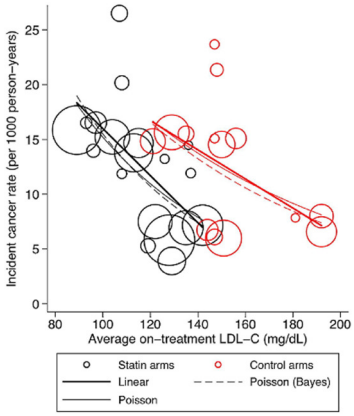
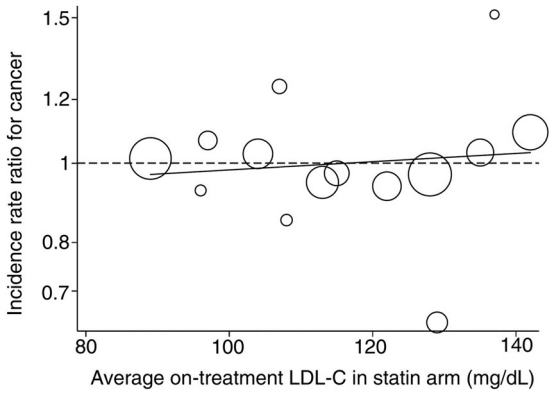
1. **What causes ischemic heart disease? 2nd DRAFT December 5, 2023**
    a. Inflammation of the endothelium by several factors, including smoking, the metabolic consequences of diabetes, hyper-homocysteinemia, iron overload, copper deficiency, oxidized cholesterol, and micro-organisms. If high total cholesterol (t-C) or LDL-C were the most important cause of cardiovascular disease, it should be a risk factor in both sexes, in all populations, and in all age groups. But in many populations, including women, Canadian and Russian men, Maoris, patients with diabetes, and patients with the nephrotic syndrome, the association between t-C and mortality is absent or inverse; or increasing t-C is associated with low coronary and total mortality, particularly in the elderly.[1]
    b. Periodontal disease and other infections:[2] Although the strong association of periodontal disease and atherosclerosis has not yet been proven to be causal, the first hypothesis suggests that oral bacteria involved in periodontal disease (or their by-products) can infect blood vessels or in some other way promote plaque formation and, thus, CVD. The second hypothesis postulates that inflammation as a result of periodontitis increases systemic inflammation and oxidative stress, and this contributes to and increases the already chronic inflammation present and in this way contributes to atherosclerosis and CVD. Infectious agents that have been linked to atherosclerotic disease include, but not limited to Chlamydia pneumoniae, Porphyromonas gingivalis, Helicobacter pylori, influenza A virus, hepatitis C virus, cytomegalovirus (CMV), and human immunodeficiency virus (HIV).[3]
    c. Stress and Type A personality:[4] It is not generally appreciated that stress is a common denominator for many cardiovascular risk factors, since stress can: increase homocysteine, C reactive protein and fibrinogen, all of which promote inflammation or coagulation; cause coronary vasoconstriction, spasm and increased platelet adhesiveness and aggregation that favors the formation of clots; cause increased visceral fat deposits that contribute to insulin resistance, diabetes, elevated triglycerides and other manifestations of metabolic syndrome; produce myocardial necrosis in the absence of coronary occlusion by increased secretion of catecholamines at nerve endings in the ventricle (also see Section 7). In the Ornish program of reversal of heart disease, the subjects who were not successful in the meditation/stress reduction component of the program saw no reversal of atherosclerosis.[5] [6]
    d. The fact that statin treatment lowers both total and cardiovascular mortality in high-risk individuals is taken as evidence that cholesterol lowering is effective. However, statins are just as effective whether cholesterol is lowered by a small amount or by more than 40%. In addition, statin treatment is effective whether the initial LDL-C is high or low. If high LDL-C were causal, the greatest effect should have been seen in patients with the highest LDL-C, and in patients whose LDL-C was lowered the most, but this is not the case.[7]
    e. The West of Scotland Coronary Prevention Study (WOSCOPS), a placebo-controlled 5-year cohort study, demonstrated that the use of pravastatin decreased low density lipoprotein (LDL) levels and associated risk of myocardial infarction. The rate of occurrence of coronary events, however, was similar across the four lowest quintiles of LDL reduction (23–41% reductions in mean LDL levels). The relationship between reduction of LDL and the reduction of risk was not linear. Further analysis indicated that even in overlap groups where patients exhibited equivalent mean LDL levels on treatment, pravastatin treatment was associated with less risk of occurrence of coronary events than placebo treatment. These results suggest that while LDL level may serve as a predictor of the risk of coronary events, other factors exist that should be considered and investigated further.[8]
2. **So why are statins effective at reducing coronary events?**
    a. Statins suppress inflammation through their effects on T-regulatory cells[9] (augment their function and number, suppressing the immune response) and Natural Killer (NK) cells[10] (reducing their function and number, suppressing the immune response).
    b. Statins have positive effects on vascular endothelial function, platelet adhesiveness and antithrombotic actions, plaque stabilization, reduction of the vascular inflammatory process and anti-oxidation.[11]
    c. Treatment of patients with elevated CRP (ie. inflammation) and "normal" LDL (median 130 mg/dl) showed that reduction of LDL (with median on-therapy LDL of 50 with some subjects as low as 44) but

without reduction of CRP had no effect on CV death. CV Death only went down with both low CRP and low LDL. So lowering LDL in isolation may not be the target, but you must also impact CRP/inflammation to have an impact on CV death and total mortality.[12]

3. **How much risk reduction do we see on statin therapy?**
    a. Rosuvastatin for Primary Prevention Among Individuals With Elevated High-Sensitivity C-Reactive Protein and 5% to 10% and 10% to 20% 10-Year Risk (Four year study),[13] Rosuvastatin 20 mg vs placebo.
        i. Achieved levels in Rosuvastatin vs Placebo: LDL 50 vs 110, HDL 50/50, TG 100 vs 120, CRP 2.0 vs 3.5
        ii. Rate of MI: 2/1000 vs 4/1000 (50% reduction, but half of subjects on-drug still had MI). Treat 500 patients to benefit one patient.
        iii. Rate of stroke: 2/1000 vs 3/1000 (1/1000 subjects benefited, but 2 on-drug subjects still had outcome) Treat 1000 patients to benefit one patient.
        iv. Rate of death: 1/1000 vs 1.25/1000. Treat 4000 patients to benefit one patient.
    b. Statin-induced reductions in low-density lipoprotein cholesterol (LDL-C) levels and the absolute and relative reductions in individual clinical outcomes, such as all-cause mortality, myocardial infarction, or stroke.[14]
        i. In this meta-analysis of 21 randomized clinical trials in primary and secondary prevention that examined the efficacy of statins in reducing total mortality and cardiovascular outcomes, there was significant heterogeneity but also reductions in the absolute risk of 0.8% for all-cause mortality, 1.3% for myocardial infarction, and 0.4% for stroke in those randomized to treatment with statins compared with control, with relative risk reductions of 9%, 29%, and 14%, respectively. So, it appears that approximately 1-2% of the treated population saw benefit from the statin therapy over the course of the treatment (ie. 98% of treated subjects had no benefit/reduction in these outcomes). A meta-regression was inconclusive regarding the association between the magnitude of statin-induced LDL-C reduction and all-cause mortality, myocardial infarction, or stroke.
        ii. These clinical outcomes are similar to what is seen in longer-term follow-up studies like the 20-year follow-up for the West of Scotland study (3.3% reduction in all cause death, which was 2.6% reduction in CV death, 0.5% increase in stroke death but not significant, cancer the same in both groups, 14.2%). So, 96.7% of treated subjects had no benefit in overall or CV mortality over 20 years of follow-up, the overall mortality being 38% versus 35.7%, and CV mortality of 15.1% versus 12.5%. Some of the subjects may have discontinued or changed therapy over the period of follow-up, so this may be an underestimate of benefit.[15]
4. **What else is cholesterol doing?**
    a. Plasma lipoproteins (VLDL, LDL, Lp[a] and HDL) function primarily in lipid transport among tissues and organs. However, cumulative evidence suggests that lipoproteins may also prevent bacterial, viral and parasitic infections and are therefore a component of innate immunity. Infections can induce oxidation of LDL, and oxLDL in turn plays important anti-infective roles and protects against endotoxin-induced tissue damage. There is also evidence that apo(a) is protective against pathogens. Taken together, the evidence suggests that it might be valuable to introduce the concept that plasma lipoproteins belong in the realm of host immune response.[16] [17]
5. **Cholesterol and Cancer**
    a. The first graph below shows the inverse association between higher rates of cancer with lower levels of LDL-C in randomized controlled clinical trials of statins versus placebo in the prevention of ischemic heart disease. The second graph shows the rate of cancer in the statin arms per average LDL-C level achieved, showing no association between statin use and cancer. But both statin and placebo arms showed the same relationship of the lower the LDL-C the higher the rate of cancer.[18]
    b. The PROSPER Trial,[19] the only statin clinical trial focused primarily on the elderly (age over 70 years), new cancer diagnoses were more frequent on pravastatin than on placebo (1.25, 1.04-1.51, p=0.020). There

was no overall benefit in total mortality because the decrease in CV mortality (1%) was offset by the increase in cancer deaths (1%).

c. 



d. Infections and malignancies: Many malignancies appear to have infections as probable causes including prostate cancer (HPV),[20] pancreatic cancer (HBV, HCV),[21] Lymphomas,[22] cervical cancer (HPV), gastric cancer. Could lower levels of LDL-C increase the risk of malignancies due to suppression of components of our immune system including cholesterol?

6. Adverse effects of statins
   a. Liver abnormalities
   b. Myopathy
   c. Immune suppression: The concern here is the NK cells are the immune cells that help control cancer through active surveillance and killing of cancer cells. Overexpression of T-regulatory cells in the tumor microenvironment is a poor prognostic finding in cancers because the T-regs suppress the immune response to cancer, promoting the growth and spread of cancer. These cells are also important in the immune response to infections.
7. Fat intake and heart disease:[23] The World Health Organization project MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease), a huge cardiovascular epidemiologic study, assessed 21 countries over 10 years. Results published in 2000 failed to find any correlation or connection between heart attacks and fat consumption or cholesterol. All the countries in the top eight of saturated fat consumption had lower cardiac mortality rates than all the eight countries that consumed the least fat. France consumed three times as much saturated fat compared to Azerbaijan but had one-eighth the rate of heart disease deaths. The heart disease death rate in Finland was four times greater than in Switzerland, even though the amount of fat consumed in the two countries was the same. See section 1.C above on the effect of stress on heart disease.
8. What is the bottom line? In a large Danish prospective cohort study,[24] the association between LDL cholesterol level and all-cause mortality was U-shaped, with both low and high levels of LDL cholesterol associated with excess mortality risk (adjusted hazard ratios, 1.25 and 1.15 for baseline LDL cholesterol levels <70 mg/dL and >189 mg/dL, respectively, compared with LDL cholesterol levels between 132 and 154 mg/dL). The LDL cholesterol level associated with lowest mortality risk was 140 mg/dL in the overall population and in those not taking lipid-lowering agents; it was 89 mg/dL in those taking lipid-lowering medications. This study suggests that low LDL cholesterol levels functioned largely as a marker of severe disease, rather than as a causal mortality risk factor. The unexpectedly high LDL cholesterol level associated with lowest mortality risk in the general population reinforces the guidance that LDL cholesterol levels should be lowered based on absolute CVD risk, not on baseline LDL cholesterol level alone. And addressing the inflammatory and stress-related risk factors first and foremost. Yes, more than just writing a prescription for medications.

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