Preventive Medicine 85 (2016) 32–35

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Commentary

Does IMPROVE-IT prove it?

Robert DuBroff

Division of Cardiology, University of New Mexico, MSC10-5550, Albuquerque, NM 87131-0001, USA

ARTICLE INFO

Available online 11 January 2016

ABSTRACT

The recently published IMPROVE-IT trial has been hailed as proof that lowering cholesterol reduces the risk of cardiovascular disease (Cannon et al., 2015). Although this study did demonstrate a modest clinical benefit with incremental low-density lipoprotein cholesterol lowering, many physicians tend to ignore the numerous clinical studies which have failed to demonstrate a benefit of cholesterol lowering. This article challenges the cholesterol hypothesis by reviewing these negative studies and our reluctance to acknowledge them. Paradoxically, cholesterol lowering remains the focus of cardiovascular disease prevention despite the inconsistent benefit demonstrated in dozens of clinical trials. The cholesterol-lowering, statin-centric approach to cardiovascular disease prevention may in fact distract us from other beneficial therapies. Dr. Alexander Leaf, former chief of medicine at Massachusetts General Hospital, commented on this paradox and the Lyon Diet Heart Study nearly 15 years ago by writing, "At a time when health professionals, the pharmaceutical industries, and the research funding and regulatory agencies are almost totally focused on lowering plasma cholesterol levels by drugs, it is heartening to see a well-conducted study finding that relatively simple dietary changes achieved greater reductions in risk of all-cause and coronary heart disease mortality in a secondary prevention trial than any of the cholesterol-lowering studies to date" (Leaf, 1999).

For nearly twenty years, cholesterol lowering has been the mainstay of many CVD prevention guidelines for both primary and secondary prevention. The IMPROVE-IT trial, recently published in the *New England Journal of Medicine*, was a large randomized trial of cholesterol lowering with the statin drug simvastatin versus simvastatin plus ezetimibe (a cholesterol absorption inhibitor) in patients with a recent acute coronary syndrome (Cannon et al., 2015). The hypothesis tested was not simply whether the simvastatin–ezetimibe combination is superior to simvastatin alone, but rather, if incremental lowering of LDL cholesterol results in further clinical benefit. At issue is the validity of the cholesterol hypothesis, which links cholesterol intake and blood levels to CVD and posits that lowering cholesterol reduces the likelihood of CVD for both primary and secondary prevention. The inconvenient truth, however, is that cholesterol lowering does not consistently save lives or reduce the risk of CVD.

Association does not equal causation

Elevated serum cholesterol levels are universally identified as a major risk factor for atherosclerotic disease. Ideally a cardiovascular risk factor should help us distinguish those who will develop CVD from those who will not. However, the distribution of cholesterol levels in individuals who did and did not develop coronary heart disease in the original Framingham Heart Study are remarkably similar except when total cholesterol is extremely high (>380 mg/dl) or extremely low (<150 mg/dl; Fig. 1) (Kannel et al., 1979). Risk factors may be associated with a disease, but that does not prove causation (Hill, 1965). For example, high levels of triglycerides and low levels of HDL cholesterol are considered cardiovascular risk factors, but treatments to correct these lipid abnormalities have failed to demonstrate a consistent clinical benefit (The FIELD Study Investigators, 2005; Michos et al., 2012). Hence, risk factors should not automatically become treatment targets, and treatment of surrogate endpoints is not without hazard.

Lower cholesterol levels are not always better

In general, there are three ways to achieve lower cholesterol levels. First, one can be born with genetically low cholesterol. Mendelian randomization studies have shown that people born with genetically low cholesterol levels are at lower risk of CVD, but it is unclear if this is due to association or causation (Ference et al., 2012). Nevertheless, we should not extrapolate these results to the broader population who lack these genetic variations. More commonly, diet and drugs are used to lower cholesterol levels. The low-fat diet has been recommended for decades but has never been proven to prevent CVD. The Women's Health Initiative Randomized Controlled Dietary Modification Trial was a primary prevention study of 48,835 postmenopausal women

E-mail address: rodubroff@salud.unm.edu.

http://dx.doi.org/10.1016/j.ypmed.2016.01.004
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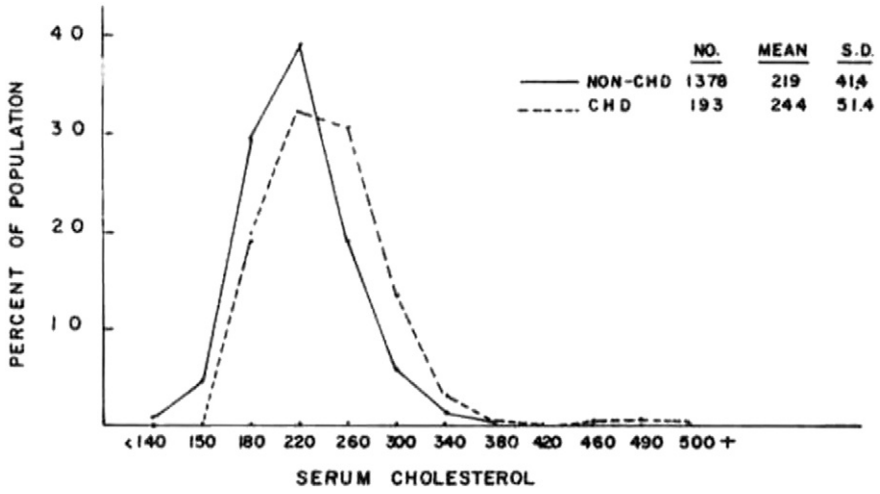

Fig. 1. Serum cholesterol levels (mg/dl) in individuals who did and did not develop coronary heart disease (CHD) from the Framingham Heart Study (Kannel et al., 1979). Reprinted with permission of the publisher.

randomized to either a low-fat diet or control diet. No reduction in cardiovascular events was observed after 8.1 years (Howard et al., 2006). An exhaustive review and meta-analysis of 72 dietary clinical trials concluded that reduced consumption of saturated fats does not reduce cardiovascular mortality (Chowdhury et al., 2014). Early studies of cholesterol lowering with bile acid sequestrants, fibrates, and niacin suggested clinical benefit, but the 2013 AHA/ACC guidelines on cholesterol management concluded that only statins have been proven to reduce cardiovascular events and mortality rates (Stone et al., 2014). If the cholesterol hypothesis is correct, why aren't these cholesterol-lowering diets and drugs equally effective? While many statin trials and meta-analyses have concluded that there is significant benefit, others have concluded otherwise. The Cholesterol Treatment Trialists meta-analysis of 27 statin trials in people at low risk of vascular disease concluded that there is a clear benefit, but a subsequent meta-analysis of the same 27 studies concluded there was no significant mortality benefit (Cholesterol Treatment Trialists' (CTT) Collaborators, 2012; Abramson et al., 2013). Similarly, a meta-analysis of 11 statin trials involving 65,229 participants in high-risk primary prevention found no mortality benefit (Ray et al., 2010). Other examples where cholesterol lowering trials have failed to demonstrate either a reduction in mortality or clinical events include statins in the elderly (primary prevention group) (Shepherd et al., 2002), statins in moderately hypercholesterolemic, hypertensive patients (primary and secondary prevention) (ALLHAT-LLT Authors, 2002), statins in heart failure (primary and secondary prevention) (Kjekshus et al., 2007; GISSI-HF Investigators, 2008), statins in renal failure (primary and secondary prevention) (Wanner et al., 2005; Fellstrom et al., 2009), statins in diabetes (primary and secondary prevention) (Wanner et al., 2005; Knopp et al., 2006), statins in individuals with extremely high coronary calcium scores (secondary prevention) (Arad et al., 2005), lipid lowering in peripheral vascular disease (secondary prevention) (Aung et al., 2007), statins in acute coronary syndromes (secondary prevention) (Vale et al., 2014), and statins post-coronary bypass (secondary prevention) (The Post Coronary Artery Bypass Graft Trial Investigators, 1997).

These contradictory and confusing results have engendered two schools of thought. The predominant view is that positive statin trials provide unequivocal proof of benefit. Proponents dismiss or refute negative statin trials by arguing that the degree of LDL lowering was inadequate, these studies were not designed or powered to reduce mortality, there were methodological errors, the negative results are due to a type II statistical error, or simply argue that the statins were started too late in the course of the disease. Conversely, some clinicians believe that statin drugs are ineffective in reducing mortality or CVD (de Lorgeril, 2014). They rebut the positive statin trials by arguing the trials were overseen by the pharmaceutical industry, many trials were stopped prematurely, there were methodological errors and biases, the positive results are due to a type I statistical error, or there is an over-reliance on combined endpoints and meta-analyses rather than mortality rates. I believe there is a third option. We can reconcile these discordant views by acknowledging that statin drugs do reduce mortality and CVD in certain individuals, but we are currently unable to accurately identify these individuals. Optimistically, future research may help us identify individuals who should or should not be treated with statin drugs based upon pharmacogenomics rather than biochemical or clinical characteristics.

Mortality results are more important than combined endpoints

The primary endpoint of the IMPROVE-IT trial was the combined endpoint of cardiovascular death, non-fatal MI, hospital admission for unstable angina, coronary revascularization after 30 days, or non-fatal stroke. While the avoidance of a stroke or heart attack is extremely important, combined endpoints may distract us from total mortality. By combining endpoints of unequal importance a positive result may lead to an exaggerated perception of benefit (Ferreira-González et al., 2007). In IMPROVE-IT, only two of the five components of the composite endpoint (non-fatal MI and stroke) achieved statistical significance, yet the study is considered positive because the primary end point achieved statistical significance ($P = 0.016$; HR, 0.936; 95% CI, 0.89–

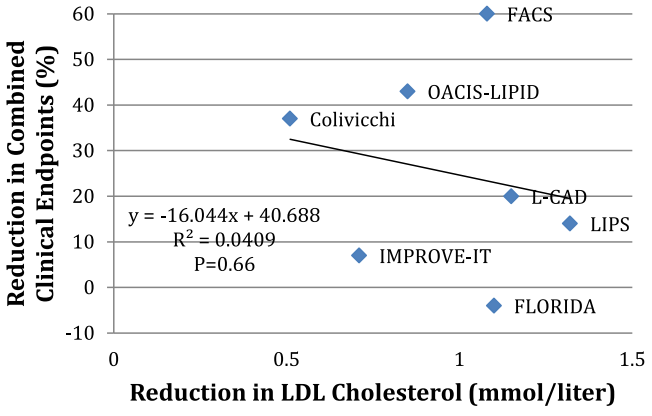

Fig. 2. Comparison of clinical benefit to degree of LDL lowering in IMPROVE-IT and statin trials of patients with acute coronary syndromes. The combined clinical endpoint includes death, non-fatal MI, or non-fatal stroke as defined in the Cochrane meta-analysis of statin trials in acute coronary syndromes (Vale et al., 2014).