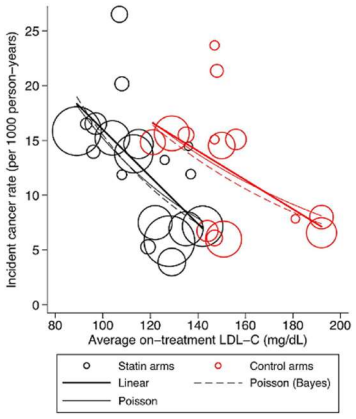
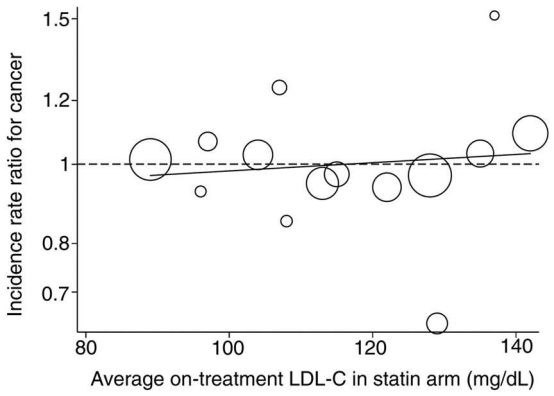
1. **What causes ischemic heart disease? 4rd DRAFT www.georgesteelemd.com April 11, 2025**
    a. Inflammation of the endothelium by several factors, including smoking, the metabolic consequences of diabetes, hyper-homocysteinemia (or may just be a marker of risk?), iron overload, copper deficiency, hypertension, 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] And the gut dysbiosis is a factor as is "leaky gut" from an inflammatory diet, leading to absorption of enterotoxins from bacteria and from the pathogenic bacteria entering the bloodstream to be found in atherosclerotic plaque.
    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). There are studies in cynomolgus monkeys showing the monkeys at the bottom of the social ladder who experienced being mobbed and stressed every day had severe atherosclerosis while those at the top of the hierarchy had little disease, even though the groups did not differ in serum lipids, blood pressure, serum glucose, or ponderosity. 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 cholesterol. 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 and Myopathy
    b. 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.

9. What to do with your cholesterol numbers: First, get all the following tests if you do not have them already:
    a. Lipid panel with total cholesterol, LDL, HDL, triglycerides. More on these below.
    b. Lipoprotein (a), called "LP little a." If this is elevated, you need to get it lower, probably need a statin.
    c. High sensitivity CRP: this is the inflammation test. You want less than 1, preferably less than 0.5.
    d. Apolipoprotein B, called Apo B. You will calculate the ratio of LDL/Apo B (LAR); greater than 1.2 is lower risk. See the Figure below following the references for the impact of the LAR on total and cardiac mortality over 10 years. This was also true for subjects over the age of 65 years.[25]
    e. Hemoglobin A1c, the test for diabetes. If this is above 6.4 you have diabetes and need to take a statin until you make your diabetes go away through what you eat and how you move.
    f. Homocysteine: if this is elevated you need to increase your intake of B vitamins.
    g. Consider a coronary artery calcium score (CAC, a CT scan of the heart). Cost about $150 per scan.
    h. Calculate the MESA score (https://internal.mesa-nhlbi.org/about/procedures/tools/mesa-score-risk-calculator). This will include the coronary calcium score and predict the 10-year probability of a cardiac event of heart attack, sudden cardiac death, or new onset angina, as well as your "coronary age."
    i. Goal is an Apo B level less than 90 with an LDL/Apo B ratio greater than 1.2 (ie. large fluffy LDL).
10. When to consider taking a statin?
    a. If your Lipoprotein (a) is elevated, even if your lipid panel is fine. LP(a) is strongly related to heart disease.
    b. If your 10-year risk of a serious cardiovascular event is greater than 7%, with an elevated Apo B above 90 with a LDL/Apo B ratio less than 1.2.
    c. Yes, if you have diabetes, which is equivalent to the risk of those who have already had a heart attack. So, you must focus on making your diabetes go away through what you eat and how you move.
11. Which statin to take?
    a. The hydrophilic statins are rosuvastatin and pravastatin. These should be taken with CoEnzyme Q10 to protect mitochondrial function and reduce myopathy. Take the lowest effective dose and watch for symptoms or signs of myopathy or liver enzyme abnormalities. Rosuvastatin is much more potent than pravastatin but may be associated with more adverse events at higher doses (above 10 mg per day). An option is dosing three times per week to reduce side effects.
    b. Do not take the lipophilic statins (atorvastatin, fluvastatin, lovastatin, and simvastatin), which cross the blood brain barrier and may reduce the brain's ability to produce cholesterol it requires to maintain itself and may cause more insomnia.
12. What about TMAO?
    a. Normal platelet function is critical to blood hemostasis and maintenance of a closed circulatory system. Heightened platelet reactivity, however, is associated with cardiometabolic diseases and enhanced potential for thrombotic events. We now show gut microbes, through generation of trimethylamine N-oxide (TMAO), directly contribute to platelet hyperreactivity and enhanced thrombosis potential. Plasma TMAO levels in subjects (N>4000) independently predicted incident (3 yr) thrombosis (heart attack, stroke) risk. Direct exposure of platelets to TMAO enhanced submaximal stimulus-dependent platelet activation from multiple agonists through augmented Ca2+ release from intracellular stores. Animal model studies employing dietary choline or TMAO, germ-free mice, and microbial transplantation, collectively confirm a role for gut microbiota and TMAO in modulating platelet hyperresponsiveness and thrombosis potential, and identify microbial taxa associated with plasma TMAO and thrombosis potential. Collectively, the present results reveal a previously unrecognized mechanistic link between specific dietary nutrients, gut microbes, platelet function, and thrombosis risk.[26]
    b. Interestingly, fish flesh contains TMAO, a dangerous compound associated with increased mortality from heart attack and stroke but the oil inhibits its production. TMAO is made through a three-step process. First, one must consume dietary choline, phosphatidylcholine or carnitine. Then the gut bacteria makes

something called TMA which goes to the liver and is converted into TMAO. TMAO is closely linked to a number of problems including kidney disease, atherosclerosis and even heart failure. This is something I am particularly interested in. TMAO is inhibited by extra virgin olive oil and the red pigment in wine. Foods commonly found in the Mediterranean diet such as cold-pressed olive oil, balsamic vinegar, and red wine are rich in the compound DMB (or 3,3-dimethyl-1-butanol), which has been shown to inhibit TMAO production. Now we know that fish oil also inhibits TMAO. If one thinks about the heart-healthy Mediterranean diet we immediately think of fish, red wine, and olive oil. Inhibition of TMAO may be one reason why this diet is associated with less cardiovascular mortality.[27]

c. Deep-sea fish: These fish often have higher TMAO concentrations due to their habitat and diet. Examples include cod, halibut, and Orange Roughy. Cod, a common deep-sea fish, is a significant source of TMAO. Generally, saltwater fish tend to have higher TMAO levels compared to freshwater fish. While salmon's TMAO content is lower than that of deep-sea fish, it can still contribute to an increase in circulating TMAO levels after consumption. Both fresh and canned tuna have relatively low TMA+TMAO levels.

13. What about Omega-3 oils and prevention of cardiovascular disorders?
    a. The problem with supplementing omega-3 oils is that oxidized omega-3 oils increase inflammation. There is little evidence from many studies that omega-3 supplementation reduces cardiovascular outcomes and there is evidence they may enhance the risk of cardiac arrhythmias.[28] The combination of omega-3 oils with extra virgin olive oil has shown the polyphenols and oleic acid in the olive oil appear to protect the omega-3 oils from oxidation in the human body, thereby reducing inflammation.[29] This may also reduce the increased platelet reactivity due to TMAO as discussed above.

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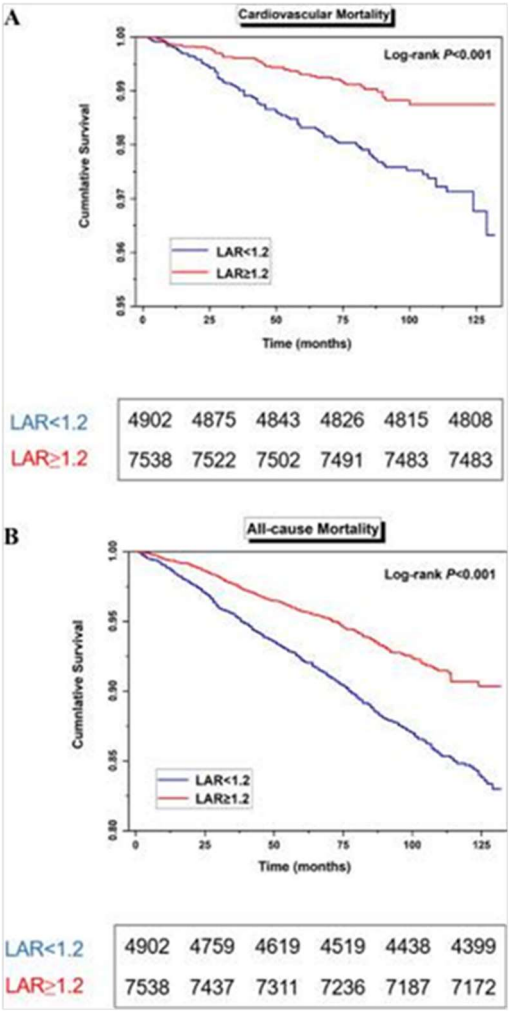
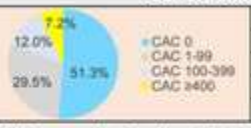
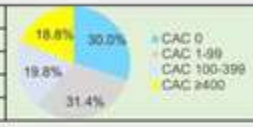


[29]These are the graphs of cardiovascular and total mortality based on the LDL/Apo B ratios of less than 1.2 (blue line) versus greater and 1.2 (red line). Diabetes and inflammation are related to lower LAR ratios. So, eat less and move more.

28,025 patients (6151 statin-users) aged 40–75 years from the CAC Consortium were followed for median 11.2 years. There were 395 CVD and 182 CHD deaths. The statin user group (22%) was older with increased classic CVD risk factor burden. Statin users had higher baseline CAC scores (281 vs. 107) with larger mean CAC area and density. Osei et al. Atherosclerosis 2021;316:79-83 [coronary heart disease (CHD) and cardiovascular disease (CVD)]. Comment: DM, HTN, Lipids the major risk factors in On Statin.

Prognostic value of CAC score, area and density among individuals not on statin vs. on statin therapy

		NOT ON STATIN THERAPY		ON STATIN THERAPY	
Cohort characteristics					
N		21,874		6,151	
Mean age		54		57	
Women		38%		28%	
White		95%		94%	
Mean CAC score		107 +/- 332		281 +/- 664	
Mortality event rates (per 1000 person-years) and Hazard ratios					
		Mortality event rate	Hazard ratio (95% CI)	Mortality event rate	Hazard ratio (95% CI)
CHD Mortality	CAC 0	0.1	Reference	0.3	Reference
	CAC 1-99	0.3	3.4 (1.5, 7.5)	0.5	0.9 (0.3, 2.7)
	CAC 100-399	0.5	4.5 (1.9, 10.8)	0.8	1.1 (0.4, 3.1)
	CAC ≥400	1.9	13.1 (5.6, 30.3)	2.5	2.2 (0.8, 5.9)
CVD Mortality	CAC 0	0.3	Reference	0.6	Reference
	CAC 1-99	0.8	1.8 (1.2, 2.8)	1.1	1.3 (0.6, 2.7)
	CAC 100-399	1.2	2.0 (1.2, 3.3)	1.7	1.5 (0.7, 3.2)
	CAC ≥400	4.0	5.3 (3.3, 8.6)	3.9	2.4 (1.2, 5.1)
Association of CAC components with CHD and CVD mortality among participants with CAC >0					
		Age and sex + volume **OR** density score adjusted		Age and sex + volume **OR** density score adjusted	
CHD Mortality	Ln (Volume score), per SD	2.3 (1.6, 3.1)		2.5 (1.6, 3.8)	
	Density score, per SD	0.69 (0.49, 0.95)		1.1 (0.7, 2.0)	
CVD Mortality	Ln (Volume score), per SD	1.8 (1.4, 2.2)		1.9 (1.4, 2.6)	
	Density score, per SD	0.78 (0.63, 0.97)		0.9 (0.6, 1.3)	