FPIN's Clinical Inquiries

Best Alternatives to Statins for Treating Hyperlipidemia

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Clinical Question

When statin therapy is not tolerated, what are the best alternative treatments for patients with hyperlipidemia?

Evidence-Based Answer

Most alternatives to statin therapy reduce cholesterol levels but do not consistently demonstrate a reduction in cardiac-related and all-cause mortality in patients with or without coronary heart disease (CHD). Fibrates and niacin decrease the risk of major coronary events; however, no statistically significant reductions in mortality have been shown. (Strength of Recommendation [SOR]: A, based on systematic review of randomized controlled trials [RCTs]).

Resins decrease cardiovascular mortality but not total mortality. (SOR: A, based on review of RCTs).

The effects of ezetimibe (Zetia) on cardiovascular outcomes and mortality are unknown. (SOR: C, based on a single RCT with disease-oriented evidence).

Omega-3 fatty acid supplementation does not clearly demonstrate reductions in mortality. (SOR: A, based on two meta-analyses of RCTs).

There is insufficient evidence to recommend the use of herbal therapy for the treatment of hyperlipidemia. (SOR: A, based on a systematic review of RCTs).

Evidence Summary

A literature search found one systematic review that included 97 RCTs comparing different classes of antilipidemic therapies.[1] Other studies focused on specific therapies and included one high-quality systematic review of 12 RCTs, 22 prospective cohort studies, four case reports, and one cross-sectional study evaluating cardiovascular outcomes for omega-3 fatty acid supplementation; one systematic review of 27 RCTs on garlic; and one systematic review of 25 limited-quality RCTs of 11 herbal products.[2,4] Additional studies included a systematic review of 48 RCTs and 41 cohort studies evaluating the effect of omega-3 fatty acid

supplementation on mortality, cardiovascular disease, and cancer; a subsequent Cochrane review that addressed omega-3 fatty acid supplementation for the prevention and treatment of cardiovascular disease; and a meta-analysis of 53 RCTs evaluating fibrates and 30 RCTs evaluating niacin therapy.[5-7]

FIBRATES

A meta-analysis of medications that increase high-density lipoprotein (HDL) cholesterol levels included eight RCTs evaluating the long-term clinical end points of fibrates.[7] Pooled results of these studies indicate a clinically significant reduction in coronary events (number needed to treat = 33 for four years). Reductions in cardiac-related and all-cause mortality were not significant, and noncardiovascular mortality was similar in the treatment and placebo groups (relative risk [RR] = 1.10; 95% confidence interval [CI], 0.96 to 1.26). An earlier systematic review, which included the World Health Organization Cooperative Trial on primary prevention with clofibrate (not available in the United States), showed that fibrates were associated with a small but statistically significant increase in mortality (RR = 1.13; 95% CI, 1.01 to 1.27).[1]

NIACIN AND RESINS

Based on a meta-analysis that included a single long-term outcome study of 2,248 men treated with immediate-release niacin, cardiovascular events were reduced by 27 percent at 10-year follow-up compared with placebo; however, it should be noted that this study had a more than 70 percent drop-out rate.[7]

A systematic review that included two RCTs of 3,107 patients with CHD did not demonstrate a clinically significant reduction in cardiovascular mortality in those treated with niacin (RR = 0.95; 95% CI, 0.82 to 1.10).[1] In this same systematic review, which included eight RCTs of resins, chole-styramine (Questran) and colestipol (Coles-tid) demonstrated significant reductions in cardiovascular death in the treatment groups (RR = 0.70; 95% CI, 0.5 to 0.99) but no significant reductions in overall mortality.[1]

OMEGA-3 FATTY ACIDS

A systematic review of 14 RCTs reported that omega-3 fatty acid supplementation resulted in a clinically significant reduction in overall mortality in patients with pre-existing CHD (RR = 0.77; 95% CI, 0.63 to 0.94).[1] This review, however, excluded one RCT of 3,114 male patients with angina in the data synthesis. When this study was included, reduction in mortality was not statistically significant and had a wide confidence interval (RR = 0.84; 95% CI, 0.66 to 1.06). Based on a pooled estimate from a subsequent review that included this RCT, there was no significant reduction in cardiovascular events or mortality with omega-3 fatty acid treatment.[5] Another concern noted in this review and an associated Cochrane review was that relative risk of mortality seemed to increase with duration of treatment.[5,6] Trials subgrouped by duration revealed a protective effect, with decreased deaths in trials lasting 24 to 47 months (RR = 0.84; 95% CI, 0.75 to 0.93) but a significant harmful effect in those lasting longer than 48 months (RR = 1.31; 95% CI, 1.07 to 1.59).[5] This harmful effect was based on a single RCT.

An Agency for Healthcare Research and Quality (AHRQ) evidence report based on a comprehensive systematic review indicated that although some studies did show benefit with omega-3 fatty acid, there was an

imbalance in the design of the studies, and data on women and the specific effects of different CHD outcomes are uncertain.[2]

EZETIMIBE

One RCT found that treatment with ezeti-mibe (a cholesterol absorption inhibitor) resulted in an average low-density lipoprotein (LDL) cholesterol level reduction of about 18 percent; however, its effect on important patient health outcomes (e.g., mortality) is unknown.[8]

GARLIC AND HERBAL MEDICATIONS

A high-quality systematic review on the effects of garlic on cardiovascular disease, which was conducted for an AHRQ evidence report, evaluted 37 studies.[3] Although some modest short-term improvements in lipid measures were found, effects on cardiovascular outcomes were either not measured or not found. Thus, there is insufficient evidence to recommend use of garlic for the treatment of hyperlipidemia.[3] Based on a systematic review of 25 RCTs, various herbal medications (guggul, fenugreek, red yeast rice, artichoke) may lower average total cholesterol by 10 to 33 percent; however, these studies are of poor quality overall, and an impact on mortality has not been established.[4]

Recommendations from Others

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines outline treatment goals in the management of hyperlipidemia with LDL cholesterol goals based on 10-year risk of CHD.[9] Statins are the preferred treatment, and resins and niacin are options for add-on therapy or for treatment in patients with modest elevations of LDL cholesterol level. Fibrates have a higher risk profile and should be reserved for use in combination with statins or in patients with moderate or severe hypertriglyceridemia (triglyceride level higher than 500 mg per dL [5.65 mmol per L]). A scientific statement from the American Heart Association recommends that patients with known CHD should consume 1 g of omega-3 fatty acids containing eicosapentaenoic acid plus docosahexaenoic acid per day, preferably from oily fish.[10]

Clinical Commentary

Reducing morbidity and mortality is the objective of treating hyperlipidemia, and statins are the drugs that have been best proven to accomplish this. Lowering LDL cholesterol level by any other means is widely accepted as the "logical" alternative for patients who cannot tolerate statins. This approach is recommended by the NCEP ATP-III guidelines; however, the effect of this practice on mortality has not been demonstrated. Pharmaceutical companies certainly benefit from physicians' enthusiasm for "treating the numbers," but this review should be a reminder that patients might not. It will be interesting to see if the Improved Reduction of Outcomes: Vytorin Efficacy International Trial or other trials now under way show the newest and most expensive nonstatin LDL-lowering drug to be any more beneficial than its predecessors.

When faced with a patient with hyper-lipidemia who cannot tolerate statins, it is important to take another look at the overall risk of cardiovascular disease and to inform the patient of the data (or lack thereof)

regarding the expected benefits and risks of alternative treatments. The informed patient who previously decided to take statins based on the explanation of proven risk reduction may choose not to consent to take a medication with less certain benefit.

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