Triglycerides in Cardiovascular Prevention

Nevrez Koylan M. D., FACC, FESC, EHS
Professor of Medicine
Anadolu Health Center
Disclosures

Nothing to disclose related to this meeting and topic
• An Overview of Triglycerides and Triglyceride Metabolism

• Triglycerides, Atherogenic Dyslipidemia and Atherosclerosis

• Triglycerides and Atherosclerotic Vascular Disease

• Treatment of Hypertriglyceridemia
• An Overview of Triglycerides and Triglyceride Metabolism

• Triglycerides, Atherogenic Dyslipidemia and Atherosclerosis

• Triglycerides and Atherosclerotic Vascular Disease

• Treatment of Hypertriglyceridemia
What is a Triglyceride?

Glycerol + 3 Fatty Acids → Triglyceride

+ 3 H₂O
An Overview of Lipid Metabolism
Cholesterol Esters in Lipoproteins

Watts GF, Ooi EMM, Chan DC. Nature Reviews Cardiology 2013, 10, 648–661
Dietary Carbohydrate Transforms to VLDL

Hudgins LC. Et al. J Lipid Res 2000, 41:595
Development of Hypertriglyceridemia

- VLDL
- Chylo-microns
- Remnants

Defective Lipolysis by Lipoprotein Lipase

Miller M. U Maryland Unpublished data
• An Overview of Triglycerides and Triglyceride Metabolism

• **Triglycerides, Atherogenic Dyslipidemia and Atherosclerosis**

• **Triglycerides and Atherosclerotic Vascular Disease**

• **Treatment of Hypertriglyceridemia**
Multiple Lipid Fractions Associated With CHD Risk

Risk of CHD by Triglyceride Level

*Framingham Heart Study*

Castelli WP. *Can J Cardiol* 1988, 4:5A-10A
Hypertriglyceridaemia, Triglyceride-rich Lipoproteins, And Atherogenesis

Proinflammatory lipolysis products (e.g. Oxidized lipids, saturated FFA)

Inflammation
Coagulation
Endothelial dysfunction
Oxidative stress
Thrombosis

Watts GF, Ooi EMM, Chan DC. Nature Reviews Cardiology 2013, 10, 648–661
Possible Atherogenic Changes Accompanying Hypertriglyceridemia

- Increased VLDL Cholesterol rich remnants
- Low HDL
- Small dense LDL
- Increased chylomicron remnants
- Coagulation changes
Atherogenic Dyslipidemia

Atherogenic dyslipidaemia: the combination of elevated TRL remnants and/or low HDL-C.

- Triglycerides are predominantly carried in fasting conditions in very low-density lipoproteins (VLDLs) and their remnants, and postprandially in chylomicrons and their remnants.
- The generic term ‘triglyceride-rich lipoprotein remnants’, therefore, relates to chylomicron and VLDL particles which have undergone dynamic remodelling in the plasma after secretion from the intestine (chylomicrons) or liver (VLDL)
- **Pattern of high TG, small, dense, LDL-C, and low HDL-C**
Pathogenesis of Atherogenic Dyslipidemia

**Diabetes, Insulin resistance**

**Dietary Fat**

**Dietary Carbohydrates**

**Sugar**

**Triglyceride**

**Small dense LDL**

**HDL**

**LDL**

**VLDL**

**VLDL Remnants**

**Chylomicron Remnants**

**Apo B100**

**Apo B48**

**Apo A1**

**LPL**

**Plasma pool of triglyceride rich lipoproteins**

**CETP**

**CE**

**Watts GF, Ooi EMM, Chan DC. Nature Reviews Cardiology 2013, 10, 648–661**
Triglycerides and Lipoprotein Remnants

Nordestgaard BG, unpublished results, 2010
Remnant (Non- (HDL-C+LDL-C)) Cholesterol

• An Overview of Triglycerides and Triglyceride Metabolism

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• Treatment of Hypertriglyceridemia
Triglycerides and CAD

- Difficult to show TG as an independent risk factor for CAD
- “Little old man in traffic”
- Elevated TG is a risk when LDL/HDL ratio is > 5
- In mixed dyslipidemia trials, apo B is a better risk predictor than LDL
- Role of Non HDL
Predictors of CHD Events in the ARIC Study

In 10-year follow-up of 12,339 men and women without CHD:

Multivariate predictors

LDL-C  HDL-C
Lp(a)    TG  (in women only)

Hazard Ratios for CHD or Ischemic Stroke Across Quantiles of Usual Triglyceride, HDL-C, and Non-HDL-C Levels

Hypertriglyceridemia Increase CHD Risk in Patients with Low HDL Levels

Increase in CVD Risk Due to Hypertriglyceridemia (Univariate analysis)

Relative risks (RR) and 95% confidence (CI) were calculated and standardized with respect to a 1 mmol/L increase in triglyceride.

Available Prospective Studies Of Triglycerides And CHD In Essentially General Populations

Risk ratio (95% CIs) (top third vs. bottom third)

<table>
<thead>
<tr>
<th>Study Description</th>
<th>No. of CHD cases</th>
<th>a Un-corrected for within-individual triglycerides variations</th>
<th>b Corrected for within-individual triglycerides variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western European and North American Populations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reykjavik Study\textsuperscript{32}</td>
<td>2459</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIC-Norfolk Study\textsuperscript{33}</td>
<td>1123</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies published between 1995-2005\textsuperscript{2,4,9,11,13,16,21,25}</td>
<td>3785</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies published before 1995\textsuperscript{3,10,12,14-17,19,20,22-24,26-28}</td>
<td>2791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian and Pacific Populations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APCSC\textsuperscript{30}</td>
<td>850</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Triglycerides and MI Risk in 12510 Middle Aged Men

Seri 1

Stevanow L, Kjellstrom T; Atherosclerosis 1999, 142:243-247
Non-HDL Cholesterol and CVD Risk

• Non-HDL-C calculation
  • Non-HDL-C = TC – HDL-C
  • Non-HDL-C goal
  • 30 mg/dL above goal for LDL-C

• Significance of non-HDL-C
  • Encompasses all known and potential atherogenic lipid particles
  • (linearly proportional to Apo B)
  • Has been shown to be a stronger predictor of cardiovascular death than LDL-C, especially in women

LDL-C and Non-HDL-C as Targets of Therapy

- LDL: major atherogenic lipoprotein
- VLDL: additional atherogenic lipoprotein
- Non-HDL: LDL + VLDL
- LDL cholesterol (LDL-C): traditional primary target for clinical intervention
- Non-HDL cholesterol (Non-HDL-C): appropriate target for clinical intervention
Advantages of Non-HDL-C as Target for Clinical Intervention

• Sum of all atherogenic lipoproteins (LDL + VLDL)

• Does not require fasting for accurate measurement

• Subsumes most cases of elevated triglycerides

• Growing evidence for greater predictive power than LDL-C

• Essentially equivalent to apolipoprotein B in predictive power
Postprandial Triglyceride Levels in Subjects with and without Coronary Artery Disease (CAD)


*P=0.025; †P≤0.001.
Remnant Cholesterol As A Causal Risk Factor For Ischemic Heart Disease

Remnant Cholesterol and CHD Risk

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Lowering LDL-C Decreases CHD Risk

**LDL-C mg/dL (mmol/L)**

- 40 (1.0)
- 60 (1.6)
- 80 (2.1)
- 100 (2.6)
- 120 (3.1)
- 140 (3.6)
- 160 (4.1)
- 180 (4.7)
- 200 (5.2)

**event (%)**

- 0
- 5
- 10
- 15
- 20
- 25
- 30

**Rx - statin**
**PRA – pravastatin**
**ATV - atorvastatin**

**Primary prevention**

- WOSCOPS – Placebo
- LIPID – Placebo
- CARE – Placebo
- HPS – Placebo

**Secondary prevention**

- PROVE-IT – ATV10
- TNT – ATV80
- HPS – Rx
- AFCAPS – Placebo
- ASCOT - Rx

**Event (%)**

- 0
- 5
- 10
- 15
- 20
- 25
- 30
Residual Risk in Statin Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>% RRR</th>
<th>Risk Reduction</th>
<th>Residual Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TECAPS</td>
<td></td>
<td></td>
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<tr>
<td>JUPITER</td>
<td></td>
<td></td>
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<tr>
<td>HPS</td>
<td></td>
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<tr>
<td>AS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CARE</td>
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<tr>
<td>LIPID</td>
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<tr>
<td>PROSPER</td>
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<tr>
<td>CARDS</td>
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<tr>
<td>ASCOT</td>
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</tbody>
</table>

1º prevention  | High risk | 2º prevention

[Bar chart showing residual risk and risk reduction across different trials]
## Risk Difference vs Placebo of High TG Subgroups
### Large-scale, Primary and Secondary CVD Prevention Trials

<table>
<thead>
<tr>
<th>Trial (drug)</th>
<th>Primary endpoint: entire cohort (P)</th>
<th>Lipid subgroup criterion</th>
<th>Primary endpoint: subgroup post-hoc (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (gemfibrozil)</td>
<td>−34% (&lt;0.02)</td>
<td>TG &gt;204 mg/dL LDL-C/HDL-C ratio &gt;5.</td>
<td>−72% (0.005)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>−9% (0.26)</td>
<td>TG ≥200 mg/dL</td>
<td>−39.5% (0.02)</td>
</tr>
<tr>
<td>VA-HIT (gemfibrozil)</td>
<td>−22% (0.006)</td>
<td>TG ≥150 mg/dL</td>
<td>−27% (0.01)</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>−11% (0.16)</td>
<td>TG ≥204 mg/dL HDL-C &lt;40 mg/dl (men) or &lt;50 mg/dl (women)</td>
<td>−27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (fenofibrate)</td>
<td>−8% (0.32)</td>
<td>TG ≥204 mg/dL HDL-C ≤34 mg/dL (Prespecified)</td>
<td>−31% (&lt;0.05)</td>
</tr>
<tr>
<td>JELIS (EPA)</td>
<td>−19% (0.011)</td>
<td>TG ≥150 mg/dL HDL-C &lt;40 mg/dl</td>
<td>−53% (.043)</td>
</tr>
<tr>
<td>AIM-HIGH (niacin)</td>
<td>+2% (0.79)</td>
<td>TG ≥200 mg/dL HDL-C ≤32 mg/dl</td>
<td>−36% (0.032)</td>
</tr>
</tbody>
</table>

ACCORD=Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH=Atherothrombosis Intervention in MetS with Low HDL/High TG: Impact on Global Health Outcomes; BIP=Bezafibrate Infarction Prevention; FIELD=Fenofibrate Intervention and Event Lowering in Diabetes; HHS=Helsinki Heart Study; JELIS=Japan EPA Lipid Intervention Study; VA-HIT=Veterans Affairs HDL Intervention Trial.

Low Carb vs. Low Fat Diets on Triglycerides

- Triglycerides (mg/dL)

- Low Carb

- Low Fat

(1) Foster GD, et al. 2003
(2) Samaha FF, et al. 2003
(3) Sendikke SB, et al. 2003
(4) Brenna BJ, et al. 2003
(5) Aude YW, et al. 2004
(6) Yanoy WS JR, et al. 2004
(7) Meckling KA, et al. 2004
(8) Dyer ME, et al. 2004
(9) Toor NC, et al. 2005
(10) Dyson PA, et al. 2005
(12) Shai L, et al. 2005
(13) Volek JS, et al. 2005
(14) Tey J, et al. 2005
(15) Brinkworth GD, et al. 2005
(17) Kraus NF, et al. 2005
(18) Guldbrand, et al. 2005
(19) Ateroskleroz Demeği
(20) Association with Johns Hopkins Medicine
### Statins Reduce CVD Events in HTG Patients

<table>
<thead>
<tr>
<th>Trial (Subgroup, mg/dL) (Drug)</th>
<th>Risk difference vs placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Main Study</td>
<td>Subgroup</td>
</tr>
<tr>
<td>WOSCOPS (TG ≥148) (Pravastatin)</td>
<td>−31%</td>
<td>−32%</td>
</tr>
<tr>
<td>CARE (TG ≥144) (Pravastatin)</td>
<td>−24%</td>
<td>−15%</td>
</tr>
<tr>
<td>PPP Project (TG ≥200) (Pravastatin)</td>
<td>−23%</td>
<td>−15%</td>
</tr>
<tr>
<td>4S (TG &gt;159, HDL-C &lt;39) (Simvastatin)</td>
<td>−34%</td>
<td>−52%</td>
</tr>
<tr>
<td>JUPITER (TG ≥150) (Rosuvastatin)</td>
<td>−44%</td>
<td>−21%</td>
</tr>
<tr>
<td>CTT (TG &gt;177) (Various)</td>
<td>−21%</td>
<td>−24%</td>
</tr>
</tbody>
</table>
EPA+DHA & Lipid Levels in Patients w/ TG>500 mg/dL vs. Simvastatin

# n-3 Fatty Acid Randomized Controlled Trials Assessing Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Trial, Year</th>
<th>Population</th>
<th>Interventions Compared</th>
<th>Duration years</th>
<th>Lipid Effects</th>
<th>Endpoint</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DART 1989</td>
<td>2,033 men with recent MI (mean 41 days)</td>
<td>2 servings/wk fatty fish (or fish oil capsules) vs other dietary advice</td>
<td>2</td>
<td>No change in TC</td>
<td>IHD events Total deaths</td>
<td>0.84 (0.66-1.07) 0.71 (0.54-0.93)</td>
</tr>
<tr>
<td>GISSI-P 1999</td>
<td>11,324 men with recent MI (≤ 3 mo)</td>
<td>Usual care plus 882 mg/day EPA+DHA, vitamin E, both or neither</td>
<td>3.5</td>
<td>No change in TC, LDL-C or HDL-C; 5% decrease in TG</td>
<td>Major CV events</td>
<td>0.90 (0.82-0.99)</td>
</tr>
<tr>
<td>JELIS 2007</td>
<td>18,645 patients with total cholesterol ≥ 6.5 mmol/l (with and without CHD history)</td>
<td>1.8 g/day EPA vs usual care</td>
<td>4.6</td>
<td>No change in TC, LDL-C or HDL-C; 6% decrease in TG</td>
<td>Coronary events Non-fatal events Coronary deaths Sudden deaths</td>
<td>0.81 (0.69-0.95) 0.81 (0.68-0.96) 0.94 (0.57-1.56) 1.06 (0.55-2.07)</td>
</tr>
<tr>
<td>GISSI-HF 2008</td>
<td>6975 patients with heart failure</td>
<td>840 mg/day EPA+DHA vs placebo (not defined)</td>
<td>3.9</td>
<td>No change in TC, LDL-C or HDL-C; 5% decrease in TG</td>
<td>Death or hospitalization for CVD</td>
<td>0.94 (0.89-099)</td>
</tr>
</tbody>
</table>

Recent n-3 Fatty Acid Randomized Controlled Trials Assessing Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Trial, Year</th>
<th>Population</th>
<th>Interventions Compared</th>
<th>Duration years</th>
<th>Lipid Effects</th>
<th>Endpoints</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMEGA 2010&lt;sup&gt;178&lt;/sup&gt;</td>
<td>3,851 patients with recent MI (≤ 2 wks)</td>
<td>840 mg/day EPA+DHA vs placebo (olive oil)</td>
<td>1</td>
<td>No change in LDL-C; 4% decrease in TG</td>
<td>Major CV events Sudden deaths</td>
<td>1.21 (0.96-1.52)</td>
</tr>
<tr>
<td>Alpha-Omega 2010&lt;sup&gt;149&lt;/sup&gt;</td>
<td>4,837 patients with history of MI (median 3.7 yrs)</td>
<td>376 mg/day EPA+DHA vs placebo margarine and ALA (1.9 g/day) groups combined</td>
<td>3.4</td>
<td>No change in any lipid class</td>
<td>Major CV events CHD deaths</td>
<td>1.01 (0.87-1.17)</td>
</tr>
<tr>
<td>SU.FOL.OM3 2010&lt;sup&gt;179&lt;/sup&gt;</td>
<td>2,501 patients with recent coronary or cerebral ischemic event (median 101 days)</td>
<td>600 mg/day EPA+DHA vs placebo (not defined) and B vitamin groups combined</td>
<td>4.2</td>
<td>NR</td>
<td>Major CV events CHD deaths</td>
<td>1.08 (0.79-1.47)</td>
</tr>
<tr>
<td>ORIGIN 2012&lt;sup&gt;189&lt;/sup&gt;</td>
<td>12,536 patients with diabetes, IGT, or IFG, most with CVD</td>
<td>840 mg EPA+DHA vs olive oil placebo</td>
<td>6.2</td>
<td>No change in TC, LDL-C or HDL-C; 11% decrease in TG</td>
<td>CVD deaths Major CV events</td>
<td>0.98 (0.87-1.10)</td>
</tr>
<tr>
<td>Risk and Prevention 2013&lt;sup&gt;181&lt;/sup&gt;</td>
<td>12,513 patients at increased risk for CHD but without MI</td>
<td>850 mg EPA+DHA vs olive oil placebo</td>
<td>5.0</td>
<td>NR</td>
<td>Death, non-fatal or stroke CVD death</td>
<td>0.98 (0.88-1.08)</td>
</tr>
</tbody>
</table>
JELIS: Patient Subgroup - TG >150mg/dL and HDL <40mg/dL

Hazard ratio and P value adjusted for age, gender, smoking, diabetes, and hypertension. HR = hazard ratio; CI = confidence interval.
Fibrate Trials and CVD Events

The Effect of Fibrates on CVD Events

Effects of Fibrates on CHD Events by Cholesterol and TG Levels

<table>
<thead>
<tr>
<th>Trials, n</th>
<th>Mean baseline HDL concentration (mmol/L)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1.00</td>
<td>0.773 (0.606-0.985)</td>
</tr>
<tr>
<td></td>
<td>≥ 1.00</td>
<td>0.868 (0.787-0.957)</td>
</tr>
<tr>
<td>Mean baseline triglyceride concentration (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 2.00</td>
<td>0.888 (0.822-0.960)</td>
</tr>
<tr>
<td></td>
<td>≥ 2.00</td>
<td>0.682 (0.530-0.877)</td>
</tr>
<tr>
<td>Mean LDL concentration (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 3.5</td>
<td>0.866 (0.798-0.940)</td>
</tr>
<tr>
<td></td>
<td>≥ 3.5</td>
<td>0.672-0.466-0.970</td>
</tr>
</tbody>
</table>

AIM-HIGH
Niacin Plus Statin to Prevent Vascular Events

Inclusion Criteria
- Age ≥45
- History of vascular disease
- Atherogenic dyslipidemia
  - LDL-C ≤160 mg/dL
  - HDL-C ≤40 mg/dL men or ≤50 mg/dL women
  - TG ≥150 mg/dL ≤400 mg/dL
- For patients entering the trial on a statin
  - HDL-C ≤42 mg/dL men or ≤53 mg/dL women
  - TG ≥125 mg/dL ≤400 mg/dL

Primary Endpoint
Composite Endpoint for first
- CHD death
- nonfatal MI
- ischemic stroke
- hospitalization for high-risk non-STEMI ACS

Secondary Endpoint
- composite of CHD death, nonfatal MI, or ischemic stroke out to common date
AIM HIGH: Primary Outcome

Cumulative % with Primary Outcome

- **Combination Therapy**
- **Monotherapy**

HR 1.02, 95% CI 0.87, 1.21
Log-rank P value = 0.79

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>N at risk (Monotherapy)</th>
<th>N at risk (Combination Therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>1</td>
<td>1581</td>
<td>1606</td>
</tr>
<tr>
<td>2</td>
<td>1381</td>
<td>1366</td>
</tr>
<tr>
<td>3</td>
<td>910</td>
<td>903</td>
</tr>
<tr>
<td>4</td>
<td>436</td>
<td>428</td>
</tr>
</tbody>
</table>

16.4% (Combination Therapy)
16.2% (Monotherapy)
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- 5-year study against a background of usual care, including the option to add other lipid-lowering therapies

9795 Type 2 Diabetes Patients

No clear indication for lipid lowering therapy at baseline

Fenofibrate 200 mg/day, n = 4895
+Other lipid-lowering therapies

5 Years or 500 CHD Events

Placebo, n = 4900
+Other lipid-lowering therapies

FIELD: Primary and Secondary Endpoints

11% Reduction  
$P = 0.16$  
(Primary EP)

24% Reduction  
$P = 0.01$  

19% Increase  
$P = 0.22$  

21% Reduction  
$P = 0.003$  
(Secondary EP)

FIELD: Total CVD Events in Patient Subgroups

**Patients With Low HDL-C**

- **14% Reduction**
- **ARR = 2.1%**
- **NNT = 48**
- **P = 0.02**

**Patients With Dyslipidemia**

- **14% Reduction**
- **ARR = 2.3%**
- **NNT = 44**
- **P = 0.06**

- **<40 mg/dL (men) and <50 mg/dL (women) at baseline**
- **Triglycerides ≥150 mg/dL and low HDL-C at baseline**

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study

- Question: Would statin plus a fibrate as compared with statin monotherapy reduce CVD in diabetics at high risk for CVD?
- 5518 patients with type 2 DM treated with open label simvastatin were treated with either masked fenofibrate or placebo
- Primary outcome measure: nonfatal MI, nonfatal stroke, or death from CV causes
- Follow-up: 4.7 years

- Results: Annual primary outcome was 2.2% in fenofibrate group and 2.4% in placebo group (NS)
- Annual rate of death was 1.5% in fenofibrate group and 1.6% in placebo group (NS)
- Prespecified subgroup analysis suggested heterogeneity in treatment according to sex, with a benefit for men and possible harm for women (P = 0.01 for interaction)
- Possible benefit seen in fenofibrate group if baseline triglycerides high (>204 mg/dL) and HDL-C low (<34 mg/dL): primary outcome rate 12.4% in fenofibrate group vs. 17.3% in placebo (P = 0.057 for interaction)

Primary Outcome & Total Mortality

Kaplan-Meier Estimates of Cumulative Incidence
Lipid Trial - Primary Outcome

Kaplan-Meier Estimates of Cumulative Incidence
Lipid Trial - Total Mortality

# ACCORD: Primary Outcome By Treatment Group and Baseline Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate % Events (# in grp)</th>
<th>Placebo % Events (# in grp)</th>
<th>Feno to Placebo Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.5% (2765)</td>
<td>11.3% (2753)</td>
<td></td>
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</tr>
<tr>
<td>LDL-c Tertile</td>
<td></td>
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</tr>
<tr>
<td>&lt;=84 mg/dl</td>
<td>9.4% (938)</td>
<td>12.2% (891)</td>
<td></td>
<td>0.1212</td>
</tr>
<tr>
<td>85-111 mg/dl</td>
<td>9.9% (934)</td>
<td>11.2% (922)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=112 mg/dl</td>
<td>12.4% (877)</td>
<td>10.6% (927)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-c Tertile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=34 mg/dl</td>
<td>12.2% (964)</td>
<td>15.6% (906)</td>
<td></td>
<td>0.2374</td>
</tr>
<tr>
<td>35-40 mg/dl</td>
<td>10.1% (860)</td>
<td>9.5% (866)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=41 mg/dl</td>
<td>9.1% (925)</td>
<td>9.0% (968)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride Tertile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=128 mg/dl</td>
<td>9.9% (891)</td>
<td>11.3% (939)</td>
<td></td>
<td>0.6422</td>
</tr>
<tr>
<td>129-203 mg/dl</td>
<td>10.5% (924)</td>
<td>9.9% (913)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=204 mg/dl</td>
<td>11.1% (934)</td>
<td>12.8% (888)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trig/HDL combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG204+/HDL&lt;=34</td>
<td>12.4% (485)</td>
<td>17.3% (456)</td>
<td></td>
<td>0.0567</td>
</tr>
<tr>
<td>All Others</td>
<td>10.1% (2264)</td>
<td>10.1% (2264)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1c Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1c &lt;= 8.0</td>
<td>8.7% (1324)</td>
<td>10.6% (1335)</td>
<td></td>
<td>0.2045</td>
</tr>
<tr>
<td>A1c 8.1+</td>
<td>12.2% (1435)</td>
<td>11.9% (1415)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ACCORD: Conclusion

• ACCORD Lipid does not support use of the combination of fenofibrate and simvastatin, compared to simvastatin alone, to reduce CVD events in the majority of patients with T2DM who are at high risk for CVD

• Subgroup analyses suggesting heterogeneity in response to combination therapy by gender or by the presence of significant dyslipidemia require further investigation
## Comparison Of ACCORD Subgroup Results With Those From Prior Fibrate Studies

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (Gemfibrozil)</td>
<td>-34% (0.02)</td>
<td>TG &gt; 200 mg/dl LDL-C/HDL-C &gt; 5.0</td>
<td>-71% (0.005)</td>
</tr>
<tr>
<td>BIP (Bezafibrate)</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 200 mg/dl</td>
<td>-39.5% (0.02)</td>
</tr>
<tr>
<td>FIELD (Fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG ≥ 204 mg/dl HDL-C &lt; 42 mg/dl</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-8% (0.32)</td>
<td>TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl</td>
<td>-31%</td>
</tr>
</tbody>
</table>
Association Estimated By Meta-regression Between Extent Of TG-lowering And Reduction In Risk Of A Major CV Event In Large Controlled Trials Of Fibrates

Approach for DM Patients with Dyslipidemia

• Start a Statin in any case!

• Combination therapy if necessary to achieve nonHDL targets

• DM with renal disease: statin plus ezetemibe(SHARP)/ba resin, statin plus fish oil, statin plus niacin (avoid feno)

• DM without renal disease but poorly controlled triglycerides or glucose: statin plus feno or fish oil/, niacin with caution
New Drugs: DGAT Inhibitors

Harris WS, Bulchandani D. Curr Opin Lipidol 2006;17:387-393
Apo C3 Inhibitors

- Apolipoprotein C-III (ApoC-III) is a small protein that resides on various lipoproteins
- Inhibits lipoprotein/hepatic lipases
- Impairs hepatic uptake of triglyceride (TG)-rich lipoproteins (such as lipoprotein remnants)
- Generally promotes hypertriglyceridemia.
- May contribute to insulin resistance
- May contribute to atherosclerosis
Hypertriglyceridemia and CVD - Conclusion

• Hypertriglyceridemia is an important but underestimated risk factor in the pathogenesis of atherosclerosis and must be treated
• Lifestyle modifications is the most important intervention
• For TG ≥1000 mg/dL, consider fibrate, high-dose long chain Ω-3 fatty acids and niacin; for 500-999 mg/dL and no history of pancreatitis, consider statins or any of the above
• For TG 200-499 mg/dL, targets of therapy are non-HDL-C and LDL-C, generally using statins
• If LDL-C falls to <40 mg/dL, therapy may be continued in absence of intolerance