"Tailored Treatment" with Statins for Primary Prevention of Cardiovascular Disease May Be More Effective Than the Current "Treat-to-Target" LDL Strategy

Hayward R, Krumholz H, Zulman D, et al. Optimizing statin treatment for primary prevention of coronary artery disease. Ann Intern Med 2010;152:69–77.

Study Overview

Objective. To determine whether statin treatment based solely on coronary artery disease (CAD) risk improves outcomes more than a treatment strategy based on LDL cholesterol targets.

Design. Simulated models using population data from the National Health and Nutrition Examination Survey (NHANES) and efficacy data on statins from randomized controlled trials.

Methods. Authors simulated the population effects of 3 strategies for using statins in the primary prevention of CAD: (1) standard treat-to-target—statin treatment to achieve LDL < 190 mg/dL for individuals at low risk for CAD (0–1 risk factors), < 160 mg/dL if moderate risk (≥ 2 risk factors and 10-year CAD risk < 10%), and < 130 mg/dL if high risk (coronary heart disease [CHD] equivalent or ≥ 2 risk factors for CAD and 10-year CAD risk > 10%); (2) intensive treat-to-target—statin treatment to achieve LDL < 160 mg/dL for low risk, LDL < 130 mg/dL for moderate risk, and < 100 mg/dL for high risk patients; and (3) tailored treatment—fixed dose of a moderate-potency statin (simvastatin 40 mg) if 5-year CAD risk was 5% to 15% and high-potency statin (atorvastatin 40 mg) if 5-year CAD risk was > 15%. The first 2 strategies allowed for stepped therapy with statins from 20 mg of simvastatin to 80 mg of atorvastin to achieve goal LDL levels. The models used population data from a simulated national population of 1 million people aged 30 to 75 years based on data from 4503 eligible subjects in NHANES III (data collected 1988–1994). The efficacy and harms data for statins came from randomized controlled trials for each of the statin options evaluated. Authors determined CAD risk using the Framingham risk score [1]. Experts in lipids reviewed the assumptions underlying the simulation models. Multiple sensitivity analyses were conducted to examine the effect of underlying assumptions: varying the range of LDL cholesterol reduction expected from statins, decreasing the goal LDL to < 70 mg/dL in the intensive treat-to-target strategy for individuals with a CHD risk equivalent, altering the accepted accuracy of the Framingham risk score, altering the risk stratification methods, changing the number of steps in statin treatment allowed for the treat-to-target strategy, altering the mortality benefit expected from escalating statin therapy, altering the length of treatment from 5 to 10 years, and combinations of these sensitivity analyses.

Main outcome measure. Quality-adjusted life-years (QALYs).

Main results. The standard treat-to-target strategy led to use of statins in 37.9 million individuals and an increase in 48 QALYs per 1000 persons treated for 5 years or 1.83 million total QALYs saved in the United States compared with no treatment. The intensive treat-to-target strategy led to treatment of 53.4 million individuals, with an additional 570,000 QALYs saved compared with the standard strategy. This strategy had a slightly lower relative benefit with only 45 QALYs saved per 1000 persons treated. The tailored treatment strategy resulted in treatment of 53 million individuals, 520,000 more QALYs saved and 10 more QALYs per 1000 persons treated for 5 years than the intensive treat-to-target strategy. The tailored treatment strategy led to more treatment among moderate-risk individuals with low LDL levels, and treating this group lead to 1 QALY saved per 39 people treated for 5 years. In contrast, the intensive treat-to-target strategy led to more treatment among individuals with high LDL but low CAD risk, with only 1 QALY saved for every 172 individuals treated. Sensitivity analyses showed similar results for tailored treatment and the intensive treat-to-target strategy only if using the more aggressive goal of LDL < 70 mg/dL among high-risk individuals, use of full risk stratification equation rather than a more limited risk stratification equation, and if the Framingham risk score provided a lower predictive accuracy for CAD risk.

Conclusion. Use of a tailored therapy strategy, with administration of statins based on CAD risk alone, may be more effective as a population strategy than strategies that require treatment to a LDL target.

Commentary

Statins are a mainstay of treatment for the primary preven-

tion of cardiovascular events. Numerous clinical trials have confirmed the benefit of statins for CAD prevention, and the National Cholesterol Education Program (NCEP) has recommended aggressive use of statins, with therapy guided by both CAD risk and LDL treatment goals [2]. However, using statins to reach a specific LDL treatment goal can be challenging. Individual responses to statins vary widely and cholesterol level monitoring is subject to measurement error [3]. Furthermore, use of specific LDL levels to trigger treatment decisions might limit treatment among individuals with a high risk for CAD but low LDL. Recent data have emerged to suggest that even individuals with moderate CAD risk and low LDL benefit from statins [4]. An alternative strategy for use of statins, based solely on total risk for CAD without any LDL targets for beginning or titrating therapy, might simplify treatment and ensure that more high-risk individuals are treated [5]. This simulation study by Hayward et al tests this alternative strategy.

The study found that a tailored treatment strategy, using statins based solely on CAD risk, leads to more total QALYs saved and more effective treatment with more QALYs per 1000 people treated than either a standing treat-to-target strategy (with conservative LDL targets) or an intensive treat-to-target strategy (with aggressive LDL targets). As with any simulation, the results are only as strong as the assumptions used for the simulation. Yet, the authors used rather conservative assumptions about the effect of statins on LDL and the overall effect of statins on reducing CAD risk, which would favor a treat-to-target strategy. The results were robust regardless of these assumptions, and multiple sensitivity analysis confirmed the improved results with a tailored treatment strategy.

The major limitation of this study was the use of LDL targets in both the standard and the intensive treat-to-target strategies. Lower LDL targets, including a target of < 70 mg/dL for those individuals at highest CAD risk (CHD equivalent) and a target of < 100 mg/dL for those at moderately high risk (≥ 2 risk factors for CAD and 10-year CAD risk of 10%–20%), are commonly accepted and embraced as optional targets by the National Cholesterol Education Program [6]. Only one of these very intensive LDL targets was tested in sensitivity analysis—the LDL goal of < 70 for those at highest risk. Using this very intensive target LDL, along with some higher estimates of uncertainty about the risk assessment calculations, was equivalent to the tailored treatment strategy.

Another limitation arises from the use of NHANES data from 1988 to 1994 to create the simulated population. Authors used these data because they assumed a limited effect of statin treatment on average LDL levels in the population because of less frequent use of statins during this time period when compared with more recent NHANES data collection periods. However, use of this population also limits the applicability of these data to the current population. Much progress in cardiovascular risk reduction has been made since this time, with more aggressive treatment of blood pressure and use of aspirin in primary prevention, and statin treatment may have weaker effects in a more aggressively treated present-day population. Weaker effects of statin treatment on outcomes could decrease the total population benefit found in this study; however, the relative benefit of different treatment strategies should not change.

Regardless of these limitations, tailored treatment is a tempting strategy because of its simplicity even if it is equivalent to an intensive treat-to-target strategy. Tailored treatment could be employed easily in resource-poor settings, which are not suited to the frequent monitoring of cholesterol levels and dose titration of statins that is required in a treat-to-target strategy. Cost savings would also result. Based on this simulation, tailored treatment would lead to the same number of individuals treated with statins as the intensive treat-to-target strategy. Yet, the decreased need for frequent laboratory monitoring of cholesterol that would be a result of tailored treatment would substantially reduce costs.

These simulation data are promising. If confirmed in actual randomized clinical trials, a new paradigm of statin treatment could emerge that is both simple and perhaps more effective in preventing CAD.

Applications for Clinical Practice

For the use of statins in the primary prevention of CAD, tailoring treatment strategy according to CAD risk alone may be a more effective strategy that treating to specific LDL targets. This simulation study shows promising evidence of this benefit, but further studies, including randomized controlled trials, should be conducted to further demonstrate a benefit to tailored treatment. Even if tailored treatment and treat-to-target are similar in achieving outcomes, tailored treatment may still be a preferred strategy secondary to its simplicity and possible cost savings.

—Review by Jason P. Block, MD, MPH

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