Residual Macrovascular Risk

Residual Risk Reduction Initiative (R3i) defines residual CV risk as the risk of CV events that persists in people despite achievement of treatment goals for low-density lipoprotein (LDL) cholesterol, blood pressure, and glycaemia according to current standards of care.

New data appear to challenge the importance of low HDL cholesterol as a driver of residual CV risk, a contribution further confounded by the presence of different HDL subclasses.

Fruchart JC et al. Cardiovascular Diabetology 2014, 13:26
Cholesterol Synthesis and Absorption Markers

Potentially Treatable Residual Risk Issues

- Smoking
- Hypertension
- Dyslipoproteinemia
- Diabetes, prediabetes, insulin resistance —
- Endocrine Issues (thyroid, etc)
- Cardiac comorbidities (valvular disease, cardiomyopathy)
- Renal Dysfunction
- Coagulation issues
- Inflammatory comorbidities
- Homocysteine
- Hyperuricemia
- Vitamin deficiencies

Plus many others

Lipid Levels in In-Patients with Documented Coronary Artery Disease

Cholesterol Treatment Guidelines Use of Statin Therapy

Kearney JF et al New Eng J Med 2014;370:275-
An anticipated increase in statin utilization may result in more patients experiencing statin intolerance or dose-limiting AEs; thus, combination of non-statin drugs with optimized standard ('spared') statin doses towards optimal lowering of LDL-C appears a particularly suitable clinical approach.

Many patients are at increased risk of CVD due to an underlying co-morbidity, including metabolic syndrome, type 2 diabetes mellitus, CKD, FH, and AS.

**National Health And Nutrition Examination Survey (NHANES) 2003-2012**

Age Specific Prevalence of Metabolic Syndrome

Comparisons of prevalence estimates were performed using \( \chi^2 \) test: patients aged 20-30 years in each age group were used as reference. All comparisons yielded \( p < 0.01 \).

**The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial**

Despite achieving a mean LDL-C of 80 mg/dL, patients in the atherogenic dyslipidaemia\(^*\) subgroup had a 70% higher rate of major CV events compared to those without atherogenic dyslipidaemia.

\*TG > 204 mg/dL and HDL-C \leq 34 mg/dL

An anticipated increase in statin utilization may result in more patients experiencing statin intolerance or dose-limiting AEs; thus, combination of non-statin drugs with optimized standard (‘sparking’) statin doses towards optimal lowering of LDL-C appears a particularly suitable clinical approach.

Many patients are at increased risk of CVD due to an underlying co-morbidity, including metabolic syndrome, type 2 diabetes mellitus, CKD, FH, and AS.

The adoption of individualized patient management is becoming increasingly evident with recent guidelines advocating that care decisions should be made by the healthcare provider and patient together, in consideration of the circumstances presented by the patient, and also that the intensity of therapy should be adjusted in accordance with the patient’s absolute risk.

\[ \text{ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults} \]

Less than anticipated therapeutic response: approximately ≥50% reduction in LDL-C from baseline for high-intensity statin and 30% to <50% for moderate-intensity statin.

- Reinforce improved adherence to lifestyle and drug therapy.
- Evaluate for secondary causes of hyperlipidemia if indicated.
- Increase statin intensity, or if on maximally-tolerated statin intensity, consider addition of nonstatin therapy in selected high-risk individuals.

\[ \text{ACC Pathway for Nonstatin Therapy} \]

The ACC pathway supports the recently introduced concept of LDL-C thresholds to trigger consideration of additional nonstatin therapy.

Niacin substantially increases adverse events and is not recommended.
The Simvastatin and Ezetimibe In Aortic Stenosis (SEAS) Trial

Secondary outcomes were events related to aortic-valve stenosis and ischemic cardiovascular events. There was no difference between groups in overall mortality.


Multi-Ethnic Study of Atherosclerosis (MESA)

LDL-C vs LDL-P Discordance

Relations between LDL-C and LDL-P among 5598 MESA participants

Otros JD et al. Journal of Clinical Lipidology (2011) 5, 105–113

Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets

A claims analysis was conducted among 15,569 high-risk patients identified from the HealthCore Integrated Research Database where the impact of LDL levels on risk was compared across cohorts who achieved LDL-P <1000 nmol/L or LDL-C <100 mg/dL.

Atherosclerosis 2014;235:585-591
On-treatment CV risk: LDL-P

Risk for future CHD events by LDL-P

- Hazard Ratio (HR) for future CHD events across LDL-P thresholds adjusted for baseline demographics, comorbidities, and LDL-C.
- Median follow-up was 10.1 months.
- Sample sizes indicate the number of patients with LDL-P levels at or above the designated thresholds.

Toth PP et al. Atherosclerosis 2014;235:585-591

On-treatment CV risk: LDL-C vs LDL-P

Kaplan Meier Curves for Combined CHD/Stroke Risk at 36 months of follow-up
Comparative Effectiveness Analysis of LDL-P vs. LDL-C on CHD/stroke risk

Toth PP et al. Atherosclerosis 2014;235:585-591

Effect of PCSK9 Inhibition by Alirocumab on Lipoprotein Particle Concentrations Determined by Nuclear Magnetic Resonance Spectroscopy

Conclusions: Alirocumab significantly reduced LDL-C and LDL-P concentrations in hypercholesterolemic patients receiving stable atorvastatin therapy. These findings may be of particular relevance to patients with discordant LDL-C and LDL-P concentrations.

J Am Heart Assoc. 2015;4: e002224
Efficacy of Alirocumab in Reducing LDL-P

Samples were collected from patients receiving alirocumab 150 mg every 2 weeks (n=26) or placebo (n=31) during a phase II, double-blind, placebo-controlled trial in patients (LDL cholesterol >100 mg/dL) on a stable atorvastatin dose. Alirocumab significantly reduced mean concentrations of total LDL-P (63.3% versus 1.0% with placebo) and large (71.3% versus 21.8%) and small (54.0% versus +17.8%) LDL-P subfractions and VLDL-P concentrations (36.4% versus +33.4%; all P<0.01).

Efficacy of Alirocumab on NMR Lipoprotein Biomarkers

An ongoing large clinical outcomes study of alirocumab (ODYSSEY OUTCOMES will provide a more definitive analysis of the effects of alirocumab for secondary prevention of cardiovascular complications and will include patients with metabolic syndrome and others who may have LDL-C and LDL-P discordance.

LDL Particle Number Measures as Targets of Therapy

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Population</th>
<th>Framingham</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;75</td>
<td>130</td>
<td>100</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>&lt;80</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>NMR LDL-P (nmol/L)</td>
<td>&lt;600</td>
<td>1100</td>
<td>1400</td>
</tr>
</tbody>
</table>

- American College of Cardiology/ American Heart Association [1]
- American Diabetes Association / American College of Cardiology Foundation Consensus Statement [1]
- American Association of Clinical Endocrinologists/ American College of Endocrinology Comprehensive Diabetes Algorithm [8]
- National Cholesterol Education Program [5]
Cholesterol Synthesis and Absorption Markers

ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

- Less than anticipated therapeutic response: approximately ≥50%

National Lipid Association Consensus Statement High Density Lipoproteins

- Low serum levels of HDL-C have been found repeatedly to be the best predictor of CHD in observational studies, especially in men older than 50 years
- After adjustment for established covariates, high levels of HDL-C in general correlate with low risk, whereas low levels correlate with higher risk of CHD

Most studies did not adjust for LDL particle concentration or apoB levels that may confound this association

National Lipid Association Consensus Statement High Density Lipoproteins

- The cholesterol content of HDL does not represent many important HDL functions that are related to CVD risk
- Currently, evidence from clinical trials is insufficient to recommend HDL-targeted therapy
- No evidence supports raising HDL-C levels to some arbitrarily defined HDL-C threshold (i.e., ≥40 mg/dL in men or ≥50 mg/dL in women)
No new guideline for the management of dyslipidemia will be recommending pharmacologic intervention for low HDL-C, given the absence of positive data from randomized, prospective studies.


Mean carotid IMT in MESA adjusted for age, sex, ethnicity, HTN, & smoking in high and low HDL-C tertiles, each subdivided according to HDL-P level tertiles:

- p=NS for HDL-C trend within each HDL-P tertile
- p<0.05 for HDL-P trend for both low and high HDL-C tertiles
- p=NS for medium HDL-C tertiles (not shown)

Entire sample

• p=NS for HDL-C trend within each HDL-P tertile
• p<0.05 for HDL-P trend for both low and high HDL-C tertiles
• p=NS for medium HDL-C tertiles (not shown)
Residual Macrovascular Risk

- In HPS-THRIVE2 there were safety issues with niacin/laropiprant, notably significant increases in diabetes complications, new-onset diabetes, infections, and gastrointestinal, musculoskeletal, bleeding and skin adverse events, leading to subsequent world-wide withdrawal of this therapy.
- Niacin remains a therapeutic option in North and South America, but is no longer an option in Europe.
- Combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes, possible increase in risk of ischemic stroke, and side effects.

ABA Guidelines – CVD & Risk Management section
Diabetes Care Volume 40, September 1, January 2017 S75-87

Residual Macrovascular Risk

Meta-analysis of major fibrate outcomes studies, showing the impact of fibrate treatment on residual CV risk in patients with atherogenic dyslipidemia defined as elevated TG (≥204 mg/dL) and low HDL-C (≤34 mg/dL).

<table>
<thead>
<tr>
<th>Subgroups with dyslipidemia</th>
<th>No dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>0.75 (0.64-0.87)</td>
</tr>
<tr>
<td>FIELD</td>
<td>0.84 (0.74-0.96)</td>
</tr>
<tr>
<td>BIP</td>
<td></td>
</tr>
<tr>
<td>VA-HIT</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>0.94 (0.84-1.05)</td>
</tr>
</tbody>
</table>

Odds ratios (95%) CI

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial

9.7 Year Follow-up

JAMA Cardiology | Original Investigation

Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes

All participants were preselected subgroups.

Cholesterol Synthesis and Absorption Markers

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial 9.7 Year Follow-up

An additional 5 years of follow-up of survivors ACCORD-Lipid study cohort members extends the original overall neutral outcome of the ACCORD study and provides additional support for possible benefits of fenofibrate on cardiovascular outcomes in a subset of patients with diabetes and hypertriglyceridemia, especially those with low HDL-C. Our findings support the hypothesis that patients with abnormal dyslipidemia may derive some benefit from addition triglyceride lowering therapy.


Primary Outcome

Cardiovascular Mortality

Total Mortality

Fenofibrate therapy may reduce CVD in patients with diabetes with hypertriglyceridemia and low HDL-C.


Hazard ratios for Primary Outcome in prespecified subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin + Fenofibrate</th>
<th>Events/No. (% )</th>
<th>Statin + Placebo</th>
<th>Events/No. (% )</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>508/2739 (18.5)</td>
<td>539/2732 (19.7)</td>
<td>0.93 (0.83-1.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>197/956 (20.6)</td>
<td>224/903 (24.8)</td>
<td>0.81 (0.67-0.98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C 35-40</td>
<td>159/852 (18.6)</td>
<td>157/858 (18.3)</td>
<td>1.01 (0.81-1.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 41</td>
<td>150/916 (16.3)</td>
<td>155/959 (16.1)</td>
<td>1.02 (0.81-1.27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &lt; 129</td>
<td>146/879 (16.6)</td>
<td>186/930 (20)</td>
<td>0.83 (0.67-1.03)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>129-203</td>
<td>171/918 (18.6)</td>
<td>160/908 (17.6)</td>
<td>1.04 (0.84-1.29)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥ 204</td>
<td>189/927 (20.3)</td>
<td>190/882 (21.5)</td>
<td>0.93 (0.76-1.13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG &gt; 204 &amp; HDL-C &lt; 34</td>
<td>99/482 (20.5)</td>
<td>121/454 (26.6)</td>
<td>0.73 (0.56-0.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>134/841 (15.9)</td>
<td>106/832 (12.7)</td>
<td>1.30 (1.01-1.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>374/1898 (19.7)</td>
<td>433/1900 (22.7)</td>
<td>0.84 (0.73-0.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1.30 (1.01-1.68)</td>
<td></td>
<td>0.84 (0.73-0.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>407/2242 (18.1)</td>
<td>415/2266 (18.3)</td>
<td>0.99 (0.86-1.13)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

American Diabetes Association CVD & Risk Management Guidelines

- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended.
- However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥ 204 mg/dL and HDL cholesterol level ≤ 34 mg/dL.

ADA Guidelines – CVD & Risk Management section
Diabetes Care Volume 40, Supplement 1, January 2017 S 75-87
For the primary endpoint, hazard ratio with rosuvastatin was 0.46 (95% CI: 0.32 – 0.69), and the expanded endpoint (bottom) by baseline Lp(a) mass concentration:

- For the primary endpoint, hazard ratio with rosuvastatin was 0.46 (95% CI: 0.32 – 0.69).
- For the expanded endpoint, hazard ratio with rosuvastatin was 0.47 (95% CI: 0.30 – 0.62).

Hazard ratios and 95% confidence intervals were calculated for participants with baseline Lp(a) mass concentration below the median and above the median respectively (p-interaction = 0.10).

- Although the median change in Lp(a) mass concentrations was similar between the control and rosuvastatin groups, the use of rosuvastatin nonetheless resulted in a small but statistically significant positive shift in the overall Lp(a) distribution (P<0.0001).

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) Study: Lp(a) lipoprotein(a) mass concentrations

- Current therapeutic options to reduce the risk of CHD (Coronary Heart Disease) are limited (P-H: .001; I²: 66.1)
- Several small and large prospective studies have investigated the association between EPA & DHA intake and the risk of CHD
- Omega 3 Fatty Acids intake is shown to have an inverse association with Lp(a) concentration

No FDA indication to treat Lp(a)

Efficacy of rosuvastatin according to baseline lipoprotein(a) concentration

- For the primary endpoint, hazard ratio with rosuvastatin was 0.46 (95% CI: 0.32 – 0.69).
- For the expanded endpoint, hazard ratio with rosuvastatin was 0.47 (95% CI: 0.30 – 0.62).

Streppel et al, 2008
- Median overall Lp(a) distribution: 23 mg/dL (Caucasians) & 60 mg/dL (Blacks)
- Median overall Lp(a) distribution: 23 mg/dL (Caucasians) & 60 mg/dL (Blacks)

Omega 3 Fatty Acids

- Current therapeutic options to reduce the risk of CHD (Coronary Heart Disease) are limited (P-H: .001; I²: 66.1)
- Several small and large prospective studies have investigated the association between EPA & DHA intake and the risk of CHD
- Omega 3 Fatty Acids intake is shown to have an inverse association with Lp(a) concentration

No FDA indication to treat Lp(a)
Cholesterol Synthesis and Absorption Markers

Targeting Inflammation in Atherosclerosis
Pathways of Atherosclerosis Progression

- ApoB elicits inflammation in plaques and progresses atherosclerosis via other paths
- Inflammation may be caused by factors other than apoB
- Clinical trials are underway to test this strategy with anti-inflammatory drugs developed for other conditions, such as methotrexate, colchicine, and the inhibiting interleukin-1β antibody canakinumab

Brenton JF. JACC 2016;68:2794-96

Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus: Cardiovascular Risk

Prevalences of carotid atherosclerosis in groups of control subjects and patients with SLE and RA matched for age and gender with comparable cardiovascular disease risk factor profiles

Circulation 2007;116:2346-2355.

IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT)

Prespecified LDL-C and hs-CRP target achievement at 1 month by randomized treatment

Number and proportion of subjects achieving each target (LDL-C<70 mg/dL and hs-CRP<2 mg/L), LDL-C<70 mg/dL only (hs-CRP<2 mg/L), hs-CRP<2 mg/L only (LDL-C≥70 mg/dL), or both LDL-C<70 mg/dL and hs-CRP<2 mg/ L by randomized treatment

Patients were obtained using multivariable-adjusted logistic regression with indication of the described adjustment factors as covariates

Bihora EA et al. Circulation 2010;122:1224-33
Cholesterol Synthesis and Absorption Markers

Prognosis of CKD by GFR and Albuminuria Categories

KDIGO 2012
Kidney Disease Improving Global Outcomes
GFR is the best overall index of kidney function in health and disease

Relationship of Cardiovascular Mortality with GFR and Albuminuria Categories

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

Study of Heart and Renal Protection (SHARP)

Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease

9270 patients with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularization

Prespecified outcome was first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure)

**Cholesterol Synthesis and Absorption Markers**

### Study of Heart and Renal Protection Study (SHARP)


- There was no evidence of excess risks of hepatitis (21 [9.3%] vs 18 [9.4%]), gallstones (108 [2.3%] vs 108 [2.3%]), or cancer (436 [8.4%] vs 439 [8.5%], p=0.9) and there was no significant excess of death from any non-vascular cause (666 [14.4%] vs 612 [13.2%], p=0.13).

- Placebo
- Ezetimibe / simvastatin

Reduction of LDL-C with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.

- Risk ratio 0.83 (0.74 – 0.94)
- Logrank 2P=0.0022

### National Health And Nutrition Examination Survey (NHANES): Vitamin D

NHANES (2001-2004) data of 10,170 people ≥ age 18 combined with National Death Index revealed an inverse association between 25(OH)D and all cause and cardiovascular disease mortality in healthy adults with serum 25(OH)D levels of < 21 ng/mL.

- Clinical trials for the primary prevention of cardiovascular disease with 25(OH)D supplementation may target healthy adults with serum 25(OH)D levels of 21 ng/mL to validate these findings.

### Vitamin D Deficiency Is Not Good for You

Diabetes Care 2011;34:1249-46

- Endocrine Society Clinical Guidelines Vitamin D
- Recommends screening for vitamin D deficiency in individuals at risk for deficiency; does not recommend population screening for vitamin D deficiency in individuals who are not at risk.
- All adults who are vitamin D deficient can be treated with 50,000 IU of vitamin D3 or vitamin D2 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a targeted level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1500–2000 IU/day.

J Clin Endocrinol Metab 2011;96(7):1911–1930
Vitamin D

- Genetically lowered 25OHD levels were not associated with increased risk of CAD in a large, well-powered study, suggesting that previous associations between circulating 25OHD levels and CAD are possibly confounded or due to reverse causation.
- The results provide no rationale for the use of vitamin D to prevent CAD.
- Vitamin D is essential for efficient calcium absorption and thus for bone health.
- Taken with supplemental calcium, vitamin D can reduce postmenopausal bone loss and improve BMD and improve muscle strength and reduce risk of falls.


Summary Slide: Residual Risk

- Dyslipoproteinemia: going beyond LDL-cholesterol.
- Statins remain initial apolipoprotein treatment of choice.
- Apolipoproteins discordance/concordance issues with LDL-C.
- Fall of HDL-cholesterol in risk assessment and goal of therapy.
- Reduced Omega 3 levels increase risk.
- Lp(a) – Statins may benefit.
- Diabetes: High TG and low HDL-C define residual risk.
- Aortic Stenosis – Rx benefit ischemic heart disease risk.
- Renal Issues – eGFR & albuminuria define risk.
- Inflammatory comorbidities increase CV risk.
- Hypovitaminosis D.

Thanks for your attention.