Lipid Management in Diabetes

Kyaw Soe, March 10th, 2012
Diabetes Dyslipidemia

- The major contributor for the CV mortality and morbidity in DM.
- Moderately increased LDL-c (or normal LDL).
- High TG.
- Decrease HDL-c.
- Lp abnormalities are manifested earlier than hyperglycemia; Prediabetes.
Mechanisms of DM Dyslipidemia

Fat Cells

Insulin

IR

↑ FFA

↑ TG

↑ Apo B

↑ VLDL

CETP

TG

CE

↑ VLDL

CETP

↓ HDL

Apo A-1

(tipoprotein or hepatic lipase)

Small Dense LDL
Hypertriglyceridemia

- ↑ TG is just a marker or mediator of CAD risk?
- Data regarding arthrogenic role of high TG are not as robust as that of LDL-c.
- When ↑ TG occurs in the setting of low HDL → a clear risk.
High TG raises the Risk of CAD at All Levels of HDL-c


TG, HDL-c and Associated Risk for Premature CAD
653 pt with premature familial CHD and 1029 control
High TG as a risk factor of CHD.

- Meta-analysis of the population based prospective studies.
- After adjusting the HDL-c and other risk factors.
- ↑ fasting TG were associated with ↑ CAD risk in both men and women.

CAD risk can be reduced to a maximum of approximately 45% with statin and/or fibric acid Rx. To achieve the reduction of residual 55%, raising HDL-C becomes Critical.

1Duffy & Rader Circulation 2006; 113
Residual Cardiovascular Risk in Major Statin Trials

CHD events occur in patients treated with statins

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients Experiencing Major CHD Events, %</th>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>28.0</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>LIPID</td>
<td>15.9</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>CARE</td>
<td>13.2</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>HPS</td>
<td>11.8</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>7.9</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>10.9</td>
<td>6.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Δ LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>4444</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
</tr>
<tr>
<td>HPS</td>
<td>20 536</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>6595</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>6605</td>
</tr>
</tbody>
</table>

Secondary  High Risk  Primary

TNT: Events in HDL-C and LDL-C Quintiles
CHD risk equivalents

- DM.
- Symptomatic carotid artery disease.
- PAD.
- Abdominal aortic aneurysm.
- Multiple risk factors that confer a 10 years risk of CHD ≥ 20%.
- CKD with Cr >1.5 mg/dL or eGFR <60.
DM = CAD risk?

- Calculate patient-specific risks rather than simply considering all DM pts as CHD risk.
- Framingham risk score ( >5000 white; 6% DM).
- Framingham Not differentiate the severity, duration and control of DM.
UKPDS Risk Engine

- UKPDS risk engine (53,000 DM).
- Input: age, sex, A Fib, Ethnicity, smoking, duration of DM, HgbA1c, SBP, Total Chol, HDL
- Output: CHD, fatal CHD, stroke and fatal stroke
- 95% confidence interval
- www.dtu.ox.ac.uk/riskengine

UKPDS risk engine, Clinical Science 2001 (UKPDS group)
ADA: Position Statement-2012

- **Statin Rx is indicated**, regardless of baseline lipid levels in **high risk** pt.
  - with overt CVD.
  - without CVD: > 40 years and who have one or more other CVD risk factors.

- **Lower risk** (<40 and without overt CVD) consider statin if LDL > 100 or those with multiple CVD risks.
### ADA/ACC 2008 Consensus Statement: Treatment Goals in Patients With Cardiometabolic Risk and Lipoprotein Abnormalities

#### Goals

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-Risk Patients</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td>Known CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes plus ≥1 additional major CVD risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-Risk Patients</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>&lt;90 mg/dL</td>
</tr>
<tr>
<td>No diabetes or known CVD but ≥2 major CVD risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes but no other major CVD risk factors</td>
<td></td>
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<td></td>
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</tbody>
</table>

Goal by ADA

- TG < 150 mg/dL.
- HDL-c >40 in men and >50 in women
- LDL-c 30-40% ↓ from baseline - acceptable alternative.
- All Placebo-controlled Statin trials generally achieve LDL reduction 30-40% from baseline to see the CV benefit.
New Lp Parameters

- LDL-c measurement by reference method, β quantitation is complex and expensive.
- **Friedewald** equation underestimates LDL-c when TG is high.
- “Direct “ LDL measurement is not standardized.
- LDL measurement may not accurately reflect the true burden of atherogenic LDL particles.
NMR (Nuclear Magnetic Resonance)

- Measurement of LDL particles number and size.
- Better risk discriminator than LDL-c.
- Small dense LDL particles are atherogenic.
- Discrepancy in standard LDL-c measurement and LDL particle size and number in Dyslipidemic condition (high TG and low HDL).
**NMR (Nuclear Magnetic Resonance)**

**Indication**: LDL-c at goal (<70 mg/dL) and yet artherosclerosis has progressed angiographically or clinically.

**Limitations**:
- 1. Expensive.
- 2. Need independent verification of accuracy of method and consistency of CVD predictive power across various ethnicities, ages, and conditions that affect lipid metabolism.
Lipoprotein(a) [Lp(a)]

- ApoB containing LDL-like particle.
- Has enhanced binding to intimal proteoglycans.
- Prothrombotic effect.
- Predicts CVD.
- Little evidence that insulin resistance or diabetes influences Lp(a) concentrations.
- Clinical utility of routine measurement of Lp(a) is unclear.
Non-HDL Cholesterol

- Reflects the concentration of cholesterol within all atherogenic Lp.
- **ATP III**: in high TG, non-HDL-c is secondary goal after targeting LDL-c.
- Non-HDL-c is a better predictor of CVD risk than LDL-c (especially for statin treated pt).

Lu W et al Diabetes care 26,2003
Lui J et al Diabetes Care 28, 2005
Pischon T. Circulation 112, 2005
Apo B-100

- Each LP {CML, VLDL, IDL, LDL, and Lp(a)} contains a single ApoB molecule.
- Measurements of ApoB represent the total burden of atherogenic Lp particles.
- Not require a fasting sample.
- Standardized assay.
- A better predictor than LDL-c (particularly the on treatment LDL-c).
- More effective way to assess residual CVD risk and for medication adjustments.
# Cardiovascular Outcome in Fibrate Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Fibrate</th>
<th>Follow-up</th>
<th>Patient Population</th>
<th>Primary End Point</th>
<th>Absolute Event Rate (%)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (1982)</td>
<td>Gemfibrozil, 1200 mg</td>
<td>5.0</td>
<td>4081 men with non-HDL cholesterol ≥200 mg/dl (primary prevention)</td>
<td>Fatal or nonfatal MI, or CAD death</td>
<td>84/2030 (4.1)</td>
<td>0.66 (0.47–0.92)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>VA-HIT (1991–1993)</td>
<td>Gemfibrozil, 1200 mg</td>
<td>5.1</td>
<td>2531 men with CAD and HDL cholesterol &lt;40 mg/dl (secondary prevention)</td>
<td>Nonfatal MI or CAD death</td>
<td>275/1267 (21.7)</td>
<td>0.78 (0.65–0.95)</td>
<td>0.006</td>
</tr>
<tr>
<td>BIP (1990–1992)</td>
<td>Bezaﬁbrate, 400 mg</td>
<td>6.2</td>
<td>3090 men and women with previous MI or angina (secondary prevention)</td>
<td>Fatal or nonfatal MI or sudden death</td>
<td>232/1542 (15.1)</td>
<td>0.91 (0.76–1.08)</td>
<td>0.26</td>
</tr>
<tr>
<td>FIELD (1998–2000)</td>
<td>Fenofibrate, 200 mg</td>
<td>5.0</td>
<td>9795 men and women with type 2 diabetes (primary and secondary prevention)</td>
<td>Nonfatal MI or CAD death</td>
<td>288/4900 (5.9)</td>
<td>0.89 (0.75–1.05)</td>
<td>0.16</td>
</tr>
<tr>
<td>ACCORD (2001–2005)</td>
<td>Fenofibric acid, 160 mg</td>
<td>4.7</td>
<td>5518 men and women with type 2 diabetes on statin therapy (primary and secondary prevention)</td>
<td>Nonfatal MI, nonfatal stroke, or death from cardiovascular causes</td>
<td>310/2765 (11.2)</td>
<td>0.92 (0.79–1.08)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* ACCORD denotes Action to Control Cardiovascular Risk in Diabetes trial, BIP Bezaﬁbrate Infarction Prevention study, CAD coronary artery disease, FIELD Fenofibrate Intervention and Event Lowering in Diabetes study, HHS Helsinki Heart Study, MI myocardial infarction, and VA-HIT Veterans Affairs High-Density Lipoprotein Intervention Trial.

Goldfine AB et al. NEJM 2011 ;365
Helsinki Heart Study

- Primary prevention trial with Gemfibrozil in middle-aged men with dyslipidemia.
- Safety of treatment, changes in risk factors and incidence of coronary heart disease.
- ↓ CVD events but no effect on overall mortality.
VA-HIT (Veteran Affairs HDL intervention Trial)

- Gemfibrozil in men with CHD, (HDL <40 mg/dl and TG >300).
- 22 % ↓ in RR for non-fatal MI or death from coronary cause.
- More benefit: ↓ 35% in DM or Metabolic syndrome (a high fasting plasma insulin level).
BIP (Benzafibrate infarction Prevention)

- No effect on all-cause and cardiac mortality.
- 31% relative risk reduction of MI in pt with metabolic syndrome.
FIELD (Fenofibrate Intervention and Event Lowering in Diabetes)

- Failed to reduce the risk of primary outcome (MI and CHD death).
- ▼ Secondary outcomes (total fatal and non-fatal CVD event) and microvascular complications.
- Significant drop-in rate for statin use in the placebo group.
- Higher rate of Rhabdo in statin and fibrate group.
Post Hoc analysis by Scott et al.
No benefit in pt without metabolic syndrome.
Marked dyslipidemia (high TG and low HDL) had the greatest CV risk reduction.
ACCORD Lipid Trial

- 5518 DM pt.
- Simvastatin in all pt.
- Fenofibric acid 160 mg daily Vs Placebo.
- No significant difference in primary outcome (CVE) despite significant reduction in TG and slight increase in HDL in treatment arm.
ACCORD Lipid Trial - Lipid Values

ACCORD Lipid Trial: Primary and Secondary Outcomes

Subgroup analysis of ACCORD

- Highest baseline TG (>204 mg/dL) and lowest baseline HDL (<31 mg/dL) showed 30% ↓ in primary end points.
- “Dilution effect” by Inclusion of pt with less extreme dyslipidemia. (baseline TG of all participants =162 mg/dL).
ACCORD Eye Trial

- Fenofibrate- fewer composite events.

- Progression by at least 3 steps on diabetic retinopathy scale  Or

- Proliferative retinopathy necessitating photocoagulation or vitrectomy (6.5 Vs 10.2%).
Verdict for Fenofibrate

- **FIELD** and **ACCORD-Lipid**.

- Fenofibrate should only be used in patients with TG > 200 mg/dL.

- The greatest benefit seen in those with both TG>200 mg/dL and HDL-c <35 mg/dL.
Niacin

- Most potent agent available to increase HDL-c.
- The only one that reduce Lp (a).
- ↓ circulating FA by inhibiting the release of FA in adipose tissue mediated by hormone sensitive lipase.
- Concern for DM control.
Effect of nicotinic acid on DM control

- The prospective Arterial Disease Multiple Intervention Trial (ADMIT) and
- The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT).

- No statistically significant worsening of blood glucose levels.
- Require additional anti-diabetic medication.
Aim-High

- 3000 (1/3 DM).
- Statin +/- extended release niacin.
- Significant ↓ TG, LDL and ↑ HDL in treatment arm.
- Halted early due to no difference in the primary CVD outcome and a possible increase in ischemic stroke.
- Unclear etiology.
- Causal association or possibly the statistical “play of chance.”

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy (NEJM Dec 2011)
HPS2-THRIVE

- Treatment of HDL to Reduce the Incidence of Vascular Events.
- Extended Release Niacin/Laropiprant.
- Flushing and pruritus – mediated by PG-D.
- Laropiprant: selective PG D r/c antagonist.
- Phase III safety and efficacy trial for high risk pts (CAD, CVD, PAD and DM).
- Primary outcome (non-fatal MI or cardiac death) stroke (fatal or non-fatal).
Bile acid binding Resin

- Cholestyramin, Colestipol and Colesevelam.
- Interrupt the entero-hepatic recirculation of bile acid.
  - ↓ the bile acid returning to the liver ➔ ↑ conversion of hepatic cholesterol to bile acids.
- Up-regulation of gene of hepatic LDL r/c.
- Side effects - nausea, cramping, bloating, ↑ liver enzymes.
- Bind to certain medications, inhibiting their absorption (i.e., digoxin, warfarin), and limit absorption of fat soluble vitamins.
Bile acid binding Resin

- Cholestyramine and Colestipol reduce LDL -25%.
- Low compliance.
- Colesevelam lower LDL by 20%, better compliance.
- Colesevelam lowers HgbA1c-0.5 %
- No systemic toxicity.
- Raise VLDL ,TG production.
- Addition to statin or for statin-intolerant patients.

Omega 3 Fatty acid

- Lower post-prandial TG.
- Bioactive eicosanoids (Docosahexanoic acid and eicosapentanoic acid).
- Lipid lowering, anti-inflammation, reduce platelet aggregation, vasodilatation and plaque stability.
- Italian study (GISSI) and Japanese study (JELIS) showed clinical benefit (CVE and mortality).
- Risk of bleeding with ASA.
Ezetimibe

- Inhibit cholesterol absorption in the small intestine.
- Addition to statin or intolerant to statin.
- None of combination lipid lowering therapy trials with Ezetimibe have been evaluated for event reduction.

Statin+Ezetimibe \( \leq \) Statin+Niacin.

- Evidence-based approach: Maximizing statin dosage before adding Ezetimibe to statin.


Future therapies for Raising HDL

- Many novel therapies.
- CETP inhibitor.
- Dual and pan-PPAR agonists.
Dual PPAR α/Υ agonist
Aleglitazar

- PPAR α → ↑ LP lipase activity → ↓ TG secretion from liver and increased β oxidation in liver.

- Result in ↓ TG and ↑ HDL-c.

- PPAR Υ → improve insulin sensitivity.

- Muraglitizar- 2006 – increased CV events.

- Tesaglitazar- Renal toxicity.
Aleglitazar

**ALECARDIA**
- Phase III Randomized.
- Aleglit Vs Placebo.
- Safety and Efficacy Study.
- 6000-7000 pt with recent ACS and DM II.
- CV mortality and morbidity.

**SYNCHRONY**
- Phase-II Randomised.
- Dose-Ranging and safety profile Study (Aleglit Vs Pio Vs Placebo) in DMII.
- Dose related Reduction A1c (1.35% with Max dose of 600 mg).
- Increased HDL -20.7%.
- Reduced LDL-15.5%.
- ↓ Apo B.
CETP INHIBITORS

- Torcetrapib- ILLUMINATE Trial
- Dalcetrapib- (JTT-705)
- Anacetrapib- (MK-0859)
Dalcetrapib

- Irreversibly binds to CETP via disulfide bond.
- No effect on BP and aldosterone.
- Less potent than Torcetrapib in raising HDL and apo A-I (36% vs 16%).
- Diarrhea and infection.
- No effect on fasting glucose or HgA1c.
- Dal-outcome trial – ongoing.

• Stein EA et al. Safety and tolerability of dalcetrapib. Eur Heart J 2010.
• Kallend D et al. Dalcetrapib safety and tolerability in DMII and/or metabolic syndrome. Diabetologia 2009.
DEFINE: Determining the efficacy and tolerability of CETP Inhibition with Anacetrapib

- Anacetrapib Vs Placebo
- LDL-39.8% ↓ (P<0.001).
- HDL-138.1% ↑ (P<0.001).
- Acceptable Safety Profile.
- No changes in BP, electrolyte or aldosterone.
- Cardiovascular events - in 16 pt in anacetrapib (2.0%) Vs 21 pt in placebo (2.6%) (P=0.40).

CP Cannon: NEJM: Nov 2010
REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification)

- On going phase III efficacy study.
- Randomized Placebo control trial.
- Major coronary event.
- 30,000 pt with 4 years follow up.
Take Home Messages

- **Combination therapies** (Statin+Fibrate or Statin +Niacin) are beneficial only in selected pt. (baseline high TG and low HDL )

- **LDL-c goal** should not only be the numbers (<70 or 100 mg/dl), it should be the amount of reduction.( at least 30 %)

- **New Lp parameters** (such as Lp (a) and LDL particles and size) should be used in high risk pt and to assess the medication adjustment in pt already on statin and LDL-c is at goal.
Future Work

- Functionality test of HDL, not only quantity.
- Better tools to assess the CV risk.
- Novel Therapy for residual CV risk reduction.
More Work and More Hope

“Let’s do the good cholesterol, bad cholesterol bit.”

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