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CLINICAL COMMENTARIES

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Conquering cholesterol: a report from the front lines

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Strong genetic and observational data, along with the results of clinical lipid-lowering trials, have established the causal link between cholesterol and atherosclerosis. If the population maintained the cholesterol concentrations typically present at birth, atherosclerosis might indeed become an orphan disease. The basic science and experimental basis for the cholesterol hypothesis has been well documented.[1] The pursuit of lower LDL cholesterol, a major atherogenic lipoprotein, arose from events in the 1950s. The myocardial infarction sustained by the sitting President of the USA in 2955, Dwight D. Eisenhower, was emblematic of the epidemic of myocardial infarction afflicting mostly middle-aged men in mid-century.[2,3] These events galvanized the solons of the day who mostly matched the demographics of the then typical heart attack victim to support research into fighting atherosclerosis. The National Heart Institute, now the National Heart, Lung, and Blood Institute (NHLBI), began the Framingham Heart Study in 1948. By the early 1960s, the results of this study helped define the relationship between serum cholesterol and coronary heart disease.[4] These findings provided the prelude for the Coronary Drug Project initiated in 1966.[5] This clinical trial enrolled over 8000 male patients assigned randomly to six treatments including two doses of conjugated estrogens, clofibrate, dextrothyroxine, niacin, or lactose placebo. Suffice it to say that the participants taking the milk sugar control were better off than any of the drug-treated individuals.

The NHLBI then launched the Lipid Research Clinic's Coronary Primary Prevention Trial. This study also enrolled exclusively middle-aged men ($n = 3806$) with elevated LDL-C. They received cholestyramine, a bile acid sequestrant. This rather unpalatable treatment lowered LDL-C by ~14% and produced a 19% reduction in the primary endpoint of coronary heart disease death or nonfatal myocardial infarction.[6,7] The modest benefit of this intervention and the lack of a mortality reduction unleashed multiple commentaries in the lay and professional press, castigating the quest to lower cholesterol therapeutically.[8,9]

Further advances in basic science pointed to the path forward. Bloch[10] elucidated the >30 steps in the biosynthetic pathway of cholesterol from acetate. Hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase) was identified as the rate-limiting step in this biosynthetic pathway. Endo *et al.*,[11] working in the laboratories of Sankyo Pharmaceutical Company in Japan, discovered the first effective inhibitor of this enzyme, the precursor of the statin class of drugs, by testing natural products elaborated by soil bacteria. Alfred (Al) Alberts at the Merck Research Laboratories engaged in a parallel path. The introduction of statins into clinical practice provided highly effective tools for lowering LDL cholesterol. A burgeoning family of clinical trials established the efficacy of statin-induced lowering of LDL in reducing cardiovascular events.

Statins have revolutionized preventive cardiology, but some individuals do not tolerate statins because of muscle symptoms, some attributable to the nocebo effect, but others related to the drug therapy. The drug ezetimibe arose from a search for inhibitors of acyl-CoA:cholesterol acyltransferases (ACAT). Ezetimibe appeared to lower cholesterol, however, by mechanisms distinct from the statins and independent of ACAT inhibition. A brilliant series of investigations emerging from the laboratory of Schering-Plough established a target of ezetimibe as the Niemann-Pick C1-Like Protein 1 (NPC1L1) and identified this molecule as an intestinal cholesterol transporter.[12] Ezetimibe lowered LDL cholesterol by some 15–18%, providing a nonstatin therapy shown to produce a modest decrement in cardiovascular events when added to simvastatin. The pioneering work of Catherine Boileau, Marianne Abifadel, and Nabil Seidah identified gain of function of proprotein convertase subtilisin/kexin type 9 (PCSK9) as the genetic defect in autosomal-dominant hypercholesterolemia.[13] This discovery led rapidly to therapeutic antibodies that profoundly lower LDL and, even when added to statins, yielded further reduction in cardiovascular events.

Further exploration of the cholesterol–biosynthesis pathway led to the development of an additional nonstatin LDL-lowering agent, bempedoic acid.[14] This substituted dicarboxylic acid small molecule inhibits adenosine triphosphate (ATP) citrate lyase (ACLY), an enzyme proximal to HMG-CoA reductase (*Figure 1A*). Bempedoic acid is a prodrug requiring CoA conjugation to attain its inhibitory capacity. The enzyme that catalyzes the activation of bempedoic acid resides in the hepatocyte but not in muscle cells. Hence, bempedoic acid can lower LDL by 15–25% without affecting muscle metabolism. The recent CLEAR Outcomes trial showed in individuals who could not tolerate statin treatment that bempedoic acid therapy reduced major adverse cardiovascular events.[15] This intervention did not cause an increase in muscle symptoms compared with placebo, although there was a slight increase in serum uric acid and gout and in cholelithiasis. Note that the development of each of these agents proven clinically effective involved cooperation between discovery in industry laboratories and academic investigators who carried out the clinical trials. Thus, the conquest of cholesterol required close collaboration between these two sectors.

No doubt that lifestyle furnishes the foundation of cardiovascular prevention. But lifestyle modification alone seldom suffices to achieve the desired reduction in cardiovascular risk. We can justly celebrate the conquest of LDL-C, but where do we go to further address the residual risk? The attempts to achieve clinical benefit by raising HDL through a variety of pharmacologic interventions have proven disappointing. Triglyceride-rich lipoproteins do contribute causally to cardiovascular risk. The mechanisms likely do not involve triglycerides *per se*, but cholesterol carried within

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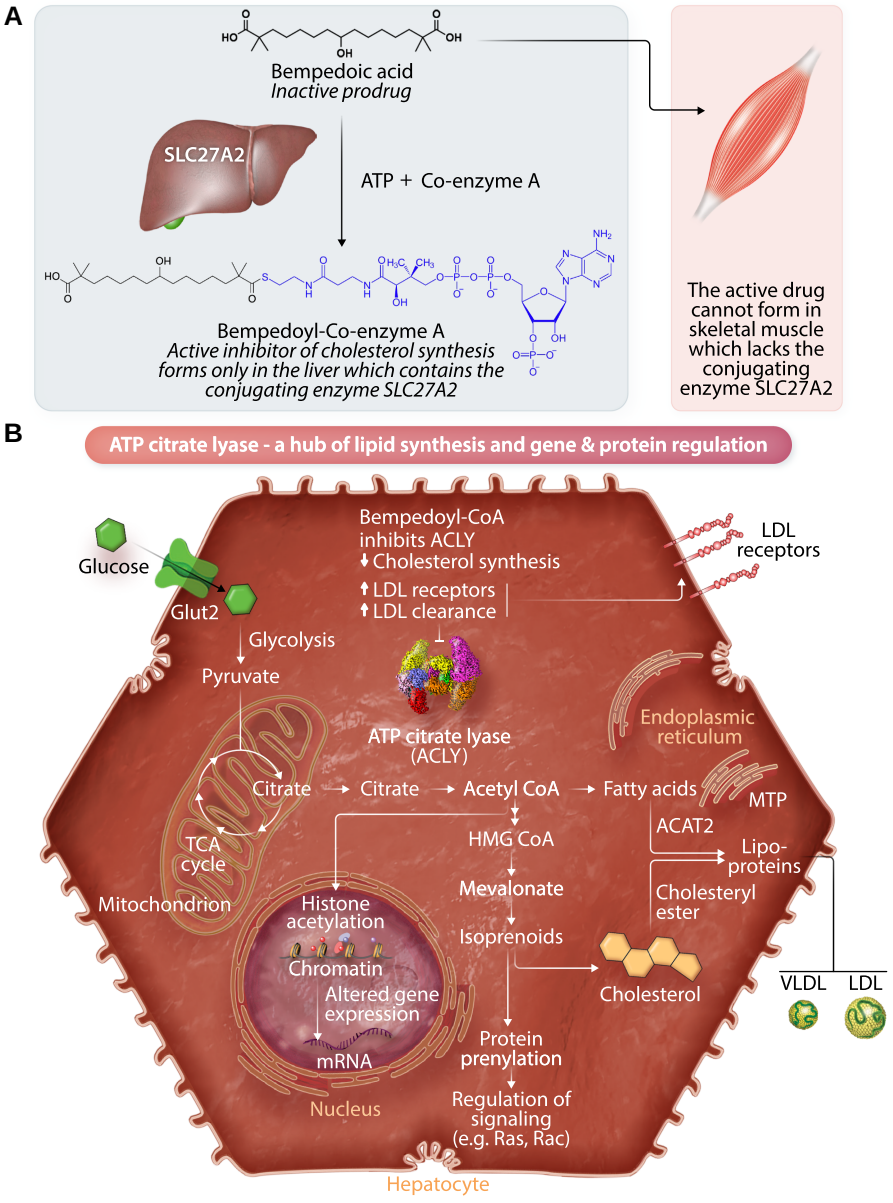

Figure 1 ATP citrate lyase—a hub of lipid and energy metabolism, and gene and protein regulation. Glucose generates pyruvate through glycolysis. Pyruvate enters the Krebs tricarboxylic acid cycle (TCA, also known as the citric acid cycle) in the mitochondrion. Citric acid produced by the TCA is transported into the cytoplasm. The key enzyme ACLY generates acetyl-CoA from citrate. This multifunctional metabolite enters the biosynthetic pathway for cholesterol. Downstream from ACLY, HMG-CoA reductase, the target of statins, gives rise to mevalonic acid and its downstream products that can regulate intracellular signaling by prenylation of proteins pivotal in biologic control such as Ras and Rac. Inhibition of ACLY by bempedoic acid lowers intracellular concentrations of cholesterol by limiting its synthesis. Finely tuned transcriptional regulatory mechanisms increase the expression of the receptor for LDL. This control mechanism raises cell surface LDL receptors that clear LDL, lowering plasma levels of this atherogenic lipoprotein. Acetyl-CoA also furnishes substrate for fatty acid synthesis. Thus, ACLY promotes the production of both cholesterol and fatty acids that can then combine to form cholesteryl esters, a reaction catalyzed by acetyl-CoA acetyltransferase 2 (ACAT2). A microsomal transport protein (MTP) helps to package the cholesteryl esters into lipoproteins including LDL and very LDL (VLDL). Acetyl-CoA, the product of the ACLY reaction, also participates in the acetylation of histones and other proteins. The epigenetic changes in chromatin regulate gene expression. These manifold fates of acetyl-CoA, the product of ACLY, thus exert widespread influences on energy metabolism, polyisoprenoid and sterol synthesis, lipoprotein production, LDL clearance, and the transcriptional control of gene expression. Inhibition of ACLY can thus have broad pleiotropic effects beyond mere LDL lowering.

these particles and associated apolipoproteins such as CIII. The omega-3 fatty acid icosapent ethyl has shown cardiovascular event reduction in some clinical trials to an extent not likely attributable to the magnitude of decreased triglycerides. Fibric acid derivatives have not shown reduction in macrovascular events when added to statins. Yet, signals for benefit for microvascular complications with diabetes such as retinopathy and peripheral arterial disease have emerged from several fibrate trials including the recent PROMINENT trial with pemafibrate.[16] Agents that target angiopoietin-like factors and apolipoprotein CIII do hold promise for treating hypertriglyceridemia.[17,18] Trials including those aimed at raising

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HDL and lowering triglycerides have challenged some of our cherished preconceptions. The lessons learned underscore the absolute necessity of rigorous and properly powered randomized clinical trials to establish efficacy of agents regardless of the results of observational, experimental, and biomarker studies.

Beyond the lipids, inflammation certainly contributes to residual risk in statin-treated patients. Bempedoic acid, but not ezetimibe or PCSK9 inhibition, lowers the biomarker of inflammation, high-sensitivity C-reactive protein (hsCRP).[15] Targeted anti-inflammatory therapies are hotly pursued for the atherosclerosis treatment. Neutralization of interleukin-1 beta (IL-1β) with the monoclonal antibody canakinumab first established the efficacy of an anti-inflammatory therapy in preventing atherothrombotic events.[19] The recent colchicine trials have supported the concept of targeting inflammation in this disease.[20,21] While the mechanisms that underlie hsCRP lowering by bempedoic acid are not fully understood, we now recognize that ATP citrate lyase plays a broad role in metabolism beyond hepatocyte cholesterol biosynthesis (*Figure 1B*). In most cell types, ATP citrate lyase links carbohydrate and fatty acid catabolism to cholesterol and fatty acid production by catalyzing the cleavage of mitochondrial-derived citrate into acetyl-CoA, the building block for cholesterol and fatty acids. Cells exploit this energy nexus to shift metabolism when energy and biosynthetic demands are high. Elevated levels of cellular acetyl-CoA also drive the acetylation of transcription factors and histones, further propagating metabolic reprogramming through changes in gene expression (*Figure 1*). Upon activation, many cell types, including inflammatory cells, immune cells, endothelial cells, and hepatic stellate cells, augment ATP citrate lyase activity to sustain proliferation and cell-specific effector function. Since constitutive ACLY activity and subsequent maladaptive metabolism in these cell types participate in many pathogenic processes, inhibitors of this enzyme such as bempedoic acid may confer benefits beyond reductions in myocardial infarction stroke such as mitigating fatty liver disease.[22,23] These interesting hypotheses merit further clinical evaluation.

These are exciting times in cardiovascular prevention. We can look forward to further progress in addressing the now global epidemic of atherosclerosis aggravated by obesity and diabetes mellitus. As we move forward, we need to strive as a community to provide equitable access to new therapies. We must partner effectively with patients and the public to reap the harvest of our scientific and clinical advances by making proven therapies more broadly available and by encouraging their use by individuals shown to benefit in clinical trials.

The tale of the conquest of cholesterol holds several lessons for us. First, fundamental basic research served as the underpinning of the development of novel therapeutics and understanding their mechanisms. Second, tight collaboration between industry and academic investigators was a prerequisite to progress. Third, we must demand rigorous clinical trials to establish the efficacy of novel therapeutics. Ultimately, having therapies available provide no benefits without access and implementation in practice. Heeding these lessons should accelerate further progress in the quest to combat cardiovascular disease.

Conflict of interest: P.L. is an unpaid consultant to or involved in clinical trials for Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Moderna, Novo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron. P.L. is a member of the scientific advisory board for Amgen, Caristo Diagnostics, Cartesian Therapeutics, CSL Behring, DalCor Pharmaceuticals, Dewpoint Therapeutics, Eulicid Bioimaging, Kancera, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, TenSixteen Bio, Soley Thereapeutics, and XBiotech, Inc. P.L.'s laboratory has received research funding in the last 2 years from Novartis, Novo Nordisk, and Genentech. P.L. is on the Board of Directors of XBiotech, Inc. P.L. has a financial interest in XBiotech, a company developing therapeutic human antibodies, in TenSixteen Bio, a company targeting somatic mosaicism and clonal hematopoiesis of indeterminate potential (CHIP) to discover and develop novel therapeutics to treat age-related diseases, and in Soley Therapeutics, a biotechnology company that is combining artificial intelligence with molecular and cellular response detection for discovering and developing new drugs, currently focusing on cancer therapeutics. P.L.'s interests were reviewed and are managed by Brigham and Women's Hospital and Mass General Brigham in accordance with their conflict of interest policies. S.L.P. is an employee of and shareholder in Esperion Therapeutics, Inc. S.E.N. reports that the Cleveland Clinic Center for Clinical Research has received funding to perform clinical trials from Abbvie, AstraZeneca, Amgen, Bristol Myers Squibb, Eli Lilly, Esperion, Medtronic, MyoKardia, New Amsterdam Pharmaceuticals, Novartis, Pfizer, and Silence Therapeutics. S.E.N. is involved in these clinical trials but receives no personal remuneration for his participation. S.E.N. consults for these pharmaceutical companies but does not accept compensation.

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Data availability

No new data were generated or analysed in this paper.

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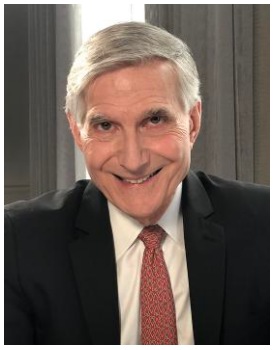

Biography: Peter Libby, MD, is a cardiovascular specialist at Brigham and Women's Hospital in Boston, MA, and holds the Mallinckrodt Professorship of Medicine at Harvard Medical School. His areas of clinical expertise include general and preventive cardiology. His current major research focus is the role of inflammation in vascular diseases such as atherosclerosis. Dr Libby has a particular devotion to translate his basic laboratory studies to pilot and then large-scale clinical cardiovascular outcome trials. He instigated and helped to lead the large-scale CANTOS trial that provided clinical validation of the role of inflammation in atherosclerosis. Dr Libby has received numerous awards for his research accomplishments, including the Gold Medal of the European Society of Cardiology in 2011 and the Anitschkow Prize in Atherosclerosis Research of the European Atherosclerosis Society in 2013. He was the laureate of the Ernst Jung Gold Medal for Medicine in 2016. In 2019, he was honored with the Research Achievement Award of the American Heart Association and was the recipient of the 2020 Paul Dudley White Award of the American Heart Association. An author and lecturer on cardiovascular medicine and atherosclerosis, Dr Libby has published extensively in top-ranked medical journals. He is the Editor-in-Chief for the 12th edition of *Braunwald's Heart Disease*. Dr Libby earned his medical degree at the University of California, San Diego, and completed his training in internal medicine and cardiology at the Peter Bent Brigham Hospital (now Brigham and Women's Hospital). He also holds an honorary MA degree from Harvard University; Doctorat honoris causa from the Université de Lille, France, and Université Laval in Québec, Canada; and a Doctor Medicinæ Honoris Causa degree from Goethe University, Frankfurt am Main, Germany.

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Biography: Steven E. Nissen, MD, is Chief Academic Officer for the Heart and Vascular Institute at the Cleveland Clinic, the Lewis and Patricia Dickey Chair in Cardiovascular Medicine, and Professor of Medicine at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University. From 2006 to 2019, he served as Chair of the Department of Cardiovascular Medicine at the Cleveland Clinic. In 2006–07, he served as President of the American College of Cardiology (ACC). His initial research focused on the application of intravascular ultrasound (IVUS) imaging to the assessment of progression and regression of coronary atherosclerosis, conducting more than a dozen randomized controlled trials, most published in the *NEJM* or *JAMA*. More recently, he has served as Study Chairman for large global cardiovascular outcomes trials studying lipid-modifying therapies. His contributions to scientific literature include more than 650 journal articles. He is co-author of a book for patients with heart disease, *Heart 411*, released by Crown Books on 31 January 2012. He has also written extensively on the subject of drug safety. In 2001, he co-authored the first manuscript (*JAMA*) that raised concerns about the cardiovascular safety of rofecoxib (Vioxx™). In 2007, he authored a *NEJM* manuscript that demonstrated that the widely used diabetes drug rosiglitazone (Avandia™) raised the risk of myocardial infarction. In 2007, *Time Magazine* selected Dr Nissen as one of the world's 100 most influential people. He was named by Thompson Reuters as one of the world's most highly cited physician–scientists.

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