Combination Therapy with Statins: Who Benefits?

Amita Singh, MD, Michael Davidson, MD*

KEYWORDS

• Lipids • Cholesterol • Statin • Niacin • Fibrates • Ezetimibe • Omega-3 fatty acids • Cardiovascular risk

KEY POINTS

- When therapies have been studied in addition to statins, which remain the standard of treatment, it has been challenging to consistently show an additional clinical benefit in terms of cardiovascular (CV) event reduction, although overall safety seems acceptable.
- Combination therapy is a viable and often used strategy, which allows more patients to successfully reach their ideal lipid targets.
- There may be particular benefit with fenofibrate and niacin in patients with more severe atherogenic dyslipidemias who are unable to achieve intensive low-density lipoprotein (LDL) reduction with statins alone.
- Patients with very high CV risk because of recurrent events on therapy, or those with statin intolerance, are potential candidates for combination strategies.
- Further testing of novel therapies, particularly the PCSK9 class of medications, may introduce an era of potent LDL lowering without dependence on statins, but until then, they remain the mainstay of therapy.

INTRODUCTION

Cardiovascular (CV) disease (CVD) has been the leading cause of death in the United States since the early twentieth century, with worldwide rates similarly on the increase.[1] Increased low-density lipoprotein cholesterol (LDL-C) and, to a lesser extent, low high-density lipoprotein cholesterol (HDL-C) and increased triglyceride (TG) levels are all independent risk factors for CVD. Since the introduction of lovastatin in 1987, statins (hemoglobin [HMG]-coenzyme A [CoA] reductase inhibitors) have been repeatedly shown to decrease LDL-C, thereby reducing the risk for CVD events for patients with or without established vascular disease, and have long comprised the foundation of lipid-lowering therapy.

The importance of decreasing LDL levels in modification of CV risk has driven interest in and development of several novel cholesterol-modifying drugs, many of

Section of Cardiology, University of Chicago, Chicago, IL, USA
* Corresponding author. 140 Belle Avenue, Highland Park, IL 60035.
E-mail address: mdavidsonmd@gmail.com

Endocrinol Metab Clin N Am 43 (2014) 993–1006
http://dx.doi.org/10.1016/j.ecl.2014.08.005 **endo.theclinics.com**
0889-8529/14/$ – see front matter

which are under investigation in ongoing clinical trials. However, until these pharmacotherapies are widely available, the established cholesterol-modifying drugs remain the cornerstone of therapy; among these are statins, niacin, fibrates, ezetimibe, bile acid sequestrants (BASs), and omega-3 fatty acids (OM3FAs). In the last 10 years, clinical trials of combination therapy, primarily used as add-on therapies to statins, have yielded inconsistent results with regards to CV-related morbidity and mortality outcomes. Further complicating the picture are the release of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on the Treatment of Blood Cholesterol, which shifted the focus of therapy away from LDL-C targets.[2] The juxtaposition of these guidelines with previous algorithms has invoked questions regarding the safety and efficacy of combination lipid-lowering therapies as part of an optimal medical regimen for CV risk reduction. Although combination therapy may not be broadly recommended for all patients, closer examination of the available data suggests that combination therapy is largely safe and that careful selection provides tailored lipid-lowering strategies, which may benefit specific populations.

QUESTIONING THE PARADIGM: UPDATED BLOOD CHOLESTEROL GUIDELINES

Until recently, the aim of lipid-lowering therapy had focused on an established LDL-C target, which was calculated based on the presence of CV risk factors or equivalent disease states. In turn, this risk estimate and target LDL-C mandated how medication therapies were initiated and further titrated, typically beginning with statins.[3] The National Cholesterol Education Panel delineated LDL-C as the primary target of statin therapy, with a secondary non–HDL-C goal (designated as 30 mg/dL more than the LDL-C target). Intensive therapy was geared toward patients with higher risk, as assessed by the 10-year risk estimates using the Framingham scoring system, with consideration for use of add-on therapies for achievement of LDL-C or non–HDL-C targets. Commonly cited weaknesses of the 2001 guidelines and 2004 update were the limited generalizability of the Framingham risk score in women and nonwhite populations, and the monolithic emphasis on LDL-C targets, which could possibly lead to underuse of statin therapy. Efforts to expound on these guidelines emerged from consensus statements and guidelines from the American Diabetes Association and AHA/ACC, which further elaborated on the identification of high-risk patients (so-called cardiometabolic patients and those with established CVD), for whom intensive lipid-lowering therapy would provide incremental benefit in residual CV risk reduction.[4–6]

In a hotly debated turn, the 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol abandoned the prespecified LDL-C and non–HDL-C targets in favor of the identification of 4 risk groups for whom statin therapy is most likely to be beneficial in reducing the risk of atherosclerotic CVD.[2] Furthermore, in lieu of designated on-treatment LDL-C targets, the guidelines suggested an empirical statin potency (low, mid, or high potency) without clear targets. It can be surmised that assessing a response to therapy (ie, percent LDL reduction) could be obtained from measuring on-treatment lipid values, although the panel did not recommend routine pursuit of LDL-C targets. The 2013 guidelines do not discuss details of combination therapy, although it is implied that there may be a role for add-on strategies in individuals with statin intolerance or those with a suboptimal response to therapy. Thus, the guideline-driven use of combination therapy in the era of statin therapy remains open ended, with answers likely to be clarified by the results of future clinical trials.