Shifting views on lipid lowering therapy

Harlan Krumholz and Rodney Hayward argue that preventive cardiology should be based as much as possible on strategies that are known to improve patient outcomes rather than focusing on biomarkers.

Current guidelines and performance measures concerning risk factors for coronary artery disease emphasise the importance of achieving target cholesterol levels without strong guidance about the strategies used to achieve them. Some health programmes also pay doctors whose patients achieve specific lipid targets. The target approach opened the door for marketing campaigns to promote drugs that have not been shown to affect patient outcomes. For example, ezetimibe was heavily promoted in the United States, with the manufacturers spending more than $200m (£130m; €160m) on direct to consumer advertising of Vytorin (ezetimibe plus simvastatin) in 2007. Millions of prescriptions were written, even though no clinical trial of the drug had focused on patient outcomes. The focus on targets is out of alignment with evidence from clinical trials and discounts the importance of testing whether the benefits of a treatment exceed its risks, instead suggesting that we can rely on its effects on biomarkers.

Current US guidelines

The “treat to target” model, which focuses on cholesterol levels is deeply embedded in medical dogma. Current US guidelines, last published in 2004 and now under review, propose a low density lipoprotein (LDL) cholesterol target <2.6 mmol/l (100 mg/dl) for patients with coronary heart disease, <3.4 mmol/l (130 mg/dl) for those with two or more risk factors, and <4.1 mmol/l (160 mg/dl) for those with fewer than two risk factors. Moreover, a revision of the guidelines suggested an optional goal of <1.8 mmol/l for patients with coronary heart disease. Performance measures have also focused on achieving target levels.

The approach used by the guidelines is based on the dogma best described by Daniel Steinberg, a prominent lipidologist, as the “only rule necessary is ‘the lower, the better.’” This position derives from an understanding of lipid biology and its role in the development and progression of atherosclerosis. However, knowledge of the mechanism of disease does not confer the power to know how interventions that reduce LDL cholesterol affect patient outcomes.

The view that lower is better was reflected in the first US national guidelines for the treatment of hypercholesterolaemia, published in 1988, which identified raised lipid levels as targets for intervention. Building on years of work to establish the role of cholesterol in the development and clinical manifestation of atherosclerotic disease, the experts emphasised the importance of treating to a target level. They recommended use of drugs in various combinations in patients for whom lifestyle intervention failed.

What the evidence shows about targets

The target approach assumes that changes in risk factors by an intervention will translate into a reduction in patient risk, an assumption that has often been shown to be wrong. All drugs have complex effects that go beyond the narrow effect on a single biomarker. This makes it impossible to determine the net patient benefit of any given intervention without studies adequately powered to assess important outcomes because the beneficial effects of biomarker modification may be offset by unappreciated drug specific adverse effects.

Furthermore, treat to target guidelines are not supported by direct evidence from trials. The trials of cholesterol lowering treatments tested the effect of fixed doses of drugs, not a strategy of progressively intensifying lipid therapy without regard to strategy to reach specific target ranges. No trial has yet examined progressive lowering or shown that combination lipid therapy improves patient outcomes.

To support the focus on targets, proponents have used data from the secondary prevention trials to suggest that a regression line can be plotted across the end of trial values of the intervention and control groups and show a straight line ending somewhere near 1.8 mmol/l. That regression line includes the placebo group in the Scandinavian Simvastatin Survival Study (4S) at the high end of cholesterol levels and the intervention group in the Treating to New Targets (TNT) trial at the low end. The implication is that if you could have treated patients in the 4S group to reduce their cholesterol concentrations to the level in the intervention group of the TNT trial, the benefit achieved would have been the difference in the event rates between those groups. Hayward and others, examining the trials, show that evidence is lacking to support this claim. The studies were conducted at different times, with different subjects, and under different conditions; such a relation exists is entirely speculative.

Another problem with the target based approach is the assumption that the change in cholesterol level is more important than the strategy used to achieve it. However, the evidence shows that the strategy matters. Many interventions that lower cholesterol levels, and particularly LDL levels, fail to reduce patient risk. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial showed that torcetrapib, which lowered LDL levels by about 25%, increased the risk of death. Other interventions, such as the use of oestrogen, clodibrate, and dextrothyroxine, reduce LDL cholesterol but do not reduce risk. Most recently, questions are
being raised about ezetimibe, which effectively reduces LDL but has not been shown to improve patient outcomes; trial evidence has raised questions about its safety.11,12

**Statins**

Instead, the trial evidence most strongly supports the use of statins in patients at high risk of coronary artery disease. Statins reduce the risk of major coronary events, revascularisation, and stroke13–14 regardless of the initial lipid level. They also reduce the risk of death by roughly 12% in high risk patients. Higher potency or higher dose statins deliver slightly more benefit,15 at least for secondary prevention. Although the most likely explanation for the benefit of statins derives from their effect on lipids, many experts think pleiotropic effects may also contribute.16 So far, patients with heart failure are the only group identified that may not benefit from statins.17,18 These patients may have such a low risk of coronary heart disease that even if statins produce the same relative risk reduction, most patients will not accrue appreciable risk reduction, most patients will not accrue appreciable absolute benefit.

The safety of statins also seems assured, though there are some risks. More than 20 years after the US Food and Drug Administration approved the first statin, concerns about cancer have not been suppressed.19,20 Muscle symptoms are usually reversible, and rhabdomyolysis is very rare, especially in patients who are not also taking fibrates.21 The risk of diabetes may be increased by a modest amount but not enough to overcome the large benefit in high risk patients.22,23 However, we need continued vigilance to assess long term effects, which will be particularly important if statins are used in people without a high risk of coronary artery disease.

Given the strong evidence that statins reduce risk across the range of LDL levels, the best pre-ventive strategy may be to use the patient’s global cardiovascular risk to determine treatment.24–25 The absolute benefit of statins is greatest for those at higher risk—and those at highest risk would tend to benefit most from higher dose or higher potency statins. The benefit diminishes with decreasing risk. A recent analysis of statins for primary prevention showed that a strategy using statins based on patient risk rather than LDL levels can prevent more cardiovascular events while treating fewer people with high dose statins.26

In contrast to statins, the evidence that other treatments affect patient outcomes is variable, ranging from reasonable evidence for niacin and resins to no supportive evidence for ezetimibe. For patients who still have high cholesterol levels after treatment with statins, the choice of which other drugs to use will be made with more uncertainty about the net benefit. For patients with conditions that carry very high risk, such as those with familial hypercholesterolaemia, the target approach may be worth the uncertainty, though there should still be an emphasis on using drugs supported by the strongest evidence. Most patients, however, may wish to stay with strategies that have proved benefit to patient outcomes. In any case, the uncertainty about benefit and the limitations of the studies should be disclosed to the patient when strategies are used that do not have evidence of benefit to patients. Also, patient preferences should be respected by both provider and guidelines. We should avoid recommendations that might encourage the use of drugs whose safety and effectiveness have yet to be proved.

Harlan M Krumholz

Harold H Hines, Jr, professor of medicine, Section of Cardiovascular Medicine and Robert Wood Johnson Clinical Scholars Program, Department of Medicine, Yale University School of Medicine, New Haven, CT 06510, USA, Section of Health Policy and Administration, School of Public Health, Yale University School of Medicine; Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven

Roderic A Hayward co-director, Health Services Research and Development Center of Excellence, Ann Arbor, VA Medical Center, Michigan, USA; Schools of Public Health and Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

Correspondence to: M K Krumholz

harlan.krumholz@yale.edu

Accepted: 21 April 2010

Contributors and sources: RAH has studied and reported widely on improving methods for analysing and reporting both experimental and observational clinical studies and has a long interest in producing evidence bases and systems for facilitating more personalised patient care and clinical guidelines. This article arose from a series of conversations at the National Robert Wood Johnson Foundation Clinical Scholars Meeting. This article was envisioned and drafted by HMK, with critical revision and substantive contribution by RAH. HMK is the guarantor.

Competing interests: None declared

Provenance and peer review: Commissioned; externally peer reviewed.


The uncertainty about benefit and the limitations of the studies should be disclosed to the patient when strategies are used that do not have evidence of benefit to patients.


Cite this as: BMJ 2010;341:c3531

ANALYSIS