Editorial

Triglyceride and cardiovascular risk: A critical appraisal

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Triglyceride (TG) in lipidology has been mired with several issues including its measurement, role in inducing atherosclerotic cardiovascular disease (ASCVD), disconnect in outcome between epidemiological and genetic studies, and the discordant findings in randomized clinical trials (RCTs) versus subgroup analysis. Table 1 summarizes some of these controversies.

First, the measurement of TG in the evaluation of cardiovascular (CV) risk has long been associated with multiple issues. This include skewed distribution that necessitates categorical definitions or log transformations, increasing variability with rising TG levels, inverse association with high-density lipoprotein cholesterol (HDL-C)/apolipoprotein (Apo) AI and finally its way of measurement fasting versus nonfasting.[1,2] Further compounding to already existing problem could be an elevated TG level to be a simple epiphenomenon of insulin resistance or the metabolic syndrome or diabetes, and thus elevated TG may represent only a biomarker of risk, rather than a cause. In addition, many subjects with high-TG levels and impaired glucose who subsequently develop type 2 diabetes mellitus are not usually adjusted in multivariate analysis and thus could not measure the actual risk perfectly and independently.[3,4]

Second, the role of TG in inducing ASCVD has been controversial and not as robust as the role of low-density lipoprotein cholesterol (LDL-C). Although Zilversmit's hypothesized in 1979 that atherogenesis is related to the postprandially raised concentrations of TG and TG-rich (remnant) lipoproteins (TGRLP),[5] the independent relationships of elevated TG to the risk of future CV events or in other words the extent to which TG directly promote CVD, still appears to remain contentious. Individuals with very high TG, so-called chylomicronemia syndrome, do not develop ASCVD and that further led to scepticism about TG relation to CVD.[6] It should be noted that although the very high TG or TGRLP are too large to penetrate arterial intima and unlikely to cause ASCVD, mild-to-moderately raised TG/TGRLP is small enough to enter into intima and may potentiate a cascade of inflammation and therefore have potential to promote atherosclerosis.[7]

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Evidence for Causality between Triglyceride and Cardiovascular Disease

In 1980, Hulley *et al*. trying to associate a causal relation of TG with CV disease (CVD) concluded that "widespread screening and treatment of healthy persons for hypertriglyceridemia be abandoned until more persuasive evidence becomes available."[8] Despite three decades of several additional researches, the controversy regarding the relation between TG and CVD still persists. This perhaps could be due to the conflicting results in the studies performed or in part due to the modest effect size.

Population-based prospective studies and meta-analysis

While several of the earlier cohort studies have found a univariate association of TG to CVD, this association has become insignificant after adjustment for either total cholesterol (TC) or LDL-C. Moreover, many of these studies did not measure HDL-C and thus, relations of TG to CVD still remain unclear.

Nonetheless, many large studies have found a significant association. Table 2 summarizes those studies. In addition, some studies also found nonfasting TG associated with even further increase in CV risk. Table 3 summarizes those studies. While these studies support the hypothesis that nonfasting TG may be another important predictor of CVD risk than fasting levels, the lack of standardization, and reference levels impedes a general implementation.[9] Thus, currently, the diagnosis of hypertriglyceridemia is still based on 12 h fasting levels.

Interestingly, the measurement of fasting TG is currently recommended in most of the countries except Denmark, where nonfasting TG is a standard practice since 2009.

Table 1: Controversies and consensus on triglyceride

Question	Answer
What is the role of TG in CVD?	Elevated TG represents elevated remnants rich in cholesterol, which upon entrance into the intima leads to low-grade inflammation (apart from influence on coagulation, endothelial dysfunction, and oxidative stress), foam cell formation, atherosclerotic plaques, and thus can ultimately led to CVD
Should we measure TG and lipid profiles non-fasting or fasting?	Fasting: Although bothersome but stable minimal value which is required for LDL-C calculation. Currently practiced worldwide Non-fasting: Simple, improve compliance however monitor average lipid levels. Currently practiced in Denmark
Is it elevated TG rather than low HDL-C that cause CVD?	Genetic studies and failed randomised trials (AIM-HIGH, HPS-2 THRIVE) found low HDL likely is not a cause of CVD. This has generated renewed interest in TG and triglyceride-related lipoprotein (TGRLP)
Is it TG per se, TG-RLP (remnant cholesterol), or other lipid fraction that cause CVD?	Most would agree that it is not TG per se that cause CVD. Researchers often debate whether it is all remnant cholesterol combined or whether a certain remnant sub-fraction is more important for development of CVD
What is TGRLP (remnant cholesterol)?	TGRLP (Remnant cholesterol) can be calculated as nonfasting total cholesterol minus HDL-C minus LDL-C. Different subfractions of remnants or remnant cholesterol of intestinal and/or hepatic origin can also be measured directly
Should elevated TG be treated?	The differences in opinion exist among guidelines. Although majority found no benefit, significant benefit observed in atherogenic dyslipidemia (high TG and low HDL-C). Treatment of mild-to-moderately elevated TG awaits randomised trial evidence
Are all fibrates same in their pleotropic properties?	Each fibrates may have a different spectrum of effects. Bezafibrate needs special mention. Bezafibrate being a pan-PPAR (alpha, beta, gamma) agonist may have unique beneficial effects on glucose metabolism, insulin resistance. Bezafibrate has been associated with long-term stabilization of insulin sensitivity and pancreatic beta-cell function, reduced HbA1C and has reduced the incidence of T2DM by 30-40% compared to placebo. Thus, it appears that bezafibrate carries the neutralizing effect on adverse pro-diabetic effect of statins and appears as a strong proponent to statin therapy. Furthermore, bezafibrate significantly increase serum adiponectin level, in contrast to the other fibrates. Bezafibrate also appears to have the strongest, while fenofibrate has the weakest effect on raising HDL-C
Is fenofibrate only agents in the class to show significant microvascular benefit as observed in FIELD trial?	Although fenofibrate has been found to be effective in reducing microvascular complications of diabetes (retinopathy, nephropathy and risk of limb amputations), there is no reason to suggest that other fibrates does not carries the similar potential. Bezafibrate has been seen to effectively reduce microvascular complications in preclinical studies. Moreover, the LEADER study with bezafibrate found significantly reduced severity of intermittent claudication (up to 3 years). Similarly, clofibrate has been associated with an increased rate of absorption of hard exudates of diabetic retinopathy. Thus, this effect appeared to be due to PPARα effect of fibrates as a class irrespective of changes in lipid changes
Can all fibrates be combined with statins?	The muscle pain, myositis, rhabdomyolysis, reduction in eGFR and increase in creatinine is a known side effect of statin/fibrate combination which is significantly higher with gemfibrozil and thus combination with statin is not recommended. However, bezafibrate and fenofibrate are safer and better tolerated with statins

CVD: Cardiovascular disease, TG: Triglyceride, TGRLP: Triglyceride-related lipoprotein, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

In Denmark when nonfasting TG is >4 mmol/L, only then a fasting TG can be requested by the attending physician.[10] This could be due to some advantage with nonfasting TG. A simple advantage of nonfasting over fasting lipid measurements is its ease for patients, physician, and laboratory. As most people eat regularly throughout the day, nonfasting lipid might be a better indicator of average lipid concentrations in the blood. This also has the potential of increased compliance for regular monitoring. Moreover, TG on average increase only by 0.2–0.4 mmol/L after eating normal meals over the next 2–6 h.[11] However, the measurement of fasting TG may have certain advantage. First, TG concentrations are more stable in the fasting than nonfasting state (it is believed, although no evidence suggests so). Second, LDL-C measured by original Friedewald equation is designed for fasting TG and thus easier, although directly measured and calculated LDL-C values are highly correlated with each other, both in fasting and nonfasting state. Finally, the lack of standardization and reference value for nonfasting TG impedes generalized implementation unlike fasting TG, although modified Friedewald equations are also available for more accurate LDL-C calculations.[12]

Taken together, majority of the cohort studies largely support TG as a CV risk factor. Ironically, the results from the largest Emerging Risk Factors Collaboration which assessed

over 300,000 participants from 68 prospective studies found a CAD hazard ratio (HR) of 1.37 (95% confidence interval [95% CI]: 1.31–1.42) with increased TG, which attenuated to an insignificant hazard of 0.99 (95% CI: 0.94–1.05) after adjustment for HDL-C and non-HDL-C. This largest epidemiological study thus concluded that "for population-wide assessment of vascular risk, TG measurement provides no additional information about vascular risk with given knowledge of HDL-C and TC levels, although there may be separate reasons to measure TG concentration (e.g., prevention of pancreatitis)."[13]

Genetic studies

While genome-wide association studies (GWAS) have found a causal association between raised TG and CVD, the functions of many GWAS-identified genetic variants are largely unknown. A Mendelian randomization candidate gene approach has suggested that the around 30 genes variants or more, in association to lifestyle factors and obesity, can modestly increase TG. Of these, mutations in at least six different genes such as lower plateau limit (LPL), APOC2, APOA5, LMF1, GPIHBP1, and GPD1A can increase TG substantially and are identified as monogenic disorders. A number of these studies have clearly linked high TG with increased CV risk. Table 4 summarizes the CVD risk with high TG in those genetic studies.

Interestingly, a significantly reduced risk of ischemic CVD has also been found with genetically reduced TG. Since LPL is the principal TG-metabolizing enzyme and apo's C3 and A5 modulates LPL function as well as modulate liver uptake of remnant cholesterol, targeting these three important proteins may yield reduced CV risk.

In this regard, some studies have found a 24% and a 46% relative risk reduction, in ischemic CVD for APOA5 and LPL, respectively (with corresponding reduction in nonfasting TG by 35–36%), compared with non-TG reducing alleles.[14-17] In Copenhagen general population, a 41% ischemic CVD reduction was seen with APOC3 loss-of-function heterozygosity (along with the corresponding reduction in nonfasting TG by 44%).[18] Another study from 18 different cohorts found a 40% reduction in CHD observed with 39% corresponding reduction in TG.[19] Recently, angiopoietin-like 3 and 4 (ANGPTL3 and ANGPTL4) mutations have also been found to cause reduced TG and LDL-C, making this protein an another new drug target.[20]

Taken together, it is increasingly appearing through genetic studies that high concentrations of TG-rich lipoproteins or remnant cholesterol are causal risk factors for CVD and all-cause mortality.

Clinical intervention trial

The effect of lowering TG to CVD risk reduction has been complicated by some major issues. First, although a number of trials of statin or fibrate monotherapy have examined the potential role of baseline TG with or without HDL-C level

Table 2: TG and cardiovascular risk in cohort studies

First author (study name)	*n*	FU (yr)	CV risk without adjustment of other risk factors	CV risk after adjustment of one or more other risk factors
Fontbonne *et al.* (Paris prospective study)	7038	11	-	plasma TG level was the only factor positively and significantly associated with coronary death
Bass *et al.* (Lipid Research Clinics' Follow-up Study)	1405	14	-	TG 200-399 mg/dl, RR=1.65 (95% CI 0.99-2.77) TG>400 mg/dl, RR=3.44 (95% CI 1.65-7.20)
Laakso *et al.*	313	7	TG>204 mg/dl=2-fold	-
He *et al.*	1696	24	-	RR=2.13 (95% CI 1.46-3.17) with each mmol/L increase
Reykjavik study	18569	-	aOR=1.76 (95% CI, 1.39-2.21)	-
European Prospective Investigation of Cancer (EPIC)-Norfolk study	25668	-	aOR=1.57 (95% CI, 1.10-2.24)	1.31 (95% CI, 1.06-1.62)
Tirosh *et al.* (MELANY study)	13953	5.5	-	HR=4.05 (95% CI, 2.68-8.61) with top quartile of TG
Hokanson *et al* (meta-analysis of 17 studies)	57277	-	RR=1.32 (95% CI 1.26-1.39) and 1.76 (95% CI 1.50-2.07) in men and women respectively	RR=1.14 (95% CI 1.05-1.28) and 1.37 (95% CI 1.13-1.66) in men and women respectively
Sarwar *et al.* (meta-analysis of 27 studies)	262525	-	OR=1.4	1.72 (95% CI, 1.56-1.90) after correcting "regression dilution bias" (intra-individual variation of TG).
Patel *et al.* (Meta-analysis of 26 studies)	96224	-	-	70% (95% CI, 47 to 96) greater risk of CHD death, 80% (95% CI, 49 to 119) higher risk of CHD, and a 50% (95% CI, 29% to 76%) increased risk of stroke with highest quartile of TG
Emerging Risk Factors Collaboration (ERFC) (meta-analysis from 68 studies)	300,000	-	HR=1.37 (95% CI, 1.31-1.42)	HR=0.99 (95% CI, 0.94-1.05) after adjustment for HDL-C and non-HDL-C

CV: Cardiovascular, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, AOR: Adjusted odds ratio, HR: Hazard ratio, CI: Confidence interval

Table 3: TG and cardiovascular risk: Fasting versus non-fasting

Author (study name, follow-up) (*n*)	CV risk in fasting sample	CV risk in non-fasting sample
Eberly *et al.* (Multiple Risk Factor Intervention Trial)	HR=1.64 for CAD with average fasting TG of 187 mg/dl	HR=1.46 with average non-fasting TG of 284 mg/dl
Nordestgaard *et al.*, (The Copenhagen City Heart Study, median 26-year follow-up) (*n*=13,981)	Not studied	HR=1.20 (95% CI 1.05-1.37) for MI, HR=1.18 (95% CI 1.10-1.27) for total death in F HR=1.08 (95% CI 1.03-1.13) for total death in M with highest quintile of non-fasting TG
Nordestgaard *et al.*, (Combined analysis from the Copenhagen City Heart Study and Copenhagen General Population Study)	Not studied	HR=5·1 (95% CI 3·5-7·2) for MI HR=3·2 (95%CI 2·5-4·1) for IHD HR=3·2 (95% CI 2·2-4·7) for ischemic stroke HR=2·2 (95% CI 1·8-2·7) for all-cause mortality with mean non-fasting TG of 6·6 mmol/L versus 0·8 mmol/L
Bansal *et al.*, (Women's Health Study, median 11.4-year follow-up) (*n*=26,509)	Compared to non-fasting	HR=1.98 (95% CI 1.21-3.25) with TG level >171 mg/dl. Only non-fasting TG levels were independently associated with an increased CV events

MI: Myocardial infarction, CV: Cardiovascular, TG: Triglyceride, CAD: Coronary artery disease, MI: Myocardial infarction, IHD: Ischemic heart disease F: Female, M: Male, HR: Hazard ratio

on CVD risk, most clinical trials have excluded the patient with high TG of >400 mg/dL. Thus, it is yet unknown whether reducing TG and TGRLP provides CV benefit. Second, no large-scale randomized trials have directly examined the effect of reducing TG on CVD risk, in people with raised TG. Thus, only the secondary subgroup analyses from these trials have been left out to assess the CVD risk in patient with high TG, with or without low HDL.

The major CV outcome trials of statin and fibrates as a monotherapy or combination therapy, in order of their publication, have been cited as a timeline in Figure 1. Overall statin therapy has been associated with significant reduction in almost all the CV outcomes, irrespective of severity of baseline risk, gender, with or without background diabetes, and intensive statin therapy additionally lowered the risk by ~15–16%.[21-26] Nevertheless, a significant amount of residual risk still appears to remain. Figures 2 and 3 depict the residual risk in major statin trials. Figure 4 depicts the relative risk reduction with conventional versus intensive statin therapy. Figure 5 depicts the residual risk with intensive statin therapy. Figure 6 summarizes the outcome with statins in patient with diabetes versus no diabetes. Figure 7 depicts residual CV risk with statins in patients with diabetes versus no diabetes. These findings clearly suggest that additional agents are required to reduce remaining CV residual risk with statins. The big question is, does lowering of TG reduce CV risk in clinical trials?

Although several statin trials such as Scandinavian Simvastatin Survival Study (4S), the cholesterol and recurrent events (CARE) trial, the West of Scotland Coronary Prevention Study (WOSCOPS), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), and the treating to new targets (TNT) study found increased CV risk with higher baseline TG. Only 4S and CARE found a greater CVD risk reduction in high TG subgroup with statin therapy. Interestingly, in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), the Heart Protection Study and WOSCOPS, CVD reductions were similar across all baselines of TG. Intriguingly, the Anglo-Scandinavian Cardiac Outcome Trial found higher CVD reduction in those without having the feature of metabolic syndrome. Taken together, these perhaps suggest that statin therapy could be beneficial in subgroups with or without high TG.[27-36]

Some statin trials have also assessed the potential effect of on-treatment TG levels on CVD risk, mainly in the secondary analyses and found mixed results. AFCAPS/TexCAPS found no association of on-treatment TG level to CVD risk, similar in line to Veterans Affairs HDL Intervention Trial (VA-HIT) where TG level was not predictive of CVD event, despite significant benefit observed in CV outcome in these trials.[37,38] In contrast, the LIPID study found 11% decrease in CVD risk (14% after adjustment for other risk factors) with each 1 mmol/L decrease in TG with pravastatin, despite no association of baseline TG level to CVD risk in the placebo arm. It should be noted, however, that in LIPID trial, the lipids subtype most strongly associated with CVD risk were apo-B, LDL-C, and the ratio of TC to HDL-C.[39] Similarly, in the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction (PROVE IT-TIMI) trial each 10 mg/dL decrease in on-treatment TG level was associated with 1.8% CVD risk reduction (1.4% after adjustment for other risk factors). Beside, reduction of on-treatment TG to <150 mg/dL was associated with a 27% reduction in CVD risk. Interestingly, a combined data (*post hoc*) from the Incremental Decrease in Endpoints through Aggressive Lipid Lowering study and TNT, also found ~ 30% higher

CVD risk with on-treatment TG of >150 mg/dL although after adjustment for all confounders there found to be no association.[40]

These findings collectively suggest that statin-treated patients with high TG may exhibit an increased risk for CVD. However, these patients also displayed several other metabolic abnormalities including high non-HDL-C and Apo-B. Thus, the predictive effect of TG to CV risk still remains unknown.

The results from TG lowering trials with fibrates are another conflicting area. The first trial with gemfibrozil monotherapy in primary prevention of the Helsinki Heart Study (HHS) and subsequent trial of gemfibrozil monotherapy in the secondary prevention of VA-HIT found a significant benefit in CV outcome.[41,42] However, subsequent studies with other fibrates failed to demonstrate any benefit. Bezafibrate Infarction Prevention (BIP) study failed to show any significant benefit in CV reduction in secondary prevention trial in monotherapy.[43] Two studies with fenofibrate in combination to statin, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and Action to Control CV Risk in Diabetes (ACCORD-LIPID) trial also failed to demonstrate any significant CV benefit.[44,45] While gemfibrozil demonstrated a reduction in CV risk across all the categories of baseline TG in VA-HIT, benefit was only observed in subgroups with increased baseline TG level, with or without low HDL in HHS, BIP, FIELD, and ACCORD-LIPID study. Table 5 shows the results from these fibrates trial. A meta-analysis from 18 trials (n = 45058) with fibrate therapy with or without

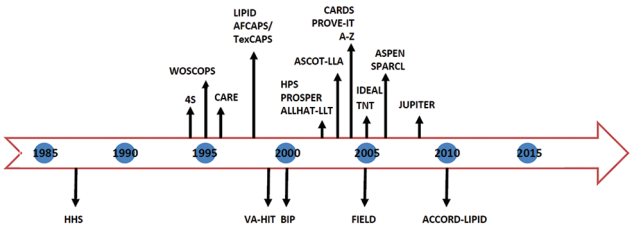

Figure 1: Major statin and fibrates trials in order of their publication

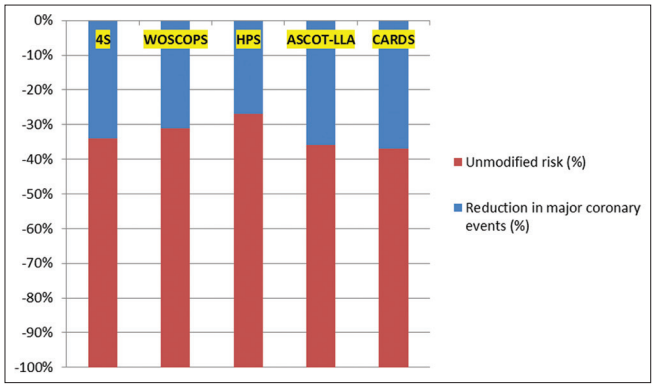

Figure 3: Residual risk still persisting with statins in major statin trials

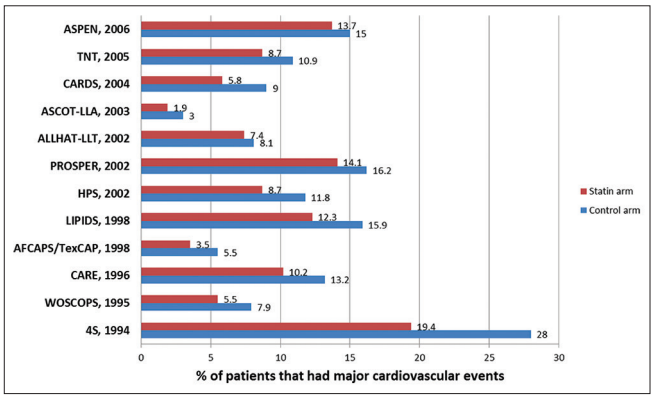

Figure 2: Residual cardiovascular risk in major statin trials (statin vs. control)

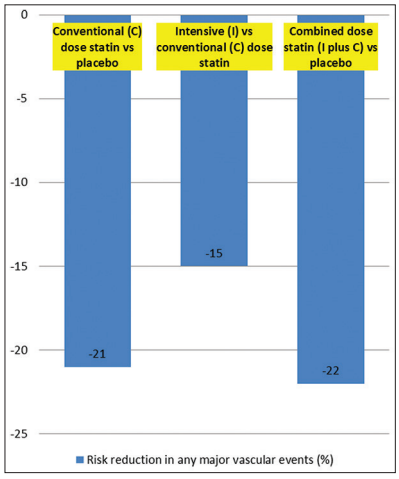

Figure 4: Risk reduction with conventional versus intensive statin therapy

Table 4: Genetic studies linking TG with cardiovascular risk

Author	N	Gene studied	Risk for CVD
Varbo *et al.*	11984	15 genetic variant	Odds ratio 2.8 (95% CI 1.9 to 4.2) with each 1 mmol/l (39 mg/dl) increase of nonfasting remnant cholesterol when corresponding observational HR was 1.4 (95% CI 1.3 to 1.5)
Jorgensen *et al.*	10391	APOA5	Study found a causal genetic odds ratio of 1.94 (1.40-1.85) and 2.23 (1.48-3.35) for doubling in non-fasting triglycerides and calculated remnant cholesterol respectively, while the observational hazard ratio was 1.57 (1.32-2.68) and 1.67 (1.38-2.02) respectively
Sarwar *et al.*	56048	APOA5	Odds ratio for coronary heart disease was 1.18 (95% CI 1.11-1.26) per C allele
Thomsen *et al.*	13957	LPL	1 mmol/L increase in triglycerides was associated with a 2·0-times increased risk of all-cause mortality, with a corresponding observational estimate of 1·2-times. This suggests that a 1 mmol/L reduction in TG was associated with a halved risk of all-cause mortality

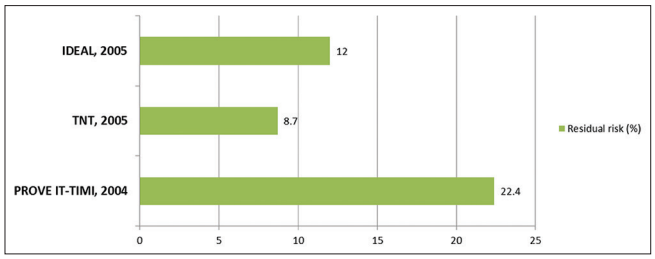

Figure 5: Residual cardiovascular risk after intensive statin therapy

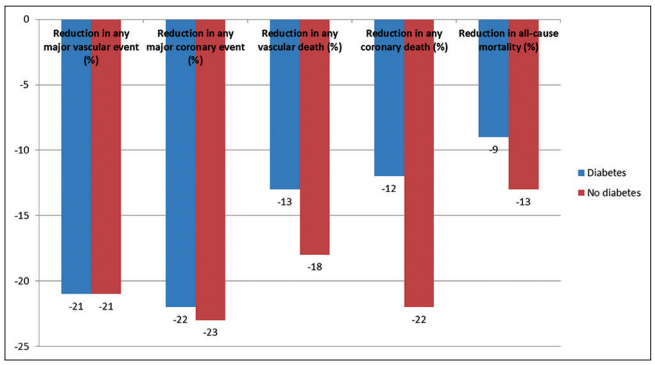

Figure 6: Outcomes with statins in diabetes versus no diabetes

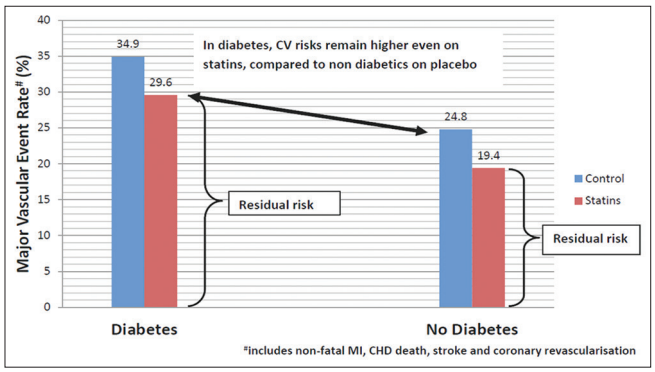

Figure 7: Residual risk with statins in diabetes versus no diabetes

atherogenic dyslipidemia found 13% relative risk reduction for any CV events ($P < 0·0001$) although no benefit on stroke, CV mortality, and risk of all-cause mortality was noted and significant increase in serum creatinine was also observed (HR: 1·99, 95% CI: 1·46–2·70; $P < 0·0001$). This reflects a blend of effects.[46] However, a random-effect meta-analysis from 5 fibrate study [Figure 8] from subgroups with atherogenic dyslipidemia ($n = 4726$) found a 35% relative risk reduction in CV events as compared to insignificant 6% reduction in those without atherogenic dyslipidemia (high TG with low HDL-C).[47] Similarly, a recent meta-analysis also found 28% relative risk reduction in CV events in subgroups with atherogenic dyslipidemia.[48] It is worthwhile to note that median TG and HDL level were modestly high and low, respectively, across these trials, and thus, the effect of lowering moderately high TG to CV risk reduction is truly unknown [Table 6] at this point of time. Figure 9 demonstrates the difference in TG lowering and HDL raising properties of different fibrates across the trial.

Other TG lowering medications such as omega-3 fatty acids have minimal beneficial evidence with regards to CVD risk reduction. This could be either due to the lack of efficacy or benefit that is not mediated directly to TG reduction but by other unidentified mechanisms. For example, the Japan eicosapentaenoic acid (EPA) Lipid Intervention Study (JELIS) found no benefit in CVD risk reduction in relation to baseline TG. However, subgroup analysis found that combination therapy with statin plus EPA (up to 1.8 g/d) reduced CVD risk by 53% (compared to statin monotherapy), in patients with baseline TG ≥150 mg/dL and HDL-C <40 mg/dL. Interestingly, this CV benefit in JELIS was not attributed to TG lowering (difference in TG reduction was only 5% between groups).[49] REDUCE-IT (clinical trials number NCT01492361) and STRENGTH (clinical trials number NCT02104817) are two large-scale, randomized, placebo-controlled trial of purified n-3 fatty acids along with statins which are currently undergoing with expected result in 2016 and 2019, respectively.

Several other newer drugs are also in a clinical development program that has TG-lowering properties. This includes proprotein convertase subtilisin/kexin type-9 inhibitors, microsomal TG protein inhibitors (lomitapide), antisense oligonucleotides (mipomersen), antisense therapies targeting Apo-B - Apo-C, cholesteryl ester transfer protein inhibitors, peroxisome proliferator-activated receptor agonists, and diacylglycerol O-acyltransferase-1 inhibitors. However, currently, their role in treating high TG is unclear.

Taken together, it is still unclear whether lowering of TG reduces CV risk unlike statin and this can be further perceived by discordant stance by different international guidelines summarized in Table 7.

Only nonstatin drugs which have shown any significant benefit in CV outcome along with statins is ezetimibe. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial, which compared ezetimibe plus simvastatin combination therapy, to simvastatin monotherapy, in patients with recently hospitalized for an acute coronary syndrome (n = 18,144) found a 6.4% (95% CI: 1–11%) proportional reduction in the major CV events during a median follow-up 6 years.[50]

Table 5: Outcome in major fibrate (except clofibrate) trials

Study	N (Median follow-up)	Drug	Prim (1^0) or Sec (2^0), (DM%)	On a statin	Primary objective	Primary objective	TG>200 mg/dL	High TG and low HDL#
HHS	4081 (5 Year)	Gemfibrozil	1^0 (DM-3%)	No	MI, CHD death	34% *P*<0.02	56% *P*<0.005	71% *P*=0.005
VA-HIT	2531 (5.1 Year)	Gemfibrozil	2^0 (DM-25%)	No	nonfatal MI, death	22% *P*=0.006	nr	34% *P*=0.004
BIP	3090 (6.2 year)	Bezafibrate	2^0 (DM-10%)	No	MI, nonfatal MI, CHD death	9.4% *P*=0.24	39.5 *P*=0.02	42% *P*=0.02
FIELD	9795 (5 year)	Fenofibrate	1^0 (78%) 2^0 (22%) (DM-100%)	1-No 2-Yes	nonfatal MI, death	11 *P*=0.16	12% *P*=0.07	27% *P*=0.005
ACCORD-LIPID	5518 (4.7 year)	Fenofibrate	2^0 (DM-100%)	Yes	nonfatal MI, CHD death, nonfatal stroke	8% *P*=0.32	31% *P*=0.05	31% *P*=0.03

*{The subgroup with dyslipidemia with prespecified criteria was as follows: In Action to Control Cardiovascular Risk in Diabete (ACCORD:Lipid): TG ≥204 mg and HDL ≤34 mg/dl; Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: TG ≥204 mg and HDL <40 mg/dl in men or <50 mg/dl in women; Bezafibrate Infarction Prevention (BIP) study: TG ≥200 and HDL <35 mg/dl; Helsinki Heart Study (HHS: TG >204 mg and HDL <42 mg/dl; and in Veterans Affairs HDL Intervention Trial (VA:HIT): TG >180 mg and HDL <40 mg/dl}, DM: Diabetes mellitus, CHD: Coronary heart disease, MI: Myocardial infarction, Prim: Primary prevention, Sec: Secondary prevention, nr: Not retrievable

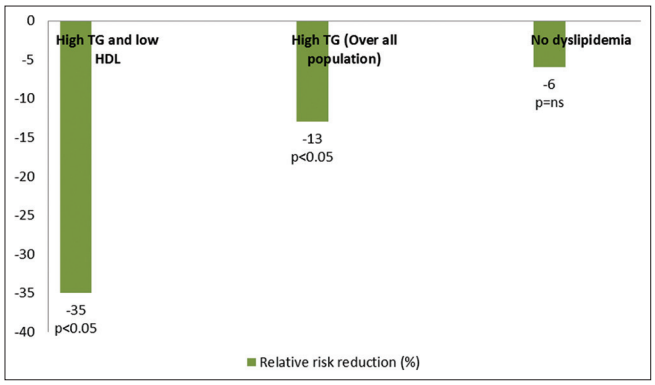

Figure 8: Cardiovascular risk reduction in different subgroups across fibrate trials

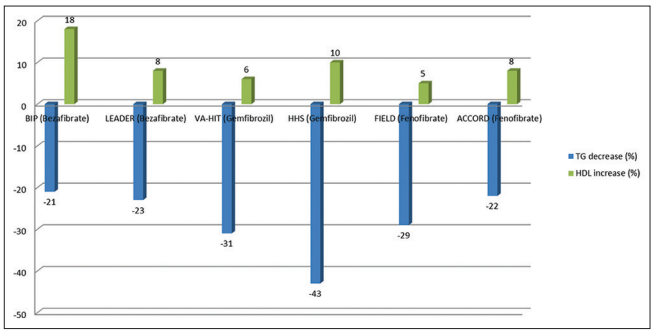

Figure 9: Difference in triglycerides and high-density lipoprotein with different fibrates

Evidence for Causality between Nonhigh-density Lipoprotein Cholesterol and Cardiovascular Disease

Non-HDL-C implies TC minus HDL-C. Non-HDL encompasses all cholesterol present in potentially atherogenic lipoprotein particles that include VLDL-C, IDL-C, Lp(a), and LDL-C. Thus, it is sometimes considered even a better marker than LDL-C as there is no need to measure Apo-B (considered a surrogate for Apo-B). Potential advantage of non-HDL are measurement of non-HDL need not require fasting, it is more practical, reliable, and inexpensive and thus non-HDL could be an important risk factor in the presence of high TG and appears more relevant in patients with diabetes.

In 1998, Frost and Havel first proposed the value of non-HDL-C in CVD risk assessment.[51] Since then several studies including Lipid Research Clinics Follow-up Study, the Pathobiological Determinants of Atherosclerosis in Youth Study, Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe study, Bypass Angioplasty Revascularization Investigation, and PROVE IT-TIMI 22 have recognized as well as demonstrated its relationship to CV risk.[52-59] Liu *et al.* in the analyses from Framingham study cohort found a strong association between non-HDL-C and CV risk within all strata of LDL-C values. Moreover, interestingly non-HDL-C is appearing to be a stronger predictor of CV risk compared to LDL-C, irrespective of TG level.[56]

The earlier ATP III guidelines did recommend that non-HDL-C should serve as a secondary target once LDL-C target levels have been achieved but TG still remained >200 mg/dL. Moreover, non-HDL-C target was set at 30 mg/dL higher than LDL-C (based on the fact that a TG level of 150 mg/dL corresponds to a VLDL-C of 30 mg/dL).[60] A meta-analysis of clinical trial data supports a 1:1 relationship between the percent of non-HDL-C

Table 6: Median TG and HDL level in fibrates trial and other important outcomes

Study	Mean TG (mg/dl)	Mean HDL-C (mg/dl)	Other important findings
HHS	175	47	48% risk reduction in patients with BMI >26 Kg/m^2 and 78% reduction in CHD in those with BMI >26 Kg/m^2 plus TG >200 mg/dl and HDL <40 mg/dl. Non-fatal MI reduced by 37%. No change in total mortality
VA-HIT	161	32	34% risk reduction in patients with diabetes or a high fasting plasma insulin level. Total mortality reduced insignificantly by 11%
BIP	149	35	31% relative risk reduction in the risk of MI in patients with metabolic syndrome. No change in total mortality
FIELD	154	43	11% decrease in total CVD events (P=0.035) including 21% reduction in coronary revascularisation (P=0.003). While 24% reduction in nonfatal MI (P=0.01) observed, a 19% insignificant increase in fatal MI (P=0.22) also seen. Although no benefit was seen in 2^0 prevention subgroup (P=0.85), a 24% reduction observed in the 1^0 prevention monotherapy group (P=0.001). Total mortality increase insignificantly by 19%
ACCORD-LIPID	162	38	Increase in creatinine significantly observed in fenofibrate arm compared to placebo (P<0.001). However, incidence of micro- (P=0.01) and macro-albuminuria (P=0.04) were significantly lesser in fenofibrate arm. Total mortality decrease insignificantly by 9%

HHS: Helsinki Heart Study, VA:HIT: Veterans Affairs HDL Intervention Trial, BIP: Bezafibrate Infarction Prevention study, FIELD: Fenofibrate Intervention and Event Lowering in Diabetes study, ACCORD:LIPID: Action to Control Cardiovascular Risk in Diabetes , BMI: Body mass index, MI: Myocardial infarction, CVD: Cardiovascular disease, CHD: Coronary heart disease, 1^0 – Primary, 2^0 – Secondary

lowering and the percent of CV reduction.[61] However, no dedicated trial has directly examined the effect of non-HDL to CV risk and thus cannot be recommended over LDL-C reduction.

Conclusion

Statins are standard of care for virtually all high-risk patients. Intensive statin therapy further lowers the risk by additional ~15%. However, a considerable amount of residual CV risk still remains. To further lower the residual risk although several other approaches have been tried, no substantial success is seen with nonstatin agents. Human genetic studies manipulated to increase HDL-C and HDL-C raising drugs such as niacin and CETP inhibitors have measurably failed so far in RCTs. This apparently suggests that the role of increasing HDL-C to reduce CVD is negligible at this point of time.

TG lowering with fibrates has shown somewhat mixed results. While human genetic studies strongly implicate TGRLP to be associated with increased CVD, RCTs with TG-lowering therapies have been clearly inconsistent. Similarly, TG lowering drugs have not been associated with improved CV outcome along with statins although some subgroups of patient (those with atherogenic dyslipidemia, metabolic syndrome, and perhaps diabetes) did appear to benefit. These mixed results could have happened at least due to two important reasons. First, none of these trials have specifically targeted individuals with sufficiently high TG. Second, fibrates may not be optimal agent to lower TG. To answer these burning questions, currently two studies such as REDUCE-IT and STRENGTH are currently ongoing. These studies with the newer generation of fish oils in patients with high TG may answer and enlighten about TG reduction to CV events. Moreover, several new targets that have been identified through genetic studies such as APOC3, APOA5, and ANGPTL for lowering TRLP are also being actively pursued, which will further enhance the knowledge and importance of TG-lowering.

Table 7: Major world guidelines on treating elevated triglyceride

Society	Year	Country	Does reduction of mild-to-moderate elevated TG (or elevated non-HDL) reduces CVD?
EAS	2011	Europe	Yes
ESC/EAS	2011	Europe	Yes[a]
AHA	2011	US	No
US Endocrine Society	2012	US	Yes
ESC, EAS, ESH	2012	Europe	No
ACC/AHA	2013	US	No
JBS3/NICE	2013	UK	No
EAS	2014	Europe	Yes
ADA	2016	US	No[b]

Yes: In high risk cases, No: Treatment not recommended, [a]Yes in some cases in high risk, [b]yes in some subset of patients with high TG and low HDL, EAS: European atherosclerosis society, ESC: European society of cardiology, AHA: American heart association, ACC: American college of cardiology, AHA: American heart association, JBS3/NICE: Joint British society/National institute of clinical excellence, ADA: American diabetes association, CVD: Cardiovascular disease

Thus, only nonstatin drug which has currently found to be associated with any significant benefit in CV reduction to date along with statins is ezetimibe (primarily lowers LDL-C with only modest effect on TG). The role of fibrates in reducing CV risk is currently unsettled although some patients with atherogenic dyslipidemia and metabolic syndrome may benefit from these combinations.

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