FRCP, FACC, FESC; Domenico Galzerano², FESC; Olga Vriz², MD

1 Ministry of National Guard-Health Affairs, King Saud Bin Abdulaziz University for Health Sciences, COM-WR, King Abdullah International Medical Research Center, Jeddah, Saudi Arabia;

2 King Faisal Specialist Hospital and Research Centre and Alfaisal University.

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Correspondence to: Abdulhalim Jamal Kinsara, FRCP, FACC, FESC, Department of Cardiology, Ministry of National Guard-Health Affairs, King Saud Bin Abdulaziz University for Health Sciences, COM-WR, King Abdullah International Medical Research Center, Jeddah, Saudi Arabia.
Email: akinsara@yahoo.com

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ABSTRACT

All major studies generated evidence that validated the association between hyperlipidemia and cardiovascular disease. Low-Density Lipoprotein (LDL) has always been the target for risk reduction and the most frequently used therapeutic option. Statins reduce the LDL and improves the cardiovascular (CV) outcomes. However, in specific clinical cases where statins cannot be used, the therapy must include non-statin drugs. There are many options available, but the not all improve the CV outcome. Ezetimibe and PCSK9 inhibitors had clear evidence of benefit to reduce atherosclerotic cardiovascular

disease risk, while other therapy are showing less evidence. The current review highlights the evidence related to non-statin in the reduction of CV outcomes.

Key words: Ezetimibe; Proprotein convertase subtilisin kexin type 9 Inhibitor; Lomitapide; Mipomersen; Inclisiran; Bempedoic acid; Nexletol & Nexlizet; Bile acid sequestrants; Fibrates; Nicotinic acid; Plasmapheresis

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INTRODUCTION

The cardiovascular (CV) benefit of non-statin lipid-modifying therapies vary significantly according to the class of the medication. Evidence is available in terms of a reduction of atherosclerotic cardiovascular disease (ASCVD) morbidity with some non-statin such as ezetimibe and proprotein convertase subtilisin kexin type 9 inhibitor (PSCK9 inhibitors)^[1]. The reduction is linear with low-density lipoprotein (LDL) reduction, however, whether this effect is the same with the new therapeutic modalities, is not clear yet. The context is a situation where a statin cannot be used or the LDL target was not achieved, and an alternative option must be considered. Some of the newer modalities are weak LDL reducers, with others achieving a significant LDL reduction.

DISCUSSION

Why we need a non-statin?

Although statins has a high safety profile, some patients cannot tolerate a statin-based regimen at any dosage, or the target reduction of LDL was not achieved. Recent guidelines created a category of Very High Risk ASCVD, which include recurrent acute coronary syndrome, as well as a patient who had an additional event, for example a stroke, peripheral arterial disease or severe chronic kidney

Table 1 Summary of Statin/Non-statin drug effect on the lipid profile.

type	LDL	Triglyceride	HDL	Non-HDL	Apolipo-protein B	Lp-a
Statin	↓↓	±↓	↑	↓	↓	±
Ezetimibe	↓↓	↓	↑	↓	↓	±
PCSK9I	↓↓	↓	↑	↓	↓	↓
Bempedoic acid	↓↓	±		↓	↓	±
Bile acid sequestrants	↓	±↑	↑	↓	↓	±

disease (CKD). Such patients will require a much lower target that may not be achieved with a statin^[1]. It is important to consider a non-statin in cases where the ApoB analysis used for risk assessment, indicated a high TG, DM, or metabolic syndrome. It is also important to consider a non-statin if the patient has a high total risk estimation using the SCORE or another risk assessment tool, or if the arterial ultrasonography plaque burden measured in the carotid or femoral artery or the CAC score assessment with a CT, shifted the patient to a higher risk category^[1].

Human genetic data directed scientists to the discovery of many lipid-lowering drugs, for example the statin inhibitors GCR gene, evolocumab and alirocumab inhibit PCSK9 and ezetimibe inhibit NPC1L1^[2]. In addition, evidence from genetic, Mendelian randomization studies, epidemiological and randomized control trials of LDL reducing drugs, indicated a log-linear relation between the LDL level and the risk of ASCVD.

All the guidelines are consistent in prescribing the first step as ensuring the healthy lifestyle through modifying the patient's practices. Modifying such practice will reduce the ASCVD risk in all ages. It might be useful to consider the patient's social and religious background to modify the lifestyle and diet^[1]. The Messenger of Allah said, "The son of Adam cannot fill a vessel worse than his stomach, as it is enough for him to take a few bites to straighten his back. If he cannot do it, then he may fill it with a third of his food, a third of his drink, and a third of his breath."^[3] Subsequent to lifestyle modification, is the addition of different groups of drugs to increase LDL reduction from 30-50% to 65-85%^[4]. Table 1 summarize the effect of these non-statin drugs on the lipid profile.

Ezetimibe

Simvastatin and ezetimibe in the Aortic Stenosis (SEAS) trial and the Study of Heart and Renal Protection (SHARP) trial investigated the potential benefit related to cardiovascular morbidity and mortality. The therapy reduced the incidence of ischemic cardiovascular events but not events that occurred due to a stenotic aortic valve^[5,6]. The LDL was reduced with 25%. The combination with the statin in acute coronary syndrome showed a significant reduction of 170 events compared to a statin alone in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). The combination reduced the primary outcome by 1.8% over 7 years with 56 patients needing to be treated and a significant lower incidence of ischaemic stroke by 21%. The absolute CV benefit due to the addition of ezetimibe was small^[7]. The beneficial effect of ezetimibe is also supported by genetic studies with mutations in NPC1L1. This is a naturally occurring mutation and its inactivation is associated with a reduction in plasma LDL and the risk for CAD^[2].

Proprotein convertase subtilisin kexin type 9 Inhibitor (PCSK9 Inhibitor)

The Cardiovascular Outcomes Research with PCSK9 Inhibition in participants with Elevated Risk (FOURIER) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome

During Treatment with Alirocumab (ODYSSEY Outcomes) trials showed a significant reduction in CV events that was proportionate to the reduction in LDL^[8,9]. The result was a 15-20% reduction in the risk of the primary endpoints (composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) [hazard ratio (HR) 0.85, 95% CI 0.790.92]. In total, 67 patients needed treatment over 2 years, and the primary outcome decreased by 1.5%. In patients using statins, the LDL reduced up to 60%.

Homozygous familial hypercholesterolemia (HoFH) specific drug: Lomitapide

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor, prescribed orally as a once daily treatment for HoFH that reduces the LDL-C and TG. MTPI is usually used with statins, and with apheresis, the reduction of LDL was 50% at 26 weeks and by 44% at 56 weeks. Although Lomitapide reduces the frequency of apheresis, the CV outcome has yet to be determined^[10].

Mipomersen

Mipomersen is an anti-apolipoprotein B, antisense oligonucleotide, which triggers the selective degradation of mRNA molecules, the drug reduce LDL with 25-33%. The CV outcomes data are still pending^[11].

Inclisiran

Inclisiran is an anti-PCSK9 small RNA, antisense oligonucleotide that reduces LDL in heterozygous FH and uncontrolled LDL. It has the major advantage of being taken as a biannual dose. A small study showed a LDL reduction of 40% with two doses 3 months apart. The CV outcomes data are still pending^[12].

Bempedoic acid derivative: Nexletol and Nexlizet

The oral adenosine triphosphate citrate lyase (ACL) inhibitor reduces LDL in a patient at risk for ASCVD, FH, and statin intolerance by 13% to 43%. If added with ezetimibe, the LDL is reduced by 48%^[13].

Bile acid sequestrants

The benefit of bile acid sequestrants is proportional to the LDL reduction, varying from 15-25%. The drug was investigated before many of the current options were available^[14,15].

Fibrates

Fibrates are agonists of peroxisome proliferator-activated receptor- α (PPAR- α), acting via the regulation of transcription factors, and result in a < 20% reduction of the LDL compared to a 50% reduction in TGs and TG-rich lipoprotein remnant particles. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), Action to Control Cardiovascular Risk in Diabetes (ACCORD) in the (fenofibrate +statin), Lower Extremity Arterial Disease Event Reduction (LEADER) trials did not show a reduction in the total CVD outcomes. The Helsinki Heart Study (HHS) reported a

significant reduction in CVD outcomes with gemfibrozil. The risk reduction appeared to be proportional to the degree of non-HDL-C lowering in the context of elevated TG/low HDL-C levels. No overall benefit was reported in two recent meta-analyses. The CV benefits of fibrates require further confirmation^[16-19].

Nicotinic acid

Nicotinic acid inhibits the Liver diacylglycerol acyltransferase-2 secretion of VLDL, and primarily raises HDL and ApoA1 by stimulating ApoA1 production in the liver. Two large randomized trials with extended-release niacin and with niacin plus laropiprant showed no beneficial effect and an increased frequency of adverse effects^[20].

Extracorporeal removal of lipoproteins

Extracorporeal removal of lipoproteins are done through plasmapheresis or nonspecific plasma exchange to remove LDL or Lp(a). However, randomized ASCVD outcome trials are still lacking^[21-23].

CONCLUSION

In a systematic review of the evidence for adding non-statin lipid-modifying therapies to statins to reduce ASCVD risk, we found evidence of benefit for ezetimibe and PCSK9 inhibitors but not for niacin or cholesterol-ester transfer protein inhibitors. However, new therapeutic options are being developed. Future therapy will investigate monoclonal antibodies or anti-PCSK9 vaccines and targeted gene editing.

Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Disclosure

All authors had full access to the articles reviewed in this manuscript and take complete responsibility for the integrity and accuracy of this manuscript. The content published herein solely represents the views and opinions of the authors.

Authorship

All named authors met the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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