Research on Cholesterol and Statins

Introductory Explanation

My lack of concern about my "high LDL-C" and "high total cholesterol" and my decision not to take statins is based on many hours of reading and research. This research has led me to conclude that:

1. Lowering cholesterol may not be desirable [1 page]
2. High cholesterol is neutral or beneficial for the elderly [1 page]
3. There are valid challenges to the cholesterol hypothesis [1 page + table]
4. There are other surrogate markers than total cholesterol or LDL-C [1 page]
5. Statins offer minimal or no benefit for primary prevention [2 pages]

Each page includes quotes taken from medical journals with online links. It may be easier to read and follow online here:

https://mbabco.netlify.com/cholesterol-2019/index.html

(or, for less typing: http://tinyurl.com/y6byqsav)

Is Lowering Cholesterol Desirable?

Studies With No Mortality or Minimal Cardiovascular Benefit

"Table 1 lists 44 cholesterol-lowering RCTs that reported no mortality benefit. Most reported no reduction in CV events, and several reported substantial harm . . ."

– From Cholesterol Paradox: A Correlate Does Not a Surrogate Make, Robert DuBroff, Evid Based Med, 2017;22(1):15-19.

https://ebm.bmj.com/content/22/1/15

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"The table summarizes 29 major RCTs of cholesterol reduction reported after the publication of these regulations. Notably, only 2 of these 29 studies reported a mortality benefit, while nearly two-thirds reported no cardiovascular benefit at all."

– A Reappraisal of the Lipid Hypothesis, by Robert DuBroff, MD, The American Journal of Medicine, September 2018, Volume 131, Issue 9, Pages 993–997.

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

Framingham – Lowering Cholesterol Produced Harm

"There is a direct association between falling cholesterol levels over the first 14 years of the study and mortality over the following 18 years. 11% overall and 14% CVD death rate increase per 1mg/dl per year drop in cholesterol levels."

– Cholesterol and mortality. 30 years of follow-up from the Framingham study, by Anderson KM, et. al., JAMA, 1987, Apr 24;257(16):2176-80.

https://www.ncbi.nlm.nih.gov/pubmed/3560398

Higher LDL-c Improved Outcomes, Lowest LDL-C Highest Mortality

"Patients with the highest baseline LDL-c levels had significantly improved outcome, whereas those with the lowest LDL-c levels had the highest mortality."

– A longitudinal 20 years of follow up showed a decrease in the survival of heart failure patients who maintained low LDL cholesterol levels, by Charach G, et. al., QJM, 2018 May 1;111(5):319-325.

https://www.ncbi.nlm.nih.gov/pubmed/29733423

High Cholesterol is Neutral or Beneficial for the Elderly

One Meta-analysis and One Study

"We identified 19 cohort studies including 30 cohorts with a total of 68 094 elderly people, where all-cause mortality was recorded in 28 cohorts and CV mortality in 9 cohorts. . . . **High LDL-C is inversely associated with mortality in most people over 60 years.**" [Emphasis added.]

– Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review, Ravnskov, et. al., BMJ Open Journal, Vol. 6, Issue 6.

http://bmjopen.bmj.com/content/6/6/e010401.full.pdf+html

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"These associations indicate that high lipoprotein levels do not seem to be definitely harmful in the general population."

– Association of lipoprotein levels with mortality in subjects aged 50 + without previous diabetes or cardiovascular disease: A population-based register study, Lisa Bathum et al., Scand J Prim Health Care, 2013 Sep; 31(3): 172–180.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3750440/

Framingham

"After age 50 years there is no increased overall mortality with either high or low serum cholesterol levels."

– Cholesterol and mortality. 30 years of follow-up from the Framingham study, Andersn KM et. al., JAMA, 1987 Apr 24;257(16):2176-80.

https://www.ncbi.nlm.nih.gov/pubmed/3560398#

18 Studies Showing Cholesterol Protective in Elderly

The following page has 18 studies from the most respected peer-reviewed journals. Here's 1 example:

"Neither high-density lipoprotein cholesterol nor low-density lipoprotein cholesterol was associated with mortality."

– Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study, Fried LP et. al. JAMA, 1998 Feb 25;279(8):585-92.

https://jamanetwork.com/journals/jama/fullarticle/187277

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/

Other Surrogate Markers than TC or LDL-C

Triglycerides to HDL Ratio

"Elevation in the ratio of TG to HDL-c was the single most powerful predictor of extensive coronary heart disease among all the lipid variables examined."

– High Ratio of Triglycerides to HDL-Cholesterol Predicts Extensive Coronary Disease, Protasio Lemos da Luz, et. al., Clinics, 2008 Aug; 63(4): 427–432.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664115/

High HDL

In a large cohort of patients hospitalized with CAD [136,905], . . . [m]ore than half the patients have admission HDL levels <40 mg/dL, whereas <10% have HDL ≥60 mg/dL.

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

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

IR: Insulin Resistance

"Emerging evidence shows that insulin resistance is the most important predictor of cardiovascular disease and type 2 diabetes."

– The cholesterol and calorie hypotheses are both dead — it is time to focus on the real culprit: insulin resistance, Maryanne Demasi, et. al, Clinical Pharmacist, 14 Jul 2017.

http://tinyurl.com/yy6hsg49

CAC (Coronary Artery Calcification) Score

"A zero CAC score in patients undergoing CT scanning for suspected stable angina has a high negative predictive value for the exclusion of obstructive CAD and is associated with a good medium-term prognosis."

– A zero coronary artery calcium score in patients with stable chest pain is associated with a good prognosis, despite risk of non-calcified plaques, Xue Wang, et. al., BMJ Open Heart, Vol. 6, issue 1.

https://openheart.bmj.com/content/6/1/e000945

Statins and Primary Prevention (2 pages)

NNT – Number Needed to Treat: Statin Drugs Given for 5 Years for Heart Disease Prevention (Without Known Heart Disease) (Updated November 2017)

Benefits in NNT

- 98% saw no benefit, no lives were saved
- None (0%) were helped (life saved)
- 1 in 104 (0.96%) were helped (preventing heart attack)
- 1 in 154 (0.65%) were helped (preventing stroke)

Harms in NNT

- 1 in 50 (2%) were harmed (develop diabetes)
- 1 in 10 (10%) were harmed (muscle damage)

http://www.thennt.com/nnt/statins-for-heart-disease-prevention-without-prior-heart-disease-2/

Little Benefit for Extending Life

"Results 6 studies for primary prevention and 5 for secondary prevention with a follow-up between 2.0 and 6.1 years were identified. Death was postponed between −5 and 19 days in primary prevention trials and between −10 and 27 days in secondary prevention trials. The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively."

– The effect of statins on average survival in randomised trials, an analysis of end point postponement, Malene Lopez Kristensen, et. al., BMJ Open Journal, Volume 5, Issue 9.

https://bmjopen.bmj.com/content/5/9/e007118.full

Statin Mechanism May Cause Harm

" . . .we present a perspective that statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels . . ."

– Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms, Okuyama H, et. al., Expert Rev Clin Pharmacol, 2015 Mar;8(2):189-99.

https://www.ncbi.nlm.nih.gov/pubmed/25655639

[See also: Statin Adverse Effects: A Review of the Literature and Evidence for a Mitochondrial Mechanism, Beatrice A. Golomb, et. al., Am J Cardiovasc Drugs, 2008; 8(6). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2849981/]

Study and 3 Analyses: Statins have No Benefit for Primary Prevention

”No benefit was found when a statin was given for primary prevention to older adults."

– Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults The ALLHAT-LLT Randomized Clinical Trial, by Benjamin H. Han, MD, MPH, et. al., JAMA Intern Med. 2017;177(7):955-965.

https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2628971

“Conclusions:. Therefore, statins have not been shown to provide an overall health benefit in primary prevention trials.”

– Do Statins have a Role in Primary Prevention?” Therapeutics Letter #48, posted on October 16, 2003.

http://www.ti.ubc.ca/pages/letter48.htm

“Conclusion This literature-based meta-analysis did not find evidence for the benefit of statin therapy on all-cause mortality in a high-risk primary prevention set-up.”

– Statins and All-Cause Mortality in High-Risk Primary Prevention: A Meta-analysis of 11 Randomized Controlled Trials Involving 65 229 Participants, Kausik K. Ray, et. al., Arch Intern Med, 2010;170(12):1024-1031.

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/416105

“. . . statin treatment, in particular when used as primary prevention, is of doubtful benefit.”

– 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

Statin Benefits Overstated

"We have described the deceptive approach statin advocates have deployed to create the appearance that cholesterol reduction results in an impressive reduction in cardiovascular disease outcomes."

– How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease, Diamond DM, et. al., Expert Rev Clin Pharmacol, 2015 Mar;8(2):201-10.

https://www.ncbi.nlm.nih.gov/pubmed/25672965