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Residual Cardiovascular Risk Despite Optimal LDL-Cholesterol Reduction with Statins: The Evidence, Etiology, and Therapeutic Challenges

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Abstract

Purpose of review—This review captures the existence, cause, and treatment challenges of residual cardiovascular risk (CVR) after aggressive low-density lipoprotein cholesterol (LDL-C) reduction.

Recent findings—Scientific evidence implicates low high-density lipoproteins cholesterol (HDL-C) and high triglycerides (TG) in the CVR observed after LDL-C lowering. However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial with fenofibrate, the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) study with torcetrapib, and the recently terminated Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study with niacin, do not clearly attribute risk reduction value to HDL-C/TG modulation.

Summary—The optimum approach to long-term lipid-modifying therapies for CVR reduction remains uncertain. Consequently, absolute risk modulation via lifestyle changes remains the centerpiece of a strategy addressing the physiological drivers of CVR associated with HDL-C/TG, especially in the context of diabetes/metabolic syndrome.

Keywords

Statins; LDL cholesterol; CV risk reduction; residual CV risk

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Introduction

The deposition of atherogenic lipoproteins in the vessel wall is the major driver for atherosclerosis, a degenerative inflammatory disease that underpins most cardiovascular (CV) events. Consequently, CV disease treatment algorithms target low-density lipoprotein cholesterol (LDL-C) to prevent atherothrombosis and plaque rupture, which portend high CV morbidity and mortality. In this context, cumulative evidence from over two decades of clinical trials involving over 170,000 participants, have demonstrated the beneficial effects of statins, or 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, in the reduction of CV event rates.[1] Thus, statins now stand as a bulwark in the frontier of therapeutic strategies for modulation of cholesterol levels and inflammation for primary and secondary prevention of atherosclerotic CV events, including stroke.[2–5] However, despite the chronicled successes from the use of statins, analyses of clinical trial data reveal significant residual CV risk in all patients treated with statins, even in the setting of optimal LDL-C reduction, thus highlighting the need to retool our CV risk reduction algorithms beyond the focus on LDL-C levels and/or the use of statins.

In this article, we discuss the large-scale placebo controlled and standard care-controlled trials of statin therapy on CV outcomes, which provide evidence for residual CV risk despite statin-induced optimal LDL-C reduction per existing treatment guidelines. Based on clinical and epidemiologic studies, we evaluate the potential underlying factors for residual CV risk, with a focus on the functional relationship between LDL-C and CV risk, other lipid culprits such as low high-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG), as well as notable co-morbidities such as diabetes/metabolic syndrome and inflammation. We highlight the counterintuitive results from recent drug intervention trials designed to modulate HDL-C and/or TG levels and support the use of global CV risk assessment and lifestyle changes in the quest for maximal CV risk reduction.

Evidence for residual CV risk

The Scandinavian Simvastatin Survival Study (4S) evaluated patients with known coronary heart disease and high levels of LDL-C. A significant reduction of CV events was observed with statin treatment compared to placebo, however, a 20% CV event rate was noted in statin treated patients.[6] Significant residual CV risk was also noted in other major trials of statin therapy, which prompted the focus on optimal statin use.[7–12] Consequently, additional studies have evaluated the incremental benefits of high-dose statin for intensive LDL-C lowering in high-risk patients. Three landmark trials that shaped our understanding in this regard include the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI) study, the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study, and the Treating to New Targets (TNT) study.[13–15] These studies compared statin lowering of LDL-C to 100 mg/dl versus intensive reduction of LDL-C to 70 mg/dl using high dose statin. In all of these trials, intensive statin therapy with 80 mg atorvastatin led to greater CV risk reduction, but residual CV risk was still apparent in the intensive statin arms; 22.4% in the PROVE IT-TIMI study despite reduction of LDL-C to 62 mg/dl, 12% in the IDEAL study where LDL-C was reduced to 81 mg/dl, and 8.7% in the TNT study which reported LDL-C of 77 mg/dl.[13–15] In the A to Z Trial, early initiation of an intensive simvastatin regimen in patients with acute coronary syndrome (ACS) did not show a significant reduction in the composite primary CV endpoint compared to delayed initiation of a less intensive regimen.[16] However, a meta-analysis of these four studies that compared conventional statin therapy to more intensive treatment in patients with chronic stable coronary heart disease (TNT and IDEAL) or ACS (PROVE-IT and A to Z) showed a further 16% benefit in reducing coronary heart disease and a 18% further benefit in reducing stroke

with more intensive treatment.[17] It is worth noting that the ACS trials (PROVE_IT and A/Z) were of shorter duration ~ 2 years, whereas TNT and IDEAL lasted 5 years. Generally, the aggregate of clinical studies indicate that treatment with statins reduces the risk of major CV events by 21% for every 39 mg/dl decrease in LDL-C, and that when LDL-C is lowered below 70 mg/dl further reduction in CV risk is accomplished.[18] However, despite aggressive LDL-C reduction, residual annual risk that approximates 9% in patients with established coronary artery disease remains a reality that has prompted questions about etiology and a therapeutic course of action. More recent reports corroborate the association between dyslipidemia and vascular events despite statin therapy, and therefore support the need for effective measures to combat residual CV risk.[19, 20] In general, it is important to note that residual CV risk remains after optimal reduction of LDL-C levels in major statin trials regardless of dose (Figure 1), in niacin and fibrate monotherapy trials, and in trials of combination therapies.[7–15, 21–23]

What is optimal LDL-C reduction?

Observational studies suggest a log-linear relationship between LDL-C concentrations and CV events.[24, 25] In this context, the Heart Protection Study (HPS) demonstrated a proportional produced by reduction of LDL-C concentration in the study participants. That is, a 1 mmol/dl reduction in LDL-C from 4 mmol/l to 3 mmol/l or from 3 mmol/l to 2 mmol/l led to the same one-quarter reduction in the risk of CV events.[8] This proportional reduction was consistent across the panorama of LDL-C concentrations among the study participants including concentrations below 2 mmol/l (77 mg/dl). The findings from the HPS put an end to the speculations in its era that a threshold of LDL-C might exist at 3.2 mmol/l (125mg/dl) below which further CV risk reduction would be futile.[10, 26] However, residual CV risk following optimal statin therapy has garnered attention, and precipitates the question as to what optimal reduction of LDL-C really is, given the log-linear association between LDL-C and vascular risk, and the fact that no clear threshold has been identified. Is further risk reduction feasible at LDL-C concentrations below the current target level of 70 mg/dL for high-risk CV patients? What impact will LDL-C of < 55 mg/dl have on CV risk reduction? In this context, what is the importance or clinical benefit of additional relative risk reduction when absolute risk is the clinically relevant parameter? Furthermore, a recent Cholesterol Treatment Trialists' (CTT) meta-analyses of data from 170 000 participants in 26 randomized trials has substantiated the initial report from the HPS; essentially, there is no evidence, as of yet, of a threshold of LDL-C within cholesterol ranges studied, where additional CV risk reduction becomes futile.[1] Furthermore, this CTT meta-analysis suggested a 12% reduction in CV events per 1 mmol/L decrease in LDL during the first year of treatment with an additional 25% reduction for each subsequent year (mean CV event reduction of 22% per 1 mmol/L decrease in LDL), indicating that continued benefits in terms of CV event reduction accrue over time with persistent statin therapy. The question of what optimal LDL-C reduction should mean is worth contemplating as we grapple with the realities of residual risk reduction.

Beyond LDL-C

In the recent past, there has been increased recognition of the relationship between cardiovascular risk and other lipid parameters, most notably HDL-C and TG. Consequently, a lot of enthusiasm now surrounds the potential contribution of these non-LDL-C parameters to residual CV risk in optimally treated statin patients. This interest is further increased by the prospect of using existing and novel pharmacological agents in modulating the serum concentrations of HDL-C and TG with the aim to achieve further reduction in CV risk during statin therapy.

HDL-C

In a landmark report from the Framingham study cohort, Gordon et al. showed that HDL-C concentrations of <1.03 mmol/l (40 mg/dl) in men and <1.29 mmol/l (50 mg/dl) in women were associated with increased CV risk.[27] In another report, Gordon et al. demonstrated that CV risk decreases by 2 to 3% for every 0.03 mmol/l (1 mg/dl) increase in HDL-C.[28] Numerous population-based studies have confirmed the association between low HDL-C and CV risk in men and women.[29–32] Consequently, low HDL-C is accepted as a major independent risk factor and treatment target for coronary heart disease, according to guidelines of The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[4] This independent association is maintained after adjusting for other risk parameters such as TG concentrations, obesity, and diabetes.[33] The magnitude of the problem is enormous, as recent studies have reported a 30 to 40% prevalence of low HDL-C in adult populations of men and women.[34, 35]

A recent meta-analysis of 20 randomized controlled trials that aggregated 543,210 person-years of follow-up indicated that the relationship between HDL-C and CV risk is not altered during statin use.[36] In this report by Jafri et al. there was an inverse relationship between on-treatment HDL-C levels and CV risk, which was statistically significant and independent of on-treatment LDL-C level, potency of the statin, age, hypertension, diabetes mellitus, and tobacco use.[36] A post hoc analysis of the TNT trial suggested that low levels of HDL were predictive of increased CV events for treatment with 10 mg of atorvastatin, but this relationship was attenuated when evaluated for 80 mg.[37]However, this trial also evaluated the subgroup with on-treatment LDL < 70 mg/dL (mean LDL 58 mg/dL) and suggested increased events in those with HDL < 42 mg/dl. The potential attenuation of low HDL in predicting CV events was also noted in PROVE-IT [38] and JUPITER [39] when on treatment LDL was < 70 mg/dL.

This report reinforces the prevailing notion that low HDL-C levels contribute to a significant portion of the residual CV risk in subjects on optimal statin therapy. Lifestyle changes that influence HDL-C levels include smoking cessation,[40, 41] weight loss and dietary manipulation,[42–48] and aerobic exercise.[49–51] Known pharmacologic strategies for raising HDL-C include fibrates,[23, 52–55] niacin,[21, 56–63] and agents under development, such as apoAI mimetics[64–68], apoAI expression stimulators, such as RVX208,[69, 70] and cholesteryl ester transfer protein (CETP) inhibitors, such anacetrapib and dalcetrapib.[71, 72] It is worth mentioning that the first CETP inhibitor, torcetrapib, failed to show CV risk reduction in the ILLUMINATE study, and indeed caused an excess of CV disease which warranted discontinuation of the trial only 10 months from its start.[73] The increase in CV events with torcetrapib has been attributed to off-target effects such as increase in blood pressure and aldosterone and electrolyte abnormalities.[74] Anacetrapib and dalcetrapib do not appear to have these off-target effects;[75] clinical outcomes trials of anacetrapib (REVEAL: Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification) and dalcetrapib[70] are underway.

Among the currently approved agents for treatment of dyslipidemia, niacin is known as the most effective HDL-C raising agent. Furthermore, studies of niacin monotherapy,[76] as well as a recent meta-analysis supported its ability to reduce cardiovascular events.[77] Similarly, regression studies of niacin used in combination with a statin have shown the ability of this combination to promote regression of atherosclerosis.[21, 22] Therefore, niacin has been a strong candidate for reducing residual risk in statin-treated patients with low HDL-C. However, the utility of extended release niacin in reducing residual CV risk in statin-treated patients with established atherosclerotic cardiovascular disease with low HDL-C but optimally treated LDL-C is now questioned by the recent early termination of the AIM-HIGH study due to lack of treatment benefit. In AIM-HIGH, 3414 subjects with

atherosclerotic cardiovascular disease, low HDL-C, and high TG were all treated with simvastatin, and randomized to either high-dose (2000 mg per day) extended-release niacin (n=1718) or placebo (n=1696). In addition, 515 were additional given the cholesterol absorption inhibitor ezetimibe in order to maintain LDL-C between 40 and 80 mg/dL. Mean baseline lipid levels in the 94% of participants taking a statin at baseline were LDL-C 71 mg/dL, HDL-C 35 mg/dL, and TG 161 mg/dL. Taken at face value, the results of AIM-HIGH indicate that the addition of niacin did not benefit this population with LDL-C well controlled by simvastatin during the 3 years of this study. Is it possible that in the setting of a low LDL-C it may take more than 3 years for the benefits of HDL-C raising with niacin to surface? In this regard, it is worth noting that the benefits of niacin in Coronary Drug Project on major cardiovascular events were noted in a follow up study 15 years later,[76] indeed suggesting delayed benefits from niacin therapy. Furthermore, it will be important to see if subjects with significant hypertriglyceridemia or with elevated Lp(a) may have benefited, although the relatively small size of AIM-HIGH may limit the power to detect differences in subgroup analyses. However, further insights on the relationship between niacin use and residual CV risk in statin treated patients will have to wait for the detailed analyses and publication of AIM-HIGH study results, and the completion of the larger international study of high-dose extended-release niacin in a population of patients with a panorama of HDL-C levels (HPS2-THRIVE: the Heart Protection Study 2 Treatment of HDL-C to Reduce the Incidence of Vascular Events). At this point, it would not be appropriate to extrapolate the results of AIM-HIGH to patients unable to achieve their LDL-C goal on statin therapy alone or to patients with very low HDL-C.

Clinical and epidemiologic evidence that supports the association between levels of HDL-C and CV risk; thus, it is puzzling that recent effort at modulating HDL-C levels have failed to reduce residual CV risk. Given recent evidence that HDL-C function can contribute to CV risk independent of HDL-C levels,[78] it is possible that heterogeneity of HDL-C function in the study populations may have confounded the results. Alternatively, it is possible that the functionality of HDL raised by pharmacologic means may fall short of the functional integrity of elevated particle levels naturally achieved by lifestyle changes. The development of clinical assays for HDL-C function may allow targeting of appropriate HDL therapies to populations with high residual risk.

TG and non-HDL-C

Numerous studies have demonstrated an association between high TG level and CV risk. This is captured in the meta-analyses of data from 262,525 participants in 29 prospective studies, showing that the TG level is a strong and independent predictor of CV risk.[79] In their report, Sarwar et al noted that the association between high TG levels and CV risk is independent of duration of follow-up, gender, or fasting.[79] Adjustment for HDL-C level attenuated, but did not eliminate, the strength of the association between high TG level and CV risk.[79] The meta-analyses by Sarwar et al predated the completion of the PROVE IT-TIMI 22 study. Analyses of the data from the latter revealed that TG levels, independent of LDL-C levels, had a substantial impact on the CV outcomes in patients with acute coronary syndromes.[80] Notably, among statin treated patients, on-treatment TG level <150 mg/dl was associated with reduced CV risk independent of LDL-C concentration. Furthermore, the beneficial effect of reducing LDL-C to <70 mg/dl was maximal in subjects with TG levels <150 mg/dl.[80] Our knowledge of the impact of TG lowering therapies on cardiovascular events is limited by the fact that no major outcomes trials have been done in patients with moderate to severe hypertriglyceridemia, as these patients were excluded from statin and fibrate outcomes trials. Fibric acid derivatives are very effective at lowering plasma triglyceride levels, moderately effective in raising HDL-C, but have only modest LDL-C lowering effects. The mean baseline TG levels in the 5 major fibrate outcomes trials ranged

from 175 mg/dL in Helsinki Heart Study (HHS)[55] to 149 mg/dL in the Bezafibrate Infarction Prevention (BIP) Study [52] (Table I). In general, fibrates are not used in clinical practice to treat individuals with TG so mildly elevated. Gemfibrozil has been shown to be effective in both primary and secondary cardiovascular risk reduction.[23, 55] In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), gemfibrozil was effective in reducing cardiovascular events in the absence of significant changes in LDL-C (and with a baseline LDL-C level of 111 mg/dL).[23] In contrast, two major trials with fenofibrate in patients with Type 2 Diabetes Mellitus have failed to demonstrate reductions in major cardiovascular events (Table I). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 diabetic patients with mean levels of TG 154mg/dL, HDL-C 43mg/dL, and LDL-C 119mg/dL to placebo and fenofibrate over a 5-year study period, and did not demonstrate a significant reduction in the primary combined endpoint for CV risk between study groups.[54] A higher rate of statin therapy commencement in the placebo group (17% versus 8%) may have masked the treatment benefit of fenofibrate. FIELD did provide support for potential safety of combination therapy (fibrate + statin).[54] In addition, post hoc analysis of data from the FIELD study demonstrates that patients with elevated TG (>200mg/dl) or low HDL-C (< 40 mg/dl in men and < 50 mg/dl in women) derived greater CV risk reduction with fenofibrate.[81] The efficacy and safety of using a statin and fibrate in combination was recently evaluated in the Action to Control Cardiovascular Risk in Diabetes lipid trial (ACCORD Lipid), which reported no effects on the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or CV death) of fenofibrate added to simvastatin; however there was an overall trend toward increased risk in women as compared to men.[82] Of note, in a prespecified subgroup analysis, there was a trend towards benefit of fenofibrate in patients with TG level of ≥ 204 mg/dl (2.30 mmol/l) or HDL-C of ≤ 34 mg/dl (0.88 mmol/l).[82] Indeed, post hoc analyses of all of the fibrate trials have shown reductions in cardiovascular events in subgroups with features of the metabolic syndrome, including overweight participants with high TG and low HDL-C levels (Table I).[83, 84] Therefore, the hypothesis that fibrate therapy may reduce residual CV risk in patients with T2DM with elevated TG and low HDL-C has not been adequately tested and should be investigated in a major cardiovascular outcome trial.

Non-HDL-C has been shown to predict CV risk as well as correlate with most lipid parameters associated with CV risk.[85–88] Evidence for the association between non-HDL-C and CV risk has also come from epidemiologic data reported by Liu et al.[89] In their analyses of data from 2,693 men and 3,101 women in the Framingham study cohort, a strong association between non-HDL-C and CV risk was noted within all strata of LDL-C values.[89] In this study, non-HDL-C was apparently a stronger predictor of CV risk than LDL-C, and this finding was independent of whether the TG level was < 200 mg/dl or > 200 mg/dl.[89]

A recent report from the INTERHEART study shows that the ApoB/ApoAI ratio was strongly associated with risk of myocardial infarction,[90] more so in patients with type 2 diabetes and metabolic syndrome.[91] Residual CV risk in patients treated with statins is particularly high among diabetics. Kearney et al. in their meta-analyses of data from 18,686 patients with diabetes in 14 randomized trials of statin therapy demonstrated a 9% proportional reduction in all-cause mortality per 1 mmol/L reduction in LDL-C in participants with diabetes (rate ratio [RR] 0.91, 99% CI 0.82–1.01; p=0.02), similar to the 13% reduction in those without diabetes (0.87, 0.82–0.92; p<0.0001).[92] However, residual CV risk in diabetic patients treated with statins was higher than in non-diabetic patients randomized to placebo treatment.[92]

Beyond Lipids

Recent evidence indicates that regardless of the lipid endpoint adopted, a low systemic burden of inflammation, as determined by the concentration of high sensitivity C reactive protein (hsCRP), confers a better prognosis in statin treated patients.[93, 94] Justification for the Use of Statins in Primary Prevention: an intervention Trial Evaluating Rosuvastatin (JUPITER),[94] provides important experimental data that inflammation, and its modulation, is critical to the benefits of statin therapy in a population of patients with normal levels of LDL-C but elevated hsCRP. The finding from JUPITER is supported by a prior report of the importance of other lipid parameters such as the cholesterol to HDL-C ratio when combined with hsCRP.[88] Taken together, these studies add to the body of evidence that supports the notion of inflammation as a unifying hypothesis in the pathogenesis of CV disease.[95] The evidence for the independent contribution of inflammation to CV disease provides the rationale and justification for the recently launched cardiovascular inflammation reduction trial (CIRT), which will allocate 7000 stable coronary artery disease patients with persistent elevations of hsCRP to placebo or very-low-dose-methotrexate (10mg), a widely utilized anti-inflammatory agent which lowers levels of tumor necrosis alpha, interleukin-6, and CRP.[96]

Lifestyle changes

Regardless of the recent disappointments from drug trials of established and novel agents for HDL-C and TG modulation, it is important to retain the important perspective that for many individuals high TG and low HDL-C are features of the metabolic syndrome, which is highly responsive to lifestyle modification. A paramount action for overall CV risk reduction is smoking cessation, which has been reported to raise HDL-C levels by 4 mg/dl, [41] with reversion to HDL-C levels seen in non-smokers.[40] Other recommended modifications include weight reduction, dietary control, and increased physical activity. A 10-kilogram weight loss can result in a 20% increase in HDL-C level.[45] Diets rich in fruits, vegetables, low-fat dairy products, with low simple carbohydrates, and reduced content of saturated and total fat can reduce blood pressure, LDL-C, and raise HDL-C levels.[42, 43, 47, 48, 97, 98] Aerobic physical activity such as brisk walking at least 30 minutes per day, more than three days of the week can result in a 4–9 mm Hg blood pressure reduction, and an elevation of HDL-C levels by 5 to 10%. [49, 50, 99, 100]

Conclusions

The use of statins to modulate levels of cholesterol and inflammation has led to remarkable reduction in CV endpoints and consequently their ubiquitous employment in contemporary approaches for primary and secondary prevention of atherosclerotic CV disease. However, residual CV risk remains a major concern, and highlights room for additional improvement. One approach to residual CV risk reduction implicates low HDL-C and high TG levels. Consequently, the quest to modulate HDL-C and TG levels via pharmacologic approaches has led to clinical trials of novel agents as well as studies of long-term combination therapy of statins with niacin or fibrates. On both fronts, we have been plagued by disappointments, which may reflect the complexities of HDL-C and TG as biomarkers and the challenges of clinical trial design when the goal is to show incremental benefits. The recent termination of the AIM-HIGH study due to lack of treatment benefit implies that the jury on combination pharmacotherapy for dyslipidemia will remain in deliberation pending detailed analyses and publication of the study results, and the completion of the Heart Protection Study 2 Treatment of HDL-C to Reduce the Incidence of Vascular Events (HPS-2-THRIVE), a large international study of high-dose, extended-release niacin in a population of patients with a panorama of HDL-C levels. All the major fibrate outcomes trials have shown reduced

cardiovascular events in subgroups with elevated triglycerides and low HDL-C with features of the metabolic syndrome or with diabetes, supporting the need for a major outcomes trial of statin and fibrate combination therapy in a population with T2DM or metabolic syndrome and significant hypertriglyceridemia and low HDL-C cholesterol. Until then, lifestyle interventions will remain the best tool for aggressively managing residual risk in statin-treated patients.

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Key points

- Significant residual cardiovascular risk after optimum reduction of LDL-C has been clearly documented in numerous statin, non-statin, and combination therapy trials
- The most notable lipid parameters implicated in residual CV risk are HDL-C and TG.
- It is harder than previously thought to clearly attribute value to HDL-C and TG modulation; however, these parameters are still viable targets.
- Attention to global risk assessment and therapeutic lifestyle modification for primary prevention and optimal CV risk reduction is an attractive approach.

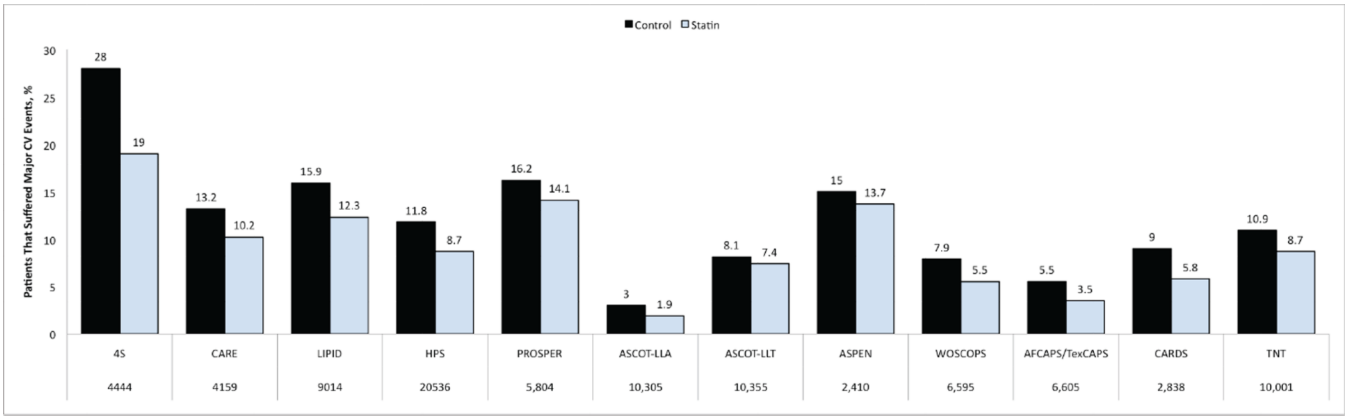

Figure 1. Presence of Residual CV Risk in Large Prospective Studies of Optimal Statin Therapy

4S = Scandinavian Simvastatin Survival Study[6]; CARE = Cholesterol and Recurrent Events trial[10]; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease[7]; HPS = Heart Protection Study[8]; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk[101]; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm[102]; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[103]; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-dependent Diabetes Mellitus[104]; WOSCOPS = West of Scotland Coronary Prevention Study[11]; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study[9]; CARDS = Collaborative Atorvastatin Diabetes Study[105]; TNT = Treating to New Targets study[14]

Table 1

Fibrates Outcomes Studies

Trial	TC	TG	HDL-C	LDL-C	Non-HDL	CVD Reduction Entire Cohort	Lipid Subgroup Criteria	CVD Reduction Subgroup
HHS[55]	269	175	47	189	222	−34% (0.02)	TG>204; HDL-C<42 *	−78%(0.002)
VA-HIT[23]	175	161	32	111	143	−22% (0.006)	TG>180	−28%(<0.05)
BIP[52]	212	149	35	148	177	−7.3% (0.24)	TG>200	−39.5(0.02)
FIELD[54]	195	154	43	119	152	−11% (0.16)	TG>204; HDL-C<40 **	−27%(0.005)
ACCORD[82]	175	162	38	100	137	−8% (0.32)	TG>204; HDL-C<34	−31%(0.03)

HHS = Helsinki Heart Study; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; BIP = Bezafibrate Infarction Prevention; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD = Action to Control Cardiovascular Risk in Diabetes.

* BMI > 26 Kg/M2;

** HDL-C < 50 mg/dl in women. Adapted from Elam MB and colleagues.[84]