COMMENTARY

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A Reappraisal of the Lipid Hypothesis

The lipid hypothesis, which postulates that lowering serum cholesterol saves lives and prevents cardiovascular disease, has been supported by a prodigious volume of evidence over the past 30 years.[1] Lowering low-density lipoprotein cholesterol (LDL-C) has become the foundation of cardiovascular disease prevention guidelines, yet not all of the evidence supports this recommendation.[2] A reappraisal of the lipid hypothesis may hold the key to understanding this inconsonance.

CLINICAL TRIAL RESULTS

The randomized controlled trial (RCT) is the gold standard for validating or rejecting a medical hypothesis. Initial proof of the lipid hypothesis came from some of the earliest RCTs of cholesterol reduction, such as the Coronary Primary Prevention Trial of cholestyramine and the first statin trials (Scandinavian Simvastatin Survival Study [4S], West of Scotland Coronary Prevention Study [WOSCOPS], and Cholesterol and Recurrent Events [CARE]). More widespread trials over the next 20 years produced mixed results, however.[2] Regrettably, some clinical trials prior to 2004 have been tainted by scandals that led to new clinical trial regulations intended to safeguard patients and lend credibility to subsequent trials.[3,4] The table summarizes 29 major RCTs of cholesterol reduction reported after the publication of these regulations (Table). Notably, only 2 of these 29 studies reported a mortality benefit, while nearly two-thirds reported no cardiovascular benefit at all. These unfavorable outcomes and inconsistent results suggest that the lipid hypothesis has failed the test of time. Alternatively, some have suggested that this lack of benefit could be due to inadequate intensity or duration of treatment, insufficiently powered studies, targeting LDL-C instead of apolipoprotein B, or perhaps these trials are attempting to lower LDL-C too late in the course of the disease.

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RISK-GUIDED LIPID THERAPY

A corollary to the lipid hypothesis postulates that those individuals at highest cardiovascular risk are most likely to benefit from lipid-lowering therapy. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines advise calculating cardiovascular risk to identify high-risk primary prevention patients for whom lipid-lowering therapy is recommended while seeking to avoid treatment in low-risk individuals. In the YOUNG-MI registry, 51% of myocardial infarction patients would not have been eligible for primary prevention statin therapy based on these 2013 cholesterol guidelines, whereas 71% would not have been statin eligible based on the 2016 U.S. Preventive Services Task Force guidelines.[5] Conversely, 44% of subjects in the Multi-Ethnic Study of Atherosclerosis study that were classified as statin eligible based on the 2013 ACC/AHA guidelines had zero coronary calcium scores.[6] These studies and others challenge the validity of the risk-guided model.[7]

CONFIRMATION BIAS AND CONFLICT OF INTEREST

Clinicians often rely upon the opinions of lipid experts in the management of their patients. Unfortunately, some experts selectively cite evidence that validates their own opinion while disregarding or misrepresenting evidence to the contrary. This behavior is called confirmation bias and risks undermining the evidence-based approach to medicine.[8] Here are some examples.

The 2014 AHA/ACC guideline on the management of non-ST-elevation acute coronary syndromes (NSTE-ACS) states, "Therapy with statins in patients with NSTE-ACS reduces the rate of recurrent myocardial infarction, coronary heart disease mortality, need for myocardial revascularization, and stroke."[9] Not referenced in this guideline was the Cochrane meta-analysis of 18 RCTs of statins for acute coronary syndrome that reported no benefit in 14,303 patients.[10] Similarly, the National Lipid Association Statin Diabetes Safety Task Force concluded that the cardiovascular benefits of statin therapy outweigh the modest risk of developing diabetes.[11] By reviewing only short-term statin studies, they overlooked the impact of long-term exposure. Omitted from their analysis was a British study reporting a

Table Randomized Controlled Trials of Cholesterol Reduction Reported After Publication of 2004 Clinical Trial Regulations

Study	Year	Patient Population Size and Characteristics	Intervention	Study Duration	Cholesterol Reduction	Mortality Benefit	CV Benefit[*]
St. Francis	2005	1005 CCS > 80th percentile	Atorvastatin 20 mg/d	4.3 y	39%-43% LDL	NR	No (P = .08)
TNT	2005	10,001 CHD, LDL < 130 mg/dL	Atorvastatin 10 mg/d or 80 mg/d	4.9 y	24% LDL	No (HR 1.01; 95% CI, 0.85-1.19)	Yes (HR 0.78; 95% CI, 0.69-0.89)
IDEAL	2005	8888 s/p MI	Atorvastatin 80 mg/d or simvastatin 20 mg/d	4.8 y	20% LDL	No (HR 0.98; 95% CI, 0.85-1.13)	No (HR 0.89; 95% CI, 0.78-1.01)
FIELD	2005	9795 T2DM	Fenofibrate 200 mg/d	6 y	12% LDL	No (HR 1.11; 95% CI, 0.95-1.29)	No (HR 0.89; 95% CI, 0.75-1.05)
4D	2005	1255 T2DM, hemodialysis	Atorvastatin 20 mg/d	4 y	42% LDL	No (RR 0.93; 95% CI, 0.79-1.08)	No (RR 0.92; 95% CI, 0.77-1.10)
ASPEN	2006	2410 T2DM	Atorvastatin 10 mg/d	4 y	29% LDL	No	No (HR 0.9; 95% CI, 0.73-1.12)
SPARCL	2006	4731 s/p stroke or TIA	Atorvastatin 80 mg/d	4.9 y	43% LDL	No (HR 1.0; 95% CI, 0.82-1.21)	Yes (HR 0.84; 95% CI, 0.71-0.99)
WHI	2006	48,835 postmenopausal women	Low-fat diet	8.1 y	7% LDL	No (HR 1.01, 95% CI, 0.81-1.27)[§]	No (HR 0.97; 95% CI, 0.9-1.06)
MEGA	2006	7932 hypercholesterolemia	Pravastatin 10-20 mg/d	5.3 y	15% LDL	No (HR 0.72; 95% CI, 0.51-1.01)	Yes (HR 0.67; 95% CI, 0.49-0.91)
ILLUMINATE	2007	15,067 high risk	Torcetrapib	2.2 y	25% LDL	No (HR 1.58; 95% CI, 1.14-2.19)	No (HR 1.25; 95% CI, 1.09-1.44)
CORONA	2007	5011 > 60 years, ischemic systolic HF	Rosuvastatin 10 mg/d	33 mo	45% LDL	No (HR 0.95; 95% CI, 0.86-1.05)	No (HR 0.92; 95% CI, 0.83-1.02)
SEAS	2008	1873 mild-moderate aortic stenosis	Simvastatin 40 mg + ezetimibe 10 mg/d	4.4 y	50% LDL	No (HR 1.04; 95% CI, 0.79-1.36)	No (HR 0.96; 95% CI, 0.83-1.12)
GISSI-HF	2008	4271 chronic HF	Rosuvastatin 10 mg/d	3.9 y	27%-32% LDL	No (RR 1.00; 95% CI, 0.90-1.22)	No (HR 1.01; 95% CI, 0.91-1.11)[**]
JUPITER	2008	17,800 LDL < 130 mg/dL, hsCRP > 2 mg/L	Rosuvastatin 20 mg/d	1.9 y	49% LDL	No (HR 0.81; 95% CI, 0.63-1.04)[#]	Yes (HR 0.55; 95% CI, 0.43-0.69)[#]
AURORA	2009	2776 hemodialysis	Rosuvastatin 10 mg/d	3.8 y	43% LDL	No (HR 0.96; 95% CI, 0.86-1.07)	No (HR 0.96; 95% CI, 0.84-1.11)
SEARCH	2010	12,064 s/p MI	Simvastatin 80 or 20 mg/d	6.7 y	0.35 mmol/L LDL	No (RR 0.99; 95% CI, 0.91-1.09)	No (RR 0.94; 95% CI, 0.88-1.01)
AIM-HIGH	2011	3414 CVD, low HDL, on simvastatin ± ezetimibe	Niacin ER 1.5-2.0 g/d	3 y	16% LDL	No (HR 1.16; 95% CI, 0.87-1.56)	No (HR 1.02; 95% CI, 0.87-1.21)
SHARP	2011	9270 CKD	Simvastatin 20 mg/d + ezetimibe 10 mg/d	4.9 y	31% LDL	No (RR 1.01; 95% CI, 0.75-1.35) CHD death	Yes (RR 0.83; 95% CI, 0.74-0.94)
SDHS	2013	458 men s/p recent coronary event	PUFA or SFA diet	39 mo	7.8% TC	No (HR 1.62; 95% CI, 1.00-2.64)	No (HR 1.70; 95% CI, 1.03-2.80)
HPS2-THRIVE	2014	25,673 vascular disease on statins	Niacin ER 2 g/d + laropiprant 40 mg/d	3.9 y	16% LDL	No (RtR 1.09; 95% CI, 0.99-1.21)	No (RtR 0.96; 95% CI, 0.90-1.03)
IMPROVE-IT	2015	18,144 s/p ACS on simvastatin 40 mg/d	Ezetimibe 10 mg/d	7 y	24% LDL	No (HR 0.99; 95% CI, 0.91-1.07)	Yes (HR 0.94; 95% CI, 0.89-0.99)
MCE	2016	9423 institutionalized	PUFA or SFA diet	41-56 mo	13% TC	No (HR 1.22; 95% CI, 1.14-1.32)	NR
HOPE-3	2016	12,705 HBP, intermediate risk	Rosuvastatin 10 mg/d	5.6 y	26% LDL	No (HR 0.93; 95% CI, 0.80-1.08)	Yes (HR 0.76; 95% CI, 0.64-0.91)
ACCELERATE	2017	12,092 high risk	Evacetrapib 130 mg/d	26 mo	37% LDL	Yes (HR 0.84;95% CI, 0.70-1.00)	No (HR 1.01; 95% CI, 0.91-1.11)
HIJ-PROPER	2017	1734 with ACS on pitavastatin	Ezetimibe 10 mg/d	3.9 y	15% LDL	No (HR 0.70; 95% CI, 0.47-1.04)	No (HR 0.89; 95% CI, 0.76-1.04)
FOURIER	2017	27,564 ASCVD LDL > 70 mg/dL on statin	Evolocumab 140 mg q 2 wk or 420 mg/mo	2.2 y	59% LDL	No (HR 1.04; 95% CI, 0.91-1.19)	Yes (HR 0.85; 95% CI, 0.79-0.92)

Table (*Continued*)

Study	Year	Patient Population Size and Characteristics	Intervention	Study Duration	Cholesterol Reduction	Mortality Benefit	CV Benefit*
REVEAL	2017	30,449 ASCVD on atorvastatin	Anacetrapib 100 mg/d	4.1 y	41% LDL	No ($P = .46$)	Yes (RR 0.91; 95% CI, 0.85-0.97)
EMPATHY	2018	5042 diabetic retinopathy	Intensive vs standard dose statin	60 mo	26% LDL	No (HR 1.21; 95% CI, 0.77-1.91)	No (HR 0.84; 95% CI, 0.67-1.07)
ODYSSEY	2018	18,924 ACS	Alirocumab 75-150 mg q 2 wk	2.8 y	55% LDL	Yes (HR 0.85, 95% CI, 0.73-0.98)	Yes (HR 0.85; 95% CI, 0.78-0.93)

ACCELERATE = Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes; ACS = acute coronary syndrome; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; ASCVD = atherosclerotic cardiovascular disease; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis—An Assessment of Survival and Cardiovascular Events; CCS = coronary calcium score; CHD = coronary heart disease; CI = confidence interval; CKD = chronic kidney disease; CORONA = Controlled Rosuvastatin in Multinational Trial in Heart Failure; CV = cardiovascular; CVD = cardiovascular disease; EMPATHY = Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy; ER = extended release; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; FOURIER = Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure; HBP = high blood pressure; HDL = high-density lipoprotein; HF = heart failure; HIJ-PROPER = Heart Institute of Japan—Proper Level of Lipid Lowering with Pitavastatin and Ezetimibe in Acute Coronary Syndrome; HOPE-3 = Heart Outcomes Prevention Evaluation—3; HR = hazard ratio; HPS2-THRIVE = Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events; hsCRP = highly sensitive C-reactive protein; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; ILLUMINATE = Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; IMPROVE-IT = Improved Reduction in Outcomes: Vytorin Efficacy International Trial; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein cholesterol; MCE = Minnesota Coronary Experiment; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI = myocardial infarction; NR = not reported; ODYSSEY = Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy; PUFA = polyunsaturated fatty acid; REVEAL = Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification; RinR = reduction in risk; RtR = rate ratio; RR = risk ratio; SDHS = Sydney Diet Heart Study; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SEAS = Simvastatin and Ezetimibe in Aortic Stenosis; SFA = saturated fatty acid; SHARP = Study of Heart and Renal Protection; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TC = total cholesterol; TNT = Treating to New Targets; T2DM = type 2 diabetes mellitus; WHI = Women's Health Initiative; 4D = Die Deutsche Diabetes Studie.

*Defined as the primary endpoint of the trial unless specified otherwise.

**Admitted to hospital for cardiovascular reasons.

#Reported among white subjects.

§CHD death.

363% increased risk of diabetes after 15-20 years of statin treatment.[12] The American Diabetes Association recommends statins for most adults with diabetes because "trials in patients with diabetes (41,42) showed significant primary and secondary prevention of atherosclerotic cardiovascular disease events and coronary heart disease death in patients with diabetes."[13] Within the quotation, reference 41 is the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus study, an RCT of atorvastatin that actually reported no mortality or cardiovascular benefit.[14]

Financial conflicts of interest also demonstrably influence physician behavior.[15] In 1 survey, 71% of clinical policy committee chairs and 90.5% of co-chairs had financial conflicts.[16] In 2009, the Institute of Medicine issued recommendations intended to limit the undue influence of industry on physicians.[17] These proposals include restricting physicians with financial conflicts from participating in guideline panels as well as participating in human research. Years later, little progress has been made, and one can only speculate as to whether financial conflicts may have influenced current lipid recommendations.[18,19]

UNINTENDED CONSEQUENCES

Promoting foods that are low in cholesterol but typically high in refined carbohydrates is supposed to help prevent coronary heart disease. Paradoxically, there is now evidence that these dietary changes have contributed to the epidemic of diabetes that can actually lead to coronary heart disease.[20] Furthermore, some statin users mistakenly believe they can eat whatever they want, leading to the phenomenon of statin gluttony.[21] Consider also that the recent expansion of statin indications may result in millions of healthy individuals being treated because of a risk score even though they may be at extremely low risk of coronary heart disease.[6]

FINAL THOUGHTS

LDL-C is considered the primary constituent of atherosclerotic plaque. Therefore, it stands to reason that lowering serum LDL-C should prevent cardiovascular disease. Three decades of RCTs, however, have yielded inconsistent and contradictory results. We must acknowledge these anomalies and either modify or reject the lipid hypothesis. Clearly, some individuals do benefit from lipid-modifying therapy. I believe the real question is how to identify them. Our current approach of focusing almost exclusively on lowering LDL-C for everyone does not consistently work, may result in unnecessary treatment of some healthy individuals, and likely reflects the fact that the pathogenesis of atherosclerosis is far more complex than originally thought. Our LDL-C-centric approach to cardiovascular disease prevention may have distracted us from investigating other pathophysiologic mechanisms and treatments. Last, we should not ignore the benefits of a healthy lifestyle. Although changing our patients' lifestyle is more difficult than prescribing a pill, the benefits are far more robust.[22]

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