

Statin Denial: An Internet-Driven Cult With Deadly Consequences

The reduction in cardiovascular morbidity and mortality during the past 3 decades represents one of the great triumphs of contemporary medicine. In 1987, the age-adjusted mortality rate in the U.S. population for cardiovascular disease was 357 in 100 000, decreasing to 167 in 100 000 by 2014 (1). Although precisely gauging the relative contributions of various public health measures to the decline in cardiovascular morbidity and mortality is impossible, most critical observers consider the introduction of statins in 1987 to be one of the keys to this success. According to the Centers for Disease Control and Prevention, the prevalence of elevated low-density lipoprotein cholesterol levels (>4.1 mmol/L [160 mg/dL], >3.4 mmol/L [130 mg/dL], and >2.6 mmol/L [100 mg/dL] for low-, medium-, and high-risk persons, respectively) declined from 59% to 28% between 1980 and 2010 (2). Average low-density lipoprotein cholesterol levels decreased from 3.3 mmol/L (129 mg/dL) in 1988 to 1994 to 3.0 mmol/L (116 mg/dL) in 2007 to 2010.

Currently, 56 million Americans are considered eligible for statin therapy, with about half actually receiving treatment (3). We know that many patients take statins intermittently rather than continuously. A recent study in patients at very high cardiovascular risk found that only 61% of those administered a statin were adherent to therapy 3 months after the initial prescription, and only 55% were adherent after 6 months (4). Among Medicare beneficiaries administered high-intensity statins after myocardial infarction, only 59% and 42% were still taking the full prescribed dosage with high ($>80\%$) adherence at 6 months and 2 years, respectively, after the event (5). For a treatment with such well-documented morbidity and mortality benefits, these adherence rates are shockingly low. Why?

Statins have developed a bad reputation with the public, a phenomenon driven largely by proliferation on the Internet of bizarre and unscientific but seemingly persuasive criticism of these drugs. Typing the term *statin benefits* into a popular Internet search engine yields 655 000 results. A similar search using the term *statin risks* yields 3 530 000 results. One of the highest-ranking search results links to an article titled "The Grave Dangers of Statin Drugs—and the Surprising Benefits of Cholesterol" (6). We are losing the battle for the hearts and minds of our patients to Web sites developed by people with little or no scientific expertise, who often pedal "natural" or "drug-free" remedies for elevated cholesterol levels. These sites rely heavily on 2 arguments: statin denial, the proposition that cholesterol is not related to heart disease, and statin fear, the notion that lowering serum cholesterol levels will cause serious adverse effects, such as muscle or hepatic toxicity—or even worse, dementia. Once armed with the suggestion of harm, patients commonly experience these adverse reactions (the nocebo effect), challenge

their physician about the risks of treatment, or simply stop taking their medication. Indeed, some patients do have statin-related adverse effects, as we documented recently in a prospective randomized trial, but intolerance in many patients undoubtedly represents the nocebo effect (7).

The societal costs of the statin denial cult are well-documented by Zhang and colleagues (8). Among patients with a reported adverse reaction, 70.7% continued receiving a statin; after 4 years, 12.2% of patients who continued statin therapy had a cardiovascular event (death, stroke, or myocardial infarction), compared with 13.9% of those who discontinued treatment. This 1.7% difference translates to a number needed to harm of 1 excess event for every 59 patients who stopped statin therapy. For the mortality component of the primary composite outcome, the number needed to harm is staggering: 1 excess death for every 83 patients who discontinued treatment. This study is not the first to suggest that statin discontinuation or nonadherence has grave consequences. A review of 19 studies reported a relative risk for statin discontinuation ranging from 1.22 to 5.26 for cardiovascular disease and 1.25 to 2.54 for death (9).

All these studies, including the recent one by Zhang and colleagues (8), have important limitations. The studies are observational and retrospective, and generally use administrative data to assess the extent and effect of statin withdrawal. Most thoughtful observers consider the reliability of epidemiologic research to be relatively low unless the observed relative risk or odds ratio is less than 0.5 or greater than 2.0. Observational studies, no matter how large, invariably have unmeasured confounders that may significantly influence the findings and interpretation. Despite these limitations, the current article is reasonably convincing: Discontinuing statin treatment has serious negative consequences.

How did the problem of statin nonpersistence arise, and how do we combat this threat to public health? The widespread advocacy of unproven alternative cholesterol-lowering therapies traces its origins to the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Incredibly, this law places the responsibility for ensuring the truthfulness of dietary supplement advertising with the Federal Trade Commission, not the U.S. Food and Drug Administration. The bill's principal sponsors were congressional representatives from states where many of the companies selling supplements are headquartered. Nearly 2 decades after the DSHEA was passed, the array of worthless or harmful dietary supplements on the market is staggering, amounting to more than \$30 billion in yearly sales. Manufacturers of these products commonly imply benefits that have never been confirmed in formal clinical studies. An Internet search of the term

dietary supplements to lower cholesterol yields 889 000 results advocating such products as garlic capsules, policosanol, lavender oil, green tea capsules, artichoke leaf extract, and many others.

Contributing to the confusion, a series of fad diets offer patients the promise of nearly miraculous reversal of heart disease by dietary means. An Internet search yields 1 220 000 results for the term *diet to reverse heart disease*. One of the top-listed results links to the Web site for the Dr. Oz television show and an article titled "Reverse Your Heart Disease in 28 Days" (10). Nowhere in the article are statins mentioned. Patients are easily seduced by these wonder diets. In many cases, the advocates aggressively promote their dietary approach as an alternative to statins, promising all of the benefits with none of the risks.

What can thoughtful physicians do to counter these dangerous cults? We must work together to educate the public and enlist media support, and we must take the time to explain to our patients that discontinuing statin treatment may be a life-threatening mistake. Passive acceptance of harmful pseudoscience is not an option.

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