Review Article

Lipid Conundrum: Residual Risk - The "Atherosis" of Lipid Management

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ABSTRACT

Since 1980s, following the discovery of the low-density lipoprotein receptor, and the development of lipid lowering pharmacological agents, the risk of cardiovascular morbidity and mortality improved in leaps and bound especially in the developed world despite limited implementation of guidelines for management of atherosclerotic cardiovascular diseases. Yet cardiovascular disease risk and mortality remains the number one cause globally. This review teases the reason of this residual risk viz; Lp(a), triglyceride rich lipoproteins, high-density lipoprotein, thrombotic prevalence, and inflammation and the evidence in literature to address the possibility of reducing this residual risk and suggest some patient profiles that could be targeted for a possible benefit without resolving to expensive investigations or genetic evaluation for primary and secondary preventive strategies.

Keywords: High-density lipoproteins, Inflammation, Residual risk, Lp(a), Thrombosis, Triglyceride, Triglyceride rich lipoproteins.

INTRODUCTION

In the new age of technology and computer security "residual risk" is considered as the potential for the occurrence of an adverse event after adjusting for the impact of all in-place safeguards.[1] It is considered a part of "total risk" and for general security purposes is an "acceptable risk". Minimum level of protection that allows full functioning of the technology "ad Infinitum" till a "hack" or "insurgence" proves otherwise is acceptable. Translate that to the human body focusing only on the lipids and lipoproteins only as a start is not acceptable.

Epidemiologically, residual cardiovascular risk (CV) could be considered as the risk of incident vascular events or progression of vascular damage persisting despite treatment with evidence based therapeutic interventions for reduction of the inherent risk (including those with overlapping factors of risks) in an individual. Much of this reduction is based on reduction in low-density lipoprotein cholesterol (LDL-C) since the 1980s (Figures 1 and 2) with the discovery of the LDL receptor and the invention and therapeutic development of HMG-CoA reductase inhibitors and later PCSK-9 receptor blockers.[2]

Despite the "robust" influence of LDL reduction and preventive guidelines for management of LDL dyslipidemia in varied population, debate continued on the residual risk conferred due to low high-density lipoprotein-cholesterol (HDL-C) or high triglycerides (TGs). A meta-analysis of 53 fibrates (16,802 subjects) and 30 niacin trials (4,749 subjects) revealed an average HDL-C increase of 10% with fibrates and 16% with niacin, a triglyceride decrease of 36% with fibrates and 20% with niacin, and a LDL-C decrease of 8% with fibrates and 14% with niacin.[3] These lipid changes resulted in similar overall reductions in major coronary events evidenced by a 25% decrease with fibrates and 27% with niacin.[3] However, analyses of the primary and secondary prevention trials like JUPITER, TNT and PROVE-IT TIMI 22 suggest that HDL-C was useful in the initial risk assessment but when LDL-C was aggressively lowered, predictive value of HDL-C for estimated residual risk was attenuated.[3] Furthermore, an adequately treated high blood pressure and high glucose is associated with a sizeable reduction of cardiovascular risk and so residual cardiovascular risk should be better studied in cardiovascular epidemiology; requiring repeated measures and cohortal follow-up.[3]

Given the above, the questions that come to mind are (a) Is there "residual risk" especially in high-risk populations who have adequate treatment and have LDL-C of <70 mg/dL? (b) Is there an "atherogenic lipid profile"? (c) What are the situations for considering residual CV risk factor

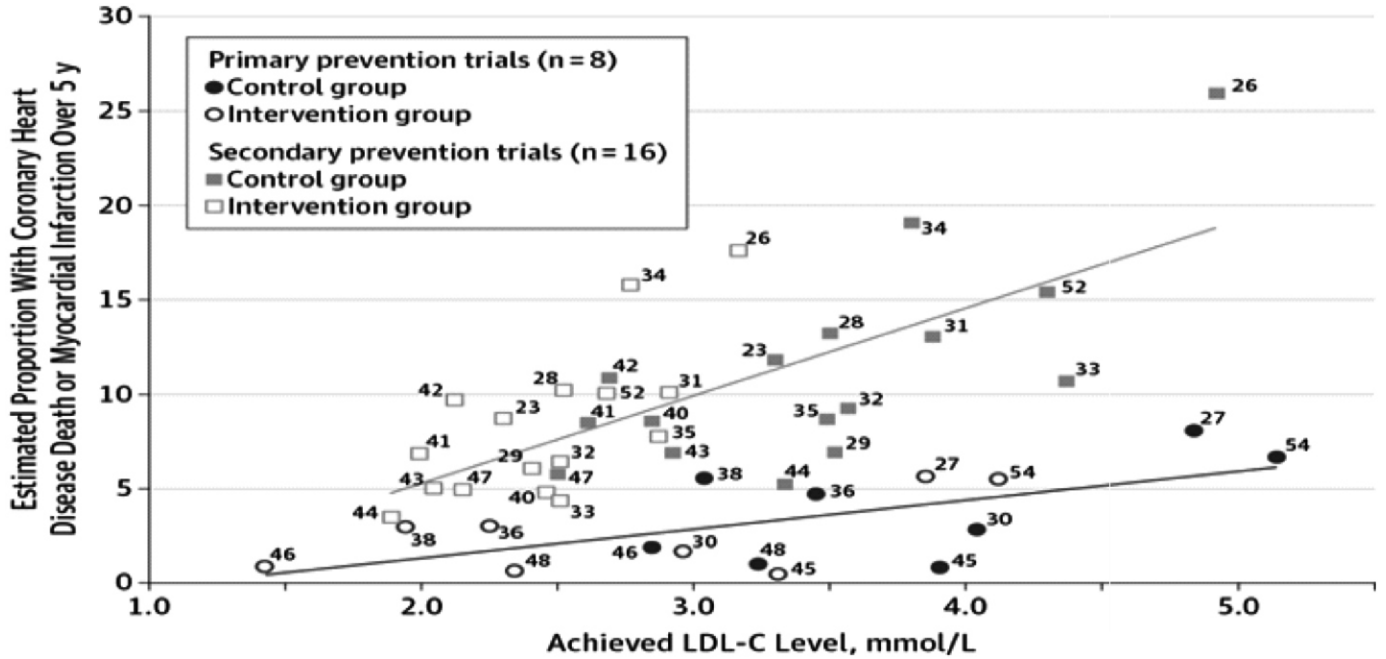

Figure 1: Association between achieved low-density lipoprotein cholesterol (LDL-C) and major coronary event rates from 24 trials of established interventions that lower LDL-C predominantly through upregulation of LDL receptor expression.[2]

***Source**: Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM et al. Association between lowering LDL-C and cardiovascular risk reduction Among different therapeutic interventions: A Systematic Review and Meta-analysis. JAMA. 2016;316(12):12891297. doi:10.1001/ jama. 2016.13985*

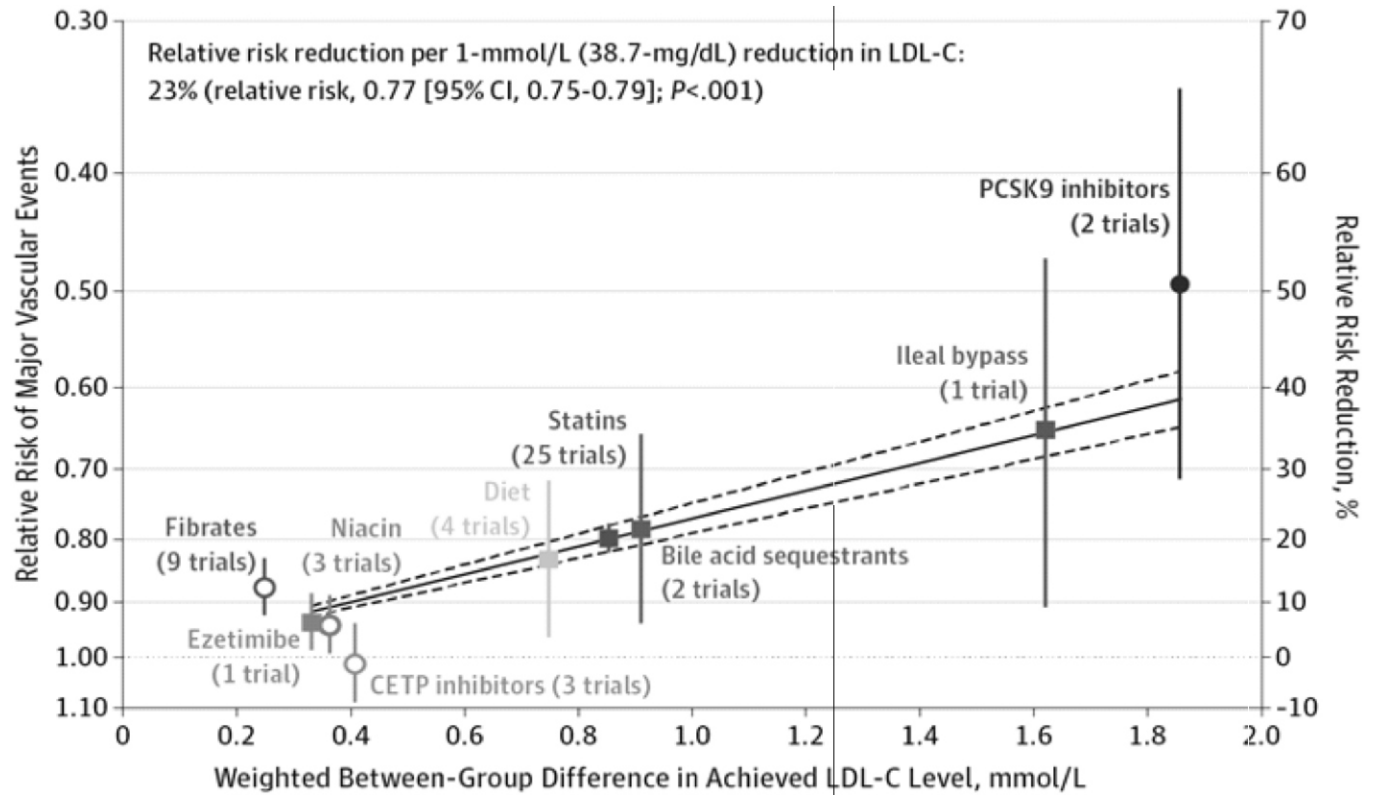

Figure 2: Weighted between-group difference in achieved low-density lipoprotein cholesterol (LDL-C) level and relative risk for major vascular events for each class of intervention.[2]

***Source:** Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A Systematic Review and Meta-analysis. JAMA. 2016;316(12):12891297. doi:10.1001/jama. 2016.13985.*

intervention after achieving LDL-C targets?

Is there "residual risk" especially in high-risk populations who have adequate treatment and have LDL-C of <70 mg/dL?

Unprecedented advances in treatment of atherosclerotic cardiovascular disease (ASCVD) have certainly increased the longevity by preventing major adverse cardiovascular event (MACE); but globally CV disease (CVD) remains leading cause of death, taking 17.9 million lives each year, one third of these deaths occur prematurely under 70 years of age and three quarters of these occur in low-and middle-income countries.[4]

Researchers assessed 3012 Framingham participants[5] (mean age 58±4 years; 55% women) free of CVD and categorized in 5 groups based on lipid lowering treatment (LLT) levels: (1) LDL-C <100 mg/dL without LLT; (2) LDL-C ≥100 mg/dL to <130 mg/dL without LLT; (3) LDL-C <130 mg/dL on LLT; (4) LDL-C ≥130 mg/dL without LLT; and (5) LDL-C ≥130 mg/dL on LLT. Individuals in groups 3 and 5 had significantly more carotid atherosclerosis compared with group 1 despite being on treatment (LLT); during follow-up (median, 13.7 years) 548 CVD events occurred. Individuals on LLT (groups 3 and 5) had substantial residual CVD risk (26.7 (95% CI 19.5 to 34.0) and 24.1 (95% CI 16.2 to 31.9) per 1000 person-years, respectively), representing approximately three times the risk for untreated individuals with LDL <100 mg/dL (group 1: 9.0 (95% CI 6.8 to 11.3) per 1000 person-years). Absolute CVD risks rose with age and were slightly greater in men than in women. After adjust-ment for traditional risk factors, groups 3 and 5 displayed increased hazards for CVD (HR = 1.47, 1.42 and 1.54, respectively) compared with group 1. Further adjustment for carotid atherosclerosis modestly attenuated these results. The authors concluded that there is "substantial residual CVD risk in individuals on LLT, compared with participants with optimal LDL-C (<100 mg/dL)." Though the LDL-C levels were optimal for the sample population free from CVD (the real world where three quarters of deaths due to CVD occur), it could be argued that residual risk may have existential presence as an inherent risk at least in the lower and middle-income countries. In contrast, between 1973-2013, in 12 middle and high income countries (Australia, Belgium, China, Czech Republic, Finland, Germany, Italy, Japan, Norway, South Korea, the UK, and the USA), a pooled analysis[8] of 267 studies with 2.3 million participants revealed that mean total and non-HDL cholesterol levels decreased in high-income western countries, whereas they increased from low levels in China and Japan. By contrast, mean HDL cholesterol declined by about 0.05-0.1 mmol/L per decade in Germany and Norway, with stagnation or possible increases in mean total to HDL cholesterol ratio despite declines in both mean total and non-HDL cholesterol. In an extended analysis by the NCD RisC[9] reported that the Global age-standardized mean total

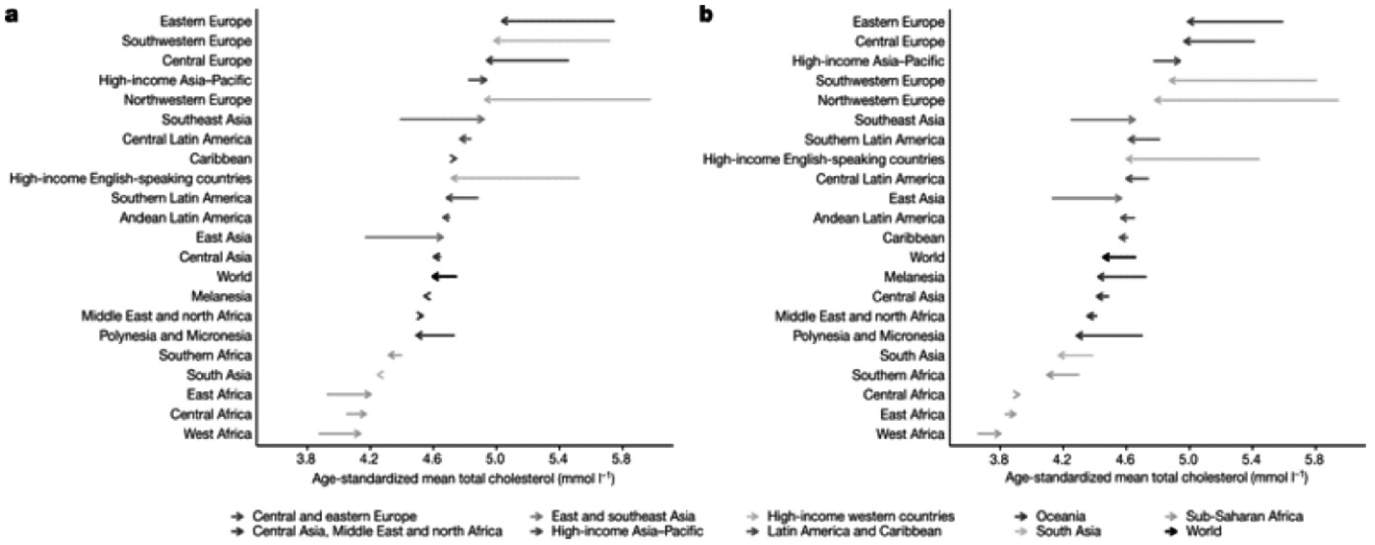

Figure 3: Change in age-standardized mean total cholesterol between 1980 and 2018 by region for women and men.[9] a, Age-standardized mean total cholesterol in women. b, Age-standardized mean total cholesterol in men. The start of the arrow shows the level in 1980 and the head indicates the level in 2018. Mean HDL cholesterol. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

Source: *NCD Risk Factor Collaboration (NCD-RisC). Repositioning of the global epicenter of non-optimal cholesterol. Nature 582, 7377 (2020). https://doi.org/10.1038/s41586-020-2338-1*

cholesterol changed little over these nearly four decades, (Figure 3). Regionally, total cholesterol decreased the most in high-income western regions and in central and eastern Europe. The decrease was the largest (around 0.3 mmol l^{-1} per decade) in northwestern Europe, where mean total cholesterol levels had been the highest in 1980. Mean total cholesterol changed little in most of the other regions, with the notable exception of east and southeast Asia, where it increased by more than 0.1 mmol l^{-1} per decade in both women and men. The increase in east and southeast Asia was largely due to an increase in non-HDL cholesterol.

Furthermore, the decrease in total cholesterol in high-income western regions and central and eastern Europe was largely due to a decline in non-HDL cholesterol and yet the deaths due to CVD remains the primouno cause of mortality. Thus, it may be pragmatic to speculate that residual risk exists in middle and high income countries despite adequate control or no change in non-HDL-C and co-exists in low to middle income countries as a part of inherent risk for CVD and its mortality. This pragma is further supported by recent study[10] suggesting the high levels of triglyceride molecules in LDL-C are linked to an increased risk of ASCVD. The study[10] enrolled 68,290 patients from the Copenhagen General Population study; 38,081 were assigned to direct automated assay to measure their LDL triglycerides and 30,208 had nuclear magnetic resonance (NMR) spectroscopy. Median follow-up was 3 and 9.2 years for the respective cohorts. In the automated assay group, each 0.1 mmol/L (9 mg/dL)higher direct LDL triglycerides carried a 22%-38% higher risk for the following outcomes: ASCVD (hazard ratio, 1.26; 95% confidence interval, 1.17-1.35). In the group that had NMR spectroscopy to measure LDL triglycerides, risks were similar, ranging from HRs of 1.13 (95% CI, 1.05-1.23) for ischemic stroke to 1.41 (95% CI, 1.31-1.52) for myocardial infarction. The investigators noted that apoprotein B levels didn't entirely explain these results. The principal investigator stated that the purpose of the study was to disprove the hypothesis that LDL triglyceride was not related to ASCVD, but the study ended up confirming it.

Is there an atherogenic lipid profile?

A panel of experts in Europe simplified the nomenclature and defined[11] the presence of atherogenic dyslipidemia (AD) as high fasting TG levels of ≥2.3 mmol/L (≥200 mg/d/L) and low HDL-c levels of ≤1.0 and ≤1.3 mmol/L (≤40 mg/dL; ≤ 50 mg/dL) in males and females, respectively in high-risk patients on maximally tolerated statin therapy. It is expected that the LDL-C levels are normal or moderately increased in AD, and the LDL particles are typically smaller and denser. Insulin resistance is consi-

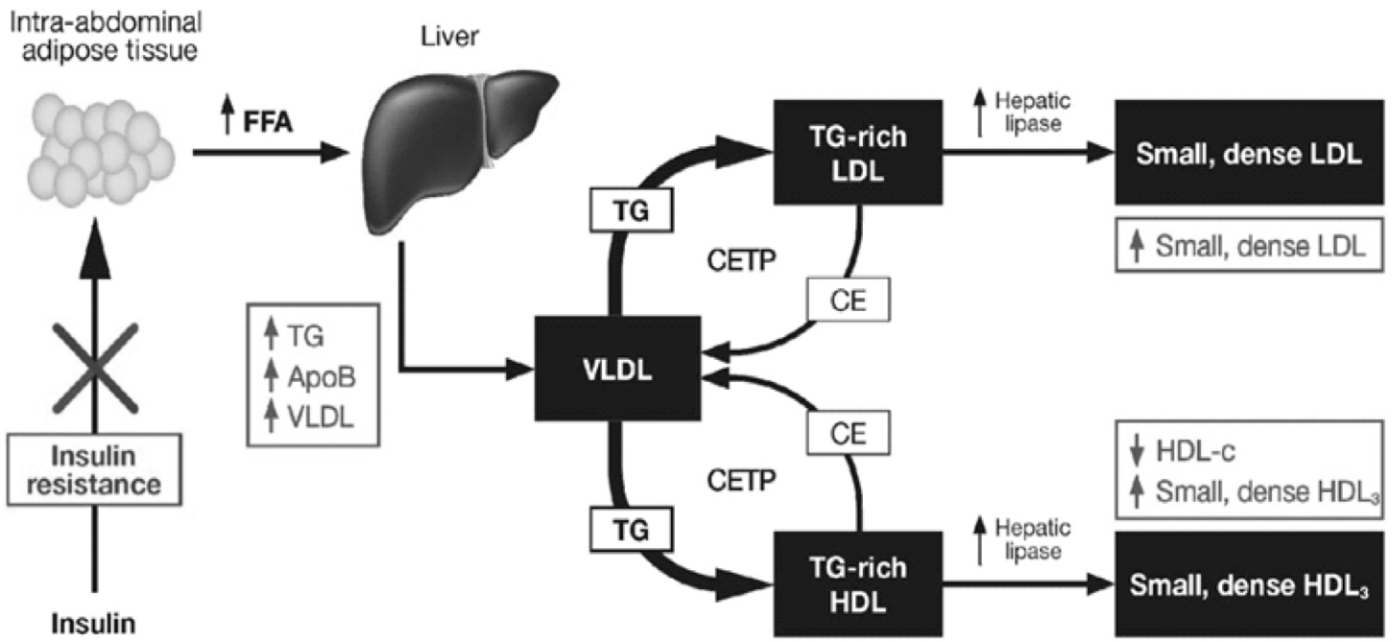

Figure 4: Pathophysiology of atherogenic dyslipidemia.

Source: *Roberto Ferrari, Carlos Aguiar, Eduardo Alegria, Riccardo C. Bonadonna, Francesco Cosentino et al, Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia, European Heart Journal Supplements, Volume 18, Issue suppl_C, April 2016,* https://doi.org/10.1093/eurheartj/suw009

dered to be the pathophysiologic domino effect of development of AD (Figure 4). In adipose tissue[12], insulin resistance leads to impaired inhibition of TG hydrolysis and release of an increased amount of FFA, resulting in an increased production of TG and VLDL particles by the liver. CETP transfers TG from TG-rich VLDL to LDL (the resulting TG-rich LDL particles can undergo hydrolysis by hepatic lipase and lead to small, dense LDL particles) and HDL (with the hydrolysis of TG-rich HDL leading to lower levels of HDL cholesterol, increased proportion of small, dense HDL[13] and increased release of free Apo A-I). Apo, apolipoprotein; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; VLDL, very low density lipoprotein.

Though it is uncertain whether pharmacological reduction of very low density lipoproteins (VLDLs) and their triglyceride/cholesterol component could reduce the residual risk of ASCVD; evidence from 9423 participants in the JUPITER trial when compared between those on statins vs placebo; demonstrated dose response reduction of ASCVD risk[14] for greater reductions in LDL-C, VLDL cholesterol mass and small VLDL lipoprotein concentration; the latter two remained significant after incremental adjustment of LDL-c ($p \leq 0.006$). Conversely, greater reductions of TGs or large/medium VLDL lipoprotein particles had no additional risk reduction.

It thus, is prudent to postulate that there is mechanistic evidence of AD due to its biological plausibility of insulin resistance and despite adequate treatment for LDL-C additional benefit is possible by control of this residual risk in subjects with AD in specific population demography and ethnicities.

Given that, what are the additional risk factors that justify this residual risk despite achieving LDL-C targets?

Residual Risk - Inflammation (hsCRP, Lp-PLA2, IL-1β, and others)

Consistent anti-inflammatory properties of statins is a pleiotropic effect of statins. In Jupiter trial, 20 mg Rosuvastatin daily reduced mean high-sensitive C-reactive protein (hsCRP) by 37% when compared to placebo[15] and the magnitude of reduction of hsCRP was proportional to the reduction of CV risk (55% reduction; $p = 0.007$, in subjects achieving < 2 mg/L hsCRP than those with hsCRP ≥ 2 mg/l); which was also documented in the PROVE-IT TIMI22 trial.[16] The direct causal association of inflammation was demonstrated in CANTOS trial[17], where 10061 subjects with history of myocardial infarction (MI), optimized LDL-C and hsCRP ≥ 2 mg/dL were randomized to OMT+P (optimized medical therapy + placebo) vs OMT + Canakimumab (a human monoclonal antibody targeted to interleukin 1 β). Lowering of hsCRP to levels <2 mg/L lead to a 25% reduction in major adverse cardiovascular events (MACE) and a 31% reduction in cardiovascular death and all-cause mortality, and a reduction in cancer mortality with high dose (300 mg) Canakinumab, without any effect on LDL-C. Neutropenia and death due to sepsis were more common in the treatment arm than placebo (incidence rate 0.31 vs. 0.18 events per 100 person-years; $p = 0.02$) and the FDA did not grant Canakinumab an indication for cardiovascular risk reduction. Other studies are summarized in the table 1 below.

One biomarker of inflammation, lipoprotein-associated phospholipase A2 (Lp-PLA2), has demonstrated that an increase in Lp-PLA2 was associated with increased risk of adverse cardiovascular outcomes[21,22] in observational studies. However, when Darapladib (a potent inhibitor of Lp-PLA2), was tested in a randomized controlled trial of subjects with stable coronary heart disease, there was no benefit seen in cardiovascular outcomes.[23] Importantly, 96% of patients enrolled in the trial were on statins, which

Table 1: Clinical trials with unique anti-inflammatory medicines and CV risk

Study	n	Sample population	Baseline hsCRP	Comparison	Duration	Outcome
CIRT[18]	3000	History of MI or multivesse disease + T2 DM or metabolic syndrome	1.5 mg/L	OMT+ P vs OMT+ Methotrexate 15-20 mgs weekly	8 months	No effect on CV events or all-cause mortality
COL COT[19]	4745	30 days post MI	-	P vs Colchicine 0.5 mgs daily	22.6 months events	131 events v/s 170 (HR 0.77; 061-0.96); p=0.02 Death 43 v/s 44 in P

themselves are known to reduce LP-PLA2 by 35%.[24-26] This inhibition of Lp-PLA2 with associated reduction of inflammation and plaque stabilization may be one of the several mechanisms through which statins exert their benefit.

Recently, clonal hematopoiesis of indeterminate potential (CHIP) has emerged as a risk factor for ASCVD through inflammatory pathways.[20] CHIP is surprisingly common, occurring in up to 20% of septuagenarians, and though it rarely transforms to acute leukemia (occurring 0.51% per year in carriers), and confers a 40% increased risk of CVD[21] and thus has emerged as a novel cardiovascular risk factor. Intense investigation is underway to determine optimal approaches to recognition and management of this non-traditional ASCVD risk factor.[27]

Table 2: Effect on Lp(a) and other lipid variables and CV Risk

Study	Outcome
JUPITER[29]	Lp(a) was a strong predictor of residual risk in patients already on a statin (adjusted HR 1.27; 95% CI 1.01-1.59, $p = 0.04$), independent of LDL-C and other risk factors.
INTERHEART[30]	Lp(a) level >50 mg/dL was associated with an increased risk of MI (OR 1.48, 95% CI 1.32-1.67, $p < 0.001$).
FOURIER[31]	Evolocumab reduced Lp(a) levels by a median of 26.9%, which was moderately correlated with change in LDL-C. Subjects with above the median baseline Lp(a), Evolocumab demonstrated 23% reduction in the risk of CHD death, MI or urgent revascularization (compared to placebo), whilst a 7% reduction was observed in those with Lp(a) below the median.
ODYSSEY[32,33]	In a *post-hoc* analysis of phase 3 trials, Lp(a) reductions were not significantly associated with MACE reductions independently of LDL-C. In subjects with the highest baseline values of Lp(a) (?105 nmol/L), reductions of Lp(a) using alirocumab translated to significant reductions in risk beyond LDL-C lowering.
Others[34,35]	AKCEA apo(a)-LRx, an apo(a) antisense oligonucleotide, reduced Lp(a) up to 80%. A monoclonal antibody targeting oxidized phospholipids (of which Lp(a) represents the major plasma carrier) demonstrated promising in vitro data. CV outcomes of these are awaited.
TLR[36-39]	Studies have indicated and epidemiological evidence exists that triglyceride rich lipoproteins (TLRs) are contributors or associated with ASCVD and a causal role was supported by Mendelian randomization studies. Remnant cholesterol (which is mostly TRL) calculated as total cholesterol minus HDL-C minus LDL-C, consistently demonstrates an association with cardiovascular disease and mortality.
TG[40-45]	Debate of role of TG reduction to improve CV outcomes continues due to inconsistent results. JELIS an open-label blinded study of supplementation with 1.8 g/day of EPA and a statin (pravastatin 10 mg or simvastatin 5 mg) vs. statin alone in a primary prevention Japanese population, demonstrated a statistically significant ($p = 0.01$) 19% reduction in major coronary events. In a sub-analysis of JELIS evaluating individuals with triglycerides >150 mg/dL and a HDL-C <40 mg/dL, EPA treatment led to a large reduction in incident coronary artery disease (HR 0.47; 95% CI 0.23-0.98; $p = 0.043$). The REDUCE-IT (Reduction of Cardiovascular Events With EPA-Intervention) trial enrolled patients with established ASCVD or diabetes with other risk factors and mild-moderate hypertriglyceridemia.77 All patients were on background statin therapy and had fasting triglyceride levels of 135 to 499 mg/dL and LDL-C levels of 41 to 100 mg/dL. Subjects were randomized to 4 grams of EPA daily or a mineral oil placebo. The intervention arm exhibited a 25% relative risk reduction in the primary composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina (17.2% in the EPA group vs. 22.0% in the placebo group; HR 0.75, 95% CI 0.68-0.83; $p < 0.001$). Interestingly, the large reduction in the primary end-point was accompanied with only a modest decrease in plasma triglyceride concentration (median 18.3%, 39 mg/dL).Additional mechanisms beyond TG reduction (e.g., antithrombotic, antiarrhythmic, antioxidant, anti-inflammatory, etc.) have been suggested as possible mechanisms as the reduction in ASCVD events was similar regardless of whether or not triglycerides were reduced to below 150 mg/dL.
HDL-C[46-58]	Framingham cohort, there was a graded decrease in risk for every 1 mg/dL increase in HDL-C concentration. Despite strong consistent epidemiological relationship between low HDL-C and ASCVD, raising HDL-C with Niacin or CETP inhibitors have failed to convincingly provide a favorable outcome on ASCVD. It could be because support of a causal relationship between low HDL-C and ASCVD in the Mendelian randomization studies is not supported. It could be that functional measures of HDL like cholesterol efflux capacity has demonstrated the ability to predict both prevalent and incident coronary artery disease At present, low HDL-C does serve to identify patients at risk for adverse events, though no pharmacological treatment (targeting HDL-C) has demonstrated efficacy reducing ASCVD.

Residual Risk Other Lipoproteins [Lp(a), TRL, HDL-C and TGs]

AHA/ACC guidelines recommend moderate to high intensity statin therapy in young subjects (40 -75 years age) with a 10-year ASCVD risk of 7.5% or more (up to 20%) and Lp(a) ≥100 nmol/L. For LDL ≥70 mg/dL or non-HDL ≥100 mg/dL and Lp (a) ≥100 nmol/L Ezetimibe and PCSK9 inhibitors for intensive lowering of LDL-C is recommended.[28] Clinical trials have generated some evidence though not convincing or showing independence from LDL-C to support robustly the guidelines (Table 2).

Recent evidence on ASCVD risk reduction in subjects with T2DM with GLP-1RA agonists and SGLT-2[59-66] inhibitors is generating immense interest and curiosity in diabetes care and ASCVD care. Though the jury is still out and except evidence for SGLT2 inhibitors in heart failure; details review and discussion on this beyond the scope of the residual risk focus of this script.

Residual Risk Thrombosis

COMPASS trial[67,68] randomized low-dose Rivaroxaban plus Aspirin vs. Aspirin alone and demonstrated a 24% reduction in primary outcome and a 22% reduction in the net clinical benefit endpoint (composite of primary outcome, fatal bleeding, and symptomatic bleeding into a critical organ/area); especially in those with high atherosclerotic burden (subjects with peripheral arterial disease) thus promising an avenue for further reduction of residual thrombotic risk. Does that mean routine anti thrombotic or antiplatelet administration needs further exploration? Early indications from Anti-thrombotic Trialist Collaboration (ATTC) suggest that subjects could benefit from intensification of antithrombotic or anticoagulant therapy. ATTC researchers analyzed 16 secondary prevention randomized trials of 17,000 patients. Aspirin reduced the risk of serious vascular events, this endpoint still occurred in 6.7% of patients, as compared with 8.2% in the placebo group, suggesting a residual risk. In subjects known ASCVD, antiplatelet agents are an essential component of optimal medical management but intensified anti-platelet (dual therapy) or addition of anti-thrombotic (anti-coagulant) must not offset the benefit in risk reduction by an increase in major bleeding and intracranial bleeding (2.6% vs 0.6%; $p<0.001$) as demonstrated in the ATLAS ACS TIMI-51 trial.[69] Additionally, Dual Anti-Platelet Therapy (DAPT), beyond 1 year post PCI is not clear. A meta-analysis[70] of 6 trials evaluating the efficacy of long-term DAPT in the post-ACS stable cardiovascular disease setting could demonstrate a benefit up to 16%, but this benefit of prolonged DAPT was offset by an increased risk of major (but not fatal) bleeding.

What are the situations for considering residual CV risk factor intervention after achieving LDL-C targets?

Review of evidence is persuasive on the existence of residual risk globally whether it is a covert part of inherent risk or has an overt existential presence. Given that and with universal unavailability of genetic tests or more in depth of endothelial function, vascular reactivity, platelet adhesiveness, lipoprotein sub-particle estimations, or functional analysis, estimation of finer and specific markers of inflammation and advent of precision medicine; what situations exists where clinicians, academicians, and researchers could agree to qualitatively identify subjects that may or could benefit with a targeted approach towards mitigation or minimization of the residual risk without increasing the risks of adverse events or the costs of therapy and keeping in mind the complex behavioral motivation (or lack of compliance) towards poly pharmacy.

A tall order and so, at this stage in our opinion a primary prevention or a population strategy for primordial prevention is expected to either not take off or crash and burn. The best is a secondary prevention in identified very high-risk subjects and a targeted intervention of combination of FARMACY and PHARMACY. This entails high motivation of the subject and intense coaching support of the health care practitioner (preventive cardiac rehabilitation centers); in adjustments in slow but consistent adjustments of behavior towards diets that are considered less inflammatory, 30 minute daily brisk walks or aerobic exercises, optimal BMI for height age and ethnicity, meditative periods to reduce stress AND fine tuning the polypharmacy with periodic compliance check-up.

Phenotypically, such situations or subjects may be identified or targeted post-acute coronary syndrome, post transient ischemic syndrome, and those with difficult to control dysglycemia or dyslipidemia or blood pressure and/or with a very high/ premature history of family history of CV deaths. In short, those with (a) post-acute ischemic episodes (b) those with high/premature CV deaths in the family, and (c) those who can be phenotypically defined as having metabolic syndrome. The pharmacology adjustment post optimal medical therapy may require additional tests like NMR assessment of lipid profile for a knowledge and evidence based fine tuning of the pharmacy and good control of blood sugar and blood pressure to have a synergistic impact of ASCVD residual risk reduction. The

other candidate for intensive modification of interventions are subjects who usually have a high atherosclerotic burden as evidenced by presence of peripheral arterial disease or thickened carotid intima or calcium score that signify burden and/or plaque vulnerability. Regretfully, at this stage of medical therapeutics, tests that are specific to screen subjects with residual risk or sensitive to rule out residual risk are not there or have not been evaluated. But collectively with a targeted identification of subjects, a consistent and sustainable patient care approach, judicious use of specific detailed investigations and above all the subject's own motivation for his/her health and well being is the name of the game and art of minimizing dis-ease and maximizing well-being.

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