Peter Attia MD Keypoints — Heart Health, Lipids & Blood Pressure

Peter Attia MD Keypoints

Episodes in this pack: 20

407 Preventing cardiovascular and Alzheimer’s disease: lowering LDL early, APOE4, and more

Guest: Michael Davidson
Date: 2026-09-14 · Duration: 2:19:15
URL: https://www.youtube.com/watch?v=EuPcbF9YVTo

KEYPOINTS

• Atherosclerosis is driven by cumulative LDL exposure—the '8 gram rule'.
Davidson, a lipidologist whose father died of a heart attack at 47, frames risk as lifetime cholesterol burden: roughly 200 mg/dL for 40 years, 100 mg/dL for 80 years, or 80 mg/dL for 100 years all add up to the same exposure that produces heart disease. Plaque forms relatively rapidly in the 20s–40s, so that decade is when the most effective treatment matters.

• Prevention should target causal drivers, not 10-year risk scores.
Peter credits Allan Sniderman with reframing the argument: instead of treating 5-, 10- or 15-year risk, treat the causes of disease. A 30-year-old's 10-year risk is low by any calculator, but Davidson says the goal is preventing heart disease at 80 or 90. He notes extra care around pregnancy for women.

• HDL-raising was a seductive hypothesis that failed repeatedly.
Observational data suggested every 1% rise in HDL cut risk about 3%, so CETP inhibitors—which raise HDL 50–75%—looked like a cure. Pfizer's torcetrapib failed (~2006) with off-target harms; Roche's dalcetrapib raised HDL ~30–40% with no LDL effect and no MACE benefit; Lilly's evacetrapib was stopped for futility after about two years despite ~75% HDL increases. Niacin on top of statins (HPS2-THRIVE) also failed.

• Merck's REVEAL proved the benefit tracks LDL, not HDL.
In about 30,000 patients, anacetrapib lowered LDL-C ~17% (~11 mg/dL absolute), and the modest event reduction matched what LDL lowering predicts: about 22% relative risk reduction per 1 mmol/L (38.7 mg/dL). Mendelian randomization similarly says HDL-C is not causal; some high-HDL genes such as SR-B1 variants raise risk.

• Obicetrapib is a far more potent, low-dose CETP inhibitor.
Earlier CETP inhibitors were dosed at 100 mg-plus; obicetrapib at 5–10 mg lowered LDL 40–50% and raised HDL ~150% in the short TULIP study (8–12 weeks). NewAmsterdam, which raised $200 million in its Series A in early 2021, ran phase 3 and the PREVAIL outcomes trial in parallel.

• The phase 3 program shows consistent additional LDL lowering.
ROSE and ROSE2: ~45–50% as monotherapy, ~55% with ezetimibe. BROOKLYN in familial hypercholesterolemia: about 40% further reduction, roughly 100 to 60 mg/dL at 12 months. BROADWAY in ASCVD patients on maximal statins (70% high-intensity): ~35% at 12 weeks, sustained to 52. TANDEM with ezetimibe: ~50%. PREVAIL, at 400+ sites globally, would support approval for secondary prevention.

• ApoB and LDL-P may move less than LDL-C on CETP inhibition.
Davidson acknowledges discordance among LDL-C, LDL particle number and apoB with CETP inhibitors—relevant for clinicians tracking apoB. Obicetrapib also lowers Lp(a), similar to PCSK9 inhibitors' 15–20%, though the reason is unclear.

• APOE4 is a lipid gene, and HDL is the lipoprotein that touches the brain.
About 20–25% of people carry one E4 and ~2–3% are homozygous, with roughly 10x Alzheimer's risk. Davidson's model: E4 impairs astrocyte cholesterol clearance; excess cholesterol leaves only as 24- or 27-hydroxycholesterol, becomes toxic and inflammatory, and amyloid and tau follow. HDL may deliver antioxidants and remove cholesterol and amyloid. He argues statins don't cause Alzheimer's.

• Biomarkers suggest an effect, especially in E4 homozygotes.
A pilot of about 13 E4 patients with MCI showed CSF 24- and 27-hydroxycholesterol falling (not seen with statins) and stable cognition, though it was open-label and unpowered. In a prespecified BROADWAY substudy (2,500 patients), p-tau217 rose less overall; in E4/E4 participants it was over 20% better than placebo, with p-tau181, A;#C"óC Â t`AP and neurofilament light all improving.

• Davidson argues high-dose statins are outdated.
80 mg atorvastatin made sense 25 years ago when nothing else existed; now ezetimibe, PCSK9 inhibitors, bempedoic acid and others allow combinations. He calls pricing PCSK9 inhibitors at $16,000 a year a blunder that slowed adoption.

• Small companies can take risks big pharma won't.
Davidson argues biotech's nimbleness—no corporate hierarchy, willingness to start an outcomes trial alongside phase 3—is why obicetrapib was revived after big companies abandoned the class. NewAmsterdam bet on starting PREVAIL early, and phase 3 success then let it raise the cash to finish. He also notes competitive pressure from China, where he says chemists vastly outnumber those in the U.S.

EXAMPLES

• Two brothers
Davidson started a statin early; his brother started later and fared differently—an n of one he finds persuasive for early treatment. His wife's grandfather also died at 47.

• Longevity genetics
The Bronx aging study of Ashkenazi centenarians found CETP loss-of-function among the most common variants, supporting the Alzheimer's hypothesis.

• p-tau217 as a future endpoint
GLP-1 trials (EVOKE, EVOKE+) showed no cognitive benefit and no p-tau217 change, while Lilly's TRAILBLAZER anti-amyloid trials showed cognition tracking p-tau217—why Davidson thinks it could become a regulatory endpoint.

• Omega-3 lesson

High-dose omega-3s lower triglycerides, but some raised LDL about 9–10%, which he says changed how he thinks about them.

- **Compliance and AI**

  Peter asks how many trial participants were truly adherent; Davidson suggests compliant-only trials could shrink a 10,000-person study to 2,000, and hopes AI can cut drug costs from ~$4 billion and 10 years.

OTHER RELEVANT

- **Lower LDL/apoB early and keep it low.**

  The cumulative-exposure model argues for action in the 30s–40s rather than waiting for 10-year risk to rise.

- **Combination therapy beats maxing one drug.**

  Moderate statin plus ezetimibe or other agents may achieve deep lowering with fewer side effects.

- **Treat high HDL with skepticism.**

  A very high HDL-C does not reliably protect and isn't a treatment target.

- **E4 carriers: watch this space, not off-label hype.**

  Obicetrapib's Alzheimer's data are early biomarker signals; a prevention trial of conversion to MCI is still planned.

- **Ask how a drug's benefit compares with its LDL drop.**

  The REVEAL lesson is a useful rule of thumb: expect roughly a 22% relative event reduction per 38.7 mg/dL of LDL lowering sustained over years. A therapy that claims more than that via HDL or other effects deserves skepticism until outcome trials such as PREVAIL report.

Blood pressure: how to measure, manage, and treat high blood pressure (AMA #48 rebroadcast)

Date: 2026-09-07 · Duration: 1:16:49
URL: https://www.youtube.com/watch?v=n42zMaH2Jgc

KEYPOINTS

• Blood pressure is one of three main drivers of atherosclerosis, along with apoB and smoking, because it mechanically damages the endothelium.

Peter frames them as complementary attacks: hypertension is a mechanical injury to the vessel lining, smoking is a chemical one, and apoB is the particle that gets through the damaged wall. All three are 'area under the curve' problems that compound over decades, so a 35-year-old with untreated hypertension is accruing risk for 40 years, not the 3 years of a typical trial.

• Current US categories: normal is below 120/80, elevated is 120–129/<80, stage 1 is 130–139 or 80–89, stage 2 is "e140 or "e90.

Tightened in 2017 after SPRINT. Note 120/83 is stage 1 despite a normal systolic. Peter would be happy with 119/78 but won't rush to medicate a borderline 123/79 average, because unlike apoB, pressure can go too low and overtreatment causes orthostasis, fainting and falls.

• SPRINT showed intensive control below 120 systolic cut cardiovascular events by about 25% and all-cause death by 27%.

About 9,400 high-risk, non-diabetic adults with systolic pressure of 130 or higher were treated to below 120 or below 140. After one year they averaged 121.4 versus 136.2. The trial was stopped early at a median of a little over 3 years. The composite outcome had a hazard ratio of about 0.75 (roughly 0.54% absolute reduction per year), cardiovascular death halved, and all-cause mortality fell 1.2% in absolute terms, including fewer kidney and even accidental deaths. Peter calls it about as conclusive as trials get.

• Hypertension mostly damages three small-vessel organs: heart, brain and kidneys.

Meta-analyses of 40–70-year-olds show each 20 mmHg rise in systolic (or 10 diastolic) doubles the risk of death from stroke, heart disease or vascular disease, so 140/90 carries about twice the risk of 120/80. The kidneys are 1–2% of body weight but get 20–25% of cardiac output, which makes them highly pressure-sensitive. In SPRINT MIND, intensive lowering cut dementia risk by about 16% in relative terms.

• About 46% of US adults have hypertension, and it's largely silent.

Prevalence is roughly 30% in men and just under 20% in women aged 20–44, about half of men at 45–55, and over 80% for both sexes at 75 and older. It's highest in African Americans (about 59% of men, 56% of women). There are no reliable symptoms; the only way to know is to measure accurately.

• Sloppy technique can move a reading by 10–30 mmHg, so home measurement under protocol beats office readings.

The errors Peter lists: wrong cuff size or measuring over clothing; unsupported back or feet (5–10 mmHg); crossed legs (5–8); skipping a 5-minute silent rest (10–20); talking (10–15); pain (10–30); a full bladder (10–15); and about 2 mmHg for every inch the arm sits above or below the heart. He ignores his own office readings. Before judging anything he wants two weeks of readings taken two or three times a day.

• Manual readings are the gold standard, and automated cuffs read 10–15 mmHg high for Peter.

He describes the manual method: inflate about 30 mmHg past the point where the pulse disappears, then release slowly; the first tapping sound is systolic and the point where the sound vanishes is diastolic. His two expensive automated cuffs consistently read high systolic against several manual checks. His guess is that automated devices estimate from mean arterial pressure. Automated cuffs are still fine for most people if they're used correctly.

• Pressure should dip 10–20% at night; during exercise systolic rises normally, but a rising diastolic is a red flag.

Lying down and parasympathetic tone should lower nighttime pressure, which is what 24-hour ambulatory monitors look for. Stress alone can push Peter over 140. During VO2 max testing a systolic of 180–200 is normal, because widening arterioles lower vascular resistance and keep diastolic flat. People with dilated aortas may need to avoid heavy breath-holding lifts that spike pressure.

• About 10% of hypertension has a fixable underlying cause (secondary hypertension).

Clues include resistance to medication, readings over 180, sudden onset, or high pressure in a young person with no risk factors. Causes to rule out include kidney disease, narrowed renal arteries, thyroid disease, excess aldosterone and adrenal tumors. 'Primary' hypertension, Peter says, is really code for 'we don't know the cause.'

• Lifestyle moves blood pressure far more than it moves lipids, and might let about half of hypertensives avoid drugs.

Each kilogram lost lowers systolic by a little over 1 mmHg and diastolic by nearly 1. Aerobic training of 90–150 minutes a week at 65–75% of max heart rate (zone 2) lowers systolic by up to 8 and diastolic by about 5 within weeks. Dynamic resistance training lowers it by about 2/3, and isometric work by about 6/3. Insulin resistance raises pressure by reducing nitric oxide availability (ADMA and SDMA are markers). Sleeping under 5 or over 10 hours is linked to up to 40% higher hypertension risk.

EXAMPLES

• An athlete friend's 190/120 turned out to be an adrenal tumor.

Around 2013–14, a friend's very high morning pressure didn't respond to several drugs. Peter suspected a pheochromocytoma; the friend's doctor refused the urine catecholamine test. An earlier chest MRI showed an adrenal nodule the radiologist hadn't flagged. Testing elsewhere confirmed the tumor, and after surgery his pressure normalized.

• STEP trial (2021): replicating SPRINT in older Chinese adults.

About 8,500 people aged 60–80 with isolated systolic hypertension (baseline about 146/83) were treated to 110–130 or 130–150. Cardiovascular events fell 26% and cardiovascular death 28%, about 1% absolute per year, but all-cause mortality didn't

change.

- **Both of Peter's parents are hypertensive.**
  He measures often so that if his genes eventually overpower his habits, he starts medication immediately rather than missing a year or two.

- **Sodium restriction cuts both ways.**
  Going from the typical 3.5–4.5 g a day down to 1.5 g can lower systolic by 5–6 mmHg in hypertensives, but one Institute of Medicine analysis linked it to higher all-cause mortality. Nephrologist Rick Johnson suggests drinking water before or with a salty meal; sensitivity to salt is higher in older people, African Americans, and people with metabolic syndrome or kidney disease.

OTHER RELEVANT

- **Run a proper home protocol before acting on any number.**
  Use a correctly sized cuff on bare skin, back and feet supported, legs uncrossed, an empty bladder, the arm at heart level, and 5 silent minutes first. Take readings two or three times a day for about two weeks and decide on the averages.

- **Max out lifestyle first: weight, zone 2, lifting, sleep, potassium from food.**
  Combined lifestyle changes can match a drug's 12–15 mmHg. Get potassium from foods like potatoes and bananas rather than supplements. If you're already on medication, taper with your doctor as you lose weight to avoid fainting.

- **Drug choice: Peter's practice favors ARBs, with thiazides and calcium blockers as add-ons.**
  The four first-line classes (thiazides, calcium channel blockers, ACE inhibitors, ARBs) each lower pressure by about 12–15 systolic and 9–11 diastolic; beta blockers aren't first-line. His team's review found ARBs equal or slightly better than ACE inhibitors, which are cheaper but can cause a cough. Avoid calcium blockers in heart failure, be cautious with thiazides if you have gout or diabetes, and avoid ACE inhibitors and ARBs in pregnancy, angioedema or renal artery stenosis. In African Americans, thiazides and calcium channel blockers may work better. Titrate up from about half the maximum dose.

- **Check cystatin C, not just creatinine.**
  Peter treats a 'normal' GFR of 60 at age 50 as too low and often a clue to hidden hypertension.

402 NMR blood analysis: how mortality risk and more can be assessed from a single blood sample

Guest: Jim Otvos
Date: 2026-08-03 · Duration: 2:27:11
URL: https://www.youtube.com/watch?v=IMbghqZ1iXI

KEYPOINTS

• NMR lipoprotein testing was born from debunking a flawed 1986 cancer test.
A New England Journal paper claimed the width of a plasma NMR signal could diagnose any cancer. Otvos ran six leftover plasma samples; half looked 'cancerous,' but three came from women who had just given birth. The signal turned out to be a superposition of VLDL, LDL and HDL lipid signals. 'Cancer' samples simply had higher triglycerides and lower HDL, which narrowed the peak. He turned that composite signal into a way to count lipoprotein particles.

• Most reported LDL cholesterol is still estimated, not measured.
Labs measure total and HDL cholesterol, then estimate VLDL cholesterol as triglycerides ÷ 5 (Friedewald) and subtract. Unless a report says 'direct,' LDL-C was probably calculated this way. Otvos helped develop a more accurate NIH equation used by LabCorp, but many labs still divide by five. Triglyceride assays measure glycerol, so rare free-glycerol states can falsely suggest high triglycerides.

• NMR counts particles because particle size shifts the signal frequency.
Identical lipid methyl groups resonate at slightly lower frequency in larger particles. A 30-second spectrum is deconvoluted into contributions from each VLDL, LDL and HDL size subclass. Because NMR can't tell cholesterol from triglyceride inside, results are particle concentrations in nmol/L, not mg/dL.

• Small dense LDL's extra risk is explained by particle number, not particle size.
At a given LDL-C, small LDL looks about threefold riskier. But smaller particles carry less cholesterol each, so the same LDL-C means more particles. Stratify by LDL-P instead, and size adds nothing. This matters because drugs that enlarge particles—niacin, fibrates, CETP inhibitors—failed outcome trials despite 'better' size profiles.

• 'Large, fluffy' LDL is not benign.
Asked about patients with LDL-P above 2,000 nmol/L who feel reassured by pattern A, Otvos calls it a specious idea. Familial hypercholesterolaemia patients have very high counts of large LDL particles; untreated homozygotes can die at 30–35.

• When LDL-C and LDL-P disagree, risk follows particle number.
In Framingham (2007) and MESA (2011), Otvos ranked LDL-C and LDL-P as percentiles and called people within 12 percentile points 'concordant,' splitting the cohort roughly into thirds. Event curves were identical when the measures agreed. When LDL-P exceeded LDL-C, events rose faster; when cholesterol was high but particles low, events were lower. Discordance rises with each metabolic-syndrome criterion and is almost guaranteed with all five.

• LDL-P/apoB is a management tool more than a risk-prediction tool.
Adding LDL-P to standard risk equations barely improves prediction, Otvos argues, because HDL-C in those models already captures the same signal indirectly. Where particles win is treatment: on statins, LDL-C often falls further than particle count. As LDL falls, triglyceride replaces cholesterol ester in the particle core, which can reveal residual risk and a case for adding drugs like PCSK9 inhibitors.

• LP-IR detects insulin resistance years before glucose rises.
Insulin resistance is to diabetes what LDL is to atherosclerosis: the cause, integrated over time. Yet medicine waits for glucose, by which point roughly half of beta-cell function may be gone. LP-IR combines six lipoprotein size/subclass measures into a 0–100 score. In unpublished Diabetes Prevention Program data, it beat fasting insulin. Its fall with lifestyle change, and less with metformin, predicted lower diabetes incidence. The Diabetes Risk Index adds branched-chain amino acids.

• GlycA is a stable, cheap marker of systemic inflammation.
The signal was first quantified just to subtract it from a fatty-acid peak. It comes from glycan decorations on acute-phase proteins, so it reflects both their levels and their glycosylation. Unlike hs-CRP, which can jump a thousandfold with infection and needs repeated measures, GlycA might double. It tracks IL-6 and falls with treatment of rheumatoid arthritis or psoriasis, but misses local inflammation.

• MVX predicts dying, more than getting a disease—'metabolic frailty.'
The Metabolic Vulnerability Index combines GlycA and small HDL-P (the inflammation subscore, IVX) with citrate and the three BCAAs (the malnutrition subscore, MMX). Low BCAAs signal wasting, the opposite of the diabetes signal. Its predictive power holds across sex, obesity, diabetes, heart failure and kidney disease. Otvos argues composite fatal plus non-fatal endpoints make it look disease-specific, when it really reflects susceptibility to dying of whatever comes.

• The technology is at risk because diagnostics economics don't reward free information.
One 150 µL plasma run yields a lipid panel, apoB via machine learning, glucose, LP-IR, GlycA and MVX at near-$1 marginal cost on $400–500k analyzers with no consumables. LabCorp bought LipoScience about a decade ago for lab revenue, not the in-vitro-diagnostics vision. It pulled the Vantera analyzers from places like Mayo and Cleveland Clinic, and the 15-year-old units are aging.

EXAMPLES

• Duke CATHGEN cohort
About 7,000 cath-lab patients, mean age ~60; 17% died within five years and about 60% of deaths were non-cardiac. Small HDL-P and GlycA predicted mortality, and a separate Salt Lake City cath cohort replicated MVX before the 2023 paper.

• MESA healthy 60-year-olds
After excluding anyone with disease, MVX still showed a stepwise mortality gradient. Hazard ratios were weaker than in cath patients, but the top versus bottom quartile meant roughly two- to threefold risk.

- **MVX in 30-year-olds (paper being submitted)**
  In 3,000+ healthy people aged 25–30 with roughly 35 years of follow-up, the MVX distribution matched 60-year-olds. Top-quartile average was ~51 versus ~27 in the bottom, scores were stable over time and barely associated with age, and it predicted premature death. Attia can't think of a comparable biomarker outside extremes like untreated FH.
- **Older-adult cohort: 186 variables**
  In a Minnesota study of older adults, small HDL particles were the strongest of 186 variables at predicting two-year mortality. Physical frailty correlated only ~0.2 with MVX; each added information.
- **CETP inhibitor obicetrapib (BROADWAY/BROOKLYN)**
  LDL-P fell more than apoB in the trials because an old algorithm couldn't separate huge HDL from small LDL and excluded small LDL. Reanalysis brought LDL-P in line with apoB. Otvos speculates CETP inhibitors' 10–20% cut in small HDL-P could blunt the expected benefit.
- **Reimbursement absurdities**
  A 14-test metabolic panel bills about $60 in components but Medicare pays about $12. ApoB pays roughly $20 versus about $13 for a lipid panel, and the NMR LipoProfile about $30.

OTHER RELEVANT

- **Manage to particles, not just cholesterol**
  If you're on treatment, check apoB or LDL-P; low LDL-C can hide residual particles, especially with insulin resistance or high triglycerides.
- **Don't chase particle size**
  Making LDL or HDL 'bigger' hasn't improved outcomes in trials; target total particle burden.
- **Act on insulin resistance before glucose rises**
  Glucose is a late signal. LP-IR, fasting insulin or an oral glucose tolerance test can flag the cause earlier. Otvos notes his wife has stayed prediabetic at ~105 mg/dL for 25 years, so prediabetes doesn't always progress.
- **Interpret hs-CRP and GlycA in context**
  Very high CRP usually means something acute; persistent low-grade elevation is more concerning. GlycA is steadier, but recent infection can still raise it.
- **Treat MVX as a promising but unproven lever**
  It's available at LabCorp and could help with surgical-risk screening, trial enrichment or predicting treatment response. Otvos stresses it raises more questions than answers: whether it's causal or modifiable remains to be tested in intervention trials.

334 - Cardiovascular disease, the number one killer: development, biomarkers, apoB, and more

Guest: Thomas Dayspring
Date: 2025-02-03 · Duration: 2:24:02
URL: https://www.youtube.com/watch?v=5hiLY5oFprY

KEYPOINTS

• Atherosclerosis is cholesterol deposited in the artery wall, delivered by apoB particles.

Dayspring, a lipidologist, calls it 'a dump job': the artery isn't making the cholesterol. Coronary and cerebral arteries matter most because their lumens are pencil-dot small and the tissue is oxygen-hungry. Narrowing usually causes no symptoms until about 75–80% blockage. Plaque rupture triggers clotting that can kill in minutes; Attia notes that close to half of first heart attacks are fatal.

• The disease starts in childhood and takes decades.

Autopsy studies show fatty streaks in the aortas of children aged 4–8 and subclinical disease in young soldiers. Fetal studies of mothers with high cholesterol show early lesions. About 50% of men's and 33% of women's first major cardiac events happen before 65. Hence the push for pediatric lipid testing around age 8–9 and 'primordial prevention.'

• Separate causal risk factors from risk markers.

Causal: age, smoking, apoB-containing lipoproteins and high blood pressure. Diabetes and kidney disease act largely through dyslipidemia and hypertension, plus other circulating irritants such as homocysteine, ADMA blocking nitric oxide, and uric acid. Markers include calcium scores, hs-CRP and homocysteine. Attia notes that a cause can be neither necessary nor sufficient: smoking raises lung cancer risk enormously, yet about 15% of lung cancer patients never smoked.

• ApoB counts the particles, and particle number drives entry into the artery wall.

Each LDL, VLDL, IDL and Lp(a) particle carries exactly one apoB, so the standardised immunoassay is a direct particle count. About 95% are LDL. Once inside, particles stick to proteoglycans, aggregate and oxidise. Monocytes become macrophages and then foam cells (first seen in Anichkov's 1913 cholesterol-fed rabbits). Smooth muscle caps the plaque, and calcium comes late. Smoking, hypertension, high insulin and homocysteine make the endothelium leakier.

• Insulin resistance shows up in lipoproteins years before glucose rises.

A 1990s NMR study found big VLDLs, small LDLs and small HDLs in clamp-confirmed insulin resistance, before post-meal insulin, fasting insulin or glucose rose. Dayspring considers insulin resistance and lipoprotein abnormalities inseparable. Attia leans toward some independent harm from hyperinsulinemia, citing diabetes trials where insulin-driven glucose control seemed to damage large vessels.

• Triglycerides above about 100 mg/dL quietly raise apoB.

In insulin resistance, the liver makes large apoC-III-laden VLDLs that linger. CETP swaps their triglycerides into LDL and HDL. Lipases then shrink those particles: HDL breaks apart (hence low HDL-C), and small LDLs change apoB shape so LDL receptors clear them poorly. That spreads cholesterol over more particles, which is why LDL-C and apoB disagree. Dayspring calls the 150 mg/dL 'normal' cutoff the 75th percentile and gets nervous above 80–100. His own triglycerides of 102–105 hid a high particle count.

• Remnants and Lp(a) pack more punch per particle than LDL.

Lp(a) is an LDL with apo(a) attached, carrying oxidised phospholipids—'gasoline on the fire.' Dayspring says it's about 7–8 times more atherogenic per particle. About 20% inherit it, so test once in life. Remnant VLDLs carry 5–7 times more cholesterol per particle. If apoB looks fine but non-HDL cholesterol (total minus HDL) is high, suspect remnants.

• HDL cholesterol tells you nothing about HDL function.

HDL function depends on more than 150 associated proteins and its surface phospholipids, neither measurable clinically. Low HDL-C with disease nearly always comes with high apoB and triglycerides. Very high HDL-C can be dysfunctional. Attia's friend had HDL-C over 100 and LDL-C under 100, yet a high calcium score; he's now on two drugs with apoB at 20–30.

• Lowering apoB through diet works best through triglycerides and saturated fat.

Saturated fat signals the liver to make fewer LDL receptors, raising apoB. Dietary cholesterol matters less. Reducing calories and refined carbs lowers triglycerides. Attia reserves drastic fat cuts for people who clearly overeat saturated fat. Fibrates lowered triglycerides in trials but didn't reduce events because they didn't lower apoB—so apoB is the goal.

• The brain makes all its own cholesterol, and desmosterol may flag over-suppression.

The brain is the most cholesterol-rich organ, with a half-life of about five years. No plasma lipoprotein crosses into it. In adults, astrocytes make cholesterol via the desmosterol pathway and ship it to neurons on apoE particles; apoE4 versions work worse. Neurons export excess as 24S-hydroxycholesterol. Low serum desmosterol has been associated with cognitive impairment, so Dayspring watches it in E4 carriers on statins.

EXAMPLES

• Attia's own early calcium

At 35, he had coronary calcium with LDL-C around the 50th percentile, normal Lp(a), normal blood pressure and no insulin resistance. That points to non-lipid family risk. He's seen no progression in 16 years of treatment.

• hs-CRP's limits

Dayspring treats over 2 as concerning and over 4 as serious. Attia sees people with CRP under 1 who already have a calcium score of 10 in their 40s, so inflammation markers are neither sensitive nor specific enough to rule disease out.

• Statins and dementia

Across more than a dozen trials with dementia as a secondary outcome, statins were neutral or protective, and the lipophilic-versus-hydrophilic difference didn't hold up. Dayspring says it began as marketing between simvastatin and pravastatin.

• Low-dose statin plus add-ons

Most LDL lowering comes from the lowest dose; each doubling adds about 6%. Dayspring prefers a 'baby statin' plus ezetimibe, bempedoic acid or PCSK9 inhibitors, none of which enter the brain.

OTHER RELEVANT

- **Get apoB, triglycerides and Lp(a) tested**

  Dayspring says apoB and triglycerides are the only blood measurements truly needed, plus a one-time Lp(a). Bring the results to someone who understands them; many doctors and some insurers resist.

- **Don't wait for calcium**

  No validated test detects pre-calcified plaque cheaply. Dayspring argues for treating modestly elevated apoB rather than waiting for the 80th–90th percentile.

- **Lp(a) drugs are still unproven**

  Outcome trials are pending. For now, high Lp(a) means controlling every other risk factor more aggressively.

- **Nobody needs to tolerate lipid-drug side effects**

  With statins, ezetimibe, bempedoic acid, PCSK9 inhibitors and more coming, apoB can be lowered without side effects in almost everyone.

255-Latest therapeutics in CVD, APOE’s role in Alzheimer’s disease, familial hypercholesterolemia

Guest: John Kastelein
Date: 2023-05-22 · Duration: 2:04:18
URL: https://www.youtube.com/watch?v=Jduj5SL5FNs

KEYPOINTS

• Cardiovascular disease dwarfs every other killer.
Kastelein, a professor of genetic medicine at the University of Amsterdam who has spent decades running a large lipid clinic, frames the conversation with global numbers: atherosclerotic disease kills far more people each year than cancer (about 12–13 million), so it is 'not even close'. Early in his career he still saw fatal or severe heart attacks in FH patients aged 20–30.

• Familial hypercholesterolemia is common and starts in childhood.
Heterozygous FH is now thought to affect about 1 in 250 people, making it the most frequent autosomal dominant disorder. More than 3,500 mutations can produce the phenotype. In children with a clinical diagnosis a mutation is found about 95% of the time (roughly 95% LDL receptor, 4.5% APOB, 0.5% PCSK9 gain-of-function), versus maybe 50–60% in adults.

• FH is a syndrome diagnosis, not a single LDL number.
An LDL cutoff of about 190 mg/dL is common, but many people at 200 have secondary causes like high triglycerides, type 2 diabetes, untreated thyroid or kidney disease. Heterozygous and homozygous FH distributions overlap, so diagnosis needs family history, pedigrees and physical signs. Referral bias meant his early patients all had LDL over 300.

• Physical signs appear as cholesterol deposits.
Tendon xanthomas on the backs of the hands and the Achilles, the corneal arcus and eyelid deposits (xanthelasma) are classic, though the first real symptom used to be a heart attack. A milder genetic subset exists; among about 25,000 heterozygous patients found, he has never seen that subset have heart attacks in their 20s or 30s.

• Treating early likely adds 15–20 years of life.
Children start statins (plus ezetimibe if needed) with a modest pediatric target below 130 mg/dL. Attia pushes back that healthy kids have LDL around 20–30 and newborns roughly 10 mg/dL, a natural experiment showing low LDL is safe. Their pediatric cohort, followed for 10 years after a NEJM trial, supports early treatment.

• About 10% of heterozygous FH is 'severe' and resists triple therapy.
Starting from 300 mg/dL, a statin's roughly 45% cut plus ezetimibe and a PCSK9 inhibitor may still leave some patients above 100–120. For homozygous FH the state of the art is high-dose statin, ezetimibe, evolocumab and evinacumab (Regeneron's ANGPTL3 antibody), with apheresis as an option.

• LDL causality is settled.
Kastelein says he 'doesn't even listen' anymore to claims that LDL isn't causal; Mendelian randomization across many genes, not just FH, shows the same dose-response. The thrifty-gene idea: FH may have protected against infection and was less dangerous around 1860, before modern diets.

• CETP inhibitors failed for clear reasons.
Pfizer's torcetrapib raised blood pressure in phase 2 and in the large trial 'killed more people than it saved' (2006). Others failed on HDL-focused thinking. Merck's anacetrapib REVEAL trial, done by Oxford with 30,000 patients, worked only modestly because it lowered LDL just 17% from a baseline of about 60, an absolute drop of only about 11 mg/dL.

• Obicetrapib is far more potent.
At 1 mg in phase 1 it lowered LDL 27%; at 10 mg it inhibits CETP about 97%, cutting LDL roughly 50% on top of high-intensity statins, raising HDL about 165% and lowering Lp(a) 56% (43% at 5 mg) in the ROSE trial. Kastelein is directly involved in its development, so treat his optimism accordingly. Phase 3 includes BROADWAY (~2,400 patients, 52 weeks), BROOKLYN (~300 heterozygous FH) and PREVAIL (~9,000 with established ASCVD and baseline LDL near 100).

• APOE4 fails at moving cholesterol in the brain.
About 65% of Alzheimer's patients carry at least one E4. Kastelein cites roughly 16-fold risk for E4/E4 and 4.5-fold for E3/E4; Attia thinks the data suggest closer to 10-fold and four-fold. Mechanistically E4 is a poor acceptor and a poor donor of cholesterol, failing both to clear excess and to supply deficient brain cells.

EXAMPLES

• The untreated aunt
Cascade screening of one family turned up a 76-year-old aunt who had never been treated and had LDL of about 250, alongside siblings with wildly different cholesterol, which shows how variable FH can look.

• The man whose doctors said it was too high
A patient with LDL around 200 since his late teens ignored warnings for decades and presented at 50 with disease, a common pattern in men first measured at military entry.

• Attia's PCSK9 misprediction
Attia thought a trial adding a PCSK9 inhibitor to patients already at LDL 70 couldn't run long enough to show a difference; it stopped early at about 2.3 years with benefit, which Kastelein uses to argue PREVAIL can also succeed.

• A planned Alzheimer's proof-of-concept
Kastelein's group is running an obicetrapib trial in E4 carriers that taps cerebrospinal fluid and tracks about 50 biomarkers, hoping CETP inhibition improves brain cholesterol transport.

• Diabetes signal
Higher HDL from CETP inhibition may protect pancreatic beta cells from apoptosis, and trials have shown roughly 16–20% fewer new-onset type 2 diabetes cases. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Screen families.**
  If you or a relative has LDL near or above 190 mg/dL or early heart disease, look for FH and test children; diagnosis is easiest and most accurate in kids.
- **Rule out secondary causes first.**
  Check triglycerides, glucose, thyroid and kidney function before labeling high LDL as genetic. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Lower is better, earlier is better.**
  Adult targets keep falling (below 70, 55, even 20), and lifetime exposure drives risk. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Know your APOE status in context.**
  E4 raises both cardiovascular and Alzheimer's risk; metabolic factors like insulin resistance and fatty liver compound it, so manage apoB and metabolic health aggressively.

247 Preventing cardiovascular disease: the latest in imaging, blood pressure & metabolic health

Guest: Ethan Weiss
Date: 2023-03-20 · Duration: 2:24:55
URL: https://www.youtube.com/watch?v=vxA2jKZylnE

KEYPOINTS

• A calcium scan is cheap and useful, but a zero doesn't rule out disease, especially in younger people.
Weiss, a cardiologist who now volunteers as clinical faculty at UCSF after leaving his lab to start a biotech company, says he did 'a full 180' on CAC scans. They're low-risk, need no dye, and can cost about $200, though some places charge $2,000. His two-by-two: a zero in a 40-year-old with risk factors teaches little and shouldn't stop aggressive treatment, and a zero in a high-risk 80-year-old has its own false-negative problem. Attia cites data that about 15% of people with a zero score have something on CT angiography, and about 1.5–2% have an unstable plaque.

• CT angiography sees soft plaque and small calcium that CAC misses, at higher cost and some radiation.
Attia says CTA often runs $700 to $2,000–2,500. Prices can differ tenfold between institutions, and fewer than half of Weiss's patients have coverage. A modern scan delivers about 2 mSv, roughly 4% of the annual allowance mentioned, but some older scanners use about 20 mSv. Attia advises shopping for both price and dose.

• Weiss treats causal risk factors, not end-stage findings.
Waiting for 30% stenosis or a calcium score of 200 before acting is 'insane,' he says, comparing it to waiting for lung damage before telling someone to quit smoking. He describes 'eye-bleeding' fights with insurers who want a heart attack before approving PCSK9 inhibitors. With low enough apoB over a long enough runway, both argue, atherosclerosis could become largely irrelevant.

• For stable plaque, optimal medical therapy usually beats stenting.
COURAGE, ISCHEMIA and ORBITA showed that optimal medical therapy works well even in mildly symptomatic patients. Clear stent cases are an active MI, rest or unstable symptoms, heart failure, or chest pain that doesn't respond to medicine. FAME and FAME 2 used fractional flow reserve (the pressure drop across a lesion) to show which lesions matter. Weiss notes that the plaques that rupture and cause sudden death are often smaller ones of about 30%, not 80–90% blockages.

• Statins can increase calcification while lowering events, so calcium isn't always a direct proxy for risk.
Weiss calls it 'incontrovertible' that statins probably increase calcification even as they cut event risk, likely by stabilizing plaque. Whether heavy endurance exercise is similar is unknown. He wouldn't tell anyone not to exercise but is 'on the fence' about the most extreme volumes.

• Statin fear far exceeds actual statin harm.
Weiss estimates that about 5% of patients have muscle side effects real enough to stop. A similar or larger group refuses statins out of fear fed by documentaries and online claims that they are 'poison,' even after 25–30 years of successful use. Liver enzyme rises also occur, especially combined with ezetimibe.

• Normal blood pressure is about 120/80 at any age, and drifting higher with age is disease.
The old view allowed 'permissive hypertension' in older people. Weiss now tells patients the goal is to get as close to 120/80 as possible without side effects. He traces the definitions from JNC 6 to JNC 7, which called 120–140 'prehypertension,' and says the evidence, not opinion, now ties lower pressure to lower mortality.

• SPRINT showed a mortality benefit from intensive control, with manageable costs.
The NIH-funded, drug-agnostic trial compared targets of about 120 against about 140 systolic and achieved roughly 121 versus 136. The results were strong enough that the trial was stopped early. Blood pressure was measured with automated cuffs, seated and alone, three readings five minutes apart. The intensive arm had more falls, syncope and kidney dysfunction, all reversible. STEP, published the year before this conversation, eased worries that SPRINT's early stop had overstated the effect.

• Fat storage capacity, not body weight alone, drives metabolic risk.
Weiss uses a bathtub analogy. Each person's genetically set capacity to store fat safely under the skin differs, and overflow into the viscera, muscle, pancreas and pericardium does the damage. People with congenital lipodystrophy or severe insulin resistance have extreme coronary risk; he mentions women needing bypass surgery in their 30s and 40s. Gerald Shulman's insulin-resistant mice got fatter and healthier when given more subcutaneous fat. A DEXA fat-mass ratio (central versus peripheral fat) helps identify this pattern.

EXAMPLES

• Attia's own scans
At 35, training at least 24 hours a week with LDL-C around 110–120 and apoB around 85–90, he had a CAC score of 6, a single speck in the proximal LAD and around the 75th–90th percentile for his age. Nobody seemed concerned. In 2016 his CAC was 0, but CTA found the same tiny speck. Radiologist Bob Peters told him a speck that small could be missed on half of repeat scans. In 2022 his CAC was 2 and his CTA was unchanged. He now targets an apoB of 30–40 mg/dL with medication.

• Measuring blood pressure honestly
Attia's resting readings averaged about 110/70 and then crept to 125–130/80 from August on. A reading right after climbing stairs might be 140/90, then fall a few minutes later. He averaged below 120/80 for six months but felt he was 'cheating' by resting five minutes first. Weiss recommends 24-hour ambulatory monitoring, because pressure varies with sleep, stress and exercise and is normally checked only briefly once or twice a year.

• ALLHAT's verdict on drug classes
The early-2000s NIH trial compared calcium channel blockers (amlodipine), ACE inhibitors and thiazide diuretics (chlorthalidone, which is more potent than hydrochlorothiazide). Alpha-blocker and beta-blocker arms were stopped early because they did worse. The remaining classes became first-line options for primary hypertension.

• The control gap

According to Weiss, in the 1970s national survey only about 50% of people with hypertension knew it, 30% were treated and 10% were controlled. Today he estimates awareness is above 80%, treatment is about 75–80% and control is only about 50%.

- **Kidneys and the 'phase shift'**

  Weiss tells patients that living an extra decade means a 50-year-old should meet the standard of a healthy 40-year-old in heart, brain, bone and kidneys. That includes using cystatin C rather than creatinine for eGFR. An eGFR of 70 in a 55-year-old shouldn't be accepted as 'good enough.'

OTHER RELEVANT

- **Use CAC as a cheap first look, not a final verdict.**

  With a family history, a zero shouldn't lead to complacency; consider CTA if it would change decisions.

- **Shop CTA for price and radiation dose.**

  Ask what the scanner's dose is and what you'll pay before the scan.

- **Measure blood pressure the way trials did, and over 24 hours.**

  Use a validated automated cuff, sit quietly, take several readings five minutes apart, and consider ambulatory monitoring.

- **Lower pressure toward 120/80 while watching for side effects.**

  Dizziness, falls and kidney changes are signs to back off. Older patients need special care with orthostatic drops.

- **Separate statin facts from fear.**

  Expect about 5% to have true intolerance, and don't let documentaries decide for you.

240 The confusion around HDL and its link to cardiovascular disease | Dan Rader, M.D.

Guest: Dan Rader
Date: 2023-01-30 · Duration: 1:54:09
URL: https://www.youtube.com/watch?v=cBDrK3xOZ7U

KEYPOINTS

• HDL biology is far more complex than LDL biology, which is why it is so poorly understood

Dan Rader, a lipidologist at the University of Pennsylvania, explains that apoB stays with its particle for life. ApoB100 is made in the liver and apoB48 in the gut. HDL's main protein, apoA1, behaves differently. It is secreted lipid-poor and picks up cholesterol and phospholipids from cells through the transporter ABCA1, and its other proteins swap on and off between particles. People who lack ABCA1 make plenty of apoA1 but have almost undetectable HDL, because the apoA1 can't acquire lipid and is cleared quickly.

• Humans are unusual in carrying most cholesterol on apoB particles

In a normal mouse, more than 90% of blood cholesterol is in HDL. Rader and Peter note that if humans had primate-like or mouse-like apoB levels, around 20 mg/dL instead of about 100, that five-fold difference would roughly separate developing atherosclerosis in a lifetime from never developing it. This is one reason mouse HDL research translates poorly to people.

• HDL subfraction labels are mostly noise for clinicians

HDL2 and HDL3 refer to particle size and number of apoA1 molecules (about four in HDL2 and three in HDL3). They have nothing to do with apoA2 or apoA4. Rader considers fractionation interesting biologically but relatively unimportant clinically. Peter says his practice stopped paying attention to HDL fractionation around 2016, and Rader agrees that was reasonable.

• High HDL cholesterol is not a free pass

The inverse link between HDL cholesterol and heart disease goes back to early Framingham data from the late 1970s and early 1980s. But a high HDL-C does not offset a high LDL-C or apoB. Peter calls the idea that a high HDL means you can ignore heart disease risk 'bunk' and cites two Mendelian randomization studies that fail to support a causal protective role. Rader says he would not change the treatment he'd otherwise give just because HDL is high. Both say HDL-C above about 90 deserves a closer look rather than reassurance.

• Raising HDL-C with CETP inhibitors has repeatedly failed

CETP moves cholesterol ester from HDL to apoB particles, and people deficient in it can have HDL-C above 100 mg/dL. Pfizer's first inhibitor, torcetrapib, was tested on top of Lipitor, and in September 2006 the combination did slightly worse, which Peter calls a bombshell. After three failures, Rader's reading is that raising HDL-C with CETP inhibition neither helps nor hurts. A CETP inhibitor might still be useful for lowering LDL and apoB, and that is being tested.

• Niacin raised HDL and lowered apoB, but outcome trials found little benefit

Niacin modestly lowers triglycerides, apoB, LDL and Lp(a) (roughly 15–20%) and could raise HDL-C from about 50 to 90 mg/dL at strong doses. Rader once prescribed it widely and says he has had to 'eat crow'. AIM-HIGH showed little benefit, and a large, well-powered Merck trial was also disappointing; together they 'killed niacin'. He has had to tell patients it probably wasn't helping them.

• HDL-C tracks triglyceride metabolism and insulin resistance

Rader calls HDL-C an 'integrator' of triglyceride handling, a little like HbA1c for glucose. After a fatty meal, triglycerides might rise from 100 to 400 mg/dL before clearing. Each excursion lowers HDL-C slightly (for example, 40 to 37–38), and repeated meals push it to a lower steady state. That is why a high triglyceride-to-HDL ratio (both in mg/dL) is reasonably associated with insulin resistance, though not in African-American patients, where it has long been found unhelpful.

• What matters may be HDL function, especially cholesterol efflux

Macrophages in the artery wall use ABCA1 to unload cholesterol onto apoA1. The cholesterol eventually returns to the liver through SR-B1, a process called reverse cholesterol transport. Rader's garbage-truck analogy: HDL collects cholesterol where you don't want it and dumps it at the liver. Two people with the same HDL-C of 50 can have very different flow through this pathway. A static concentration tells you nothing about velocity.

• Efflux capacity predicts events, and a trial is testing it

Rader's lab measures efflux capacity in macrophage-like cells (J774 cells and human macrophages). Using many thousands of baseline samples from EPIC-Norfolk with 10+ years of follow-up, they found efflux capacity predicted incident cardiovascular events. That is still association, not proof of causation. CSL112, an infusion of apoA1 complexed with lipid, was being tested in patients after acute coronary syndrome: four weekly infusions, with events measured at 90 days. If positive, it would be the first evidence that promoting efflux reduces events.

EXAMPLES

• The woman with HDL of 150

Rader recalls a published case of a woman with an LDL-C of about 100 and HDL-C of 150, initially assumed to be low risk. Humans who lack SR-B1 have very high HDL because they can't 'unload the garbage trucks', yet they have increased heart disease risk. That is why he suggests checking very high HDL-C, though he notes SR-B1 deficiency is not common.

• The ratio argument Peter hears from doctors

One of Peter's most vexing conversations is with physicians who say a patient's LDL-C of 140 is fine because the HDL is 80. Rader says he looks at the whole patient and calculated risk, but not in a way that lets a high HDL cancel out apoB.

• ApoE, apoA1 and the brain

ApoE4 is the major genetic risk factor for Alzheimer's disease in a dose-dependent way. ApoE2 is bad for lipids but carries about a 20% relative risk reduction. ApoA1 isn't made in the brain yet appears in cerebrospinal fluid. Rader says a fair amount of observational data suggests apoA1 protects against neurodegeneration, but it is associative and not yet clinically useful.

• HDL and nitric oxide

Rader cites Philip Shaul's work in Dallas showing in cells and mice that HDL, acting through SR-B1 on endothelial cells, promotes nitric oxide production. That could plausibly lower blood pressure and protect arteries, but its relevance in humans remains unproven.

OTHER RELEVANT

- **Focus on apoB, not HDL-C, when judging risk**
  Lowering apoB has hard-outcome evidence. Raising HDL-C with drugs does not, so don't let a high HDL-C talk you out of treating elevated apoB.
- **Treat very high HDL-C as a question**
  HDL-C well above 90 mg/dL may reflect genetic variants that don't protect the heart. Discuss it in the context of your overall risk.
- **Use the triglyceride-to-HDL ratio as a rough metabolic clue**
  A rising ratio in non-African-American patients can point to insulin resistance, which deserves attention.
- **Demand outcome trials**
  Rader's broader lesson from CETP inhibitors and niacin is that improving a lipid number is not the same as preventing heart attacks.

230 Cardiovascular disease in women: prevention, risk factors, lipids, and more

Guest: Erin Michos
Date: 2022-11-07 · Duration: 2:15:04
URL: https://www.youtube.com/watch?v=QykLgWm8h08

KEYPOINTS

• Heart disease mortality in younger women has stopped improving.
Michos, a Johns Hopkins preventive cardiologist, describes her European Heart Journal analysis of CDC WONDER data on US women under 65 from 1999 to 2019: cancer mortality kept declining, but since about 2010 progress on heart disease stalled and reversed. Worldwide, she cites roughly 18.5–19 million deaths a year from atherosclerotic cardiovascular disease versus about 10–11 million from cancer.

• Women increasingly don't know heart disease is their top killer.
In 2009, 65% of women surveyed knew heart disease was the leading cause of death in women; by 2019 only 44% did. Young patients fear breast cancer more, even though heart disease mortality is roughly 8–10 times higher. Clinicians also perceive women as lower risk than men with the same risk profile, leading to undertreatment.

• Ten-year risk scores fail younger people.
A 30-year-old with blood pressure of 160 has a 'low' 10-year risk simply because of age, yet a high lifetime risk. Michos and Attia note that at the bottom of the calculator's age range almost no input yields a high 10-year score, and that no trial enrolled people 25–45 long enough to show events prevented — yet no one doubts treating causal factors like hypertension or smoking early.

• Guidelines still lean on 10-year risk, with modifiers.
Under the 2019 ACC/AHA primary-prevention guidelines, below 5% 10-year risk lifestyle may suffice; above 20%, a high-intensity statin to cut LDL by 50% or more. Risk-enhancing factors and a coronary calcium score refine decisions, though a zero score is less reassuring under 40 because plaque takes time to calcify.

• Female-specific factors change risk.
Menarche before 11 or after 17, preeclampsia and gestational diabetes, and menopause before 45 (especially before 40) are associated with higher cardiovascular risk. PCOS is linked to about a 30–50% increased risk on average; insulin resistance appears in about 95% of obese and 75% of lean women with PCOS.

• Pregnancy dramatically raises lipids — by design.
Lipids climb and peak in the third trimester: total cholesterol up about 25–50%, triglycerides about 150–300%, LDL around 66% — normal physiology to supply the fetus. Across the menstrual cycle the swing is small, roughly 10–12 mg/dL in total cholesterol.

• Familial hypercholesterolemia is undertreated in women.
FH carries about a 20-fold increased risk and, in women, onset of disease roughly 20–30 years earlier; women with FH lose the usual female advantage, partly because they miss years of statin therapy over pregnancy concerns. Michos notes FH itself doesn't raise malformation or preeclampsia risk, and treatment in pregnancy is a shared decision.

• Statins work equally well in women.
A meta-analysis of over 18 randomized trials with more than 40,000 women showed similar relative benefit to men, scaling with each 1 mmol/L (39 mg/dL) LDL reduction. Yet in a survey representing 11 million US women with established disease, women were 45% less likely to be on statins.

• Much statin intolerance is nocebo.
Up to 30% of statin-treated patients report muscle symptoms, but blinded trials such as SAMSON suggest up to about 90% of those symptoms also occur on placebo. Michos often uses low doses of rosuvastatin (5–20 mg), notes CoQ10 lacks good evidence but is harmless if patients want it.

• Non-statin options fill the gap.
Ezetimibe adds roughly 18–21% LDL lowering; PCSK9 monoclonal antibodies lower LDL about 50–60% and Lp(a) about 25%, with outcome benefit in FOURIER and ODYSSEY; inclisiran, an siRNA, has lipid data from ORION trials. For very high-risk patients she believes optimal LDL may be around 30 or lower.

• Lp(a) is a risk enhancer even at low LDL.
Lp(a) has a variable number of kringle IV type 2 repeats (2 to over 40). In the Copenhagen General Population Study, Lp(a) above 50 mg/dL carried risk even with LDL below 70. Investigational drugs pelacarsen and olpasiran lower it 80–90%, but outcome data are pending.

• Hormone therapy is reasonable for symptomatic women near menopause.
For symptomatic women under 60 or within 10 years of menopause, Michos sees HRT as appropriate; she generally doesn't start it more than 10 years after menopause or over 65.

EXAMPLES

• The decade advantage
Attia frames it: a still-ovulating 40-year-old woman has roughly the cardiovascular risk of a 30-year-old man. Michos agrees on average, while noting people aren't averages.

• Pravastatin given too late
A trial giving pravastatin to women at risk of preeclampsia at 35 weeks showed no benefit — unsurprising, Michos says, since preeclampsia develops much earlier. A larger trial of about 1,500 high-risk women starts around 12 weeks.

• GLP-1 drugs for weight loss
Tirzepatide, a dual GIP/GLP-1 agonist, produced up to about 50 pounds of weight loss at the highest dose; semaglutide's STEP trials showed roughly 30 pounds, though they weren't compared head to head.

- **Women missing from trials**
  Her review of lipid-lowering trials from 1990–2018 found women were only about 29% of participants, and about 36% for newly approved cardiometabolic drugs through 2017; only about 10% of leadership roles in top-journal trials went to women.
- **Marathons in many states**
  Michos has run marathons in about 36 states with a goal of finishing rather than racing.

OTHER RELEVANT

- **Think in lifetime risk, not just 10-year risk.**
  Elevated blood pressure, LDL or apoB in your 30s matters even if your calculator score looks low.
- **Tell your doctor about pregnancy history.**
  Preeclampsia, gestational diabetes, PCOS and early menopause are risk enhancers that should shape prevention. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Screen for FH and Lp(a).**
  Very high LDL or a family history of early heart disease warrants evaluation; Lp(a) is worth measuring at least once.
- **Don't abandon statins on symptoms alone.**
  Discuss dose changes, alternative statins or non-statin drugs with your clinician, given how often symptoms are nocebo.

229 Understanding cardiovascular disease risk, cholesterol, and apoB

Guest: Allan Sniderman, Tom Dayspring
Date: 2022-10-31 · Duration: 1:18:53
URL: https://www.youtube.com/watch?v=UWQsbBZHHUU

KEYPOINTS

• This is a compilation on why ASCVD prevention must start early.
Attia assembles clips from earlier conversations, chiefly with Allan Sniderman and Tom Dayspring, with commentary in between, ordered as a primer on atherosclerotic cardiovascular disease, cholesterol and apoB. His premise: people under 30, 40 or even 50 think heart disease isn't their problem yet, and the data say otherwise.

• The first event is often the last.
Historically, more than half of first heart attacks were fatal, which is why a cardiologist friend once joked he saw fewer heart attacks than pathologists. Survival has improved, but sudden death remains a common first symptom, so waiting for symptoms is a poor strategy.

• Events cluster earlier than people assume.
In the data Attia shows, slightly over 50% of men who will have a cardiac event have it before 65, and almost 25% before 54. For women it's about one-third before 65; women carry the same disease burden but experience it about a decade later.

• Atherosclerosis starts in youth.
Autopsy work by Herbert Stary and colleagues, and studies of young soldiers and accident victims, showed atherosclerosis in people in their 20s and 30s. The disease gets a foothold over the first three decades, and lesions that can cause clinical events typically develop from the fourth decade onward.

• The 10-year risk model has two fatal flaws.
Sniderman credits 10-year risk calculators with a big step forward in the 1980s–90s, but under the 2019 ACC/AHA algorithms almost everyone is 'low risk' at 40, so treatment effectively starts at 55–60. First, because there are many more people under 60, the absolute number of events in 'low-risk' younger people is high even though the rate is low. Second, by 60 the disease has been progressing for decades.

• A population risk number isn't your risk.
A 4.1% 10-year estimate means about 4 of 100 similar people will have an event, but real risk within that group varies widely. Telling someone their risk is above 7.5% also implies 92.5% of the time nothing happens, a weak motivator. Sniderman prefers lifetime or 30-year risk: for a 30-year-old, the risk to 65 might be around 30%, a number people can act on, and you can show how much benefit is lost by starting at 45 or 55 rather than 35.

• There's no 'good' or 'bad' cholesterol, only lipoproteins.
Dayspring stresses that cholesterol is carried in lipoproteins, and the apoB-100 family (LDL, VLDL, IDL and Lp(a)) is atherogenic; apoB-48 on chylomicrons is set aside. Each atherogenic particle carries one apoB, so apoB counts the particles that enter the artery wall, in the presence of an injured endothelium.

• Standard lipid panels mislead.
An LDL-C of 140 mg/dL says little about particle number. Standard panels give several numbers, but treatment decisions are mostly based on LDL-C, so the others 'do nothing'. Attia is pessimistic that medical training will switch to apoB soon, even though the 2019 guidelines leaned toward it.

• Mendelian randomization makes apoB the causal metric.
Because genes are randomly allocated at conception, Mendelian randomization avoids much of the confounding that plagues 30-year observational studies. Studies in the last decade show apoB (and cholesterol) is causal while HDL is not, and that apoB outperforms LDL-C for risk.

• Lower apoB further and earlier.
Sniderman suggests at least a 50% reduction in higher-risk people. Attia argues physiologic levels are below about 50 mg/dL; PCSK9 inhibitors routinely reach 20–40. Halving plasma cholesterol barely changes total body cholesterol, so very low levels aren't dangerous, and children live safely around 40. Attia thinks apoB of 20–30 from your 20s could largely eliminate ASCVD and treats an apoB of 60 (about the 5th percentile) as a ceiling.

EXAMPLES

• The woman with an LDL of 220
One clip describes a patient with total cholesterol over 300, LDL-C around 220 and apoB about 170 mg/dL, the kind of case that would be flagged early with lifetime thinking but missed by 10-year calculators at a young age.

• A 40-year-old with a zero calcium score
Attia walks through a 40-year-old at the 50th percentile for apoB (the 20th percentile is about 80 mg/dL), not insulin resistant and with a calcium score of zero, ambivalent about therapy. He argues the zero score doesn't remove decades of future exposure.

• Two calculators, different answers
Attia notes one algorithm might say 10% and another 15–20% for the same person, both of which are meaningless to an individual who will either have an event or not.

• Hypertension's lesson
Sniderman contrasts decades of basic-science research on hypertension with the clinical reality that drugs are used simply because they work, and notes that risk factors track: someone in the high group at 35 has about a 95% chance of staying there.

• Plaque precedes events by decades
Sniderman explains that for someone who has a heart attack at 45 or 50, the disease didn't start two years earlier; it has been accumulating since early adulthood, which is the core argument for treating cumulative apoB exposure rather than waiting for risk scores to cross a threshold.

OTHER RELEVANT

- **Measure apoB, not just LDL-C.**
  Ask for apoB (and check Lp(a) once); it reflects particle number, the actual driver. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Think in 30-year or lifetime risk.**
  If you're 30–45, evaluate your exposure to age 65 and beyond rather than your 10-year estimate.
- **Start earlier and aim lower.**
  For people already tracking high in their late 30s or early 40s, lowering apoB toward the 5th–20th percentile is Attia's approach; discuss options and trade-offs with a clinician.
- **Don't be reassured by youth or a zero score.**
  Disease begins decades before events; prevention is cheapest and most effective early. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

210 - Lp(a) and its impact on heart disease | Benoît Arsenault, Ph.D.& Peter Attia, M.D.

Guest: Benoît Arsenault
Date: 2022-06-13 · Duration: 2:24:36
URL: https://www.youtube.com/watch?v=4H0mVPKsGG8

KEYPOINTS

• Genetics resurrected Lp(a) as a cardiovascular risk factor.
Lp(a) was discovered in 1963 by Swedish scientist Kåre Berg. Interest faded when studies in the 1990s and early 2000s came back negative — partly because assays were unreliable — and PubMed activity dipped. Three genetic studies published in 2009, including Robert Clarke's PROCARDIS work with about 3,000 cases and 3,000 controls, identified variants in the LPA gene linked to heart disease, and Mendelian randomization established Lp(a) as causal.

• Lp(a) is an LDL-like particle with an extra protein attached.
Every LDL carries exactly one apoB-100. Lp(a) adds apolipoprotein(a), which binds apoB — Arsenault says good evidence suggests this happens inside liver cells. Apo(a) contains kringle domains; kringle IV has 10 subtypes, and the type 2 subunit varies in copy number from one to as many as 40 repeats. Smaller isoforms are associated with higher Lp(a) levels.

• Measurement units and assays matter.
Old assays overestimated large isoforms and underestimated small ones; newer antibodies bind other regions and count particles better. Lp(a) can be reported in mg/dL or nmol/L; 50 mg/dL corresponds to roughly 125 nmol/L, so a patient tested both ways may think their level 'doubled' when it didn't.

• Lp(a) is largely genetic and stable, so measure it at least once.
Most guidelines suggest measuring once in a lifetime because levels are remarkably stable. More than 2,000 variants in the LPA region are associated with high levels, so a parent and child can both have high Lp(a) for different genetic reasons. Attia notes an apoB test costs about $14 — and the same logic applies to Lp(a).

• Risk rises with concentration.
At highish levels — around 50 mg/dL or 125 nmol/L — risk may be increased 50% to 100%; at very high levels it climbs further. Roughly 20% of people (depending on ethnicity, at least 15%) have levels above 50 mg/dL. Attia admits he had been telling patients 10%, understating it.

• Oxidized phospholipids make Lp(a) especially harmful.
Lp(a) carries far more oxidized phospholipids than LDL, affecting endothelial cells, smooth muscle cells, macrophages and aortic valve cells. Its sequence similarity to plasminogen may also impair clot breakdown, though Arsenault considers oxidized phospholipids the key.

• Aortic valve stenosis has the strongest link.
Comparing top versus bottom quintile, aortic valve stenosis shows the biggest relative risk, followed by peripheral artery disease and heart attack, then ischemic stroke. Arsenault's group studied Lp(a) particles from valve-stenosis patients, about 20 per study arm, to explore mechanisms.

• Statins don't lower Lp(a), and why.
Statins raise LDL receptor density, but Lp(a) levels are determined mainly by production rate, not clearance. Unexpectedly, PCSK9 increases apo(a) production in liver cells; PCSK9 inhibitors reduce Lp(a) production and lower it on average about 25–30%, with enormous variability.

• The PCSK9 story is a triumph of genetics.
PCSK9 was discovered in 2003 by Nabil Seidah in Montreal and Catherine Boileau in France, studying a family with familial hypercholesterolemia without an LDL-receptor mutation — gain-of-function in PCSK9. In 2006 Helen Hobbs's group at UT Southwestern showed loss-of-function variants caused lifelong lower LDL and less heart disease. People with no functional PCSK9 have LDL around 10–20 mg/dL with no apparent harm to reproduction, hormones or other disease risk.

• Niacin lowers Lp(a) but hasn't proved outcome benefit.
Niacin reduces Lp(a) on average about 20–30%. Large trials of HDL-modifying drugs, such as one of about 30,000 patients, illustrate why large outcome trials are needed in this field.

• Antisense drugs could transform treatment.
Ionis's antisense oligonucleotide (pelacarsen) showed in phase 2 data published in 2020 that monthly dosing brought about 90% of patients below 50 mg/dL. An outcomes trial in about 8,000 patients with established cardiovascular disease was expected to read out around 2025.

EXAMPLES

• High Lp(a), zero calcium
Attia describes a patient with Lp(a) of 690 nmol/L and LDL particle number around 1,800 nmol/L who had a zero calcium score — though in their 40s.

• Modest Lp(a), devastating disease
Conversely, he's seen patients with modest Lp(a) — 125–150 nmol/L — with six-vessel disease and calcium scores of 2,000, underscoring variable expression.

• FOURIER's underwhelming headline
Evolocumab's FOURIER trial showed only about a 15% relative risk reduction, disappointing many, but over just 2.2 years in patients already on maximal statins, with LDL lowered to about 30 mg/dL.

• EPIC-Norfolk
Arsenault analysed Lp(a) in about 18,000 people in the EPIC-Norfolk cohort, finding residual risk even when other factors were well controlled.

- **A residual-risk trial design problem**

  Arsenault notes most PCSK9 and statin trials were not built around high Lp(a). To test whether lowering Lp(a) itself reduces events, you would have to recruit only people with high levels — excluding about 80% of a typical trial population — which is exactly what the antisense outcome trials are now doing, using longer treatment periods to compensate for smaller enrolment.

OTHER RELEVANT

- **Get Lp(a) measured once.**

  There's at least a 10–20% chance yours is elevated; ask your physician to check it. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Know your units.**

  Compare like with like — mg/dL versus nmol/L — before concluding your level changed. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **With high Lp(a), lower apoB aggressively.**

  Attia takes a two-pronged approach: target apoB around 30–40 mg/dL, near childhood levels, and use a PCSK9 inhibitor if it achieves around a 30% Lp(a) reduction, until antisense therapies arrive.

- **Screen for valve and vascular disease.**

  Elevated Lp(a) warrants attention to aortic valve health and peripheral arteries, not just coronaries. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Tell relatives if yours is high.**

  Because Lp(a) is strongly inherited, a high result is a reason for first-degree relatives, including children, to be tested too.

Cardiovascular disease & why we should change the way we assess risk | The Peter Attia Drive Podcast

Guest: Allan Sniderman
Date: 2021-11-29 · Duration: 2:25:35
URL: https://www.youtube.com/watch?v=W1geXgNEG_0

KEYPOINTS

• The 10-year risk window hides most premature heart disease

Nearly every major guideline decides who gets a statin for prevention based on 10-year risk. Sniderman calls that a big step forward in 1980–1990 that has since become a trap. Age dominates the calculators, so almost everyone under about 55–60 scores 'low', even while atherosclerosis is building through their 30s, 40s and 50s. By the time the 10-year number looks alarming, decades of disease are already in place.

• A risk percentage is a statement about a group, not a person

A 4.1% 10-year risk means about 4 of every 100 similar people will have an event. It doesn't say whether you will. Different algorithms can give the same person 10%, 15% or 20%. Treating at a 7.5% threshold also means 92.5% of those treated would have had no event in that decade, which Sniderman says is a weak motivator.

• Particles drive atherosclerosis more than the cholesterol they carry

Each atherogenic lipoprotein (LDL, VLDL, remnants, Lp(a)) carries one apoB molecule, so apoB counts the particles that can enter the artery wall. Total and LDL cholesterol measure cargo. Sniderman has argued since his first clinical paper around 1980 that particle number beats cholesterol concentration, and says the evidence for that is now very strong.

• Standard lipid panels estimate rather than measure

The LDL number on a routine panel is almost always calculated, not measured directly. Sniderman notes that the apoB assay was standardized in 1994, while HDL cholesterol measurement is not standardized. He sees no technical reason apoB can't be routine.

• Triglycerides flag risk, but the cholesterol in VLDL particles is what does harm

Sniderman says very high triglycerides raise the risk of pancreatitis, but he hasn't seen solid evidence that triglyceride itself causes atherosclerosis. What causes it is the cholesterol inside VLDL particles and how many of them get into the artery wall.

• Remnant type III dyslipoproteinemia is missed without apoB

This highly atherogenic disorder shows high triglycerides and high cholesterol but a low or normal apoB, because the particles that pile up are cholesterol-rich VLDL remnants. Without an apoB measurement, and with old diagnostic methods abandoned, most cases in the US go unrecognized. Statins and/or fibrates usually work very well.

• Mendelian randomization has been a 'slam dunk' for apoB

Long observational studies are confounded because people change over 20–30 years. Mendelian randomization uses genetic variants assigned at conception as a natural randomized trial, often in hundreds of thousands of people. Sniderman says these studies point to apoB as the causal driver.

• Lipid status at 35 is surprisingly stable

Sniderman says groups can be classified fairly accurately at 35. Someone high at that age has about a 95% chance of staying high, and the ~5% who move don't become low. That's why he favors acting early in people who are clearly high, while noting that menopause and other changes still need follow-up.

• Early treatment should be targeted, not universal

A 2019 Circulation paper by his group modeled delaying treatment from 35 to 45 to 55. With a low non-HDL cholesterol, starting at 35 gains little. The big gains go to people with high non-HDL or apoB, roughly 20% of the population by his estimate. So pills for everyone at 35 is not the conclusion.

• Consensus culture is science's crucial weakness

Sniderman compares guideline committees to groupthink behind bad decisions such as Afghanistan and the 2008 financial crisis: 'when everybody in the room has the same opinion going in,' problems get solved badly. He says medicine has become less critical, and that 'dumbing down' recommendations for doctors who see 40 patients a day is a compromise on truth. He is pessimistic that apoB will replace LDL in US training within 10 years, despite Europe's pro-apoB 2019 guidelines.

• Think in 30-year and lifetime risk, like retirement savings

A retirement calculator that only looked 10 years ahead would be useless to a 30-year-old. Peter and Sniderman argue the same applies to arteries. A 50-year-old should care about being 80, not 60. A cut from 4% to 2% over a decade looks trivial, but it compounds by 70.

EXAMPLES

• Ancel Keys and the 200 mg/dL split

In the late 1950s, early total-cholesterol assays showed a clear difference in cardiovascular risk between people above and below roughly 200 mg/dL. That launched the cholesterol-centered model. Fredrickson, Levy and Lees later worked on lipoprotein classification in the 1970s.

• The FOURIER debate

Peter recounts an email argument about FOURIER (the PCSK9 inhibitor Repatha). People already on high-dose statins with an average LDL-C around 70 mg/dL had fewer revascularizations over roughly five years, but no change in mortality. Sniderman's view is that it's almost a miracle the trial showed anything, since patients started so low and were followed so briefly.

• A familial hypercholesterolemia result he thinks is wrong

A study reported that people with a genetic FH mutation had three to five times the risk of people with the same lipid levels but no mutation. Sniderman read it repeatedly and concluded the authors had made a methodological error, while admitting he may be wrong. His point is that FH is defined by the phenotype.

• Risk factors explain little of individual risk

Citing Michael Pencina's work (the name is uncertain in the recording), Sniderman says standard variables explain only about 20% of the variance in risk. He argues that grouping people by causal, precisely measured markers like apoB or non-HDL selects patients more accurately than noisy multi-factor calculators.

• The $10 test argument

His group's cost analysis put an apoB test at about $10, a negligible share of care costs. US health spending was about $7,000 per person per year a decade earlier and is now near $10,000. Cost, he says, is not a real barrier.

OTHER RELEVANT

• Ask for apoB and Lp(a), not just a standard panel

Sniderman measures a lipid panel, apoB and Lp(a) in every patient (Lp(a) once). High Lp(a) with normal apoB may add little, but both high is a 'double whammy' that changes how he frames risk.

• Use apoB to show patients progress

Seeing apoB fall from 120 to 60 tells both doctor and patient that the medication is being taken and working. That makes it a motivational tool, not just a diagnostic one.

• Interpret calcium scores by age

A CAC of zero doesn't rule out risk in someone with very high apoB. But any calcium under age 50 is significant, even if the 10-year model calls it about 4%. Peter's view is that prevention aims to stop lesions forming, which is '100% success', rather than treating them late.

• Embrace uncertainty instead of false precision

Sniderman wants doctors to say what they believe and why, admit that confidence intervals can be wide, and welcome open challenges, such as being confronted with a specific line of your own paper. Science that says the same thing as 30 years ago may not have learned anything.

#134 - James O’Keefe, M.D.: Preventing cardiovascular disease and the risk of too much exercise

Guest: James O'Keefe
Date: 2020-10-26 · Duration: 2:09:16
URL: https://www.youtube.com/watch?v=8kytXpshGks

KEYPOINTS

• Atherosclerosis is less a plumbing problem than a 'zit' problem

The idea that you just clear the clog has been hard to shake for 40 years. O'Keefe describes plaques as pustules under the artery's inner lining, full of oxidized LDL and triglycerides, that draw in inflammatory cells. They thin out, rupture, attract clots and heal over decades, with each episode laying down smooth muscle, collagen and eventually calcium. Opening stenoses helps in acute coronary syndromes but doesn't prevent most heart attacks.

• A calcium scan is 'the mammogram for the heart'

O'Keefe recommends a CT calcium score, with minimal radiation, for men over 40 and women over 60. He has read about 150,000 scores, and his practice has done about 600,000. One very fit, metabolically healthy patient scored just over 100 (75th–90th percentile) with 30–50% narrowings in three vessels. O'Keefe stresses that such lesions matter as sites of inflammation, not as blockages to stent.

• Exercise follows a reverse J-curve

If exercise were a drug it would be the best one we have for heart disease, dementia, osteoporosis, depression and diabetes, but the dose matters. In O'Keefe's 'Training for Longevity' review, 8 of 10 large studies showed mortality dropping steeply, plateauing, then 'fish-hooking' up at the highest volumes. Even 15 minutes of brisk walking a day cuts serious cardiovascular disease by about 30%.

• Chronic extreme endurance training can damage the heart

Sustained hours at high heart rates, often under heavy load, push cardiac output to 30–35 liters a minute, and 40 in elite cyclists. That strains the atria and right ventricle and can leave dilated chambers and scarring. O'Keefe cites atrial fibrillation rates up to about 700% higher in lifelong endurance athletes, and troponin and NT-proBNP rises after long efforts, especially after 45. Youth makes people resilient to this, but that resilience fades.

• Moderate running is the sweet spot

Copenhagen data showed moderate-dose runners lived longest, and O'Keefe suggests about 15 miles a week is enough for health. Beyond that, he says, you're doing it 'for some other reason.' He also cautions that the evidence is epidemiological and lifelong patterns can't be randomized. Peter says it took him about three years after first hearing O'Keefe (around 2011) to change his own training, by 2014.

• Social, playful sports added the most years

In the Copenhagen City Heart Study, about 10,000 Danes were followed for decades. After multivariable adjustment, tennis, badminton and soccer added roughly 6–10 years of life expectancy. Cycling, swimming and running added about 3–4, and health-club workouts only about 1.5. O'Keefe first thought it was nonsense, then concluded that sports that reduce stress, are fun, last a lifetime and build relationships matter. He cites Julianne Holt-Lunstad's work showing social connection as a top predictor of longevity.

• Train like a hunter-gatherer: mostly easy, some hard, plus strength

Tribes in the wild walk about 16,000–18,000 steps a day, mostly at a comfortable pace, often carrying loads. Elite endurance athletes train about 80% easy and 20% hard. O'Keefe suggests capping hard aerobic sessions at about 30–45 minutes and adding strength and balance work. In one study, about 8,000 steps a day cut mortality by about 50% over 12 years, with benefit peaking near 12,000.

• Resting heart rate is a useful feedback tool

O'Keefe's resting heart rate was in the mid-30s when he was very fit and is now in the 40s. He tracks it to tune training, sleep and stress. Some people simply run higher, but trends within one person are informative.

• SGLT2 and GLP-1 drugs protect the heart

After decades of failing to prove that lowering glucose prevents cardiovascular disease, about seven large trials of 3,000–17,000 patients showed SGLT2 inhibitors do. They cause about 100 g of sugar a day to be lost in urine. High-dose semaglutide (2.4 mg weekly) can cut body weight by around 10% even in non-diabetics.

EXAMPLES

• Micah True

The ultrarunner made famous by Born to Run often ran about 12 miles a day plus 50–100-mile desert races. He died suddenly on a run in his 50s, and the autopsy reportedly showed a dilated, scarred heart, especially the right ventricle and septum.

• O'Keefe's low-fat experiment

Years earlier, eating pizza crust without toppings and lots of white rice, his triglycerides rose from 80 to 300 and HDL fell from 50 to 33. He got skinnier, felt worse and raced slower. He now advocates a 'pesco-Mediterranean' diet with daily time-restricted eating of 12–16 hours.

• Omega-3 at prescription doses

In REDUCE-IT, 4 g a day of EPA in people with heart disease or diabetes and triglycerides above 150 cut cardiovascular events and mortality by roughly 25–30%. O'Keefe notes most Americans are low in omega-3s.

• Calcium score regression

O'Keefe says scores almost never fall, but he has seen one drop by 200–300 points from about 1,400 over a few years, more than the margin of error. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Use extra-virgin olive oil that burns**

  Good EVOO, as used in PREDIMED, leaves a peppery burn 10–20 seconds after swallowing, a sign of polyphenols. Buy carefully. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Take a 30–40-year view of risk**

  Like Allan Sniderman, O'Keefe looks beyond 10-year risk. A 40-year-old with a zero calcium score but apoB at the 80th percentile may still merit treatment, and he favors aggressive LDL and apoB lowering, including non-statin options such as PCSK9 inhibitors, ezetimibe and omega-3s.

- **Moderate sodium and add minerals**

  O'Keefe considers 2–3 g of sodium a day better than going below 1,500 mg. He emphasizes magnesium, potassium and collagen-rich foods, the 'bones' our ancestors ate. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#129 - Tom Dayspring, M.D.: The latest insights into cardiovascular disease and lipidology

Guest: Tom Dayspring, M.D.
Date: 2020-09-21 · Duration: 2:00:04
URL: https://www.youtube.com/watch?v=svYYprvlL_U

KEYPOINTS

• ApoB-carrying particles are the core driver of atherosclerosis.

Dayspring, a lipidologist who practiced internal medicine in New Jersey for 37 years, describes a growing consensus. Attia lays out the model: smoking and high blood pressure injure the artery lining, and apoB particles act as the 'Trojan horse' that carries cholesterol into the artery wall. There it is retained and oxidized, setting off an inflammatory repair response that builds plaque. Each atherogenic particle carries exactly one apoB molecule: apoB-100 for liver-made particles, and the shorter apoB-48 for chylomicrons from the gut.

• ApoB is the preferred metric, and cost is no longer an excuse.

Because of their long half-life, 90–95% of apoB particles are LDLs, so apoB works essentially as a particle count that also captures VLDL remnants, IDL and Lp(a). Attia's practice switched from LDL-P after going through three particle-count technologies in eight years. Dayspring cites Allan Sniderman's work showing that even non-HDL cholesterol leaves roughly 20–30% of people misclassified compared with apoB.

• Lower is better, and physiological apoB is probably under 50 mg/dL.

Dayspring notes newborns have apoB under 50 mg/dL, and trials show the greatest risk reduction when it is pushed that low. Guidelines suggest at least a 50% reduction in higher-risk people. PCSK9 inhibitors now routinely bring apoB to 20–40 mg/dL. He stresses that halving plasma cholesterol (say 200 to 100 mg/dL) barely changes total-body cholesterol, because most cholesterol sits in cell membranes and tissues, not in circulating lipoproteins.

• HDL cholesterol is a poor target.

HDL cholesterol was adopted from 40- to 50-year-old epidemiology. Decades of trials that raised it have been neutral at best and harmful at worst, and Mendelian randomization studies of HDL genes are neutral too. Dayspring calls HDLs 'fire engines' of many types: an average particle carries about 45 cholesterol molecules and can carry some 150 different proteins. HDL function matters, but there is no good clinical test for it yet.

• Lp(a) is 'the most dangerous particle you've never heard of.'

Lp(a) is an LDL-like particle with apo(a) attached. Its level is genetic, so a single test is enough: if it isn't high at 18, it won't be at 68. For heart attacks before 60 in the family, Attia's rule is 'Lp(a) until proven otherwise.' Yet some people with high Lp(a) reach 80 with little plaque, which suggests risk depends on more than concentration. A recent study found Lp(a) particles carrying apoC3, a 'double whammy' that makes them harder to clear.

• Lp(a)-specific drugs are still in trials, and Lp(a) isn't yet a treatment target.

Second-generation antisense drugs that work in the liver are in development, and Novartis has acquired one that has entered phase 3. Dayspring explains why the first trial enrolls only people with very high Lp(a): Mendelian data suggest the drop has to be large to help, and a failed first trial would kill the drug. For now the target is apoB. Statins may nudge Lp(a) up slightly, but they lower other LDLs so much that net risk falls.

• Statin strategy: there's residual risk, and the dose debate is real.

Statins reduce events but leave plenty of residual risk. Trials suggest that if you decide to use one, you should pick the most potent (atorvastatin or rosuvastatin) at maximum dose. Dayspring personally prefers to start lower, depending on risk, rather than use the 'gorilla dose' on day one. Before starting, he urges a CAC scan, an Lp(a) test, family history and blood pressure.

• Ezetimibe and bempedoic acid add non-statin ways to lower apoB.

Mendelian randomization predicted that blocking gut absorption of cholesterol would cut events before ezetimibe's outcome trial confirmed it. On its own, ezetimibe lowers LDL-C about 10–18% and apoB a bit less. Bempedoic acid blocks ATP citrate lyase upstream of HMG-CoA reductase. It is a prodrug activated only in the liver and isn't taken up by muscle, so it should avoid the muscle aches that limit statins, which Dayspring thinks are more common than trials show.

• Omega-3s only lower triglycerides at serious doses: about 4 g/day.

Dayspring says 1–2 g won't do much for triglyceride-rich lipoproteins. With Bill Harris he questions whether EPA alone is uniquely beneficial or whether 4 g of combined EPA plus DHA would work too. It is also unclear whether people with triglycerides below 150 and residual apoB risk would benefit.

• Fibrates are underappreciated in the right patient.

Earlier fibrate trials were badly designed and often didn't target people with high triglycerides. A selective PPAR-alpha modulator is in big outcome trials. Niacin is 'a dead drug' that appears in no guideline, though a few Lp(a) specialists still use it selectively.

EXAMPLES

• The untreated patient with apoB 170

Attia describes a woman in her late 60s with total cholesterol in the 300s, LDL-C 220 and apoB 170 mg/dL, but a coronary calcium score of zero. Dayspring consulted, and the practice chose not to treat her, an example of individualized risk assessment.

• REDUCE-IT

High-risk patients on statins with LDL-C under 100 and triglycerides of about 150 or more (137 was allowed because of assay variability) took 2 g of prescription EPA twice daily with food. Residual risk fell by almost 30%, which Dayspring calls mind-boggling on top of a statin.

• The EPA+DHA trial that stopped

A similar trial of free EPA plus DHA in high-triglyceride patients was halted about two years in, in late 2019, for futility, and

was unpublished at the time. It caught both men off guard.

- **The 38-year-old on 'Alone'**
  Attia describes a superbly fit contestant on the survival show who had had a heart attack at about 38. His instant thought: Lp(a) until proven otherwise. He also points to New York Times reporter Anahad O'Connor, who wrote about discovering he carries high Lp(a).
- **Trilipix turnaround**
  In one patient with triglycerides around 400 and apoB around 200, fenofibric acid (Trilipix) dropped triglycerides to about 100 and apoB to roughly 80–100. Attia's practice has a few patients on it and calls it a 'world beater' for the right case.
- **LDL triglycerides**
  Dayspring says that if he could have only one lipid measurement, he'd choose LDL triglyceride over LDL cholesterol, because it tracks inflammation and poor HDL function. The assay is simple (Denka makes one) but hard to find.

OTHER RELEVANT

- **Pick one metric and stick with it**
  Both men favor apoB. Use the same assay, and ideally the same lab, over time, because NMR, ion mobility and apoB results aren't interchangeable.
- **Test Lp(a) once**
  Combine it with family history, a CAC scan and blood pressure before deciding on treatment.
- **Match the omega-3 dose to the goal**
  For triglyceride lowering, the speakers point to about 4 g/day. Typical over-the-counter doses won't do it. This is their view, not individual medical advice.
- **Context and caveats**
  Recorded September 2020: later trial results for Lp(a) drugs, bempedoic acid and omega-3s postdate it. Dayspring served as chief scientific officer at two cardiovascular biomarker labs from 2012 to 2019.

#22 – Tom Dayspring Part III of V: reverse cholesterol transport, CETP inhibitors, & apolipoproteins

Guest: Thomas Dayspring
Date: 2020-01-01 · Duration: 1:04:19
URL: https://www.youtube.com/watch?v=3ZWLxElxIBg

KEYPOINTS

• Most cholesterol is made by peripheral cells, and it has to get out

Dayspring says the liver makes only about 20% of the body's cholesterol. The rest is made by cells throughout the body. A cell that accumulates too much must export it or die. Cells push free cholesterol out through transporters such as ABCA1 to apoA-I, the HDL protein. Lipid-poor 'baby' HDL particles are especially good at picking it up. Attia says that of all seven hours with Dayspring, he learned the most from the HDL and CETP discussions.

• Reverse cholesterol transport has more than one route

HDL can deliver cholesterol directly to the liver, small intestine, adrenal glands, ovaries or testes. It can also hand cholesterol to apoB particles via CETP (cholesteryl ester transfer protein), and the liver then clears those through LDL receptors. Red blood cells and albumin (one albumin molecule can carry up to 17 cholesterol molecules) also move cholesterol. Even excretion is leaky: the gut reabsorbs about 90–95% of bile salts.

• Remnants are cleared by apoE; LDL lingers

As VLDL and chylomicrons lose their core triglycerides, they become remnants. Dayspring compares it to being 'a remnant of my former self' after losing an arm. Remnants carry apoE, which binds both LDL receptors and LDL-receptor-related proteins, so they are cleared quickly. LDL relies on apoB-100 alone, so it can 'hang around forever' until an LDL receptor clears it. Some people carry more apoE on their LDLs.

• ApoC-III makes particles more atherogenic

An LDL particle that carries apoC-III is 'intensely more atherogenic' than one with apoB-100 alone, because apoC-III impairs clearance. Drugs targeting apoC-III were in development at a San Diego company. Dayspring considers triglycerides above about 130 mg/dL a sign of a problem.

• In insulin resistance, most of the added apoB comes from LDL

When triglycerides rise, VLDL particle numbers can double or triple, for example from 30 to 90 nmol/L. Because LDL starts from a much higher base (about 1,000 rising to 3,000 in the example given), the extra 300–400 nmol/L of LDL dominates the risk. A big relative change in VLDL can be a small share of the total apoB.

• VLDL-C is a crude marker

Dayspring once estimated VLDL remnants with VLDL cholesterol. He now calls it 'a very crude estimation that's almost useless', which he says annoys his lipid colleagues. He still tells patients to aim for VLDL-C under 15 mg/dL when nothing better is available.

• 'Good cholesterol' is a misnomer

HDL can transfer its cholesteryl ester to an LDL particle (about 95% of apoB particles are LDL). That LDL can end up in a macrophage in the artery wall. HDL particles also swap lipids with each other. Dayspring tells doctors that calling HDL-C 'good cholesterol' is 'mis-educating patients'.

• Low HDL-C is mostly a proxy for high apoB

In the Framingham-era data, low HDL-C and high triglycerides travel with very high apoB in almost everyone not on drugs or a strict diet. Dayspring says that if those studies had adjusted for apoB or LDL particle number, which they couldn't, low HDL-C would likely disappear as an independent risk factor. Insulin-resistant patients' disease is ultimately apoB-driven.

• HDL-C doesn't tell you whether HDL is working

Low HDL-C could mean poor pickup of cholesterol or fast delivery of it. High HDL-C could mean good pickup or a failure to drop cholesterol off. HDL particles carry about 200 identified proteins, and their protein and phospholipid signatures likely matter more than their cholesterol content. Functional HDL assays are still largely research tools.

EXAMPLES

• ApoA-I Milano

People in a small northern Italian village had HDL-C of only 5–10 mg/dL yet lived long lives, which contradicts Framingham's 'low HDL, you're out of here'. Their variant apoA-I was highly functional at moving cholesterol. Infusions based on it showed better-looking arteries on imaging, but Dayspring warns there are '217 ways to be fooled by an angiogram'.

• Torcetrapib's sudden end

Attia was at a 2006 meeting in San Francisco, sure the CETP inhibitor would succeed and send Pfizer stock soaring. At 11:30 that night he saw that Pfizer had terminated torcetrapib. Later CETP inhibitors raised HDL-C anywhere from 20–30% to 80–100%, without the expected benefit.

• Mendelian randomisation

Around 2010–2011, genetic studies showed that variants raising HDL-C don't protect against heart disease. That confirmed what the failed CETP trials suggested, but the drugs had been developed long before that data existed.

• A CETP inhibitor that worked, but won't be sold

One trial was stopped for futility. Merck continued its own large trial and showed a benefit. But Merck decided not to market the drug because it stays in the body for years. It still isn't clear why one CETP inhibitor works and another doesn't.

• Very high HDL-C as a warning

Dayspring had shared a case with unusually high HDL-C. Dayspring notes that oversized HDL particles may fail to bind the proteins they should carry. Treatment in such cases still comes down to lowering apoB.

OTHER RELEVANT

- **Focus on apoB, not HDL-C**
  For risk assessment and treatment, apoB or LDL particle number is the target. HDL-C should not reassure or alarm you on its own.
- **Use triglycerides as a metabolic clue**
  Triglycerides above about 130 mg/dL, especially with low HDL-C, suggest insulin resistance and rising apoB, a prompt to address diet and metabolism.
- **Be cautious about 'HDL-raising' claims**
  Raising HDL-C with drugs hasn't reliably reduced events. Judge any therapy by hard outcomes, not by HDL numbers or angiogram images. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't drop a good drug over a few bad signals**
  Using Vioxx's withdrawal as the example, they argue that restricting a drug for everyone because of risk in a small subgroup deprives many patients. Better to identify who is at risk.

#20 – Tom Dayspring, M.D., FACP, FNLA – Part I of V: an introduction to lipidology

Guest: Thomas Dayspring
Date: 2020-01-01 · Duration: 1:14:35
URL: https://www.youtube.com/watch?v=PllTHYgWpuw

KEYPOINTS

• Attia calls Dayspring 'the mentor to the mentors' in lipidology

This first part of a roughly seven-hour, five-part conversation introduces Dayspring. He practised internal medicine in New Jersey for just under 40 years, has given about 4,000 lectures including over 600 accredited medical-education programmes, and received the National Lipid Association's 2011 President's Award. Attia calls him his single most important clinical mentor and 'a national treasure'. This episode is the gentler warm-up before the technical parts.

• At 72, Dayspring lost 67 pounds in 11 months with monthly low-calorie weeks

Dayspring had lived for years with obesity, insulin resistance, fatty liver, gallbladder removal, a hip replacement and several spinal surgeries. After watching a talk Attia gave at MIT on longevity, he took on Attia's modified fast: one week a month of 700 calories or less with significant carbohydrate restriction. Attia's colleague Nicole helped plan the meals. Dayspring says days two and three were the hardest. Eleven months later he was 67 pounds lighter.

• His lab report went from red and yellow to all green

Working for a lab company, Dayspring tests nearly every cardiometabolic marker on himself. A report that was largely yellow and red a year earlier was 100% green. He also feels his orthopaedic symptoms are about 90–95% better. He can walk to dinner, where a year before he had to stop after a short block. He suspects the fasting did more than weight loss alone, but offers this as personal experience.

• Fear of cognitive decline was a big motivator

Dayspring says his biggest worry was cognitive impairment as he aged, with fatty liver and other problems 'sneaking up'. Seeing 'the light at the end of the tunnel', with US average life expectancy around 80, plus wanting to be around for his son, turned years of ambivalence into an all-in switch. Attia notes that once Dayspring commits to something, he never wavers.

• Coronary care has changed dramatically since the 1970s

As a resident in a 700-bed hospital, Dayspring might admit a dozen coronary care patients in one night. He saw transmural heart attacks with Q waves and pulmonary oedema, and patients 'dropping dead before your eyes'. A 50-50 survival chance was common. Attia's concierge-practice colleague says he can't remember his last Q-wave heart attack. Dayspring still believes early prevention could all but end the disease.

• He taught himself lipidology over a decade

Frustrated by middle-of-the-night heart attack calls, Dayspring moved into prevention: smoking, weight and aggressive blood-pressure control. After trials such as Framingham and MRFIT pointed to cholesterol, he says it took about 10 years of serious reading, often not understanding what he'd read for the first five, before it 'all made sense'. Early influences included Dan Rader, Virgil Brown, Allan Sniderman and Ron Krauss.

• His diagrams made complex lipid biology teachable

Dayspring says he can't draw a person beyond a stick figure, but he learned to build detailed, animated lipoprotein diagrams in PowerPoint. Attia, who learned PowerPoint at McKinsey, assumed a professional illustrator made them. Dayspring also wrote Lipidaholics Anonymous, a free weekly newsletter of real case discussions read by several thousand people. He jokes that what he wrote in 2002 is 'mostly all wrong' now.

• Facts have half-lives, including 'high HDL is good'

Attia contrasts very long-lived facts, like a round Earth, with the Framingham-era belief that high HDL cholesterol is protective, which he now calls grossly oversimplified and possibly incorrect. Dayspring goes further: no one should judge cardiovascular risk from HDL cholesterol or think raising it achieves anything. He considers it worth listing only for calculations like non-HDL cholesterol.

• Lipoproteins mainly carry energy and phospholipids, not cholesterol

Dayspring stresses that almost every cell makes all the cholesterol it needs. The bigger problem is cells making too much, which can crystallise and kill them, so cells have powerful ways to export it. Lipoproteins mostly deliver triglycerides, fatty acids for fuel, to muscle or for storage in fat cells. They also deliver phospholipids, which make up their outer shells.

EXAMPLES

• Phospholipids: the overlooked lipid

Lipids are water-insoluble molecules. Triglycerides are three fatty acids on a glycerol backbone. Phospholipids have two fatty acids plus a phosphorus-containing head that is water-friendly, which lets them form both lipoprotein surfaces and cell membranes. Most are made in the liver and small intestine. Dayspring calls them the glyceride nobody looks at.

• Shrinking 'dump trucks' feed HDL

Large chylomicrons from the gut and VLDL from the liver have the most surface area. When lipoprotein lipase in muscle and fat strips their triglycerides, the particles shrink and shed surface phospholipids. Phospholipid transfer protein hands those to cells or to immature apoA-I particles, helping them grow into large HDL.

• Fat structure shapes cell membranes

Attia explains that saturated fatty acids have no double bonds, monounsaturated have one and polyunsaturated have two or more. Dayspring adds that straight saturated chains make membranes rigid, while multiple double bonds take up space. That changes 'lipid rafts', the membrane zones where receptors such as the LDL receptor can sit, and he expects it to explain much of HDL function.

• Paterson firefighting and a 1962 Rangers game

The son of a Paterson, New Jersey fire chief, Dayspring built one of the most-visited historical fire department websites in the

US and a large collection of firefighting antiques. A high-school friend took him to the old Madison Square Garden around 1962, where the bright ice and helmetless New York Rangers turned him into a lifelong hockey fan.

OTHER RELEVANT

- **Don't judge heart risk by HDL cholesterol**
  Both men treat HDL-C as an outdated measure; later episodes focus on particle number and HDL function.
- **It's never too late to start**
  Dayspring's transformation at 71–72 came after decades of ignoring his own risk. He credits support from his wife, who prepared meals, and Attia's team.
- **Learn visually**
  Dayspring's own method, drawing what you read, is offered as a way into dense subjects; his diagrams are shared on Twitter at @Drlipid.

#21 – Tom Dayspring, M.D., FACP, FNLA – Part II of V: Lipid metrics and cholesterol regulation

Guest: Tom Dayspring
Date: 2020-01-01 · Duration: 1:27:02
URL: https://www.youtube.com/watch?v=bQCXbtvZrhY

KEYPOINTS

• Lipids do not float free in plasma—they ride inside lipoproteins.
Dayspring credits physicist John Gofman (the transcript sometimes says 'Hoffman') with mid-century ultracentrifuge work showing hydrophobic lipids must be packaged. Learn that first, he says, or every later cholesterol debate will be confused. Plasma is water; triglycerides and cholesteryl esters are not. Without apolipoproteins and phospholipid coats, the cargo would oil-slick out of solution.

• There are separate lipoprotein lineages, not one maturation ladder.
You do not climb chylomicron !' VLDL !' IDL !' LDL !' HDL as a single sequence. Chylomicrons are gut-derived triglyceride carriers; VLDL/LDL are liver-apoB lineage; HDL is its own system. Mixing those stories produces nonsense clinical advice. Dayspring is emphatic about that semantic hygiene because patients hear 'LDL turns into HDL' folklore that no pathway diagram supports.

• LDL-C measures cholesterol cargo; LDL-P / apoB count the ships.
A 'direct LDL-C' assay quantifies cholesterol inside LDL particles. NMR LDL-P reports particle concentration in nmol/L. ApoB counts apoB-containing particles. Discordance—low cholesterol per particle but high particle number—is exactly where risk hides from a standard panel. When particles are cholesterol-poor but numerous—common in insulin resistance—LDL-C underestimates risk and apoB corrects it.

• Ultracentrifugation is the conceptual gold standard almost nobody uses clinically.
Separating fractions and measuring cholesterol in each is too slow for routine care, so chemistry assays and NMR shortcuts evolved. Framingham-era HDL assays were an early practical win; modern NMR still cannot perfectly distinguish a huge chylomicron from a huge VLDL by size alone. Chemists built direct assays precisely because nobody could centrifuge every patient sample the way research labs once did.

• Sterol vocabulary matters: cholesterol, stanols, zoosterols, phytosterols.
Cholesterol has a double bond at carbons 5–6 and a hydroxyl at carbon 3. Saturating that bond yields a stanol. Plant foods bring dozens of phytosterols (campesterol, stigmasterol, and others). Those markers help sort synthesis vs absorption stories in advanced testing. Mislabeling a stanol as cholesterol on a slide is the kind of error that still shows up in papers Dayspring referees, which is why he drills structure.

• ABC transporters move sterols in and out of cells and gut lumen.
ABCA1 helps seed nascent HDL; ABCG5/G8 efflux sterols (including plant sterols) back into the gut. People vary widely in sterol absorption—Dayspring cites ranges from modest (~20%) to very high (reports into the 60%+ range)—so the same diet is not the same internal exposure. If ABCG5/G8 is sluggish, phytosterols accumulate; sitosterolemia is the extreme teaching case for why efflux genes matter.

• The brain makes its own cholesterol; plasma LDL is not its delivery truck.
Neurons and glia synthesize what they need behind the blood–brain barrier. That fact reframes why crashing plasma LDL pharmacologically is not the same as starving the CNS of cholesterol. That disconnect also explains why neurologic fear-mongering about 'low cholesterol starving the brain' usually misunderstands compartmentalization.

• Acute illness wrecks a lipid panel's meaning.
Peter noticed HDL plunging in ICU patients under extreme stress and kept rechecking it. Inflammatory and metabolic shifts move lipids transiently—so never make chronic risk decisions off an admission panel. Steroidogenic tissues still need cholesterol for hormones, but an ICU draw is the wrong moment to invent a lifelong HDL deficiency story.

• Cholesterol synthesis pathways (Bloch / Kandutsch–Russell) are not trivia.
Multiple routes and crossovers exist; cells still end at the cholesterol molecule they need. Understanding synthesis vs absorption helps interpret precursor sterols on advanced panels and why some drugs hit production while others hit gut uptake. Nobel politics aside (Bloch/Lynen vs later pathway workers), clinicians mainly need to know production and absorption can be independently high or low.

• This Part II is the 101 before later clinical application episodes.
Dayspring is one of Peter's core lipid mentors. The episode deliberately stays on structure, measurement, and vocabulary so later talks about residual risk, remnants, and therapy have a shared language. Listeners should treat this installment as vocabulary bootcamp before Parts III–V get more applied.

EXAMPLES

• Gofman ultracentrifuge insight
A physicist's centrifuge work reframed plasma 'fat' as organized lipoprotein particles—foundation for everything that followed in lipidology. Once you see lipids as passengers, 'cholesterol in my blood' stops sounding like dissolved grease and starts sounding like traffic counting.

• LDL-C vs LDL-P discordance
Same person can look fine on cholesterol concentration and be high-risk on particle number; NMR/apoB resolve that. Peter returns to this distinction constantly with patients who were told their LDL was 'fine' on an outdated panel.

• Phytosterol panel as absorption clue
Elevated plant sterols suggest hyper-absorption phenotypes that diet and ezetimibe-class strategies target differently than pure over-producers. Pair them with triglycerides and HDL to see the whole remodeling neighborhood, not a single villain molecule.

- **ICU HDL collapse**
  Peter's repeated inpatient observations: severe stress acutely tanks HDL—another reason timing of labs matters. Inflammatory cytokines and altered CETP activity are among the plausible acute movers.
- **ABCG5/G8 efflux**
  Pumping sterols back into the gut lumen is a major, not minor, pathway—and a big source of person-to-person variability. Combined with ABCA1's role launching nascent HDL, transporter talk becomes clinical rather than alphabet soup.

OTHER RELEVANT

- **Ask for apoB or LDL-P when stakes are high.**
  If family history, diabetes, or surprising events exist, cargo-only LDL-C is not enough. Guidelines have been moving this direction for years; Dayspring was early and loud about it.
- **Do not interpret lipids drawn during acute illness.**
  Wait until the inflammatory storm settles before rewriting a prevention plan. Recheck fasting lipids weeks after recovery when you need numbers for prevention.
- **Learn lineage before supplements and internet protocols.**
  Chylomicron vs VLDL vs HDL confusion is how people mis-blame 'cholesterol' for triglyceride problems and vice versa. If a thread cannot say which particle lineage it means, ignore the protocol.
- **Match therapy to synthesis vs absorption phenotype when data exist.**
  Advanced sterol markers plus apoB give a clearer lever than total cholesterol folklore. Hyper-absorbers and hyper-producers are not moral categories—they are levers.

#19 – Dave Feldman: stress testing the lipid energy model

Guest: Dave Feldman
Date: 2020-01-01 · Duration: 3:10:33
URL: https://www.youtube.com/watch?v=kRxeyaNWmHw

KEYPOINTS

• Peter opens already mostly unconvinced by Dave's lipid-energy model.
He estimates he entered ~20% open to being persuaded and left unconvinced. His null hypothesis remains the lipid/apoB causal framework, even while granting Dave's n-of-1 experiments are interesting and technically earnest. He repeatedly separates respect for Dave's curiosity from assent to Dave's clinical conclusions.

• Dave's personal 'catharsis' was a late-2015 lipid spike on low-carb.
About seven and a half months into the pattern, total cholesterol hit roughly 329 mg/dL with LDL-C around 200–250. That shock launched the software engineer into systematic self-experimentation and the 'cholesterol code' public project. Friends on similar diets had milder moves; Dave's magnitude made denial impossible and launched the public 'drop roll call' community.

• Lean mass hyper-responders are the phenotype under debate.
Lean people on ketogenic/low-carb diets who show very high LDL-C/LDL-P with high HDL and low triglycerides. Dave hypothesizes energy trafficking via lipoproteins explains the rise; Peter doubts the triglyceride-export math can account for the extra cholesterol mass and particle counts. Peter also argues that even garden-variety type 2 diabetes does not generate the LDL burden people casually attribute to 'energy delivery,' weakening the model's scaling claim.

• Inversion experiments: huge dietary fat can drop LDL short-term.
Dave reports multi-day high-fat runs where LDL-C fell ~73% and LDL-P dropped on the order of ~1,000+ nmol/L in three days. Peter finds the phenomenology striking but insufficient to overturn chronic risk models built on apoB exposure over years. If fat influx acutely lowers measured LDL, Dave reads that as particles being used; Peter reads it as an acute redistribution that still fails the decades-long apoB risk literature.

• Mass balance is Peter's first objection.
Where does the extra cholesterol in all those LDL particles come from if not synthesis or delayed clearance? Without a closed account of cholesterol flux, the energy model feels incomplete to him—even if Dave later refined answers after the taping. Until synthesis, absorption, and clearance are quantified together, a storytelling model remains a hypothesis.

• Genetic FH lessons cut against 'exclude my phenotype' special pleading.
Peter notes ~2,000 vaguely identified genetic routes to familial hypercholesterolemia phenotypes. He is unwilling to throw out that causal body of evidence for a low-carb subgroup that has not yet shown clean outcome data. Excluding those mutations from the debate because they are 'genetic' while treating diet-induced highs as a different species of LDL is, to Peter, special pleading.

• PCSK9 and receptor biology still dominate his clinical priors.
Even on max-dose atorvastatin (80 mg), some patients need more particle-lowering. PCSK9-related FH subsets (~3–5% in his framing) and receptor pathway genetics keep him anchored to apoB reduction as the lever with outcome trials. Fourier and ODYSSEY-type PCSK9 outcome data sit in the background of that prior even when cost-effectiveness is a separate argument.

• Dave wants atherosclerosis imaging and more stratified cohorts.
He argues trouble should show up as rising CAC or carotid intima-media thickness before panic, and that studies stratifying high HDL/low TG alongside high vs low LDL-C are the fair test. Peter agrees better data would help while refusing to treat absence of powered studies as reassurance. Dave grants imaging lag and noise; Peter answers that waiting for plaque to prove a hypothesis is a harsh experiment to run on yourself.

• Composition experiments (SFA cuts, mono swaps) are practical middle ground.
In one early case with Tom Dayspring, a keto loyalist with extreme LDL-P was urged to cut saturated fat toward ~25 g/day and lean on mono sources (olive oil, macadamia)—hard to do without creeping carbs. Lipid-P moved; ideology was the obstacle. Olive-oil-and-macadamia thought experiments show how hard pure mono eating is at weight-stable calories without sneaking carbohydrate back in.

• Remnants, oxidized LDL, and kinetics remain measurement gaps.
Both admit clinical labs poorly resolve true remnant particles without apoC-III-aware methods, and oxidized LDL assays are imperfect. Those gaps cut both ways: they limit Dave's reassurance and Peter's mechanistic certainty in any single blood draw. Better assays would help both men; they would not, by themselves, rewrite Mendelian and trial evidence favoring lower apoB.

EXAMPLES

• November 2015 panel: TC ~329
Dave's inflection point from curious low-carb eater to full-time lipid experimenter. From that lab printout came years of inversion diets, sterol panels, and public spreadsheets.

• Three-day fat load !' ~73% LDL-C drop
Inversion pattern central to his talks; Peter calls it interesting phenomenology, not outcome evidence. Directionality is clear in his logs even when exact assay ceilings (some LDL-P assays top out near 3,500) complicate extreme readings.

• Patient on 80 mg Lipitor still above particle goal
Peter's clinic reminder that max statin "` max apoB control for everyone. Add ezetimibe or PCSK9 inhibition when diet and statin leave residual particle risk.

• SFA ~25 g/day keto rescue attempt
Dayspring/Attia advice for a hyper-responder who refused to leave ketosis—diet composition as a lever inside the low-carb constraint. The case is an existence proof that composition changes can move LDL-P without abandoning low carb entirely.

• Quebec / stratified HDL-TG studies Dave cites
He wants bets settled by apoB-aware cohorts with high HDL and low triglycerides, not slogans. Peter would take the same

bet structure if apoB were measured and follow-up long enough—data he says still are not in.

OTHER RELEVANT

- **Keep apoB/LDL-P on the table even if you love low-carb.**
  Peter's closing posture: phenotype pride does not replace particle burden when lifetime risk is the question. High HDL and low triglycerides are good signs for insulin sensitivity; they are not a force field against apoB.
- **Use imaging as additional data, not a permission slip.**
  CAC/CIMT can inform urgency, but a zero CAC at 40 does not prove a 3,000 nmol/L LDL-P pattern is safe forever. Repeat imaging and lipids on a schedule; do not interpret one reassuring scan as a lifetime waiver.
- **If you stay keto with extreme LDL-P, change the fat composition.**
  Cut saturated fat hard, emphasize monos, recheck particles—before arguing on Twitter that causality is canceled. Recheck advanced lipids after 4–8 weeks of the swap before declaring victory or defeat.
- **Separate curiosity from clinical null hypotheses.**
  Dave's experiments are worth watching; they have not, in Peter's view, earned a new default for patient care. For clinicians, that means continuing to treat elevated apoB seriously in lean low-carb patients until outcome evidence says otherwise.

#24 – Tom Dayspring, M.D., FACP, FNLA – Part V of V: Lp(a), inflammation, oxLDL, remnants, and more

Guest: Tom Dayspring
Date: 2020-01-01 · Duration: 1:29:47
URL: https://www.youtube.com/watch?v=ttQY5J98Iok

KEYPOINTS

• Lp(a) is an LDL-like particle carrying an extra protein, apo(a), and the name matters.
Dayspring insists on saying 'little a', because Lp(A) with a capital A would point to apoA-I, the main protein on HDL. Lp(a) is an apoB particle with apolipoprotein(a) attached, and he calls it potentially highly atherogenic. He reminds listeners that it was covered in depth in an earlier episode and gives only a two-minute recap here.

• Measuring Lp(a) by mass is crude, and particle number is better.
Most labs report Lp(a) mass, the weight of the whole particle including cholesterol, triglycerides, phospholipids and proteins. Because the molecular weight of apo(a) varies so much between people, Dayspring calls mass a nearly useless metric unless it is very high. A particle count requires separating lipoproteins by electrophoresis and staining the Lp(a) band for apoB, which gives 'Lp(a)-P'. He stresses that this is not an NMR test, and discloses that he works for True Health Diagnostics, which owns the assay.

• Statins don't lower Lp(a), probably because apo(a) hides the receptor binding site.
Dayspring thinks LDL receptors are the main way Lp(a) is cleared. Statins increase LDL receptors, but those receptors grab ordinary LDL first, and apo(a) may hide the part of apoB that the receptor binds to. He also notes that Lp(a) levels are driven mainly by how much apo(a) the liver makes, not by clearance. So the real fix is blocking its production.

• Niacin and PCSK9 inhibitors lower Lp(a), but there is no outcome proof yet.
Niacin lowers Lp(a) by about 20%, and PCSK9 inhibitors lower it to varying degrees, but insurers won't cover a PCSK9 inhibitor for Lp(a). Any benefit could be credited to lowering LDL and remnants instead. Dayspring doesn't use niacin for this, though he notes Sam Tsimikas does. The decisive test will be an antisense drug from Ionis that blocks apo(a) production, then in phase 3 in high-Lp(a) patients who already had heart disease.

• Inflammation is 'necessary but not sufficient' for heart disease.
The anti-IL-1 drug showed fewer events but costs about $30,000 and slightly raised cancer risk, so Dayspring doubts it will ever be approved for routine prevention. Low-dose methotrexate and colchicine trials were still awaiting results. Attia argues that these drugs make sense only for patients whose problem is actually inflammation. Someone with low CRP and fibrinogen whose issue is high LDL particle number wouldn't benefit.

• The 'oxidized LDL' blood test measures something other than what its name suggests.
Truly oxidized LDL, the kind macrophages take in to become foam cells, forms inside the artery wall, not in plasma, which is full of antioxidants. The blood test detects aldehydes on apoB, a sign of 'minimally oxidized' particles, usually about 5% of the total. Dayspring uses it, myeloperoxidase (MPO), or preferably urinary F2-isoprostanes to flag a pro-oxidative state and to motivate changes in diet.

• Dayspring advises against relying on Lp-PLA2.
The FDA cleared it only for screening in primary prevention. Mendelian randomization shows its levels don't track outcomes, and two large trials that sharply suppressed Lp-PLA2 reduced no events. Attia and Dayspring have both largely stopped using MPO. Attia still finds Lp-PLA2 somewhat informative when Lp(a) is also high, and Dayspring explains why that pairing might matter inside the artery wall.

• ADMA and SDMA may give a window into endothelial function.
Both are byproducts of protein breakdown that reduce arginine available for making nitric oxide, so high levels suggest endothelial dysfunction. Dayspring notes that high homocysteine slows ADMA clearance, a plausible mechanism for homocysteine's link to heart disease. He would use these markers to push a borderline primary-prevention patient toward aggressive diet changes, or to justify more apoB lowering in someone already on maximal therapy.

• Remnants matter, but LDL particles still deliver most of the cholesterol.
VLDL particles are two to three times larger and carry more cholesterol each. LDL particles vastly outnumber them, though, so most cholesterol entering the artery wall is still LDL-delivered, 'a thousand guys versus one', as Dayspring puts it. Estimates of VLDL cholesterol, from triglycerides divided by five or non-HDL minus LDL cholesterol, often disagree and don't identify true remnants. All approved apoB-lowering drugs clear remnants too.

EXAMPLES

• An Lp(a)-heavy patient on a statin
One man had an LDL particle number of about 1,600 nmol/L, about 600 of which were Lp(a) particles. A statin only acts on the roughly 1,000 non-Lp(a) particles, so total particle number may fall less than expected.

• Earl, Dayspring's best friend
His high school friend in Paterson, New Jersey, took him to his first hockey game and became a firefighter. Despite high cholesterol and repeated invitations to come in for free care, Earl avoided doctors. He died of a sudden heart attack in his mid-50s while watching TV, and Dayspring calls it a needless death.

• Prescription EPA and omega-3 delivery forms
Dayspring says omega-3s lower apoB by about another 8–10%. He was expecting positive results from a prescription EPA trial on top of statins due that November. He points out that most supplements are esterified forms that need pancreatic enzymes to be absorbed, and that krill oil phospholipids carry only one omega-3 per molecule.

• JP and first principles
Attia recalls an engineering student who taught him to derive formulas rather than memorize them. Attia wrote only F = ma on his exam cheat sheet. He contrasts this with biology, where, as a physicist-turned-biologist once lamented, you keep getting out

of the bath to look up one more fact.

OTHER RELEVANT

- **Test red-blood-cell omega-3s, not plasma levels.**
  An RBC omega-3 index reflects about 60–90 days, much like A1c, while plasma levels reflect your last meal. Dayspring says Bill Harris might aim for about 14%. He says he has seen no data showing harm at high levels and doesn't know of omega-3s causing clotting problems, though he notes this would have to be tested.
- **Use oxidation markers to guide diet changes, not to justify drugs.**
  Since lowering apoB itself reduces inflammation, Dayspring treats oxidative markers mainly as a reason to push diet: carbohydrate restriction for insulin resistance, and fasting. Very high-risk patients, such as someone just out of bypass surgery, need both diet and medication from day one.
- **Don't put off checking your lipids.**
  Dayspring's point from Earl's story is that heart disease is the most delayable of the major killers. Many early deaths come from people never getting checked or being judged on the wrong metrics.

#23–Tom Dayspring Part IV of V: statins, Zetia, PCSK9 inhibitors, niacin, cholesterol & the brain

Guest: Tom Dayspring
Date: 2020-01-01 · Duration: 2:00:15
URL: https://www.youtube.com/watch?v=xJ6X81Gn83Y

KEYPOINTS

• Early cholesterol drugs proved that lowering cholesterol reduces events, and then the field fixated on cholesterol numbers.

Before statins there was immediate-release niacin, which most people couldn't tolerate, and an antibiotic that disrupted cholesterol recirculation through bile. Then came bile acid sequestrants, whose long outcome trial showed modest benefit. Dayspring calls the result a tragedy: for 20–30 years drug companies chased cholesterol numbers, including sequestrants' trivial one- or two-point rises in HDL cholesterol.

• Statins began with a fungus and were proven in patients with familial hypercholesterolemia.

Dayspring credits Japanese mycologist Akira Endo, who he says deserves a Nobel Prize. Lovastatin was approved in 1987. The first outcome trials enrolled people with LDL cholesterol around 180–190, likely familial hypercholesterolemia: Swedish heart-attack survivors on simvastatin, then Scottish men without prior events on pravastatin in the West of Scotland trial. Both cut events by about 25%, with Dayspring recalling a number needed to treat of roughly 40–50 for West of Scotland.

• Five-year trials underestimate a disease that develops over 50 years.

Attia credits Allan Sniderman for teaching him that lipid trials give a drug about five years to change the course of a disease that began at birth. Because statins work, it is now unethical to withhold them from high-risk patients. New drugs therefore get tested on top of statins, which, as both point out, raises the bar for showing benefit.

• Ezetimibe works in both the gut and the liver.

Dayspring explains that NPC1L1, the transporter ezetimibe blocks, sits on intestinal cells and on the liver's bile-facing surface, where the liver can reclaim cholesterol from bile. Blocking both drains liver cholesterol and switches on LDL receptor production through SREBP. Attia admits this weakens his habit of reserving ezetimibe for people who over-absorb cholesterol, though Dayspring says plant-sterol over-absorption still matters.

• Ezetimibe was hurt by trials that measured the wrong thing.

Dayspring says early imaging studies measured artery wall thickness (carotid IMT), which in his view was the wrong surrogate, and ignored the extra reductions in apoB, triglycerides and CRP. That led cardiologists to write the drug off. He also points to aortic stenosis trials that could test ezetimibe without a statin.

• PCSK9 inhibitors cut events even in patients who were already low.

Attia calls the FOURIER trial one of the most remarkable results in cardiovascular medicine. Patients on statins with an average LDL cholesterol of 92 mg/dL, around the 10th percentile of the Framingham population, still had fewer events with Repatha within about 2.2 years. Amgen's stock was hammered because the cost per life saved looked like $1 million or more. Attia stresses that this is a separate question from the science.

• Gemfibrozil has outcome data on its own, and its benefit tracked particle numbers.

The VA-HIT trial in veterans with heart disease, low HDL cholesterol and roughly normal LDL showed event reductions as large as any statin trial, despite only about a 1.5-point rise in HDL cholesterol. Dayspring says James Otvos's post hoc NMR analysis explained the benefit by lower LDL particle counts and higher HDL particle counts. Fenofibrate trials missed their primary endpoints, which he blames partly on many participants also taking statins.

• Dayspring regards niacin as having failed every rigorous test.

In the 1960s Coronary Drug Project, niacin did not improve its primary endpoint, mortality, and trended the wrong way. Other arms of that trial gave men estrogen, which triggered heart attacks, and thyroid hormone, which killed people. A follow-up a decade or more later claiming a mortality benefit is, he says, a post hoc analysis that 'would be laughed at' today. Later trials also failed, and insurers stopped paying.

• Statins and brain cholesterol: a subset of patients may be at risk.

The brain makes all its own cholesterol, mainly through the desmosterol pathway. Dayspring says blood desmosterol tracks spinal-fluid levels closely, and statins are the leading cause of suppressed desmosterol. Both stress that population data do not show statins causing dementia. Attia's concern is patients with unmeasurably low desmosterol, such as someone with LDL cholesterol of 40 and LDL particle number of 500.

EXAMPLES

• Statins and the blood-brain barrier

Lipophilic statins such as atorvastatin and simvastatin enter the brain more easily. Hydrophilic, liver-selective statins such as pravastatin and rosuvastatin need no transporters to enter the liver and have fewer drug interactions. Dayspring notes 5 mg of rosuvastatin is often enough, and pravastatin at 40–80 mg matched the roughly 25% event reduction in outcome trials.

• Fibrate drug interactions

Gemfibrozil raises statin levels and increases the risk of muscle inflammation and breakdown (myositis and rhabdomyolysis), which Dayspring says isn't seen with fenofibrate. Fenofibrate strengthens warfarin, so the warfarin dose has to come down. He prefers fenofibrate and notes it has evidence for small-vessel benefits.

• A $3,000 niacin bill

Attia had a patient billed about $3,000 for prescription extended-release niacin. Dayspring adds that cheap sustained-release niacin is the form with the most liver toxicity.

• Liver enzymes rising on ezetimibe

Attia has seen it at least four times: adding ezetimibe to a statin doubled transaminases, which returned to normal when it was stopped. Dayspring says no package insert calls for monitoring liver enzymes and the rise is inconsequential, but agrees the

decision is individual.

OTHER RELEVANT

- **Don't stop a statin because of creatine kinase (CK) levels alone.**
  Get a baseline first, since exercise and ethnicity can raise CK. Dayspring says stop for muscle aches or weakness, such as trouble getting out of a chair, not for a rise from 50 to 300. Attia still tends to switch to pravastatin if CK rises even without symptoms.
- **Make apoB or LDL particle number the target.**
  Dayspring would use whatever combination lowers apoB, for example a low-dose statin plus ezetimibe if sterol markers suggest over-absorption. He would rather do that than push one drug to its maximum dose.
- **Check whether you convert EPA to DHA.**
  Dayspring says DHA has the stronger effect on apoC-III and triglycerides, while EPA does more for apoB. He measures omega-3 levels, because some people on high-dose EPA don't make enough DHA.
- **Be wary of diets that send apoB soaring.**
  Dayspring warns that diets that raise LDL particle number sharply may be fine for two years. He questions keeping that up for 15 years in a young person, given that genetic and trial data consistently show apoB matters.

#07 – Deep Dive: Lp(a) — what every doctor, and the 10-20% of the population at risk, needs to know

Guest: Peter Attia (deep dive)
Date: 2019-12-22 · Duration: 1:16:16
URL: https://www.youtube.com/watch?v=OHQiU68Ad7s

KEYPOINTS

• Lp(a) is an LDL particle with apo(a) bonded to it

In this solo episode, with Bob Kaplan asking the questions, Attia describes Lp(a) as a garden-variety LDL particle of about 20 nm whose apoB-100 is covalently linked, through a strong disulfide bond, to an extra protein, apo(a). Which LDLs carry apo(a) is mostly genetically determined, inherited codominantly. Attia estimates somewhere between one in five and one in 10 people have elevated levels, and calls the distribution long-tailed to the right.

• Apo(a) resembles the clotting protein plasminogen

Plasminogen has five 'kringle' folding domains. Apo(a) lacks kringles 1–3 but has the same kringle 5 and a kringle 4 with 10 subtypes. Kringle 4 type 2 varies most between people, from a couple of copies to about 40. That repeat count largely sets the particle's mass, which is why Attia spends time on what he admits is a very technical detail.

• Particle number beats Lp(a) mass

Attia estimates 19 out of 20 Lp(a) tests measure mass, which counts the whole structure. Two people with the same mass can differ in risk: the one with shorter kringle 4 type 2 repeats has more particles and higher risk. A very low mass, under 5 mg/dL, makes a high particle count unlikely. He finds the Lp(a)-cholesterol test unhelpful and prefers particle number in nmol/L.

• Attia's thresholds and reference ranges

For particle number he likes under 50 nmol/L, sees 50–100 as a grey zone, and worries above 100, certainly above 125. The highest he has seen is about 650–700, and a few patients sit at 400–500. Mass-based cut-offs vary: US labs call under 30 mg/dL normal, the European Atherosclerosis Society under 50. He believes the UK and Germany cover apheresis above 60.

• High Lp(a) may once have been an advantage

Attia speculates on two evolutionary benefits. Because of its similarity to plasminogen, Lp(a) promotes clotting, which helps in trauma or childbirth bleeding. It may also scavenge oxidised phospholipids and carry them back to the liver. In today's more inflammatory setting, with hypertension and high insulin, some particles get stuck in the artery wall and bring their oxidised cargo with them.

• Three harms: atherosclerosis, aortic stenosis and blood clots

Attia believes about two-thirds of aortic stenosis cases are explained by elevated Lp(a). The particle seems drawn to the high-pressure aortic valve, where it triggers bone-forming proteins and calcification. He puts the hazard ratio for aortic stenosis at about 2–4, median around 2.5, and for venous thromboembolism at about 3. He stresses that tripling a 1% risk means 3% absolute risk, not cause for panic.

• Statins don't lower Lp(a), but are still used

Statins work mainly by switching on SREBP-2, which adds LDL receptors to the liver, but SREBP-2 also raises PCSK9, which breaks those receptors down. Tom Dayspring's explanation, as Attia relays it, is that Lp(a) is cleared 'last in line', after LDL and VLDL, so it never gets its turn. On statins alone, Lp(a) changes not at all or even rises. Attia is clear that people with high Lp(a) probably should take a statin, but to control apoB, not Lp(a).

• PCSK9 inhibitors lower Lp(a), especially combined with a statin

By blocking PCSK9, these drugs protect LDL receptors and the other receptors, such as LRP, that clear Lp(a), and combined with a statin they lower Lp(a). Attia notes they are not FDA approved for that purpose. Niacin lowers Lp(a) by about a third, but whether it saves lives is contested. He thinks the trial that sank niacin was poorly designed, and says lipidologists are split roughly evenly on using it.

• Lifestyle barely moves Lp(a)

Lp(a) levels are decided mainly by how much the liver makes, with clearance a secondary factor. LDL particle number, by contrast, depends on triglycerides, cholesterol synthesis, absorption and receptors, and diet can change all of them. That is why diet works on LDL particle number but not Lp(a).

• Antisense drugs are the first therapies designed for Lp(a)

Antisense oligonucleotides block the liver's production of apo(a), cutting levels by about 70% to as much as 99% in early data. Attia says that could normalise someone at 200. They had completed phase 1 and 2 trials and were slowly enrolling phase 3. He jokes that three years earlier he predicted results in five years and still says five. He is wary of wiping something out entirely, but says only such a trial can prove causation.

EXAMPLES

• Bob Harper's heart attack

The Biggest Loser trainer had a heart attack at a gym at 52 despite clean annual checkups. A news story reported he had perilously high Lp(a), apparently never measured before. Attia notes that Anahad O'Connor, the journalist who wrote it, is a friend whose interest he sparked. Many patients sent him the article.

• A keto patient's LDL particle number fell from over 3,500 to 1,200

A young patient refused to give up a ketogenic diet, so Attia cut his saturated fat from 75 to 25 grams a day, using olives, olive oil, macadamia nuts and guacamole. In about eight weeks his LDL particle number fell from over 3,500 to about 1,200. In all but one of roughly a dozen similar cases, swapping saturated for monounsaturated fat fixed the problem while fat stayed high. Attia calls this suggestive, not proof.

• Attia gave up blanket baby aspirin

He used to put everyone with elevated Lp(a) on baby aspirin. He now thinks that was oversimplified, since only a subset seem to benefit. He takes DVT prevention seriously instead, such as discussing options for long flights with selected patients.

- **Estrogen therapy may lower Lp(a) by up to 50%**

  Kaplan cites an UpToDate summary saying estrogen replacement reduces Lp(a) by up to 50%, an effect blunted somewhat by progesterone. The same source says hormone therapy isn't recommended for reducing heart risk. Attia finds it 'a bit too good to be true' and plans to look at levels in his patients who have gone through menopause.

- **Apheresis as a last resort**

  Apheresis filters Lp(a) out through a large IV, but because the particles' half-life is only days, patients may need it twice a week. Attia says he very rarely uses it now that PCSK9 inhibitors exist.

OTHER RELEVANT

- **Test Lp(a) at least once**

  Because it is genetic and rarely checked, a particle-number test can reveal risk that a standard lipid panel misses.

- **If it's high, screen the aortic valve**

  Attia orders at least an echocardiogram, and preferably cardiac MRI, even in patients in their 30s. BNP or NT-proBNP can flag strain on the heart.

- **Lower apoB aggressively**

  Since Lp(a) itself is hard to change, Attia controls everything else: apoB with statins and PCSK9 inhibitors, plus other drivers such as blood pressure and insulin.