World Journal of Cardiology

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DOI: 10.4330/wjc.v7.i7.404

World J Cardiol 2015 July 26; 7(7): 404-409
ISSN 1949-8462 (online)

Cholesterol confusion and statin controversy

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Author contributions: DuBroff R reviewed the literature, composed and wrote the article; de Lorgeril M made suggestions, provided literature, reviewed the article and guided the initial submission and revision process.

Conflict-of-interest statement: DuBroff R does not disclose any conflict of interest; de Lorgeril M discloses receiving research grant (through Grenoble University School of Medicine) from the European Community and from the Barilla G and R F.lli Company.

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Received: February 24, 2015
Peer-review started: February 26, 2015
First decision: March 20, 2015
Revised: April 9, 2015
Accepted: April 28, 2015
Article in press: April 30, 2015
Published online: July 26, 2015

Abstract

The role of blood cholesterol levels in coronary heart disease (CHD) and the true effect of cholesterol-lowering statin drugs are debatable. In particular, whether statins actually decrease cardiac mortality and increase life expectancy is controversial. Concurrently, the Mediterranean diet model has been shown to prolong life and reduce the risk of diabetes, cancer, and CHD. We herein review current data related to both statins and the Mediterranean diet. We conclude that the expectation that CHD could be prevented or eliminated by simply reducing cholesterol appears unfounded. On the contrary, we should acknowledge the inconsistencies of the cholesterol theory and recognize the proven benefits of a healthy lifestyle incorporating a Mediterranean diet to prevent CHD.

Key words: Cholesterol; Statins; Coronary heart disease; Mediterranean diet; Cardiovascular disease; Mortality

Core tip: Traditional efforts to prevent cardiovascular disease have emphasized the benefits of cholesterol lowering and statin drugs. Often overlooked is the fact that numerous studies of cholesterol lowering have failed to demonstrate a mortality benefit and the benefits of statins may have been overstated. The Mediterranean diet has consistently lowered cardiovascular events and mortality in numerous studies and does not typically lower cholesterol levels. Alternative theories of atherosclerosis are independent of cholesterol metabolism and may provide the key to future preventive strategies.

DuBroff R, de Lorgeril M. Cholesterol confusion and statin controversy. *World J Cardiol* 2015; 7(7): 404-409 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i7/404.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i7.404

INTRODUCTION

Nearly twenty years ago two landmark randomized clinical trials appeared in *The Lancet* which forever changed the course of medicine for patients with coronary heart disease (CHD). The 4S study employed a cholesterol-lowering statin drug and reported a 30% mortality reduction[1]. The Lyon Diet Heart Study utilized the Mediterranean diet and reported a 70% mortality reduction[2]. Subsequent studies of the Mediterranean diet have confirmed these findings and also shown a reduced risk of cancer, diabetes, and Alzheimer's disease[3-6]. Subsequent statin studies have led the United States Food and Drug Administration to issue warnings regarding the increased risk of diabetes and decreased cognition with statin drugs. Paradoxically, statins have gone on to become a multi-billion dollar industry and the foundation of many cardiovascular disease prevention guidelines while the Mediterranean diet has often been ignored. We believe this statin-centric cholesterol-lowering approach to preventing CHD may be misguided.

ASSOCIATION DOES NOT EQUAL CAUSATION

The cholesterol hypothesis links cholesterol intake and blood levels to cardiovascular disease. Because cholesterol is considered a risk factor for atherosclerosis many believe that lowering cholesterol in the blood is the best way to prevent CHD. Ideally, risk factors should help us distinguish those who will develop a disease from those who will not. However, if one examines the original Framingham Heart Study data (as an example) it is clear that the cholesterol levels of those who developed CHD and those who did not overlap except when the total cholesterol level exceeded 380 mg/dL or was less than 150 mg/dL (Figure 1). Moreover, cholesterol may be associated with CHD but that does not prove causation. Despite the fact that high triglycerides and low HDL have long been associated with CHD, studies designed to raise HDL or lower triglycerides have failed to reduce CHD mortality. Similarly, cholesterol should not automatically become a treatment target. It may be a leap of faith to assume that lowering cholesterol is the best way to prevent CHD.

LOWERING CHOLESTEROL MAY NOT LOWER CARDIOVASCULAR MORTALITY

The rare occurrence of CHD in isolated, rural societies such as Tukisenta, New Guinea has been attributed to low cholesterol levels[7]. However, it is equally plausible that the diets and lifestyles of these individuals may protect them from CHD. While we may never be certain if low cholesterol or a healthy lifestyle (or both) are responsible for preventing CHD in these societies, there is ample evidence that lowering cholesterol does not consistently lower CHD mortality. Reducing

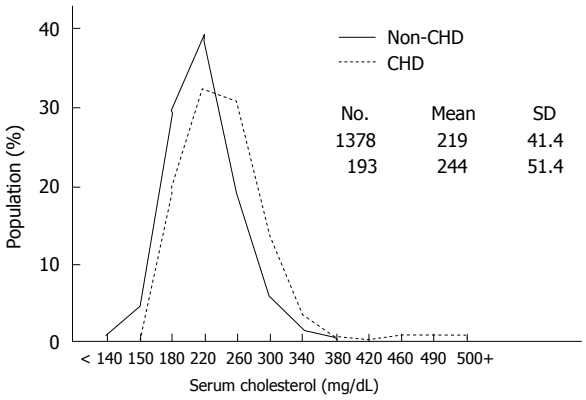

Figure 1 Serum cholesterol distribution among coronary heart disease and non-coronary heart disease patients in the Framingham Heart Study[43]. Reprinted with permission of the publisher. CHD: Coronary heart disease.

cholesterol blood levels by reducing dietary saturated fats is commonly recommended, but an exhaustive review and meta-analysis of 72 dietary studies concluded that reduced consumption of saturated fat does not reduce cardiovascular mortality[8]. Many drugs such as niacin, fibrates, and bile acid sequestrants can lower cholesterol levels, but the recent AHA/ACC guidelines on cholesterol concluded that these drugs do not lower CHD mortality rates[9]. Moreover, the results of cholesterol-lowering statin trials, as will be discussed and analyzed later, do not consistently lower mortality rates[10]. Consider also the dramatic mortality benefit of the Mediterranean diet in the Lyon Diet Heart Study which was achieved without a reduction in cholesterol levels[2-4]. Thus, the hypothesis that lowering cholesterol lowers mortality from CHD is not supported by many clinical research studies.

EARLY STATIN TRIALS MAY HAVE BEEN FLAWED

Early statin trials reported significant mortality benefits, yet serious concerns have been raised in some studies regarding biased results, premature trial terminations, under reporting of adverse events, high numbers of patients lost to follow-up and oversight by the pharmaceutical company sponsor[10]. Heightened awareness within the scientific community regarding problems in clinical trial conduct and analysis - exemplified by the unreported risk of heart attacks in patients taking the pain killers Vioxx and Celebrex - led to new regulatory rules for clinical trials in 2005[11]. Curiously, statin trials conducted after 2005 have failed to demonstrate a consistent mortality benefit[10].

MORTALITY RESULTS ARE MORE IMPORTANT THAN COMBINED CLINICAL ENDPOINTS

Cholesterol-lowering statin trials are often viewed as supporting the cholesterol hypothesis by reporting

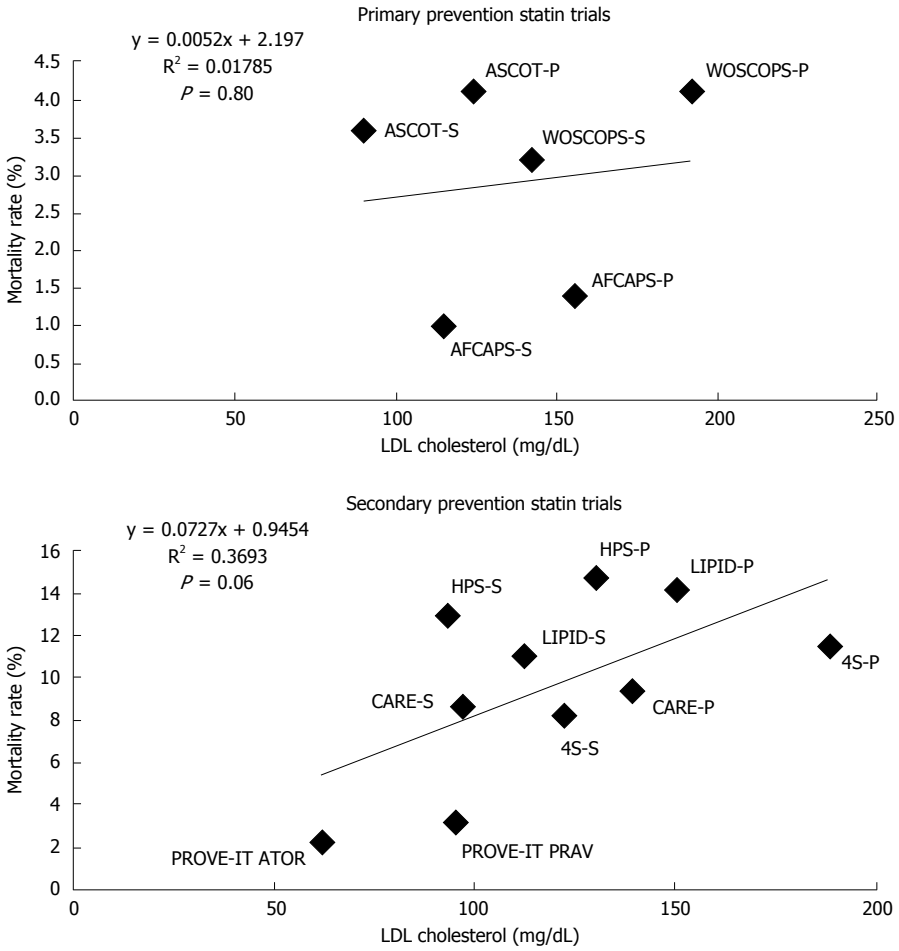

Figure 2 Comparison of mortality rates to low-density lipoprotein cholesterol levels using the randomized clinical trials cited in reference 14 (taken as an example).

significant reductions in combined clinical endpoints. Clinical endpoints are valuable and should not be ignored, but the ultimate measure of efficacy is total mortality that reflects both the treatment effect and potentially fatal side effects. Utilizing combined endpoints may lead to an exaggeration of perceived benefit by assigning equal importance to disparate clinical events such as a hospital admission for angina and death from a heart attack[12,13]. Some have argued that there is a linear relation between low-density lipoprotein (LDL) levels and CHD events[14]. This analysis may be inaccurate because it combines different types of CHD events from diverse studies into one endpoint even though each study defines CHD events differently. A more meaningful analysis compares total mortality rates to LDL cholesterol levels. When we performed such an analysis on these same statin trials - those analyzed in reference 14 - we found no statistically significant relationship (Figure 2).

MORTALITY BENEFITS OF STATINS ARE INCONSISTENT

Although a number of statin trials have reported a mortality benefit, quite a few have not. A corollary to the cholesterol hypothesis posits that patients at highest risk should derive the greatest benefit from cholesterol lowering. However, statin trials in the elderly (PROSPER), in patients with heart failure (CORONA, GISSI-HF), and in patients with renal failure (4D, AURORA, SHARP) have all failed to demonstrate a mortality benefit[10,15]. A Cochrane meta-analysis of 18 cholesterol-lowering trials (some with statins) in patients with peripheral arterial disease also failed to demonstrate a mortality benefit[16]. A separate meta-analysis of 11 statin trials for high-risk primary prevention similarly failed to demonstrate a mortality benefit[17]. Another Cochrane meta-analysis of statin usage after acute coronary syndromes concluded there was no mortality benefit[18]. The Cholesterol Treatment Trialists (CTT) performed a meta-analysis of 27 statin trials and concluded that statins were clearly beneficial in reducing cardiovascular events[19]. However, when the same 27 trials were assessed for mortality outcomes, no benefit was seen[20]. The coronary calcium score is considered to be one of the best predictors of cardiovascular risk, yet the St. Francis Heart Study showed no clinical benefit in asymptomatic patients with coronary calcium scores > 80th percentile randomized to statin therapy[21]. Finally,

diabetes mellitus is considered a CHD risk equivalent, but the three randomized controlled trials specifically designed and powered to assess the effect of statins in diabetes all failed to demonstrate a mortality benefit (CARDS, 4D, ASPEN)[22-24].

ALTERNATIVE THEORIES OF ATHEROSCLEROSIS AND CHD COMPLICATIONS ARE CHOLESTEROL INDEPENDENT

The dramatic benefits of the Mediterranean diet are likely due to multiple mechanisms which do not directly involve cholesterol. Independent of cholesterol metabolism are the true fatal complications of coronary atherosclerosis - thrombotic coronary occlusion, acute myocardial ischemia, left ventricular dysfunction, and malignant arrhythmias. The hemostatic system appears to be a principal modulator of atherosclerotic plaque formation and progression and the Mediterranean diet can favorably alter elements of the coagulation cascade[25,26]. Plaque rupture and intra-plaque hemorrhage leads to progressive atherosclerosis, thrombosis causes acute coronary syndromes, and sudden cardiac death is the main cause of cardiac mortality. At the genetic level large scale, genome-wide association studies have identified 46 loci directly linked to CHD, yet a majority of these loci have no apparent relation to cholesterol or traditional risk factors[27]. Although we can't change our genes, epigenetic studies have shown that the Mediterranean diet can favorably alter the expression of atherogenic genes[28], whereas a recent cholesterol-lowering statin trial failed to demonstrate a similar effect[29]. At the cellular level we now know that atherosclerosis is an inflammatory disease where macrophages and T lymphocytes likely play a dominant role. Whether or not specific anti-inflammatory therapies will be successful remains to be determined, but prior experience with Vioxx and Celebrex, which unexpectedly increased cardiovascular deaths, emphasizes the importance of proceeding cautiously. Recent studies have demonstrated that the Mediterranean diet can reduce markers of inflammation[26]. Accumulating evidence also implicates sugar in the pathogenesis of atherosclerosis. Diabetes is considered a coronary artery disease equivalent yet diabetics typically have average cholesterol levels. Other studies indicate that those who drink sugar-sweetened beverages are at much higher risk for CHD[30]. How elevated levels of blood glucose lead to atherosclerosis and why cholesterol lowering statins increase the risk of diabetes remains enigmatic, yet the totality of evidence suggests molecular mechanisms of atherosclerosis that are independent of cholesterol metabolism. The Mediterranean diet has been shown to reduce the risk of developing diabetes and the metabolic syndrome[31,32]. Elegant research into the gut microbiota is also providing an alternative theory of atherosclerosis[33]. Consider that L-carnitine, a component of red meat, is metabolized by the gut microbiota into trimethylamine oxide (TMAO). TMAO, in turn, promotes atherosclerosis and has been associated with a higher risk of cardiovascular events independent of traditional risk factors such as cholesterol. The gut microbiota can also adapt to changes in diet, which may explain why some vegans do not produce any TMAO after an L-carnitine challenge and how the Mediterranean diet may exert its anti-inflammatory and anti-atherosclerotic effects[34].

STATIN DRUGS HAVE UNINTENDED CONSEQUENCES

If statins have failed to consistently reduce mortality one must ask if statins improve the quality of life. Serious or fatal statin adverse events are rare, but side effects are not. The incidence of muscular aches and weakness in statin trials is highly variable, and real world experiences may differ from clinical trial reports. Consider that the adherence rates for statins in the elderly are poor with nearly 75% of primary prevention patients stopping the drug within the first two years[35]. More recently a cohort study of statin users reported a 53% discontinuation rate although a very high percentage were able to continue statin therapy after being rechallenged[36]. In the largest statin survey ever conducted, the National Lipid Association observed that roughly 30% of statin patients reported experiencing muscle pain and weakness and 57% of surveyed patients reported stopping the drug due to side effects[37]. One may debate the relationship of statins to diabetes and dementia, but the fact remains that the FDA now requires disclosure of these warnings. Most distressing is the recent report of gluttonous behavior among statin users who mistakenly believe they are "protected" by taking statins and can eat whatever they want[38].

CONCLUSION

The debate over the cholesterol hypothesis and statins has raged for decades. Some may point to the recent decline in cardiovascular deaths in the United States as proof of statin effectiveness, but this view fails to incorporate the impact of smoking cessation, lifestyle changes, and dramatic improvements in heart attack survival rates due to timely reperfusion and the availability of external and implantable defibrillators. Others may argue that statins are started too late in life to be effective (the horse may already be out of the barn) and reference Mendelian randomization studies which show that rare individuals with genetically low cholesterol levels have a much lower incidence of CHD[39].

However, this concept should not be extrapolated to the 99.99% of us who lack these genes and also fails to explain how the Mediterranean diet reduces mortality within months of initiation[2-4]. In 1996 Nobel laureates Brown and Goldstein anticipated the eradication of coronary disease in their *Science* editorial, "Exploitation of recent breakthroughs - proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors - may well end coronary disease as a major public health problem early in the next century"[40]. History has proven otherwise, and the global prevalence of CHD, despite worldwide statin usage and cholesterol lowering campaigns, has reached pandemic proportions. Coronary heart disease is an extremely complex malady and the expectation that it could be prevented or eliminated by simply reducing cholesterol appears unfounded. After twenty years we should concede the anomalies of the cholesterol hypothesis and refocus our efforts on the proven benefits of a healthy lifestyle incorporating a Mediterranean diet to prevent CHD[2-4,41,42].

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