Cholesterol paradox: a correlate does not a surrogate make

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Abstract

The global campaign to lower cholesterol by diet and drugs has failed to thwart the developing pandemic of coronary heart disease around the world. Some experts believe this failure is due to the explosive rise in obesity and diabetes, but it is equally plausible that the cholesterol hypothesis, which posits that lowering cholesterol prevents cardiovascular disease, is incorrect. The recently presented ACCELERATE trial dumbfounded many experts by failing to demonstrate any cardiovascular benefit of evacetrapib despite dramatically lowering low-density lipoprotein cholesterol and raising high-density lipoprotein cholesterol in high-risk patients with coronary disease. This clinical trial adds to a growing volume of knowledge that challenges the validity of the cholesterol hypothesis and the utility of cholesterol as a surrogate end point. Inadvertently, the cholesterol hypothesis may have even contributed to this pandemic. This perspective critically reviews this evidence and our reluctance to acknowledge contradictory information.

Nobel laureates Brown and Goldstein published an editorial in 1996 predicting that "Exploitation of recent breakthroughs … may well end coronary disease as a major public health problem early in the next century."[1] They based their optimism largely on 'proof of the cholesterol hypothesis' which posits that lowering serum cholesterol reduces the risk of coronary heart disease (CHD). Paradoxically, CHD is now pandemic. Some may argue that this pandemic is secondary to the global explosion of obesity and diabetes, but it is equally plausible that the cholesterol hypothesis is incorrect. The results of the recently presented ACCELERATE trial may hold the key to understanding this paradox.[2]

The cholesterol hypothesis has been debated for years, but in light of recent clinical trial results, a reappraisal of the evidence is warranted. Cholesterol is an ostensibly ideal surrogate target: it is present in atherosclerotic plaque; cholesterol is an established risk factor for CHD; Mendelian randomisation studies suggest benefit from lifelong reduced cholesterol levels and cholesterol-lowering drug trials have reduced the risk of cardiovascular (CV) events. Consequently, it seemed impossible that the gold standard of modern medical research—a large, double-blind, randomised controlled trial (RCT)—could undermine, rather than confirm, this theory. Yet the ACCELERATE trial reported that evacetrapib, a novel cholesteryl ester transfer protein inhibitor, reduced low-density lipoprotein (LDL) cholesterol by 37%, raised high-density lipoprotein (HDL) cholesterol by 130%, but produced no discernible reduction in CV events or mortality in high-risk patients. I believe the ACCELERATE trial adds to the chorus that cholesterol is not a valid surrogate end point.

Rudolf Virchow first described the microscopy of the atherosclerotic plaque, but Nikolay Anichkov is credited with elucidating the central role of cholesterol in atherosclerosis. Ironically, cholesterol is also essential for life as a key component of cell membranes, steroid hormones and bile acids. The Framingham Heart Study further clarified the role of cholesterol as a major risk factor for CHD.[3] Ideally, a risk factor should help us distinguish those individuals who will develop a disease from those who will not. Figure 1 illustrates this concept and the original Framingham cholesterol data. The cholesterol levels of Framingham participants who did and did not develop CHD are remarkably similar except when the cholesterol level was extremely low (<150 mg/dL) or extremely high (>380 mg/dL). For the vast majority of patients, cholesterol levels do not help us differentiate those who will and will not develop CHD.

Mendelian randomisation studies are often cited in support of the cholesterol hypothesis. Conceptually, individuals born with genetically low LDL cholesterol should be protected from CHD since their cholesterol levels are reduced throughout life. Yet the report of PCSK9 sequence variations associated with low LDL cholesterol illustrates many of the shortcomings of this model.[4] This study reported that 2.6% of 3363 black patients in the Atherosclerosis Risk in Communities study had nonsense mutations in PCSK9 associated with a 28% reduction in LDL cholesterol. The authors calculated an 88% reduction in the risk of CHD by statistically comparing one fatal myocardial infarction in the PCSK9 group with 319 composite CHD events in the control group (unspecified, but defined as "definite or probable myocardial infarction, a silent myocardial infarction detected by electrocardiographic interval changes consistent with an intercurrent ischemic event, death due to CHD, or a coronary-revascularization

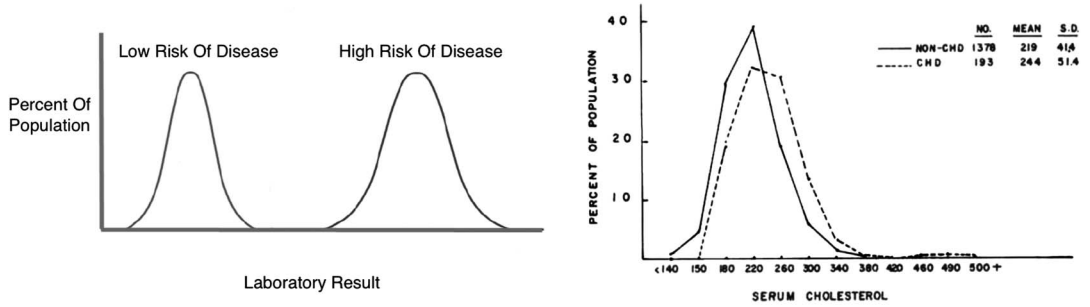

Figure 1 Comparison of ideal risk factor with Framingham Heart Study cholesterol distribution in patients who developed coronary heart disease (CHD) and those that did not develop coronary heart disease (NON-CHD).[3] Cholesterol values are mg/dL. Reprinted with permission of the publisher.

procedure"). Such a comparison may not be valid and by ascribing equal importance to different events such as a CHD death and ischaemic electrocardiogram (EKG) changes the perceived benefit can easily be exaggerated.[5] Moreover, adjudicating CHD events based on death certificates and soft end points such as EKG changes limits the validity of the primary end point. Notably, this study reported no mortality or stroke benefit. These PCSK9 sequence variations were also associated with a statistically significant lower incidence of hypertension, which raises the question of whether LDL cholesterol lowering alone explains the reduction in CHD events. Medication and statin usage that might potentially impact CHD events were not reported. Ultimately, we must ask ourselves if this study proves the cholesterol hypothesis and should it be extrapolated to support the initiation of lipid lowering therapy in our adult patients? I believe Mendelian randomisation studies are hypothesis generating, not hypothesis proving.

Many experts cite numerous RCTs of statins in support of the cholesterol hypothesis, but we should not ignore the dozens of cholesterol-lowering trials that do not. Table 1 lists 44 cholesterol-lowering RCTs that reported no mortality benefit. Most reported no reduction in CV events, and several reported substantial harm (CDP, HERS, Minnesota Coronary Experiment, Sydney Diet Heart Study, WHI, WHO). This lack of benefit was seen even with profound reductions in LDL cholesterol (50% in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial). Although several studies were not specifically designed to assess mortality, the reported lack of mortality benefit should not be disregarded. While some experts have dismissed or criticised these negative trials, the totality of evidence simply cannot be ignored. Even when researchers demonstrate a statin mortality benefit, the findings are underwhelming. A recent analysis concluded that statins would only postpone death by a median of 3.1 and 4.2 days for primary and secondary prevention, respectively.[6]

Some researchers also point to meta-analyses as proof of the cholesterol hypothesis. Meta-analysis can provide an efficient mechanism of pooling similar, smaller studies and generating robust statistical results. But not all biostatisticians concur, and some refer to meta-analysis as 'statistical alchemy for the twenty-first century'.[7] Moreover, the results of meta-analyses pertaining to cholesterol lowering are inconsistent. For example, the Cholesterol Treatment Trialists' meta-analysis of 27 statin trials in people at low risk of vascular disease concluded that there was substantial benefit, but a subsequent meta-analysis of the same 27 statin trials concluded there was no mortality benefit.[8 9] Similarly, a meta-analysis of 11 statin trials in high-risk primary prevention found no mortality benefit and no correlation between the degree of LDL lowering and mortality rates.[10] Cochrane meta-analyses of cholesterol lowering in peripheral arterial disease of the lower extremities and statin use in acute coronary syndromes also reported no benefit.[11 12] Notably, the results of meta-analyses are often discordant with the results of subsequent large RCTs.[13]

Finally, consider that the cholesterol hypothesis may have inadvertently contributed to the very disease we seek to prevent. The cholesterol hypothesis risks oversimplifying the complex interaction of cholesterol, diet and coronary disease, leading many statin users to overeat with consequent obesity.[14] Nearly 50 years ago, three Harvard researchers were paid thousands of dollars by the sugar industry to write a review in the *New England Journal of Medicine* emphasising the importance of fat and cholesterol in CHD while minimising the importance of sugar.[15] Hence, the food industry developed and continues to promote low-cholesterol foods that are nonetheless high in sugar and refined carbohydrates. These dietary changes have likely contributed to the current epidemic of obesity and diabetes that can lead to CV disease.[16]

"A correlate does not a surrogate make," and by definition, treatment of a valid surrogate end point should result in a consistent clinical benefit.[17] The empirical record is now clear that lowering cholesterol through diet or with eight different classes of drugs does not significantly prolong life or consistently prevent CHD (table 1). Yet experts continue to proclaim the success of cholesterol lowering. Fifty-four years ago, Thomas Kuhn described this reluctance to acknowledge anomalies in a

Table 1 Examples of cholesterol lowering randomised controlled trials that reported no mortality benefit

Study	Patient population size and characteristics	Intervention	Mean duration	Cholesterol reduction	CVD event reduction
A to Z	4497 ACS	Simvastatin 0–20 mg/day or simvastatin 40–80 mg/day	6–24 months	19% LDL	No (HR 0.89, 95% CI 0.76 to 1.04)
ACCELERATE	12 092 high risk	Evacetrapib 130 mg/day	30 months	37% LDL	No (HR 1.01, 95% CI 0.91-1.12)
AIM-HIGH	3414 CVD, low HDL, on simvastatin ±ezetimibe	Niacin ER 1.5–2.0 g/day	3 years	16% LDL	No (HR 1.02, 95% CI 0.87 to 1.21)
ALERT	2102 s/p renal transplantation	Fluvastatin 40 mg/day	5.1 years	32% LDL	No (RR 0.83, 95% CI 0.64 to 1.06)
ALLHAT-LLT	10 355 >55 years, HBP, moderate hypercholesterolaemia	Pravastatin 40 mg/day	4.8 years	28% LDL	No (RR 0.91, 95% CI 0.79 to 1.04)
ASCOT-LLA	10 305 HBP, low-average cholesterol	Atorvastatin 10 mg/day	3.3 years	29% LDL	Yes (HR 0.64, 95% CI 0.50 to 0.83)
ASPEN	2410 T2DM	Atorvastatin 10 mg/day	4 years	29% LDL	No (HR 0.9, 95% CI 0.73 to 1.12)
AURORA	2776 haemodialysis	Rosuvastatin 10 mg/day	3.8 years	43% LDL	No (HR 0.96, 95% CI 0.84 to 1.11)
CARDS	2838 T2DM	Atorvastatin 10 mg/day	3.9 years	40% LDL	Yes (RinR 37%, 95% CI 17% to 52%)
CARE	4149 s/p MI, average cholesterol	Pravastatin 40 mg/day	5 years	28% LDL	Yes (RinR 24%, 95% CI 9% to 36%)
CDP	8341 men s/p MI	Dextrothyroxine 6 mg/day	3 years	11% TC	No (excess mortality, premature trial termination)
CDP	8341 men s/p MI	Clofibrate 1.8 gm/day	5 years	6% TC	No (Z=1.99)
CDP	8341 men s/p MI	Niacin 3 gm/day	5 years	11% TC	No (Z=−1.49)
CDP	8341 men s/p MI	Oestrogen 2.5 mg/day	56 months	NR	No (excess DVT, PE and cancer, premature trial termination)
CDP	8341 men s/p MI	Oestrogen 5.0 mg/day	18 months	NR	No (excess non-fatal MI, premature trial termination)
CORONA	5011 › 60 years, ischaemic systolic HF	Rosuvastatin 10 mg/day	33 months	45% LDL	No (HR 0.92, 95% CI 0.83 to 1.02)
ENHANCE	720 FH on simvastatin	Ezetimibe 10 mg/day	2 years	16% LDL	No (trend towards excess CVD events)
FIELD	9795 T2DM	Fenofibrate 200 mg/day	6 years	12% LDL	No (HR 0.89, 95% CI 0.75 to 1.05)
GISSI-HF	4574 Chronic HF (40% ischaemic)	Rosuvastatin 10 mg/day	3.9 years	27–32% LDL	No (HR 1.02, 99% CI 0.92 to 1.13)
GISSI-P	4271 Recent MI	Pravastatin 10–40 mg/day	2 years	15% LDL	No (HR 0.90, 95% CI 0.71 to 1.15)
HERS	2763 women with CVD, intact uterus	CEE 0.625 mg+MPA 2.5 mg/day	4.1 years	11% LDL	No (HR 0.99, 95% CI 0.80–1.11, excess morbidity, premature trial termination)
HOPE-3	12 705 HBP, intermediate risk	Rosuvastatin 10 mg/day	5.6 years	26% LDL	Yes (HR 0.76, 95% CI 0.64 to 0.91)
Howard 2006	48 835 postmenopausal women	Low-fat diet	8.1 years	7% LDL	No (HR 0.97, 95% CI 0.90 to 1.06)
HPS2-THRIVE	25 673 vascular disease on statins	Niacin ER 2 gm/d+laropiprant 40 mg/day	3.9 years	16% LDL	No (RR 0.96, 95% CI 0.90 to 1.03)
IDEAL	8888 s/p MI	Atorvastatin 80 mg/day or simvastatin 20 mg/day	4.8 years	20% LDL	No (HR 0.89, 95% CI 0.78 to 1.01)
IMPROVE-IT	18 144 s/p ACS on simvastatin 40 mg/d	Ezetimibe 10 mg/day	6 years	24% LDL	Yes (HR 0.94, 95% CI 0.89 to 0.99)
JUPITER	17 800 LDL ‹130 mg/dL, hsCRP ›2 mg/L	Rosuvastatin 20 mg/day	1.9 years	49% LDL	Yes (HR 0.56, 95% CI 0.46 to 0.69)
MEGA	7932 hypercholesterolaemia	Pravastatin 10–20 mg/day	5.3 years	15% LDL	Yes (HR 0.67, 95% CI 0.49 to 0.91)
Minnesota Coronary Experiment	9423 nursing home and mental hospital residents	PUFA or SFA diet	41–56 months	12.8% TC	No (excess mortality HR 1.22, 95% CI 1.14 to 1.32; excess CVD RR 1.9, 95% CI 1.01 to 3.72)
LIPS	1677 s/p first PCI	Fluvastatin 80 mg/day	3.9 years	27% LDL	Yes (HR 0.78, 95% CI 0.64 to 0.95)
LRC-CPPT	3806 men, hypercholesterolaemia	Cholestyramine	7.4 years	13% LDL	Yes (RinR 19% p<0.05)
Post-CABG	1351 s/p CABG	Lovastatin 2.5–40 mg ± cholestyramine/day	4.3 years	24–25% LDL	No
PREVEND-IT	864 microalbuminuria	Pravastatin 40 mg/day	3.8 years	21% LDL	No (HR 0.87, 95% CI 0.49 to 1.57)
PROSPER	5804 elderly at risk of vascular disease	Pravastatin 40 mg/day	3.2 years	34% LDL	Yes (HR 0.85, 95% CI 0.74 to 0.97)
PROVE-IT	4162 ACS, TC ‹240 mg/dL	Pravastatin 40 mg/day or atorvastatin 80 mg/day	24 months	35% LDL	Yes (RinR 16%, 95% CI 5% to 26%)
SEAS	1873 mild-moderate aortic stenosis	Simvastatin 40 mg+ezetimibe 10 mg/day	4.4 years	50% LDL	No (HR 0.96, 95% CI 0.83 to 1.12)
SHARP	9270 CKD	Simvastatin 20 mg/day+ezetimibe 10 mg/day	4.9 years	31% LDL	Yes (RR 0.83, 95% CI 0.74 to 0.94)

Continued

Table 1 Continued

Study	Patient population size and characteristics	Intervention	Mean duration	Cholesterol reduction	CVD event reduction
St Francis Heart	1005 CCS >80th centile, asymptomatic	Atrovastatin 20 mg/day	4.3 years	39–43% LDL	No (p=0.08)
Sydney Diet Heart Study	458 men s/p recent coronary event	PUFA or SFA diet	39 months	7.8% TC	No (excess mortality p=0.05; excess CVD HR 1.7, 95% CI 1.03 to 2.80)
TNT	10 001 CHD, LDL <130 mg/dL	Atorvastatin 10 mg/day or 80 mg/day	4.9 years	24% LDL	Yes (HR 0.78, 95% CI 0.69 to 0.89)
WHI	10 739 women s/p hysterectomy	CEE 0.625 mg/day	6.8 years	13% LDL	No (HR 1.12, 95% CI 1.01 to 1.24; excess stroke, premature trial termination)
WHO	15 745 men, high cholesterol	Clofibrate 1.6 gm/day	5.3 years	9% TC	No (mortality increased 25%)
WOSCOPS	6595 men, hypercholesterolaemia	Pravastatin 40 mg/day	4.9 years	26% LDL	Yes (RinR 31%, 95% CI 17% to 43%)
4D	1255 T2DM, haemodialysis	Atrovastatin 20 mg/day	4 years	42% LDL	No (HR 0.92, 95% CI 0.77 to 1.10)

ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; CCS, coronary calcium score; CEE, conjugated equine oestrogen; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DVT, deep venous thrombophlebitis; ER, extended release; FH, familial hypercholesterolaemia; HBP, high blood pressure; HDL, high-density lipoprotein cholesterol; HF, heart failure; hsCRP, highly sensitive C reactive protein; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported; MPA, medroxyprogesterone acetate; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolus; PUFA, polyunsaturated fatty acid; RR, rate ratio; RinR, reduction in risk; SFA, saturated fatty acid; TC, total cholesterol; T2DM, type 2 diabetes mellitus.

theory.[18] Dr Kuhn wrote that a paradigm shift would only occur when the evidence contradicting a theory is overwhelming. Therefore, we must accept the empirical record even though it contradicts our long-held beliefs. Other researchers believe this reluctance can be explained by the tendency to "see what you want to see," and ignore what you do not.[19] For example, a recent editorial in the *New England Journal of Medicine* proclaimed, "Proof That Lower Is Better—LDL Cholesterol and IMPROVE-IT."[20] IMPROVE-IT, a RCT of ezetimibe added to simvastatin in patients with a recent acute coronary syndrome, reported a 24% reduction in LDL cholesterol, but an absolute risk reduction in combined CV events of only 2% after 6 years. Furthermore, the results barely achieved statistical significance (HR 0.936, 95% CI 0.89 to 0.99) and there was no mortality benefit. The conclusions of this study must also be viewed cautiously since 42% of patients discontinued their study medications. The editorial further asserts that "IMPROVE-IT is a landmark study in that it is the first clinical trial to show a benefit of adding a nonstatin lipid-modifying agent to statin therapy." Conspicuous by its absence is any mention of ENHANCE, another RCT of ezetimibe that reported no benefit when added to statin therapy in familial hypercholesterolaemic patients, or AIM-HIGH and HPS2-THRIVE, two RCTs that reported no benefit of niacin when added to statin therapy in patients with CV disease (table 1).

The debate over the cholesterol hypothesis has continued because the results of cholesterol lowering interventions are inconsistent and contradictory. Nevertheless, clinical guidelines continue to emphasise the critical importance of cholesterol lowering to prevent CHD. Unfortunately, I believe this one-dimensional approach may have impeded the advancement of science and our search for other preventive strategies. The ACCELERATE trial may well herald our tipping point and a sea change in our approach to CHD prevention.

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Notes