Comprehensive Cardiovascular Risk Reduction In the Patients With Diabetes and Insulin Resistance: Addressing the Barriers and Overcoming the Challenges

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Pathogenic Continuum: Time and Severity

‘Normal’
Impaired Glucose Tolerance
Impaired Fasting Glucose
Pre-Diabetes

Type 2 Diabetes
Yrs: 0 5 10 20+ 12+

A1C 5.8 6.4 6.5 12+

Atherosclerosis
- NSTEMI
- STEMI
- CSA
- CHF
- CVD
- PVD
- SCD

Visceral adiposity
Lipid accumulation muscle, liver
Inflammation...
Pathogenic Continuum: Time and Severity

'Normal'
Impaired Glucose Tolerance
Impaired Fasting Glucose
Pre-Diabetes

Type 2 Diabetes
Yrs: 0 5 10 20+ 12+

A1C 5.8 6.4 6.5 12+

Atherosclerosis

Undiagnosed T2D?

Variables in clinical trial outcomes?

- NSTEMI
- STEMI
- CSA
- CHF
- CVD
- PVD
- SCD
Diabetes and Pre-Diabetes Are Present in Most MI patients

Consecutive patients presenting with an AMI, $n = 181$

Oral Glucose Tolerance Test (4 wks post-MI)

- 80% Diabetic
- 25% Prediabetes
- 35% Normal
- 40% No DM by Hx

Incidence of Undiagnosed Prediabetes and T2D

Stroke (n=238, OGTT)¹
  16% Undiagnosed T2D
  23% Pre-diabetes

Coronary Bypass (n = 7310, FPG)²
  5.2% Undiagnosed T2D
  Longer intubation, worse outcomes

ACS Japan (n=134, OGTT)³
  37% Impaired glucose tolerance
  10% Undiagnosed T2D

Glycated Hemoglobin, Diabetes, and CV Risk in Non-Diabetic Adults

11,092 adults without T2D or CVD
2nd visit, Atherosclerosis Risk in Communities (ARIC) study.

A1C Predicts Coronary Heart Disease Even At Lower ‘Normal’ A1Cs

*P<0.001 for linear trend across A1C categories.*
Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
N = 25,364 aged ≥30 years

Mortality hazard (%)

Follow-up (years)

*2-hour OGTT

Increased CVD Risk Exists Prior to Dx of T2D

Elevated Risk of Cardiovascular Disease Prior to Clinical Diagnosis of Type 2 Diabetes

CVD Risk 3.2 higher adjusting for all CVD risk factors

Pre-Diabetes and the Risk for Cardiovascular Disease

A Systematic Review of the Evidence

<table>
<thead>
<tr>
<th>Definition of Pre-diabetes</th>
<th>Risk of CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG (100-125 mg/dl)</td>
<td>1.18</td>
</tr>
<tr>
<td>IFG (110-125 mg/dl)</td>
<td>1.20</td>
</tr>
<tr>
<td>IGT</td>
<td>1.20</td>
</tr>
</tbody>
</table>

- Meta-analysis: 18 studies
- 175,152 participants

Diabetes, CVD and Death

Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults

<table>
<thead>
<tr>
<th></th>
<th>HbA1c (5.5-6.5)</th>
<th>HbA1c (6.0-6.5)</th>
<th>IFG (100-125 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.9</td>
<td>4.5</td>
<td>2.2</td>
</tr>
<tr>
<td>CHD</td>
<td>1.3</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2</td>
<td>2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Death</td>
<td>1.2</td>
<td>1.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

- The Atherosclerosis Risk in Communities (ARIC)
- Community-based prospective cohort
- 15,792 middle-aged adults from four U.S. communities.
- Whites and Blacks only
- 15 years follow-up

Atherosclerosis

Diabetic Atherosclerosis
Dysfunctional Adiposity and the Risk of Prediabetes and Type 2 Diabetes in Obese Adults

Neeland, McGuire, DeLemos et al

732 participants (43 yo, 65% women, 71% nonwhite)
No T2D, CVD at baseline – normal FPG (512)
Predictors of T2D over 7 yrs:
• Higher baseline visceral fat 2.4
• Fructosamine 2.0
• Fasting glucose level 1.9,
• Family hx T2D 2.3;
• SBP 1.3
• Weight gain over follow-up 1.06

No predictive value:
• BMI
• Total body fat
• Subcutaneous fat
Expansion of Adipose Tissue Mass Contributes to Pro-inflammatory State and Metabolic Dysfunction

Reprinted with permission.
Adverse Cardiometabolic Effects of Adipose Tissue

- Hypertension
- Atherogenic dyslipidemia
- Insulin resistance & Type 2 diabetes
- Inflammation
  - IL-6
  - CRP
  - TNF
- Atherosclerosis
- Thrombosis
- Adipsin
- Angiotensinogen
- Insulin
- FFA
- Resistin
- Leptin
- Lactate
- Adiponectin
- PAI-1

Reference:
Atherosclerosis in Youth Is Linked to Obesity and “Early” Insulin Resistance

Fatty Streaks
Men: Age 15-24

Aortic Strips

BMI (kg/m²)
<25
25-30
>30

Surface area involved (%)

<25
25-30
>30

Raised Lesions
Men: Age 15-24

Surface area involved (%)

<25
25-30
>30

PPAR-delta in the liver controls release of a specific phosphatidylcholine (18:1/18:0) that induces fatty acid oxidation in skeletal muscle.

Similar integrating signals to brown fat?

A metabolic minuet

Two related nuclear receptors mediate circadian fat metabolism in two different tissues using a lipid messenger as an intermediary. This signalling pathway might be relevant to the understanding of metabolic disorders. See Letter p.550

David D. Moore

breakdown and increases muscle endurance.
Pathogenic Continuum

‘Normal’

Pre-Diabetes

Type 2 Diabetes

Glucose

Yrs: 0 5 10 20+ 12+

A1C 5.8 6.4 6.5

Atherosclerosis

- NSTEMI
- STEMI
- CSA
- CHF
- CVD
- PVD
- SCD

Shorter duration of diabetes?
Specific types of antidiabetic therapy?
- Benefit?
- Harm?
Legacy effects? Metabolic memory?
ACCORD & ADVANCE: Treatment Effect on Nonfatal MI, Stroke, CV Death

ACCORD

![Graph showing cumulative incidence over years for ACCORD study.](image)

- Standard
- Intensive

HR 0.90 (0.78 - 1.04)
P = 0.16

ADVANCE

![Graph showing cumulative incidence over years for ADVANCE study.](image)

- Standard
- Intensive

HR 0.94 (0.84 - 1.06)
P = 0.32

DCCT: Absolute Risk of Sustained Retinopathy Progression by HbA$_{1c}$ and Years of Follow-up

Mean HbA$_{1c}$ = 11%

Rate/100 person-years

Time during study (y)

UKPDS 80: The “Legacy” Effect of Intensive Glucose Control

Myocardial Infarction

- Death reduced by 13% (*P* = .007).
- Metformin group: any diabetes-related endpoint reduced by 21% (*P* = .01), MI by 33% (*P* = .005), and death from any cause by 27% (*P* = .002).

Benefits of Tight BP and Glucose Control—UKPDS

- Stroke
- Any diabetes-related endpoint
- Microvascular endpoints
- Diabetes-related deaths

Risk reduction, %

* p<.02 tight BP control (144/82 mmHg) vs less tight control (154/87 mmHg)
† p<.03 intensive glucose control (A1c 7.0%) vs less intensive control (A1c 7.9%)

Multi-factorial Intervention and CV Disease in Type 2 Diabetes
Intensive Vs. Conventional Therapy

Glycosylated Hemoglobin (%)

Conventional Therapy 0.2%
Intensive Therapy -0.5%
P<0.001

Total Cholesterol (mg/dl)

Conventional Therapy -3 mg/dl
Intensive Therapy -50 mg/dl

Years of Follow-up

Multi-factorial Intervention and CV Disease in Type 2 Diabetes Intensive Vs. Conventional Therapy

**Triglycerides (mg/dl)**
- **Conventional Therapy**: 9 mg/dl
- **Intensive Therapy**: -41 mg/dl
  - *P*=0.015

**LDL Cholesterol (mg/dl)**
- **Conventional Therapy**: -13 mg/dl
- **Intensive Therapy**: -47 mg/dl
  - *P*<0.001

Years of Follow-up

Multi-factorial Intervention and CV Disease in Type 2 Diabetes Intensive Vs. Conventional Therapy

Systolic Blood Pressure (mm Hg)

Conventional Therapy -3 mm Hg
Intensive Therapy -14 mm Hg

Diastolic Blood Pressure (mm Hg)

Conventional Therapy -8 mm Hg
Intensive Therapy -2 mm Hg

P<0.001

P=0.006

Years of Follow-up

Intensive Multiple Risk Factor Management in Patients with Type 2 Diabetes: STENO-2

N=160; follow-up = 7.8 years

Conventional Therapy

Intensive Therapy

Primary composite endpoint: conventional therapy (44%) and intensive therapy (24%).

*Death from CV causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease. †Behavior modification and pharmacologic therapy.

By paying attention to and taking better care of our patients with diabetes and prediabetes, we can ensure they will do better and live longer.

“If I had known I was going to live so long, I would have taken better care of myself”

Thank you
Understanding the Lipid-Lipoprotein Disconnect in Managing Patients with T2DM and Dyslipidemia

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Director, Cardiometabolic Disorders
Mount Sinai Heart
Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, New York
The LDL Disconnect

1. LDL-C: Is it an adequate biomarker of cardiovascular risk in societies with an obesity epidemic?
2. What is the basis for LDL heterogeneity in insulin resistance?
3. LDL-associated cardiovascular risk: Is the cholesterol content of LDL (LDL-C) as informative as LDL particle concentration?
4. What are the effects of available therapies on LDL-C vs. LDL-P?
5. What are the effects of emerging therapies on LDL-C vs. LDL-P
LDL-C: Is it an adequate biomarker of cardiovascular risk in societies with an obesity epidemic?
Lipids and CVD – Guidelines Clinical Evidence

(Meta-analysis of 14 trials, n=90,056, 1994-2004)

Reduction in incidence of **major coronary** and **cardiovascular events** and mean absolute LDL-C reduction

Residual CVD Risk Is Particularly High in Patients With Diabetes Treated With Statins

Meta-Analysis of CHD Patients in 14 Statin Trials

CVD Risk Higher Than Patients With No Diabetes on Placebo

Diabetes

No Diabetes

Major Vascular Event Rate

34.9

29.6

24.8

19.4

Control

Treatment

Residual Risk

14.3-year mean follow-up of 18,686 patients with diabetes; n = 71,370 patients with no diabetes

Nonfatal MI, CHD death, stroke, or coronary revascularization

Event rate per 1 mmol/L (39 mg/dL) reduction in LDL-C

LDL Cholesterol in IS, IR, and Type 2 Diabetic Subjects

* p=0.03 vs. IS

Metabolic Reactions Driven by Triglycerides (VLDL) Induce Variability in LDL and HDL Composition and Size

- Cholesterol ester
- Triglyceride

Large VLDL → Chol-enriched TG-depleted

CETP

TG

LDL

HDL

Lipases

Small LDL

Small HDL

TG-enriched Chol-depleted
Effects of Insulin Sensitivity and Type 2 Diabetes on Lipoprotein Particle Size

VLDL

<table>
<thead>
<tr>
<th>IS</th>
<th>IR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

LDL

<table>
<thead>
<tr>
<th>IS</th>
<th>IR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.5</td>
<td>21.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

HDL

<table>
<thead>
<tr>
<th>IS</th>
<th>IR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>9.0</td>
<td>9.5</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; IR = insulin resistant; IS = insulin sensitive
*P < 0.05; **P < 0.01 vs. IS

NMR Lipoprotein Particle Concentrations In IS, IR, and Type 2 Diabetic Subjects

- VLDL
- IDL
- LDL

IS: 79.5
IR: 83.8
DM: 99.2

* p values vs IS < 0.05
** p values vs IS < 0.01
*** p values vs IS < 0.001

LDL-C, LDL-P, and Apo B with increasing number of MetS features in Framingham men.

- **LDL-C, mmol/L**
  - N=286
  - N=407
  - N=355
  - N=233
  - N=113
  - N=30

- **LDL-P, mmol/L**
  - N=286
  - N=407
  - N=355
  - N=233
  - N=113
  - N=30

- **ApoB, mmol/L**
  - N=286
  - N=407
  - N=355
  - N=233
  - N=113
  - N=30

**MetS (-)**

**MetS (+)**

~2.3x risk

**Statistical Significance:**
- LDL-C $P=0.01$
- LDL-P $P<0.0001$
- ApoB $P<0.0001$

Alternative LDL Measures in Framingham Women with Increasing Numbers of Metabolic Syndrome Features

LDL Cholesterol and LDL Particle Numbers in T2DM Patients with LDL-C < 100 mg/dL (2.6 mmol/L) (n=2,355)

LDL Particle Number Distribution in T2DM Patients with Low LDL-C

LDL-C
70-100 mg/dL (1.8-2.6 mmol/L)
(n=1,484)

LDL-C
< 70 mg/dL (1.8 mmol/L)
(n=871)

LDL-associated Cardiovascular Risk: Is the cholesterol content of LDL (LDL-C) as informative as LDL particle concentration?
Lipoprotein Subclasses Predict Incident Type 2 Diabetes

HRs and 95% CIs were stratified according to fasting (circles) or nonfasting (diamonds) status.

# CVD Prediction by LDL-P and LDL-C in Large Cohort Studies

*(LDL-P measured in entire cohort)*

<table>
<thead>
<tr>
<th></th>
<th>MESA(^1) Carotid IMT</th>
<th>Framingham(^2) Future CVD Events</th>
<th>Women’s Health Study(^3) Future CVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=5,362</td>
<td>n=3,066</td>
<td>n=27,673</td>
</tr>
<tr>
<td>(\Delta IMT) (\text{(SE)})</td>
<td>p</td>
<td>HR (95% \text{ CI})</td>
<td>p</td>
</tr>
<tr>
<td>LDL-C</td>
<td>35.8 (4.1)</td>
<td>&lt;0.001 1.11 (1.01-1.22)</td>
<td>1.74 (1.40-2.16) &lt;0.001</td>
</tr>
<tr>
<td>LDL-P</td>
<td>39.9 (4.1)</td>
<td>&lt;0.001 1.28 (1.17-1.39)</td>
<td>2.51 (1.91-3.30) &lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) *Atherosclerosis* 2007;192:211-7. Change in IMT per 1 SD increment in LDL, from linear regression analyses adjusted for age, gender, race, hypertension, & smoking.


\(^3\) *AHA Scientific Sessions* 2007. Hazard ratios (upper vs lower quintile), from Cox regression analyses adjusted for age, rx, smoking, menopause, BP, BMI & diabetes.
Event-free Survival Stratified by LDL-C and LDL-P in the Framingham Offspring Study

NMR Lipoprotein Subclass Particle Parameters as Multivariable Predictors of CHD Events in VA-HIT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th></th>
<th>On-Trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR* (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Large LDL particles</td>
<td>1.31 (1.09-1.57)</td>
<td>0.003</td>
<td>1.34 (1.11-1.62)</td>
<td>0.002</td>
</tr>
<tr>
<td>Small LDL particles</td>
<td>1.44 (1.20-1.73)</td>
<td>&lt;0.0001</td>
<td>1.41 (1.14-1.73)</td>
<td>0.001</td>
</tr>
<tr>
<td>IDL Particles</td>
<td>0.98 (0.86-1.12)</td>
<td>0.78</td>
<td>1.13 (0.97-1.30)</td>
<td>0.11</td>
</tr>
<tr>
<td>Large HDL particles</td>
<td>0.95 (0.82-1.11)</td>
<td>0.53</td>
<td>0.92 (0.79-1.07)</td>
<td>0.30</td>
</tr>
<tr>
<td>Medium LDL particles</td>
<td>0.82 (0.70-0.96)</td>
<td>0.02</td>
<td>0.82 (0.69-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Small HDL particles</td>
<td>0.71 (0.60-0.84)</td>
<td>&lt;0.0001</td>
<td>0.67 (0.57-0.79)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*ORs (95% CIs) were calculated for a 1-SD increment in each lipoprotein in each lipoprotein subclass parameter at baseline and on-trial with the use of logistic regression models that included all lipoprotein particle parameters in 1 model. All models were additionally adjusted for treatment group, age, hypertension, smoking, body mass index, and diabetes.

What are the effects of available therapies on LDL-C versus LDL-P?
LDL-C, Apo B, and Cardiovascular Events in Low HDL-C Subjects AFCAPS/TexCAPS

Dashed line = placebo
Solid line = lovastatin

Logistic regression model adjusted for age, sex, marital status, hypertension, smoking, and family history.

### Treatment Issues

Any Intervention That Changes LDL Composition (Size or Cholesterol Content) Will Differentially Affect LDL-C and LDL-P

<table>
<thead>
<tr>
<th>Cholesterol per particle increased</th>
<th>Cholesterol per particle decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>fibrates</td>
<td>statins</td>
</tr>
<tr>
<td>niacin</td>
<td>statin + ezetimibe</td>
</tr>
<tr>
<td>glitazones</td>
<td>bile acid sequestrants</td>
</tr>
<tr>
<td>omega-3 FAs</td>
<td>estrogen replacement therapy</td>
</tr>
<tr>
<td>exercise</td>
<td>anti-retrovirals (some)</td>
</tr>
<tr>
<td>low-carb diet</td>
<td>high-carb diet</td>
</tr>
</tbody>
</table>

**LDL-P ↓ more**

**LDL-C ↓ more**

COMETS: Percent LDL Lowering by Statin Monotherapy in Metabolic Syndrome Patients

Rosuvastatin

- Baseline: 168
- 6 weeks (10 mg): 1960
- 12 weeks (20 mg): 1260

- Baseline: 1210
- 6 weeks (10 mg): 93
- 12 weeks (20 mg): 84

- Baseline: 38%

Atorvastatin

- Baseline: 171
- 6 weeks (10 mg): 1870
- 12 weeks (20 mg): 1300

- Baseline: 105
- 6 weeks (10 mg): 1260
- 12 weeks (20 mg): 95

- Baseline: 33%

Less cholesterol per LDL particle

Less cholesterol per LDL particle

Fewer LDL particles

What are the effects of emerging therapies on LDL-C versus LDL-P?
Novel Therapies Lower LDL-C more than ApoB

- CETP Inhibitors
## Lipid Effects of CETP Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>HDL-C</th>
<th>Apo A-I</th>
<th>LDL-C</th>
<th>Lp(a)</th>
<th>Apo B</th>
<th>TG</th>
<th>CETP Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dalcet.</strong> 600 mg/d</td>
<td>↑27%</td>
<td>↑13%</td>
<td>↓5%</td>
<td>ND</td>
<td>ND</td>
<td>↓3%</td>
<td>Partial (~↓22%)</td>
</tr>
<tr>
<td><strong>Anacet</strong> 100 mg/d</td>
<td>↑138%</td>
<td>↑45%</td>
<td>↓40%</td>
<td>↓36%</td>
<td>↓21%</td>
<td>↓7%</td>
<td>Very high</td>
</tr>
<tr>
<td><strong>Evacet</strong> 100 mg/d</td>
<td>↑98%</td>
<td>↑36%</td>
<td>↓26%</td>
<td>ND</td>
<td>↓16%</td>
<td>↓3%</td>
<td>High?</td>
</tr>
</tbody>
</table>

All results are with background statin therapy. ND=no data

*Stein E, et al. Am J Cardiol. 2009;104:82-91. 12 Weeks
Novel Therapies with Equal Potency on LDL-C and ApoB

- Lomitapide
- Mipomersen
- PCSK9 Inhibitors
Changes from Baseline to Week 12 by Treatment Group (mITT Population)

- % Δ LDL-C
- % Δ ApoB
- % Δ Non-LDL-C
- % Δ Lp(a)

**Placebo**
- 50 mg / 2 weeks
- 100 mg / 2 weeks
- 150 mg / 2 weeks
- 200 mg / 4 weeks
- 300 mg / 4 weeks

*Least squares mean (SE) using last observation carried forward method
+ P<.0001 for % change SAR236553 vs placebo
* P=.05 for % change SAR236553 vs. placebo
P values are not adjusted for multiplicity (descriptive only)

Conclusions

1. The “optimal” LDL target has not been established from clinical trials

2. Among insulin-resistant patients, LDL-C overestimates the risk benefit of statin therapy

3. LDL-P and ApoB have been advocated as secondary targets of therapy in MetS/T2DM patients

4. Emerging therapies afford the opportunity to reduce LDL-associated residual risk due to their additive benefits in lowering LDL-P and Apo B in statin-treated patients; however, the benefits of this therapy can only be determined from randomized clinical trials
Clinical Trial Update on Cardiovascular Risk and T2DM: What to Expect in the Near Future?

Michael Miller, MD, FACC, FAHA
Professor of Medicine, Epidemiology & Public Health
University of Maryland School of Medicine
Director, Center for Preventive Cardiology
University of Maryland Medical Center
Cardiology Division
Baltimore, MD
Understanding CV Outcome Studies in Type 2 Diabetes

**A1C (%)**

- **Build up “bad” metabolic memory**
- **Drive the risk for complications**
  - No benefit - ACCORD, VADT, ADVANCE
    - a. longer duration DM
    - b. “point of metabolic no return”
    - c. wrong med or process of care
  - PROACTIVE - right med, (even with existing ASCD, longer duration DM)

**Brownlee, No glycemic threshold Continuous risk factor**

Benefit earlier and shorter duration DM:
- DCCT/EDIC, UKPDS, Steno-2

**TIME (yrs since diagnosis)**

Given epidemiologic data, aim for <6.0, start early, use right meds, without undue risk hypoglycemia and visceral weight gain, await DeFronzo study.

Modified from Prof. Stefano del Prato. EASD Commentary, Rome, Italy, 2008.
ORIGIN: Design

Randomized, double-blind trial with 2x2 factorial design

12,537 patients at high risk for CV events and had IFG, IGT, or newly diagnosed diabetes

Subjects included in two study arms

Prescription omega-3 fatty acid
Investigated whether addition of omega-3 fatty acids reduces CV death

Glargine
Investigated whether insulin replacement therapy with insulin glargine targeting fasting normoglycemia (FPG ≤ 95 mg/dL) reduces CV outcomes more than standard approaches

ORIGIN=Outcome Reducing with Initial Glargine Intervention

Trial Design

Patients and Methods

- 12,537 patients from 573 sites treated with insulin glargine (open) vs standard care and n-3 fatty acids (1g per day) versus placebo (double-blind)

- Median follow-up, 6.2 years

- Baseline characteristics
  - Mean age, 63.5 years
  - Females, 35%
  - Median FPG, 125 mg/dL
  - Median HbA$_{1c}$, 6.4%
Primary outcomes

- CV death or MI or stroke
- CV death or MI or stroke or revascularization or CHF hospitalization

Secondary outcomes

- Microvascular composite
- New T2DM
- All cause death
Results

- Median FPG of 95 mg/dL in glargine group vs 123 mg/dL in standard therapy group

- Median HbA$_{1c}$
  - Glargine group: 6.2%
  - Standard therapy group: 6.5%

- Differences in cancer incidence were not significant (HR, 1.00; 95% CI, 0.88 to 1.13; p=0.97).
Myocardial Infarction, Stroke, or Death from Cardiovascular Causes (Coprimary Outcome)

Adjusted hazard ratio, 1.02 (0.94-1.11)
P - 0.63 by log-rank test

Proportion with Events

No. at Risk
Insulin glargine  6264  6057  5850  5619  5379  5151  3611  766
Standard care  6273  6043  5847  5632  5415  5156  3639  800

Years of Follow-up

Diabetes Prevention

- New diabetes developed in 24.7% of glargine vs 31.2% of standard therapy subjects without baseline diabetes
  - OR, 0.72; 95% CI, 0.58 to 0.91; p=0.006

- Consistent but attenuated effect noted after 2nd OGTT
  - OR, 0.80; 95% CI, 0.64 to 1.00; p=0.050

- In people at risk for future diabetes, 6 years of basal insulin glargine titrated to normal FPG reduces incidence of diabetes
Hypoglycemia

- Significantly higher rates of hypoglycemia with glargine vs standard therapy ($p<0.001$)

Weight and BMI

- Median weight change:
  - Glargine: $1.6 \text{ kg (95\% CI, } -2.0 \text{ to } 5.5)$
  - Standard therapy: $-0.5 \text{ kg (95\% CI, } -4.3 \text{ to } 3.2; p<0.001)$

- BMI change:
  - Glargine: $0.81 \text{ kg/m}^2 (95\% \text{ CI, } -0.6 \text{ to } 2.3)$
  - Standard therapy: no change ($95\% \text{ CI } -1.4 \text{ to } 1.6; p<0.001$)
Implications for Insulin Therapy

- Supplementing endogenous insulin with basal insulin slows dysglycemia progression.
- Although later benefits or harms cannot be ruled out, over 6 to 7 years exogenous basal insulin flexibly lowers glucose.
- Despite lower glucose levels, routine early use of basal insulin glargine is not better than guideline-based standard care in limiting important health outcomes.
- Basal insulin glargine currently is the best studied glucose-lowering drug available.
- No new safety outcomes limit early use when needed.
Examine: Time to First Occurrence of Primary Endpoint after Alogliptin vs. Placebo

Hazard ratio, 0.96 (upper boundary of the one-sided repeated CI, 1.16)

Cumulative Incidence of Primary End-Point Events (%)

Months

SAVOR-TIMI 53: No Increase in CV Events with Saxagliptin in Patients With or At Risk for CVD

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal ischemic stroke

HR, 1.0 (95% CI, 0.89-1.12; P=0.99 for superiority; P<0.001 for noninferiority)

Saxagliptin (n=8,280)

Placebo (n=8,212)

7.3% (n=613)

7.2% (n=619)

Saxagliptin is not FDA-approved for cardiovascular risk reduction.

SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53, CV=cardiovascular; M=myocardial infarction

Scirica BM, et al; for the SAVOR-TIMI 53 Steering Committee and investigators.

Ongoing Trials to Determine Cardiovascular Benefit of DPP-IV Inhibitors in Patients with Diabetes

- **TECOS** (Trial Evaluating Cardiovascular Outcomes With Sitagliptin)
  - Planned longer duration of follow-up than SAVOR-TIMI 53 and EXAMINE, which may help determine if a cardiovascular benefit does exist.

- **CARMELINA** (CArdiovascular safety and Renal Microvascular outcome with LINAgliptin in patients with Type 2 Diabetes mellitus at high vascular risk)

- **CAROLINA** (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes)
  - Companion to CARMELINA – combination of placebo controlled and active controlled should provide insight into whether any CV effects are due to a comparison with placebo or are independent of glycemic effects.
Ongoing Trials to Determine Cardiovascular Benefit of GLP-1 Agonists in Patients with Diabetes

- **ELIXA** (Evaluation of **Lixisenatide** in Acute Coronary Syndrome)
  - Patients with diabetes and previous ACS
- **EXSCEL** (**Exenatide** Study of Cardiovascular Event Lowering Trial)
- **LEADER** (**Liraglutide** Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)
- **SUSTAIN** (**Semaglutide** in Subjects With Type 2 Diabetes)
- **REWIND** (Researching Cardiovascular Events With a Weekly Incretin in Diabetes)
  - **Dulaglutide**
Dyslipidemia

Therapeutic Lifestyle Changes
(See Obesity Algorithm)

Lipid Panel: Assess CVD Risk

Statin Therapy

If statin-intolerant
Try alternate statin, lower statin dose or frequency, or add non-statin LDL-C-lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

If TG > 500 mg/dL, fibrates, omega-3 ethyl esters, niacin

Intensify therapies to attain goals according to risk levels
Effect of Weight Loss on Glycemic Control in Type 2 Diabetes (Look AHEAD, N=5,145)

Change in HbA1c (%)

Change in Fasting Blood Glucose (mg/dL)

Effect of Weight Loss on Plasma Lipids in Type 2 Diabetes (Look AHEAD)

Change in Triglycerides (mg/dL)

Change in HDL-C and LDL-C (mg/dL)

Look AHEAD Trial – Diet and Lifestyle Did Not Reduce CV Endpoints but Did Improve Other Comorbidities

Why study failed
1. Low event rates (<3%/y)
2. Weight changes over time

Why study worked
1. ↓ nephropathy
2. ↓ retinopathy
3. ↓ depression

Main effect, -4 (95% CI, -5 to -3), P<0.001

4-Year Randomized Controlled Trial of Orlistat as an Adjunct to Lifestyle for the Prevention of Type 2 Diabetes in Obese At-Risk Patients

Weight loss with orlistat + lifestyle reduced and maintained weight better than lifestyle alone

Change in Body Weight (kg)

Placebo + Lifestyle

Orlistat + Lifestyle

P < 0.001

“DPP-type” Intervention
-3.0 kg

Orlistat + “DPP-type” Intervention
-5.8 kg

DPP = Diabetes Prevention Program

XENDOS trial
## Recent Additions to Obesity Pharmacotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval/Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcanerin</td>
<td>- $5\text{-HT}_{2c}$ serotonin agonist</td>
<td>Approved, Summer 2012</td>
</tr>
<tr>
<td></td>
<td>- Little affinity for other serotonergic receptors</td>
<td></td>
</tr>
<tr>
<td>Phentermine/</td>
<td>- Sympathomimetic</td>
<td>Approved, Summer 2012</td>
</tr>
<tr>
<td>Topiramate ER</td>
<td>- Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)</td>
<td></td>
</tr>
</tbody>
</table>

Lorcaserin — BLOOM Study: Body Weight Over Years 1 and 2

Effect of Lorcaserin in Patients with T2DM: BLOOM-DM Study

Change in HbA1C

- Placebo (n=248): Baseline Mean A1C (%) = 8.0
- Lorcaserin 10 mg BID (n=251): Baseline Mean A1C (%) = 8.1
- Lorcaserin 10 mg QD (n=93): Baseline Mean A1C (%) = 8.1

Decreasing Use in Diabetes Medications

- Placebo (n=248)
- Lorcaserin 10 mg BID (n=251)
- Lorcaserin 10 mg QD (n=95)

*P < 0.001 vs placebo.
†P = 0.087 vs placebo.

Lorcaserin: Precautions

- Serotonin syndrome or neuroleptic malignant syndrome-like reactions
  - Safety of concomitant use of other serotonergic or antidopaminergic agents (including antipsychotics) or drugs that impair serotonin metabolism (including MAOIs) has not been evaluated

- **Valvular heart disease** – Regurgitant valve lesions (mitral and/or aortic) reported with 5-HT2B receptor agonist activity
  - Lorcaserin is selective for 5-HT2C receptors
  - Avoid in patients taking cabergoline
  - Caution in patients with heart failure

- Cognitive impairment – Impairment in attention and memory occurred in 1.9% of lorcaserin patients and 0.5% in placebo patients
  - Rates of discontinuation for cognitive impairment was 0.3% and 0.1% with lorcaserin and placebo

## Changes from baseline to week 56 in secondary endpoints

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phentermine 7.5mg/Topiramate 46 mg ER</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>↓</td>
<td>-7.6</td>
<td>-2.4</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>↓</td>
<td>-4.7</td>
<td>-2.4</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>↓</td>
<td>-3.4</td>
<td>-2.7</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>↓</td>
<td>-8.6</td>
<td>4.7</td>
</tr>
<tr>
<td>LDL–C (%)</td>
<td></td>
<td>-3.7</td>
<td>-4.1</td>
</tr>
<tr>
<td>HDL–C (%)</td>
<td>↑</td>
<td>5.2</td>
<td>1.2</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>↓</td>
<td>-2.49</td>
<td>-0.79</td>
</tr>
<tr>
<td>Adiponectin (μg/mL)</td>
<td>↑</td>
<td>1.40</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Phentermine/Topiramate ER Prevents Progression to T2DM: SEQUEL Study

Annualized Incidence of T2DM

- Placebo: 3.7%
- Phen/TPM CR 7.5/46 mg: 1.7%, $P=0.1514$
- Phen/TPM CR 15/92 mg: 0.9%, $P=0.0078$

NS, not significant; Phen/TPM CR, phentermine/topiramate controlled release.

Phentermine/Topiramate ER: Precautions (continued)

• Oligohidrosis/hyperthermia – Topiramate may ↓ sweating and ↑ body temperature (caution with carbonic anhydrase inhibitors and anticholinergics)
• **Hypokalemia** – Results from ↓ carbonic anhydrase activity
  – Additive effects when added to potassium wasting diuretics
• Laboratory testing – Bicarbonate, creatinine, potassium, and glucose at baseline and periodically during treatment

New Cholesterol Guidelines

1. Individuals with known ASCVD, without NYHA Class II-IV heart failure or receiving hemodialysis

2. Individuals with LDL-C $\geq 190$ mg/dL

3. Individuals 40 to 75 years of age with diabetes and LDL-C 70-189 mg/dL, without clinical ASCVD

4. Individuals 40 to 75 years of age with estimated 10-year ASCVD risk $\geq 7.5\%$ and LDL-C 70-189 mg/dL, without clinical ASCVD or diabetes
- Diabetes Mellitus
  - ~35% of T2DM adults have fasting TG ≥200 mg/dL with ↓HDL-C and small, dense LDL particles
  - Patients with poorly controlled type 1 diabetes mellitus (T1DM) may exhibit a similar pattern of dyslipidemia
  - Causes of HTG in DM include ↑hepatic VLDL production and defective removal of chylomicrons and CMRs, which often reflects poor glycemic control

## ACCORD Lipid Prespecified Subgroup with Dyslipidemia

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate-simvastatin % with events (N)</th>
<th>Simvastatin monotherapy % with events (N)</th>
<th>Hazard ratio (95% CI)</th>
<th>Within-group P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.5 (2765)</td>
<td>11.3 (2753)</td>
<td></td>
<td>0.324</td>
</tr>
<tr>
<td>TG ≥ 204 and HDL-C ≤ 34 mg/dL</td>
<td>12.4 (485)</td>
<td>17.3 (456)</td>
<td></td>
<td>0.032*</td>
</tr>
<tr>
<td>All Others</td>
<td>10.1 (2264)</td>
<td>10.1 (2284)</td>
<td></td>
<td>0.935*</td>
</tr>
</tbody>
</table>

*Treatment-by-subgroup interaction, p = 0.057
Reduction of CV Events with EPA – Intervention Trial

- Men & women ≥45 yo
- Prior CHD (70% patients) or T2DM + ≥1 RF
- Atherogenic dyslipidemia:
  - Hx of ↑TC (at LDL-C goal on statin)
  - TG 150–500 mg/dL

N=8000

Primary endpoint: Prevention of 1st major CV event

Study duration ~4–6 yrs

- Randomized, double-blind, parallel group design
- Secondary outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as diabetes, etc.
- Multinational trial
- Anticipated completion 2016

AMR101=icosapent ethyl

Clinical Trial Update T2DM: Summary

- RCTs (excluding statins/metformin) in T2DM have not demonstrated reduced CVD risk
- Recently approved FDA drugs for obesity effectively improve metabolic parameters in T2DM
- Await data from ongoing/soon to be initiated RCTs to determine +/- CV benefits in T2DM
A 48-year-old overweight man with type 2 diabetes presents to the ER with NSTEMI, demonstrating non-specific ST-T wave changes on ECG, with CK-MB and troponin T elevations. He smokes 1 pack of cigarettes daily and takes ASA 81 mg, ramipril 5 mg, metformin 1000 mg, sitagliptin 50 mg, glimepiride 2 mg daily and simvastatin 40 mg.

LDL-C: 106 mg/dL  
HDL-C: 40 mg/dL  
Triglycerides: 205 mg/dL  
Non-HDL-C: 147 mg/dL  
Total Cholesterol: 187 mg/dL  
Fasting glucose: 145 mg/dL  
A1C: 7.6%  
BP: 126/76 mm Hg
What is your LDL-C goal for this patient?
1. < 70 mg/dL
2. 70 mg/dL
3. 100 mg/dL
4. 130 mg/dL
What is your LDL-C goal for this patient?

1. < 70 mg/dL  
   - 76%
2. 70 mg/dL  
   - 10%
3. 100 mg/dL  
   - 14%
4. 130 mg/dL  
   - 0%
What adjustment would you make in his lipid therapy?

1. None – this patient needs better glycemic control.
2. Change simvastatin to atorvastatin 80 mg or rosuvastatin 40 mg
3. Add omega-3 acid ethyl ester
4. Add ezetimibe
5. Add fenofibrate
6. Add niacin
7. Add colesevelam
What adjustment would you make in his lipid therapy?

1. None – this patient needs better glycemic control. 4%
2. Change simvastatin to atorvastatin 80 mg or rosuvastatin 40 mg 63%
3. Add omega-3 acid ethyl ester 8%
4. Add ezetimibe 13%
5. Add fenofibrate 8%
6. Add niacin 4%
7. Add colesevelam 0%
What tests would you order to further risk-stratify this patient?
1. None – this patient is already at highest risk
2. Apo B
3. LDL-P
4. hs-CRP
5. Cardiac catheterization
What tests would you order to further risk-stratify this patient?

1. None – this patient is already at highest risk 29%
2. Apo B 13%
3. LDL-P 32%
4. hs-CRP 3%
5. Cardiac catheterization 23%
What adjustments would you make in his diabetes therapy?
1. None
2. Stop sitagliptin, substitute a GLP-1 agonist
3. Add long-acting basal insulin analog
4. Increase glimepiride to 4 mg daily
5. Increase metformin to 2000 mg daily
What adjustments would you make in his diabetes therapy?
1. None 8%
2. Stop sitagliptin, substitute a GLP-1 agonist 8%
3. Add long-acting basal insulin analog 13%
4. Increase glimepiride to 4 mg daily 17%
5. Increase metformin to 2000 mg daily 54%
A 48-year-old overweight man with type 2 diabetes and hypertension presents to your office with a desire to fully understand his long term CV risks since his father suffered a heart attack at 55. He takes ASA 81 mg, ramipril 5 mg, metformin 1000 mg, sitagliptin 50 mg, glimepiride 2 mg daily and simvastatin 40 mg.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C:</td>
<td>99 mg/dL</td>
</tr>
<tr>
<td>HDL-C:</td>
<td>32 mg/dL</td>
</tr>
<tr>
<td>Triglycerides:</td>
<td>205 mg/dL</td>
</tr>
<tr>
<td>Non-HDL-C:</td>
<td>120 mg/dL</td>
</tr>
<tr>
<td>Total Cholesterol:</td>
<td>152 mg/dL</td>
</tr>
<tr>
<td>Fasting glucose:</td>
<td>135 mg/dL</td>
</tr>
<tr>
<td>A1C:</td>
<td>6.6%</td>
</tr>
<tr>
<td>BP:</td>
<td>126/76 mm Hg</td>
</tr>
</tbody>
</table>
What tests would you order to further risk-stratify this patient?
1. None – this patient is already at highest risk
2. Apo B
3. LDL-P
4. hs-CRP
5. Cardiac catheterization
What tests would you order to further risk-stratify this patient?
1. None – this patient is already at highest risk 29%
2. Apo B 6%
3. LDL-P 23%
4. hs-CRP 26%
5. Cardiac catheterization 16%
A 61-year-old man who experienced a STEMI 3 weeks ago now presents for follow-up complaining of muscle weakness and muscle pain. He currently is taking atorvastatin 80 mg daily, clopidogrel 75 mg daily, carvedilol 12.5 mg BID, lisinopril 5 mg, and ASA 81 mg daily.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>115 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>187 mg/dL</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>152 mg/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>192 mg/dL</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>112 mg/dL</td>
</tr>
<tr>
<td>A1C</td>
<td>6.2%</td>
</tr>
<tr>
<td>BP</td>
<td>134/74 mm Hg</td>
</tr>
</tbody>
</table>
What is your LDL-C goal for this patient?

1. < 70 mg/dL
2. 70 mg/dL
3. 100 mg/dL
4. 130 mg/dL
What is your LDL-C goal for this patient?
1. < 70 mg/dL          79%
2. 70 mg/dL            9%
3. 100 mg/dL           3%
4. 130 mg/dL           9%
What adjustment would you make to his lipid management?

1. Stop atorvastatin and switch to rosuvastatin 20 mg daily
2. Stop atorvastatin and switch to fenofibrate 145 mg and ezetimibe 10 mg
3. Add ezetimibe 10 mg daily
4. Stop atorvastatin and change to pitavastatin 4 mg daily and ezetimibe 10 mg daily
5. Decrease atorvastatin to 20 mg daily and add ezetimibe 10 mg daily
6. Reduce atorvastatin to 40 mg
What adjustment would you make to his lipid management?

1. Stop atorvastatin and switch to rosvustatin 20 mg daily  
   31%

2. Stop atorvastatin and switch to fenofibrate 145 mg and ezetimibe 10 mg  
   17%

3. Add ezetimibe 10 mg daily  
   7%

4. Stop atorvastatin and change to pitavastatin 4 mg daily and ezetimibe 10 mg daily  
   14%

5. Decrease atorvastatin to 20 mg daily and add ezetimibe 10 mg daily  
   17%

6. Reduce atorvastatin to 40 mg  
   14%