Challenging the Cholesterol Hypothesis

ACCELERATE Trial – Lowering LDL Ineffective

"The recently presented ACCELERATE . . . [failed] to demonstrate any cardiovascular benefit of evacetrapib despite dramatically lowering low-density lipoprotein cholesterol . . .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."

– Cholesterol paradox: a correlate does not a surrogate make, Robert DuBroff, Evidence-based medicine, 2(1) December 2016.

http://ebm.bmj.com/content/22/1/15 Full text: http://tinyurl.com/ydh9k2vn

As Many CAD Patients Have Low-LDL as Not

"In a large cohort of patients hospitalized with CAD [136,905], almost half have admission LDL levels <100 mg/dL." [Note: Almost 75 percent of heart attack patients fell within recommended targets for LDL cholesterol.]

– Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines, American Heart Journal, Volume 57, Issue 1, January 2009.

https://www.sciencedirect.com/science/article/pii/S0002870308007175

LDL-C Does Not Cause CVD – A Comprehensive Review

"For half a century, a high level of total cholesterol (TC) or low-density-lipoprotein cholesterol (LDL-C) has been considered to be the major cause of atherosclerosis and cardiovascular disease (CVD), . . . However, there is an increasing understanding that the mechanisms are more complicated, . . ."

LDL-C Does Not Cause Cardiovascular Disease: a comprehensive review of current literature, Uffe Ravnskov, et. al., Expert Review of Clinical, Volume 11, 2018, Issue 10.

https://www.tandfonline.com/doi/abs/10.1080/17512433.2018.1519391

Lowering LDL-C Inconsistent Results

"...focusing almost exclusively on lowering LDL-C for everyone does not consistently work... Our LDL-C-centric approach to cardiovascular disease prevention may have distracted us from investigating other pathophysiologic mechanisms and treatment..."

– A Reappraisal of the Lipid Hypothesis, Robert DuBroff, MD, The American Journal of Medicine, September 2018, Volume 131, Issue 9.

https://www.amjmed.com/article/S0002-9343(18)30404-2/fulltext

LDL-Hypothesis: Pro and Con

Issue Statement: Primary Root Causes and Solutions for Premature CVD and MI need to be Prioritised

Hypothesis	For	Against
"Bad Cholesterol" or LDL (in and of itself) is a primary cause of CVD	COMPARATIVE/ASSOCIATIONAL evidence from prospective observational, epidemiological, ecological and other comparative studies indicates higher LDL, higher risk.	* Hazard ratios weak and inconsistent. * Framingham and many others show HR's disappear when HDL etc. taken into account * Many studies show significant HR only for very, very high LDL levels * Case-control generally no sig LDL difference between diseased and well - ratios dominate * Even in FH, severly premature CVD have same LDL as those aging healthily - nearly all studies of note show this phenomenon - also FH now beginning to be viewed as dependent more on clotting phenomena - and early disease FH are strongly marked by many parameters relative to healthy FH (LDL is ironically the one that fails to maintain itself) * In ~20 studies, calcification extent didn't correlate with LDL levels * In autopsies, atherosclerosis extent didn't correlate with LDL levels * Etc. etc. etc.
	MECHANISTIC evidence from scientific literature - but conflicting with better mechanistic edidence?	* LDL lipoproteins glycated, damaged or modified would make sense - but latter due to effect of other genuine causes * Hyperinsulin/IR/hyperglycemia dramatically stronger evidence base - and these stronger hypotheses in turn actually cause LDL dysfunction?
	EXPERIMENTAL evidence from various pharmaceutical RCT's which lower LDL - LDL drops in the population, event rates are lowered	* Examples of pharmaceutical RCT's which lower cholesterol greatly, yet increase in event rates observed e.g. CETPi * Some analyses show that event-reduction extent...does not correspond to LDL-lowering extent in individuals - very few papers available with this particular individual-level data though - unfortunately? * These analyses do show that the medication impacts on e.g. ferritin, CRP and other trial measures, DO actually track in dose-response fashion for individual's reduced risk rate

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You can access his excellent podcasts here:

https://thefatemperor.com/podcasts/