Treating Cholesterol With Combination Therapy

This guide summarizes clinical evidence on using combinations of lipid-lowering medications for the treatment of high cholesterol. Most of the available evidence compares combination therapy with using a statin medication alone. This guide covers the major classes of lipid-lowering medications. It does not cover dietary and lifestyle changes.

Clinical Issue

High cholesterol is one of the most commonly treated medical conditions. There is general consensus that aggressive treatment is indicated for high-risk individuals. LDL levels are the primary target of treatment. Lowering LDL cholesterol reduces the risk of coronary heart disease and ischemic stroke.

After diet and exercise, a statin medication is the first line of treatment. Several other types of medications are available for lowering cholesterol. For people who do not achieve the desired treatment goal on statin monotherapy, combination therapy may permit using a lower dose of a statin and decrease the risk of side effects.

Much of the available evidence compares combination therapy to statin monotherapy using less than maximal statin dosages. For people who have not reached their cholesterol goal on lower doses of statins, the clinical options are either to raise the statin dose or to add a second lipid-lowering medication.

The systematic review on which this guide is based compared the following medication combinations with statin monotherapy:

- Statin plus a bile acid sequestrant
- Statin plus ezetimibe
- Statin plus a fibrate
- Statin plus niacin
- Statin plus Omega-3 fatty acids

Clinical Bottom Line

The evidence is insufficient to conclude that combination therapy leads to lower rates of clinical events and death (all cause mortality and vascular death) than statin monotherapy. In these studies, clinical events included myocardial infarctions, strokes, and the need for invasive vascular procedures.
The evidence is insufficient to assess whether any combination regimen provides greater reduction in LDL cholesterol than statin monotherapy. Evidence is also insufficient for other intermediate outcomes, including total cholesterol, HDL cholesterol, and coronary artery and carotid intima thickening.
The evidence is insufficient to draw conclusions about the rates of adverse events of combination therapy compared with statin monotherapy. The adverse events assessed in these studies included elevation of liver enzymes, myalgia, rhabdomyolysis, and cancer.

The Studies

While over 100 research studies were included in the systematic review, several characteristics of these studies made it difficult to draw firm conclusions.

- Small sample size – The trials generally were unable to detect endpoints that occurred infrequently.
- Short duration – On average, the trials were about 30 weeks long; some lasted as little as 4–6 weeks.
- Inconsistent results – When a trial showed superiority of a drug combination, other trials did not confirm this result.
- Lack of ethnic diversity – Most study participants were white males.
- Different definitions of treatment success – Trials used many different thresholds to classify participants as having improved cholesterol levels.
- Little analysis of non-LDL outcomes – The studies provided little data on other treatment effects, such as HDL and triglyceride levels.

Only 15 of the 102 studies compared combination therapy with higher dose statin therapy. Most used the same dose statin in both the monotherapy and combination therapy study arms. It is not possible to derive recommended doses from these studies.

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Lipid-Lowering Medications

Drug Name[1]	Brand Name	Available as Generic?
Statins		
Atorvastatin	Lipitor®	No
Fluvastatin	Lescol®, Lescol® XL[2]	No
Lovastatin	Mevacor®, Altoprev®[2]	Yes
Pravastatin	Pravachol®	Yes
Rosuvastatin	Crestor®	No
Simvastatin	Zocor®	Yes
Bile acid sequestrants		
Cholestyramine	Questran®	Yes
Colesevelam	Welchol®	No
Colestipol	Colestid®	Yes
Cholesterol absorption inhibitors		
Ezetimibe	Zetia®	No
Fibrates		
Gemfibrozil	Lopid®	Yes
Fenofibrate	Lofibra®, TriCor®	Yes
Vitamins and supplements		
Niacin	Niacor®, Niaspan®[2]	Yes
Omega-3 fatty acids	Lovaza®	Yes
Combinations		
Ezetimibe/simvastatin	Vytorin®	No
Niacin ER/lovastatin	Advicor®	No
Niacin ER/simvastatin	Simcor®	No

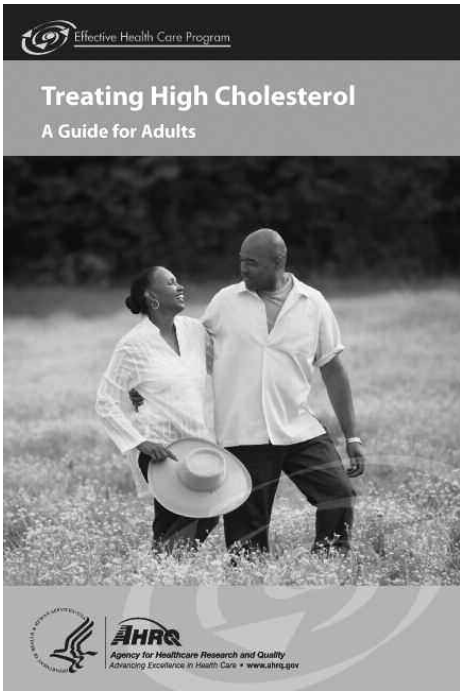
[1]These drugs were evaluated in the systematic review.

[2]Extended release. Not available as generic.

XL/ER = extended release.

Resource for Patients

Treating High Cholesterol: A Guide for Adults is a companion to this Clinician's Guide. It can help people talk with their health care professional about high cholesterol and the different types of lipid-lowering medications.



For More Information

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site: www.effectivehealthcare.ahrq.gov

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Source

The source material for this guide is a systematic review of 102 research studies. The review, *Comparative Effectiveness of Lipid Modifying Agents* (2009), was prepared by the University of Ottawa Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts. The full systematic review is available at **www.effectivehealthcare.ahrq.gov**.

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