“Cardiovascular Disease and Diabetes: What’s Left to be Accomplished with Lipids and Lipoproteins?”

Rocky Mountain Metabolic Syndrome Symposium
May 15, 2020

Robert H. Eckel, M.D.
Professor of Medicine, Emeritus
Division of Endocrinology, Metabolism & Diabetes
Division of Cardiology
Charles A. Boettcher II Chair in Atherosclerosis
University of Colorado Anschutz Medical Campus
American Diabetes Association, President Science & Medicine
American Heart Association, Past President

Duality of Interests

Consultant/Advisory Boards
• Kowa - PROMINENT
• Novo Nordisk

Medical Education
• CMHC
• Medscape
• Medical Education Resources
• Medtelligence
• VOX Media

Lipoprotein Classes

Lipoprotein (a)
What’s Left to be Accomplished with Lipids and Lipoproteins in Patients with Diabetes?

• How much LDL-C lowering is needed?
  – Should ezetimibe be used more frequently in patients with diabetes?
  – Should we be concerned about the absence RCTs for LDL lowering in patients with T1DM?
• Are elevated triglycerides truly a risk factor for ASCVD in patients with T2DM and if so, does triglyceride lowering reduce risk?
  – What’s the optimal management of severe hypertriglyceridemia?
• Lipoprotein (a) – should levels be measured in patients with diabetes and if so, will antisense therapy reduce ASCVD risk?
• HDL, ASCVD risk and diabetes; no longer a concern?

So if my patient with T2DM has experienced an ASCVD event or is at very high CVD risk, what is the treatment goal for LDL-C?
2019 ACC/AHA Guidelines: High Risk of CVD Events

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
<th>Secondary Prevention (for past 12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS (before past 12 mo)</td>
<td>History of diabetes (other than recent ACC/AHA treat limit)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
<td>Symptomatic peripheral arterial disease (history of claudication or arterial bypass or amputation N.A.S.)</td>
</tr>
</tbody>
</table>

Class I (Strong) Benefit >>> Risk

Class IIa (Moderate) Benefit >> Risk

Class IIb (Weak) Benefit > Risk

LDL-C ≥ 190 mg/dL

No risk assessment; High-intensity statin

Diabetes mellitus and age 40-75 y

Moderate-intensity statin

Diabetes mellitus and age 40-75 y

Risk assessment to consider high-intensity statin

Age >75 y

Clinical assessment, Risk discussion

Grundy SM et al, Circulation 139:1083, 2019

AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline (2018) on the Management of Blood Cholesterol:
Primary Prevention

Primary Prevention: Assess ASCVD Risk in Each Age Group Emphasize Adherence to Health Lifestyle

Class I (Strong): Benefit >>> Risk

Class IIa (Moderate): Benefit >> Risk

Class IIb (Weak): Benefit > Risk

Grundy SM et al, Circulation 139:1083, 2019

Statins in Patients with Diabetes: CTT 2008

(n=3247 major CVD events)

PCSK9 is proprotein convertase subtilisin/kexin type 9 (PCSK9)

I think that an LDL-C ~70 mg/dL is all that is needed.

The lower the LDL-C the better!

Can LDL-C Be Too Low?

- Abetalipoproteinemia & homozygous hypobetalipoproteinemia
  - Autosomal recessive
  - MTP, and/or apo B and LIMA1 gene mutations
  - Absent apo B-containing lipoproteins
    - Chylomicrons, VLDL, LDL
  - Neurological and ophthalmological sequela prevented by fat-soluble vitamins
  - Malabsorption prevented by low fat diet + essential fatty acids
  - Hepatic steatosis and AST/ALT elevations
  - No ASCVD
  - PCSK9 inhibitor trials without adverse effects

Lee J & Hegele RA, J Inherit Metab Dis 37:333, 2014
Benefits of LDL-C Lowering Begin to Plateau

Ezetimibe

Is the drug underutilized in patients with diabetes?

IMRPOVE-IT: Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke
Circulation

ORIGINAL RESEARCH ARTICLE

Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus

Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

BACKGROUND: Despite, when added to statin therapy, reduce cardiovascular events after acute coronary syndrome. We evaluated outcomes stratified by diabetes mellitus (DM).

METHODS: In IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial, 18,102 patients after acute coronary syndrome with concomitant DM were randomized to ezetimibe (10 mg) or placebo. The primary composite end point was cardiovascular death, major coronary events, and stroke. The primary composite end point was cardiovascular death, major coronary events, and stroke. The primary composite end point was cardiovascular death, major coronary events, and stroke. The primary composite end point was cardiovascular death, major coronary events, and stroke.

IMPROVE-IT: Composite Efficacy Outcomes Stratified by Treatment and Diabetes Mellitus Status

Markers of Pathways of Cholesterol Synthesis and Absorption
Cholesterol Absorption and Synthesis in T1DM

Now what about LDL-C reductions in patients with T1DM?

Relationship of HbA1c with CVD is Mediated over Time by Systolic BP and LDL-C in T1DM: DCCT/EDIC Study
Cholesterol Treatment Trialists 2010 Meta-analysis: Statin & CHD Events
(26 Trials, 170,000 Participants)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Untreated</th>
<th>Statin-Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>53.0%</td>
<td>56.6%</td>
</tr>
<tr>
<td>Age</td>
<td>36.4±17.7</td>
<td>30.4±17.7</td>
</tr>
<tr>
<td>Diabetes Duration</td>
<td>21.0±13.2</td>
<td>34.0±13.8</td>
</tr>
<tr>
<td>Diabeteens</td>
<td>12.1%</td>
<td>12.8%</td>
</tr>
<tr>
<td>BMI</td>
<td>25.1±4.3 kg/m²</td>
<td>26.4±4.5 kg/m²</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.0±1.4%</td>
<td>8.2±1.3%</td>
</tr>
<tr>
<td>eGFR</td>
<td>1.9±0.9 mL/min</td>
<td>1.9±0.9 mL/min</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>123±15 mm Hg</td>
<td>153±17 mm Hg</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.07±0.8 mmol/L</td>
<td>1.34±1.08 mmol/L</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.62±0.4 mmol/L</td>
<td>1.66±0.3 mmol/L</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.60±0.77 mmol/L</td>
<td>2.66±0.95 mmol/L</td>
</tr>
</tbody>
</table>
‘Statin’ Therapy and Death in Patients with T1DM

‘Statin’ Therapy on CVD and Death in Patients with T1DM:
Overall Cohort

‘Statin’ Therapy on CVD and Death in Patients with T1DM:
Matched Cohort (n=4025 each)
## Swedish National Diabetes Registry Statin Study: Conclusions

Benefit of statins on CVD in T1DM demonstrated but these data are:

- Observational
- Matched cohort – reduced benefit
  - Exclusion of high-risk treated T1DM patients with CVD wherein greatest benefit of treatment would be expected
- Statin doses or degree of LDL-C lowering not identified
- Unknown confounders not identified
- Is an RCT ethical?

## What’s Left to be Accomplished with Lipids and Lipoproteins in Patients with Diabetes?

- How much LDL-C lowering is needed?
  - Should ezetimibe be used more frequently in patients with diabetes?
  - Should we be concerned about the absence RCTs for LDL lowering in patients with T1DM?
- Are elevated triglycerides truly a risk factor for ASCVD in patients with T2DM and if so, does triglyceride lowering reduce risk?
  - What’s the optimal management of severe hypertriglyceridemia?
- Lipoprotein (a) – should levels be measured in patients with diabetes and if so, will antisense therapy reduce ASCVD risk?
- HDL, ASCVD risk and diabetes; no longer a concern?

## But, hypertriglyceridemia + reduced levels of HDL-C is the most common lipid/lipoprotein disorder in patients with T2DM!

But does hypertriglyceridemia cause ASCVD in patients with T2DM?
So if it’s not triglycerides that cause ASCVD in patients with hypertriglyceridemia and T2DM, what is it?

It’s Likely the Cholesterol Content of VLDL and Chylomicron Remnants

The plaque is mostly cholesteryl ester, not TG!

Differential Diagnosis of Combined Hyperlipidemia (Mixed Dyslipidemia)

- ↑VLDL (TG) + ↑LDL-C in >90%
  - Genetic
  - Acquired
    - Macroalbuminuria
- Broad beta disease (Type III) - ↑β-VLDL: <10%
  - Apo E2/E2
  - Combined hyperlipidemia requires ↑ production of VLDL
- Hepatic lipase deficiency – extremely rare
Importance of T2DM in Broad Beta Disease

- 26 Japanese patients with apoE2/2 genotype
- Lipids
  - Total cholesterol – 256 mg/dL
  - Triglycerides – 374 mg/dL
  - LDL-C – 74 mg/dL
  - Remnant cholesterol (RLP-C) – 49 mg/dL
  - RLP-C >30 mg/dL & RLP-C/TG ratio >0.1 diagnostic
- 54% with type 2 diabetes
- 66% with the metabolic syndrome
- 42% with coronary heart disease (CHD)


Unanswered Question about Hypertriglyceridemia and ASCVD in Patients with T2DM

- Does hypertriglyceridemia cause ASCVD?
- Will pemafibrate reduce CVD events and if so, is TG lowering explanatory?
- If TG lowering failed to relate to the benefit of icosapent ethyl, what is the mechanism?
  - Is icosapent ethyl (Vascepa) safe?
    - Bleeding, atrial fibrillation
  - Is icosapent ethyl (Vascepa) affordable?
  - What about other omega-3 fatty acid preparations, are they equally effective?
- Outcomes Study to Assess Efficacy of Residual Risk Reduction With EpaNova (omega-3-carboxylic acids) in High CV Risk Patients With Hypertriglyceridemia (STRENGTH) – expected completion date, Oct 14, 2020
- OTC preparations, is their composition they claim to contain?

Exam Findings Associated with Severe Hypertriglyceridemia

- Lipemia Retinallis
- Eruptive Xanthomas
- Lipemic Serum
Optimal Treatment of Severe Hypertriglyceridemia in T2DM?

• Dietary fat restriction until TG <1000-1500 without TG-lowering drugs?
  – Chait A & Eckel RH, Ann Int Med 170:626-2019
• Dietary fat restriction with TG-lowering drugs continued?
  – Berglund L et al, JCEM 97:2960, 2012
• Insulin infusion?
• Hepatin Infusion?
  – Nuchay MS et al, Arch Endo Metab 61:198, 2017
• Plasma exchange?
  – Jaglekar K et al, Thor-Ash Endo Metab 8:49, 2017
• Antisense ApoCIII RNA?
• ANGPTL3 monoclonal antibody or anti-sense RNA?
  – Chaudhry R et al, Exp Rev Clin Pharm 11:589, 2018

What’s Left to be Accomplished with Lipids and Lipoproteins in Patients with Diabetes?

• How much LDL-C lowering is needed?
  – Should ezetimibe be used more frequently in patients with diabetes?
  – Should we be concerned about the absence RCTs for LDL lowering in patients with T1DM?
• Are elevated triglycerides truly a risk factor for ASCVD in patients with T2DM and if so, does triglyceride lowering reduce risk?
  – What’s the optimal management of severe hypertriglyceridemia?
• Lipoprotein (a) – should levels be measured in patients with diabetes and if so, will antisense therapy reduce ASCVD risk?
• HDL, ASCVD risk and diabetes; no longer a concern?
Mechanisms by Which Lp(a) Mediates CVD

- Macrophage IL-1β expression
- Monocyte cytokine release
- Monocyte chemokine expression
- Oxidized Phospholipids
- Oxidation of palmitate
- SMAC expression
- Plasminogen activation
- Fibrin degradation
- EIC-PAI-1 expression
- TFPI activity
- Platelet responsiveness

Coronary Heart Disease Risk in Icelandic Patients with T2DM Based on Lipoprotein (a) Molar Concentration

To convert nM to mg/dL, divide by ~2.5
Prognostic Impact of Lipoprotein (a) on MACE over 10 Years in Patients with T2DM on Statins after PCI

Takahashi N et al; J Card, Feb. 2020

Lipoprotein(a) Reduction with Hepatocyte-directed Antisense Oligonucleotide AKCEA-Apo(a)-LRx in Persons with CVD (n=286 with Lp(a) > 60 mg/dL)

Tsamikas S et al, NEJM, 382:244, 2020

What’s Left to be Accomplished with Lipids and Lipoproteins in Patients with Diabetes?

- How much LDL-C lowering is needed?
  - Should ezetimibe be used more frequently in patients with diabetes?
  - Should we be concerned about the absence RCTs for LDL lowering in patients with T1DM?
- Are elevated triglycerides truly a risk factor for ASCVD in patients with T2DM and if so, does triglyceride lowering reduce risk?
  - What’s the optimal management of severe hypertriglyceridemia?
- Lipoprotein (a) – should levels be measured in patients with diabetes and if so, will antisense therapy reduce ASCVD risk?
- HDL, ASCVD risk and diabetes; no longer a concern?
HDL-C, Diabetes, ASCVD

• Levels of HDL-C are reduced in patients with T2DM and relate to ASCVD.
• Although levels of HDL-C are increased, HDL is dysfunctional in patients with T1DM.
• Clinical trials wherein HDL-C levels are increased by drugs have failed to reduce ASCVD.
• But, HDL mimetics that mediate reverse cholesterol transport are being tested.

Sei YJ et al, Biomaterials 170:58, 2018

Thank You!