Prediabetes

Comorbidities and Complications
Common Comorbidities of Prediabetes

- Obesity
- CVD
- Dyslipidemia
- Hypertension

- Renal failure
- Cancer
- Sleep disorders

Clinical Risks of Not Treating Prediabetes Are Substantial

- Microvascular disease
  - Retinopathy
  - Neuropathy
  - Nephropathy
- Cardiovascular disease (CVD)
  - Heart disease
  - Stroke
  - Peripheral vascular disease

The Spectrum of Cardiometabolic Disease

Genetic determinants

Insulin resistance

Obesity

Prediabetic States

Metabolic syndrome*

IFG
(FPG 100-126 mg/dL)

IGT
(2-h OGTT 140-199 mg/dL)

A1C† 5.7%-6.4% (ADA)
or 5.5%-6.4% (AACE)

Type 2 diabetes

Cardiovascular disease

*2005 NCEP criteria.

†Diagnosis of prediabetes after positive A1C screening requires confirmation with FPG or OGTT measurement.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

Prediabetes Comorbidities and Complications

OBESITY
**COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE PATIENT WITH OVERWEIGHT/OBESITY**

**STEP 1**

**EVALUATION FOR COMPLICATIONS AND STAGING**

**CARDIOMETABOLIC DISEASE | BIOMECHANICAL COMPLICATIONS**

- **BMI < 25**
  - **NO OVERWEIGHT OR OBESITY**

- **BMI ≥ 25**
  - **OVERWEIGHT OR OBESITY**

**STEP 2**

**SELECT:**

- Therapeutic targets for improvement in complications

- Treatment modality

- Treatment intensity based on staging

**Lifestyle Therapy:**

- Physician/RD counseling, web/remote program, structured multidisciplinary program

**Medical Therapy (BMI ≥ 27):**

- Individualize care by selecting one of the following based on efficacy, safety, and patients’ clinical profile: phentermine, orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg

**Surgical Therapy (BMI ≥ 35):**

- Gastric banding, sleeve, or bypass

**STEP 3**

If therapeutic targets for complications not met, intensify lifestyle, medical, and/or surgical treatment modalities for greater weight loss. Obesity is a chronic progressive disease and requires commitment to long-term therapy and follow-up.
# Older Obesity Pharmacotherapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phentermine</th>
<th>Diethylpropion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Central noradrenergic</td>
<td></td>
</tr>
<tr>
<td><strong>Approval</strong></td>
<td>Short-term use</td>
<td>DEA Schedule II-IV</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td>$</td>
</tr>
<tr>
<td><strong>Common adverse effects</strong></td>
<td>• Restlessness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase in pulse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase in blood pressure</td>
<td></td>
</tr>
</tbody>
</table>

DEA, Drug Enforcement Agency.

# Orlistat

## Mechanism of Action
- Reversible gastrointestinal lipase inhibitor

## Dosing
- 120 mg thrice daily with each main meal containing fat, taken during or up to 1 hour after eating

## Indications
- Weight loss and weight maintenance in conjunction with a reduced calorie diet
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

See prescribing information for specific instructions.

---

T2D = type 2 diabetes.

# Orlistat: Summary of Warnings and Contraindications

## Contraindications
- Pregnancy
- Chronic malabsorption syndrome
- Cholestasis

## Warnings
- Decreased cyclosporine exposure
- Multivitamin supplement containing fat-soluble vitamins recommended to ensure adequate nutrition
- Hepatocellular necrosis, acute hepatic failure
- Increased urinary oxalate; monitor renal function
- Cholelithiasis
- Increased GI events with high-fat diets (fat >30% of total daily calories)

## Adverse Effects
- Oily spotting
- Flatus with discharge
- Fecal urgency and incontinence
Orlistat: Clinical Efficacy

ITT Population, LOCF Analysis

Δ Weight (%)

-10 -8 -6 -4 -2 0

Orlistat 120 mg
Placebo

52 weeks
-8.8
P<0.001

104 weeks
-7.6
P<0.001

-5.8

-4.5

ITT = intent to treat; LOCF = last observation carried forward; TID, three times daily.

# Orlistat Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and occurring at least twice as often with orlistat as placebo, %</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orlistat 120 mg TID (N=1913)</td>
<td>Placebo (N=1466)</td>
</tr>
<tr>
<td>Oily spotting</td>
<td>26.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Flatus with discharge</td>
<td>23.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Fecal urgency</td>
<td>22.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Fatty/oily stool</td>
<td>20.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Oily evacuation</td>
<td>11.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Increased defecation</td>
<td>10.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>7.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

TID = three times daily.

# Lorcaserin

## Mechanism of Action
- Specific 5-HT$_{2C}$ (serotonin) receptor agonist

## Dosing
- 10 mg twice daily
- Discontinue if 5% weight loss is not achieved within 12 weeks

## Indications
- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m$^2$
  - BMI ≥27 kg/m$^2$ with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia
- Schedule IV Controlled Substance

---

DEA, Drug Enforcement Agency; T2D, type 2 diabetes.
Lorcaserin: Summary of Warnings and Contraindications

Contraindications
- Pregnancy

Adverse Effects
- Headache
- Dizziness
- Nausea

Warnings
- Coadministration with other serotonergic or antidopaminergic agents has not been established
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders: euphoria, dissociation, suicidal thoughts, depression
- Priapism
- Increased risk of hypoglycemia with antidiabetic medications

Effect of Lorcaserin on Body Weight in Obese Adults Over 1 Year

BLOSSOM Study

Week

Δ LS mean weight (%)

0

12 24 36 48 52

-8

-6

-4

-2

0

Placebo (n=1601)
Lorcaserin 10 mg BID (n=1602)

BID, twice daily; LS, least squares.
Effect of Lorcaserin on Body Weight in Obese Adults Over 2 Years

BLOOM Study

## Effect of Lorcaserin on Cardiometabolic Risk Markers

### BLOOM Study

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Lorcaserin 10 mg (5.8%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -6.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓ -0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↑ 2.87</td>
<td>0.049</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>↓ -21.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*P values represent comparisons to placebo.

Intent to treat, last observation carried forward analysis for total study population.

Effect of Lorcaserin on Hypertension

BLOSSOM Study

### Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lorcaserin 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>-1.2</td>
<td>-1.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>-1.4</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

### Antihypertensive Use

<table>
<thead>
<tr>
<th>Decrease</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3.1</td>
</tr>
</tbody>
</table>

BID, twice daily; LS, least squares.

Effect of Lorcaserin on Dyslipidemia

BLOSSOM Study

Lipids

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Placebo</th>
<th>Lorcaserin 10 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>-0.9</td>
<td>-4.3</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.3</td>
<td>3.7</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>ApoB</td>
<td>1.4</td>
<td>-2.9</td>
</tr>
</tbody>
</table>

P values:
- HDL-C: P<0.001
- LDL-C: P<0.001
- ApoB: P<0.001

Lipid Medication Use

- Increase: Placebo = 5, Lorcaserin = 4
- Decrease: Placebo = 1.4, Lorcaserin = 2.6

BID, twice daily; LS, least squares.

## Lorcaserin Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Lorcaserin 10 mg BID (N=3195)</th>
<th>Placebo (N=3185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16.8</td>
<td>10.1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>5.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Phentermine/Topiramate ER

**Mechanism of Action**
- Central noradrenergic effects
  - Phentermine: immediate-release sympathomimetic—affects appetite
  - Topiramate ER: delayed-release ganganergeric—affects satiety

**Indications**
- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

**Dosing**
- Once daily in morning
  - Starting dose: phentermine 3.75/topiramate ER 23 mg for 14 days
  - Usual dose: 7.5/46 mg
  - Maximum dose: 15/92 mg
- If <3% weight loss after 12 weeks on usual dose, either discontinue medication or advance to maximum dose (transition dose phentermine 11.25 mg/topiramate ER 69 mg for 2 weeks)
- If <5% weight loss after 12 weeks on maximum dose, then discontinue the medication (to discontinue take every other day for one week)

See prescribing information for specific titration and discontinuation instructions

T2D, type 2 diabetes.
Phentermine/Topiramate ER: Summary of Warnings and Contraindications

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Glaucoma</td>
</tr>
<tr>
<td>• Hyperthyroidism</td>
</tr>
<tr>
<td>• Treatment with monoamine oxidase inhibitors (MAOIs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dry mouth</td>
</tr>
<tr>
<td>• Tingling</td>
</tr>
<tr>
<td>• Constipation</td>
</tr>
<tr>
<td>• Altered taste sensation</td>
</tr>
<tr>
<td>• Upper respiratory infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fetal toxicity</td>
</tr>
<tr>
<td>• Increased heart rate</td>
</tr>
<tr>
<td>• Suicide and mood and sleep disorders</td>
</tr>
<tr>
<td>• Acute myopia and glaucoma</td>
</tr>
<tr>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td>• Creatinine elevations</td>
</tr>
<tr>
<td>• Hypoglycemia with concomitant antidiabetic therapy</td>
</tr>
</tbody>
</table>
Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 1 Year

EQUIP Study: ITT-LOCF Analysis


*P<0.0001 vs placebo.

ITT = intent to treat; LOCF = last observation carried forward; Phen/TPM ER = phentermine/topiramate extended release.
Effect of Phentermine/Topiramate ER on Weight Loss Over 2 Years

SEQUEL Study
(Completer Analysis)

Data are shown with mean (95% CI).
Phen/TPM ER, phentermine/topiramate extended release.
## Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

**CONQUER Study**

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Phentermine/Topiramate ER 7.5/46 mg (8.4%)</th>
<th>P value*</th>
<th>Phentermine/Topiramate ER 15/92 mg (10.4%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -4.7</td>
<td>0.0008</td>
<td>↓ -5.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -3.4</td>
<td>NS</td>
<td>↓ -3.8</td>
<td>0.0031</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -8.6</td>
<td>&lt;0.0001</td>
<td>↓ -10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓ -4.9</td>
<td>0.0345</td>
<td>↓ -6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓ -3.7</td>
<td>NS</td>
<td>↓ -6.9</td>
<td>0.0069</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 5.2</td>
<td>&lt;0.0001</td>
<td>↑ 6.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -2.49</td>
<td>&lt;0.0001</td>
<td>↓ -2.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>↑ 1.40</td>
<td>&lt;0.0001</td>
<td>↑ 2.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P values represent comparisons to placebo.

Intent to treat, last observation carried forward analysis for total study population.

Effect of Phentermine/Topiramate ER on Hypertension

SEQUEL Study

Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-3.2</td>
<td>-3.9</td>
</tr>
<tr>
<td>Phen/TPM ER 7.5/46 mg</td>
<td>-4.7</td>
<td>-3.7</td>
</tr>
<tr>
<td>Phen/TPM ER 15/92 mg</td>
<td>-4.3</td>
<td>-3.5</td>
</tr>
</tbody>
</table>

Antihypertensive Use

<table>
<thead>
<tr>
<th></th>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11</td>
<td>13.1</td>
</tr>
<tr>
<td>Phen/TPM ER 7.5/46 mg</td>
<td>9.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Phen/TPM ER 15/92 mg</td>
<td>5.8</td>
<td>15.6</td>
</tr>
</tbody>
</table>

BP, blood pressure; Phen/TPM ER, phentermine/topiramate extended release; T2D, type 2 diabetes.

Effect of Phentermine/Topiramate ER on Dyslipidemia

**SEQUEL Study**

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Placebo</th>
<th>Phen/TPM ER 7.5/46 mg</th>
<th>Phen/TPM ER 15/92 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>0.4</td>
<td>7.3</td>
<td>11.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-12.5</td>
<td>4.7</td>
<td>11.9</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-10.7</td>
<td>-4.6</td>
<td>-9.7</td>
</tr>
<tr>
<td>Non–LDL-C</td>
<td>-13.7</td>
<td>-5.6</td>
<td>-9.3</td>
</tr>
</tbody>
</table>

*P<0.01 vs placebo.

Phen/TPM ER, phentermine/topiramate extended release; T2D, type 2 diabetes.

## Selected Phentermine/Topiramate ER Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Phentermine/Topiramate</th>
<th>Placebo (N=1561)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.75 mg/23 mg (N=240)</td>
<td>7.5 mg/46 mg (N=498)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>4.2</td>
<td>13.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6.7</td>
<td>13.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>7.9</td>
<td>15.1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Headache</td>
<td>10.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.9</td>
<td>7.2</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Back pain</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>6.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Influenza</td>
<td>7.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Naltrexone/Bupropion SR

Mechanism of Action
• Naltrexone: opioid receptor antagonist
• Bupropion: norepinephrine-dopamine reuptake inhibitor

Dosing
• 2 tablets twice a day

Indications
• Adjunct to diet and exercise in patients with
  – BMI ≥30 kg/m²
  – BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    • Hypertension
    • T2D
    • Dyslipidemia

See prescribing information for specific instructions

T2D, type 2 diabetes.
# Naltrexone/Bupropion SR: Summary of Warnings and Contraindications

## Contraindications
- Uncontrolled hypertension
- Seizures, anorexia, or discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
- Chronic opioid use
- Use of other bupropion products or monoamine oxidase inhibitors

## Warnings
- Suicidal behavior and ideation (black box warning)
- Seizure
- Increased blood pressure and heart rate
- Hepatotoxicity
- Angle-closure glaucoma

## Adverse Effects
- GI: nausea, vomiting, constipation, diarrhea
- Headache, insomnia
- Dry mouth

Effect of Naltrexone/Bupropion SR on Body Weight

COR II Study MITT-LOCF Analysis (N=1496)

-6.5 vs -6.4

28 weeks

56 weeks

-1.9 vs -1.2

P<0.001

Naltrexone/bupropion SR

Placebo

COR II = CONTRAVE Obesity Research II; LOCF = last observation carried forward; MITT = modified intent to treat; SR = sustained release.

Effect of Naltrexone/Bupropion SR on Cardiometabolic Risk Markers

COR II Study

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Naltrexone/Bupropion SR (6.4%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↑ 0.6</td>
<td>0.039</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↑ 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓ -6.2</td>
<td>0.008</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -28.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG, mg/dL</td>
<td>↓ -2.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P value vs placebo.

BP, blood pressure; COR II, CONTRAVE Obesity Research II; FBG, fasting blood glucose; SR, sustained release.

### Naltrexone/Bupropion SR
#### Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Naltrexone/Bupropion SR 32 mg/360 mg (N=2545)</th>
<th>Placebo (N=1515)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>32.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>19.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Headache</td>
<td>17.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>8.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Liraglutide (for Obesity)

**Mechanism of Action**
- GLP-1 receptor agonist

**Indications**
- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m²
  - BMI ≥27 kg/m² with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

**Dosing**
- 3 mg once daily subcutaneous injection

See prescribing information for specific instructions

T2D, type 2 diabetes.
Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.
## Liraglutide (for Obesity): Summary of Warnings and Contraindications

### Contraindications
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- Pregnancy

### Adverse Effects
- GI: nausea, diarrhea, constipation, vomiting, decreased appetite, dyspepsia, abdominal pain
- Headache, fatigue
- Dizziness
- Increased lipase

### Warnings
- Thyroid tumors seen in rodent models
- Acute pancreatitis or gallbladder disease
- Hypoglycemia if used with sulfonylurea or glinide (in patients with T2D)
- Heart rate increase
- Renal impairment
- Suicidal behavior or ideation
- Do not use with insulin or to treat T2D

---

T2D = type 2 diabetes.
Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.
Effects of Liraglutide in Obese Patients

SCALE Obesity (N=3731)

Weight Change After 56 Weeks

-8
-10
-12
-14
-16

Δ Weight (%)

Liraglutide (n=2437)

Placebo (n=1225)

-8

P<0.001

-2.6

Effect of Liraglutide 3 mg on Cardiometabolic Risk Markers

**SCALE Study**

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Liraglutide 3 mg* (4.4%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓  -2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓  -0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓  -6.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓  -2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓  -0.9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑  0.9</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL-C, %</td>
<td>↓  -6.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>FFAs, %</td>
<td>↓  -5.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>↓  -3.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Placebo-adjusted values; P values represent comparisons to placebo (ANCOVA).

### Liraglutide (for Obesity)
#### Adverse Events

<table>
<thead>
<tr>
<th>Event occurring in ≥5% of patients and more frequently than with placebo, %</th>
<th>Liraglutide 3 mg (N=3384)</th>
<th>Placebo (N=1941)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>39.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Headache</td>
<td>13.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>19.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>5.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>5.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.
Effects of Different Types of Bariatric Surgery on Weight

Weight Loss as a Percentage of Excess Body Weight

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Follow-up Period (years)</th>
<th>1-2</th>
<th>3-6</th>
<th>7-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical banded gastroplasty</td>
<td></td>
<td>50-72</td>
<td>25-65</td>
<td>--</td>
</tr>
<tr>
<td>Gastric banding</td>
<td></td>
<td>29-87</td>
<td>45-72</td>
<td>14-60</td>
</tr>
<tr>
<td>Laparoscopic sleeve gastrectomy</td>
<td></td>
<td>33-58</td>
<td>66</td>
<td>50-55</td>
</tr>
<tr>
<td>Roux-en-Y gastric bypass</td>
<td></td>
<td>48-85</td>
<td>53-77</td>
<td>25-68</td>
</tr>
<tr>
<td>Banded Roux-en-Y gastric bypass</td>
<td></td>
<td>73-80</td>
<td>66-78</td>
<td>60-70</td>
</tr>
<tr>
<td>Long-limb Roux-en-Y gastric bypass</td>
<td></td>
<td>53-74</td>
<td>55-74</td>
<td>--</td>
</tr>
<tr>
<td>Biliopancreatic diversion ± duodenal switch</td>
<td></td>
<td>65-83</td>
<td>62-81</td>
<td>60-80</td>
</tr>
</tbody>
</table>

Weight Loss with Different Bariatric Surgeries in Severely Obese Patients

**Swedish Obese Subjects Study**
*(N=4047)*

**BMI entry criteria:** ≥34 kg/m\(^2\) men, ≥38 kg/m\(^2\) women.

**Sjostrom L, et al. JAMA. 2012;307:56-65.**

---

**Table:**

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Control</th>
<th>Banding</th>
<th>Gastroplasty</th>
<th>Bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>2037</td>
<td>376</td>
<td>1369</td>
<td>265</td>
</tr>
<tr>
<td></td>
<td>1490</td>
<td>333</td>
<td>1086</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td>1242</td>
<td>284</td>
<td>987</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>1267</td>
<td>284</td>
<td>1007</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>556</td>
<td>150</td>
<td>489</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>176</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>13</td>
</tr>
</tbody>
</table>

**Graph:**

- Control
- Banding
- Vertical banded gastroplasty
- Gastric bypass

**Years:** 0 1 2 3 4 6 8 10 15 20

**Δ Mean Weight (%):**

- Control
- Banding
- Vertical banded gastroplasty
- Gastric bypass

---

BMI entry criteria: ≥34 kg/m\(^2\) men, ≥38 kg/m\(^2\) women.

**Sjostrom L, et al. JAMA. 2012;307:56-65.**
Bariatric Surgery Reduces Mortality in Severely Obese Patients

Swedish Obese Subjects Study (N=4047)

Fatal CV Events

- Control (49 events)
- Surgery (28 events)

HR, 0.56; 95% CI, 0.35-0.88; Log-rank $P = 0.01$

Total CV Events

- Control (49 events)
- Surgery (28 events)

HR, 0.83; 95% CI, 0.69-1.00; Log-rank $P = 0.05$

BMI entry criteria: $\geq 34$ kg/m$^2$ men, $\geq 38$ kg/m$^2$ women.

Weight Loss with Different Bariatric Surgeries in Obese Patients

ACS Bariatric Surgery Center Network Prospective Observational Study
(N=28,616)

*P<0.05 vs baseline.

ACS = American College of Surgeons; BL = baseline; BMI = body mass index; LAGB = laparoscopic adjustable gastric band; LSG = laparoscopic sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass.

Effect of Different Bariatric Surgeries on Weight-Related Comorbidities at 1 Year

ACS Bariatric Surgery Center Network Prospective Observational Study
(N=28,616)

ACS, American College of Surgeons; BMI, body mass index; GERD, gastroesophageal reflux disease; LAGB, laparoscopic adjustable gastric band; LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass.

Prediabetes Comorbidities and Complications

MICROVASCULAR COMPLICATIONS
Impaired Fasting Glucose and Correlations With Diabetes, Hypertension, and Retinopathy

Population-Based Cross-sectional Studies

- Blue Mountains Eye Study (BMES) (N=3654, 99% white)
  - FPG=95.4 mg/dL
  - Patients ( % ): 8, 11.5, 71.3

- Australian Diabetes, Obesity and Lifestyle Study (AusDiab) (N=2773; ~95% white)
  - FPG=117 mg/dL
  - Patients ( % ): 33.6, 52.2, 9.3

- Multi-ethnic Study of Atherosclerosis (MESA) (N=6237; 40% white, 27% black, 22% Hispanic, 12% Chinese)
  - FPG=106 mg/dL
  - Patients ( % ): 12.8, 48.9, 15.8

Hypertension defined as >140/90 mm Hg.
FPG Thresholds Above Which Retinopathy Prevalence Rises

<table>
<thead>
<tr>
<th>Method</th>
<th>Blue Mountains Eye Study</th>
<th>Australian Diabetes, Obesity, and Lifestyle Study</th>
<th>Multi-ethnic Study of Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>On visual inspection</td>
<td>6.3-7.0 mmol/l (113-126 mg/dL)</td>
<td>7.1-7.8 mmol/l (128-140 mg/dL)</td>
<td>No clear threshold</td>
</tr>
<tr>
<td>Change point model</td>
<td>5.2 mmol/l (94 mg/dL)</td>
<td>6.3 mmol/l (113 mg/dL)</td>
<td>No clear threshold</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose.
Relationship Between FPG and 5-Year Incident Retinopathy


FPG, fasting plasma glucose.
The prevalence of retinopathy rises dramatically with increasing deciles of glycemia; for microalbuminuria, the increase in prevalence was more gradual.

FPG values corresponded well with WHO diagnostic cut points for diabetes while the 2-hour PG value did not.

A1C thresholds were similar for both retinopathy and microalbuminuria.

FPG, fasting plasma glucose; PG, plasma glucose; WHO, World Health Organization.

**Diabetic Retinopathy in the DPP**

- **Mild/moderate NPDR**: microaneurysms plus ≥1 of the following: venous loops >0/1; soft exudates, intraretinal microvascular abnormalities or venous beading; retinal hemorrhages; hard exudates >0/1; or soft exudates >0/1.

- **P=0.035 vs nondiabetic.**

---

**Legend**
- Exudates or IRMA (ETDRS 14)
- Hemorrhages (ETDRS 15)
- Microaneurysms only (ETDRS 20)
- Mild/moderate NPDR* (ETDRS 35-43)

**Graph**

- **Nondiabetic retinopathy ETDRS levels 14-15**
- **Diabetic retinopathy ETDRS levels 20-43**

---

*Mild/moderate NPDR: microaneurysms plus ≥1 of the following: venous loops >0/1; soft exudates, intraretinal microvascular abnormalities or venous beading; retinal hemorrhages; hard exudates >0/1; or soft exudates >0/1.

†P=0.035 vs nondiabetic.

DPP, Diabetes Prevention Program; ETDRS, Early Treatment of Diabetic Retinopathy Study; IRMA, intraretinal microvascular abnormalities; NPDR, nonproliferative diabetic retinopathy.

Prevalence of CKD in US Adults With Undiagnosed T2D or Prediabetes

Estimation of GFR by the MDRD Study equation, by diabetes status. Undiagnosed diabetes defined as FPG ≥126 mg/dL, without a report of provider diagnosis; prediabetes is defined as FPG ≥100 and <126 mg/dL; and no diabetes is defined as FPG <100 mg/dL.

*Plus a single measurement of albuminuria.

CKD, chronic kidney disease; FPG, fasting plasma glucose; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; NHANES = National Health and Nutrition Examination Survey; T2D, type 2 diabetes.

Prevalence of Diabetic Nephropathy in Prediabetes and T2D

**Diabetes Prevention Program**

Baseline (N=3188)

- Placebo: 5.3%
- Metformin: 6.5%
- Lifestyle: 6.8%

End of Study (N=2802)

- Placebo: 5.5%
- Metformin: 8.1%
- Lifestyle: 7.3%

ACR, albumin to creatinine ratio; DPP, Diabetes Prevention Program; T2D, type 2 diabetes.

# Diabetic Nephropathy in Prediabetes

## Diabetes Prevention Program

<table>
<thead>
<tr>
<th>End of Study Status</th>
<th>Placebo (n=940)</th>
<th>Metformin (n=931)</th>
<th>Intensive Lifestyle Intervention (n=931)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable status</td>
<td>883 (93.9%)</td>
<td>861 (92.5%)</td>
<td>863 (92.7%)</td>
</tr>
<tr>
<td>Worsened albuminuria</td>
<td>33 (3.5%)</td>
<td>35 (3.8%)</td>
<td>28 (3.0%)</td>
</tr>
<tr>
<td>Improved albuminuria</td>
<td>24 (2.6%)</td>
<td>35 (3.8%)</td>
<td>40 (4.3%)</td>
</tr>
<tr>
<td>Net increase in elevated ACR</td>
<td>9 (1.0%)</td>
<td>0 (0.0%)</td>
<td>-12 (-1.3%)</td>
</tr>
</tbody>
</table>

ACR, albumin to creatinine ratio; DPP, Diabetes Prevention Program.

Impact of TZD Therapy on Nephropathy in Prediabetes

DREAM Trial
(N=5269)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosiglitazone</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal → microalbuminuria</td>
<td>241 (9.2%)</td>
<td>285 (10.8%)</td>
<td>0.83 (0.69-0.99)</td>
</tr>
<tr>
<td>Microalbuminuria → proteinuria</td>
<td>6 (0.23%)</td>
<td>13 (0.49%)</td>
<td>0.46 (0.18-1.21)</td>
</tr>
<tr>
<td>↓ eGFR ≥ 30%</td>
<td>82 (3.1%)</td>
<td>105 (4.0%)</td>
<td>0.77 (0.58-1.04)</td>
</tr>
<tr>
<td>Microalbuminuria → normal</td>
<td>193 (52.5%)</td>
<td>185 (48.7%)</td>
<td>1.18 (0.88-1.57)</td>
</tr>
</tbody>
</table>

CI, confidence interval; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; eGFR, estimated glomerular filtration rate; HR, hazard ratio; TZD, thiazolidinedione.

prediabetes comorbidities and complications

metabolic syndrome
# Syndrome X (1988): A Historical Review

Metabolic disturbances commonly cluster in patients with cardiovascular disease, even without diabetes.

<table>
<thead>
<tr>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Resistance to insulin-stimulated glucose uptake</td>
</tr>
<tr>
<td>• Hyperinsulinemia</td>
</tr>
<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Glucose intolerance</td>
</tr>
<tr>
<td>• Increased triglycerides and VLDL</td>
</tr>
<tr>
<td>• Decreased HDL-C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Resistance to insulin-stimulated suppression of adipose tissue lipolysis increases free fatty acids</td>
</tr>
<tr>
<td>• Obesity was not a required trait, but Syndrome X was more common in overweight or obese individuals</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein cholesterol; VLDL, very low-density lipoprotein.

Clinical Identification of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor*</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>≥102 cm (≥40 in)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>≥88 cm (≥35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>≥130 mmHg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>≥85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

*≥3 criteria must be met for diagnosis.

ACC, American College of Cardiology; AHA, American Heart Association; ATP III, National Cholesterol Education Program Adult Treatment Panel III; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Abdominal Obesity and Increased Risk of Cardiovascular Events

The HOPE Study

<table>
<thead>
<tr>
<th>Waist Circumference (cm)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>&lt;95</td>
<td>&lt;87</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>95-103</td>
<td>87-98</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>&gt;103</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative risk*</th>
<th>CVD death</th>
<th>MI</th>
<th>All-cause deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.17</td>
<td>1.16</td>
<td>1.14</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.29</td>
<td>1.27</td>
<td>1.35</td>
</tr>
</tbody>
</table>

*CAdjusted for BMI, age, smoking, sex, CVD disease, DM, HDL cholesterol, total cholesterol.

BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; MI, myocardial infarction.

Incidence of Diabetes by Waist Circumference and Race/Ethnicity


Solid lines pertain to values between the race-specific 5th and 95th percentiles of waist circumference. Dotted lines are extrapolated values outside the aforementioned race-specific ranges. Adjusted for age, sex, education, and income.

Roughly One-Third of Obese Individuals Are Metabolically Healthy

NHANES 1999-2004

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td><strong>Normal</strong></td>
</tr>
<tr>
<td>Population (%)</td>
<td>Population (%)</td>
</tr>
<tr>
<td>69.9</td>
<td>78.9</td>
</tr>
<tr>
<td><strong>Overweight</strong></td>
<td><strong>Overweight</strong></td>
</tr>
<tr>
<td>48.8</td>
<td>57</td>
</tr>
<tr>
<td>*51.2</td>
<td>*43</td>
</tr>
<tr>
<td><strong>Obese</strong></td>
<td><strong>Obese</strong></td>
</tr>
<tr>
<td>29.2</td>
<td>21.1</td>
</tr>
<tr>
<td>*70.8</td>
<td>*35.4</td>
</tr>
</tbody>
</table>

*P<0.001 vs metabolically abnormal, normal weight.

NHANES, National Health and Nutrition Examination Survey.

Characteristics of Metabolically Healthy vs Insulin Resistant Obese

BMI, body mass index; IR, insulin resistant; IS, insulin sensitive.

Metabolic Syndrome vs Obesity in Cardiovascular Risk

Women's Ischemia Syndrome Evaluation (WISE) Study

BMI, body mass index; MACE, major adverse cardiac event (death, nonfatal myocardial infarction, stroke, congestive heart failure).

Metabolic Markers of CV Risk in Overweight, Insulin-Resistant Individuals

ROC Curve Analysis

TG, TG-HDL ratio, and insulin most useful metabolic markers for insulin resistance

BMI, body mass index; HDL, high-density lipoprotein; ROC, receiver-operating characteristic; TC, total cholesterol; TG, triglyceride.

# Metabolic Syndrome and Risk of Incident Cardiovascular Events and Death

#### Systematic Review and Meta-analysis*
(37 Longitudinal Studies; N=172,573)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies (N)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event</td>
<td>11</td>
<td>2.18</td>
<td>1.63-2.93</td>
</tr>
<tr>
<td>CHD event</td>
<td>18</td>
<td>1.65</td>
<td>1.37-1.99</td>
</tr>
<tr>
<td>CV death</td>
<td>10</td>
<td>1.91</td>
<td>1.47-2.49</td>
</tr>
<tr>
<td>CHD death</td>
<td>7</td>
<td>1.60</td>
<td>1.28-2.01</td>
</tr>
<tr>
<td>Death</td>
<td>12</td>
<td>1.60</td>
<td>1.37-1.92</td>
</tr>
</tbody>
</table>

*Timespan: 1971 to 1997; metabolic syndrome defined using NCEP, WHO, or modified criteria.

CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; NCEP, National Cholesterol Education Program; RR, relative risk; WHO, World Heath Organization.

Overlap Between Metabolic Syndrome and Hyperglycemia

NHANES 1988-1994
Participants Age ≥50 Years

IFG or diabetes 20.6%
Metabolic syndrome 18.4%
Both 61.0%

IFG, impaired fasting glucose; NHANES, National Health and Nutrition Examination Survey.
Risk of Developing Type 2 Diabetes

San Antonio Heart Study

Age- and Sex-Adjusted Incidence of Diabetes

IGT, impaired glucose tolerance (2-h post-load glucose ≥140 mg/dL); Met Syn, metabolic syndrome as defined in ATP III.

Prediabetes Comorbidities and Complications

MACROVASCULAR COMPLICATIONS
Baseline Proteinuria Increases Cardiovascular Risk

Systematic Review
(RCTs: N=29; Patients with DM: N=116,790; ~518,611 patient-years of follow-up)

Events/1,000 patient-years

- All-Cause Death: ~6-fold higher
  - No Proteinuria: 6.3
  - Mixed Trials: 18.6
  - All Proteinuria: 39.9

- CVD Death: ~15-fold higher
  - No Proteinuria: 1.2
  - Mixed Trials: 9.3
  - All Proteinuria: 18.7

- MI: ~13-fold higher
  - No Proteinuria: 11.6
  - Mixed Trials: 12.9

- Stroke: ~12-fold higher
  - No Proteinuria: 7.5
  - Mixed Trials: 12.4

CVD, cardiovascular disease; MI, myocardial infarction.
Risk of All-Cause and CV Mortality According to eGFR and Albuminuria

CV, cerebrovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

<table>
<thead>
<tr>
<th>Low risk:</th>
<th>Extreme risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No risk factors</td>
<td>• Progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD with diabetes, stage 3 or 4 CKD, and/or HeFH, or in those with a history of premature ASCVD (&lt;55 years of age for males or &lt;65 years of age for females)</td>
</tr>
<tr>
<td>Moderate risk:</td>
<td>• This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces better outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezetimibe with statins.</td>
</tr>
<tr>
<td>• 2 or fewer risk factors and a calculated 10-year risk of less than 10%</td>
<td></td>
</tr>
<tr>
<td>High risk:</td>
<td></td>
</tr>
<tr>
<td>• An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%</td>
<td></td>
</tr>
<tr>
<td>Very high risk:</td>
<td></td>
</tr>
<tr>
<td>• Established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH</td>
<td></td>
</tr>
</tbody>
</table>
# Dyslipidemia

## Lifestyle Therapy (Including Medically Assisted Weight Loss)

**Lipid Panel: Assess ASCVD Risk**

### Statin Therapy

- If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin
- If statin-intolerant

**Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C-lowering therapies**

**Repeat lipid panel; assess adequacy, tolerance of therapy**

**Intensify therapies to attain goals according to risk levels**

### Risk Levels

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>Desirable Levels</th>
<th>Very High Levels</th>
<th>Extreme Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

**If Not at Desirable Levels:** Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

**To Lower LDL-C:** Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin

**To Lower Non-HDL-C, TG:** Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin

**To Lower Apo B, LDL-P:** Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin

**Statin + PCSK9i**

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

*EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED**

**FAMILIAL HYPERCHOLESTEROLEMIA**

# Hypertension

**Goal:** Systolic <130, Diastolic <80 mm Hg

**For initial blood pressure >150/100 mm Hg:**

**Dual Therapy**

- ACEi or ARB
- Calcium Channel Blocker
- β-blocker
- Thiazide

**If Not at Goal (2–3 months):**

- Add calcium channel blocker, β-blocker or thiazide diuretic

**If Not at Goal (2–3 months):**

- Add next agent from the above group, repeat

**If Not at Goal (2–3 months):**

- Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

**Achievement of target blood pressure is critical**
Elevated Risk of CVD Prior to Clinical Diagnosis of Type 2 Diabetes

Nurses Health Study*
(N=117,629)

*Female nurses with no CVD at baseline aged 30-55 years and followed from 1976 to 1996.
CVD, cardiovascular disease.
Glucose Levels and Mortality in Individuals Without Known Diabetes

The DECODE Study

Postprandial glucose is an independent risk factor predicting mortality

*Adjusted for age, sex, and study center.

DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe.

Effect of Metformin and Lifestyle Change on Blood Pressure

Diabetes Prevention Program (N=3234)

**Blood Pressure Change**

- Placebo
- Metformin
- Intensive lifestyle intervention

**Hypertension Prevalence**

- Placebo
- Metformin
- Intensive lifestyle intervention

*P<0.001 vs placebo and metformin.

DPP, Diabetes Prevention Program.

Hypertension defined as blood pressure $\geq 140/90$ mmHg.

IGT, impaired glucose tolerance; STOP NIDDM, Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

## CVD Outcomes in Type 2 Diabetes Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP</td>
<td>64 of 3234 patients (89 total events)</td>
</tr>
<tr>
<td>DREAM</td>
<td>0.5 events/100 patient-years</td>
</tr>
<tr>
<td>STOP NIDDM</td>
<td>1.4 events/100 patient-years</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; STOP NIDDM, Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

Effect of Acarbose on Cardiovascular Events in Patients With IGT

STOP NIDDM
(N=1429)

CVD, cardiovascular disease; IGT, impaired glucose tolerance; RRR, relative risk reduction; STOP NIDDM, Study to Prevent Non-Insulin Dependent Diabetes Mellitus Trial.

Effect of Acarbose on CVD Events in IGT

**STOP NIDDM (N=1429)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Acarbose (N=682)</th>
<th>Placebo (N=686)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>12</td>
<td>0.09*</td>
</tr>
<tr>
<td>Angina</td>
<td>5</td>
<td>12</td>
<td>0.45</td>
</tr>
<tr>
<td>Revascularization</td>
<td>11</td>
<td>20</td>
<td>0.61</td>
</tr>
<tr>
<td>CVD death</td>
<td>1</td>
<td>2</td>
<td>0.55</td>
</tr>
<tr>
<td>Cerebrovascular event or stroke</td>
<td>2</td>
<td>4</td>
<td>0.56</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
<td>1</td>
<td>1.14</td>
</tr>
<tr>
<td>Any CVD event</td>
<td>15</td>
<td>32</td>
<td>0.51*</td>
</tr>
</tbody>
</table>

* *P<0.05

CVD, cardiovascular disease; IGT, impaired glucose tolerance; STOP NIDDM, Study to Prevent Non-Insulin Dependent Diabetes.
Effect of Intensive Lifestyle Intervention on CVD Death

Da Qing Diabetes Prevention Study

Cumulative incidence of CVD death

20-year follow-up hazard rate ratio 0.83 (95%CI 0.48-1.40)
14-year post-intervention hazard rate ratio 0.73 (95%CI 0.42-1.26)

CVD, cardiovascular disease.

Prediabetes Comorbidities and Complications

DYSLIPIDEMIA MANAGEMENT
### Common Secondary Causes of Dyslipidemia

<table>
<thead>
<tr>
<th>Affected lipids</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| ↑ Total cholesterol and LDL-C | • Hypothyroidism  
• Nephrosis  
• Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)  
• Progestin or anabolic steroid treatment  
• Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis  
• Protease inhibitors for treatment of HIV infection |
| ↑ Triglycerides and VLDL-C | • Chronic renal failure  
• T2D  
• Obesity  
• Excessive alcohol intake  
• Hypothyroidism  
• Antihypertensive medications (thiazide diuretics and b-adrenergic blocking age  
• Corticosteroid therapy (or severe stress that increases endogenous corticosteroids)  
• Orally administered estrogens, oral contraceptives, pregnancy  
• Protease inhibitors for treatment of HIV infection |

HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; T2D, type 2 diabetes; VLDL-C, very low-density lipoprotein cholesterol.

Intensive LDL-C Lowering Reduced CV Events in Patients With Low Baseline LDL-C

**Cholesterol Treatment Trialists 2010**

- For each 39 mg/dL reduction in LDL-C:
  - Individuals with baseline LDL-C <77 mg/dL had a 29% further reduction in major vascular events (P=0.007)
  - Those with baseline LDL-C <70 mg/dL had a 37% further reduction in major vascular events (P=0.004)

*Meta-analysis of randomized controlled trials of major vascular events (coronary death, myocardial infarction, coronary revascularization, and ischemic stroke) with at least 1,000 patients and ≥2 years of more vs. less intense statin dosage (N=169,138).

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

# AACE Lipid Goals by ASCVD Risk

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk factors*/10-year risk†</th>
<th>Treatment goals (mg/dL)</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
</table>
| Extreme risk  | • Progressive ASCVD including unstable angina in patients after achieving LDL-C <70 mg/dL  
• Established clinical CVD in patients with diabetes, stage 3 or 4 CKD, or HeHF  
• History of premature ASCVD (age <55 male, <65 female) | <55 | <80 | <70 |
| Very high risk| • Established or recent hospitalization for ACS or coronary, carotid, or peripheral vascular disease, or 10-year risk >20%  
• Diabetes or stage 3 or 4 CKD plus ≥1 additional risk factor(s)  
• HeHF | <70 | <100 | <80 |
| High risk     | • ≥2 risk factors and 10-year risk 10-20%  
• Diabetes or stage 3 or 4 CKD with no other risk factors | <100 | <130 | <90 |
| Moderate risk | ≤2 risk factors and 10-year risk <10% | <100 | <130 | <90 |
| Low risk      | 0 risk factors | <130 | <160 | NR |

*High LDL-C, PCOS, cigarette smoking, hypertension, low HDL-C, family history of CAD, stage 3 or 4 CKD, coronary calcification, and age ≥45 years in men and ≥55 years in women.
†Framingham risk score.
ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; HDL-C, high density lipoprotein cholesterol; HeHF, heterozygous familial hypercholesterolemia; LDL-C low density lipoprotein cholesterol; NR, not recommended; PCOS, polycystic ovary syndrome.

Classification of Elevated Triglyceride Levels

<table>
<thead>
<tr>
<th>TG category</th>
<th>TG concentration (mg/dL)</th>
<th>TG goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;150</td>
<td></td>
</tr>
<tr>
<td>Borderline high</td>
<td>150-199</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>High</td>
<td>200-499</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>≥500</td>
<td></td>
</tr>
</tbody>
</table>

TG levels that are even moderately elevated (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome. TG levels ≥200 mg/dL may indicate a substantial increase in ASCVD risk. Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension.

ASCVD, atherosclerotic cardiovascular disease; TG, triglycerides.

Very Low LDL-C Levels and Risk for Major CV Events

Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosing)

Adjusted* Hazard Ratio for Major CV Events

- LDL-C, ApoB, non-HDL-C Achieved On-Trial Atherogenic Cholesterol and Lipoprotein Concentration (mg/dL)

*Adjusted for sex, age, smoking, diabetes, SBP, HDL-C, and trial.

** >200 mg/dL for non-HDL-C.

Apo, apolipoprotein; CV, cerebrovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

IMPROVE-IT: Improved Reduction of Outcomes, Vytorin Efficacy International Trial

**Trial design:** Patients with recent ACS were randomized 1:1 to either ezetimibe 10 mg + simvastatin 40 mg or simvastatin 40 mg and followed for a median of 6 years.

**Results**

- Primary endpoint (CV death/MI/UA/coronary revasc/stroke/moderate/severe bleeding) for ezetimibe/simvastatin vs. simvastatin: 32.7% vs. 34.7% (HR 0.94, 95% CI 0.89-0.99; \( P=0.016 \))
- MI: 13.1% vs. 14.8%, \( P=0.002 \); stroke: 4.2% vs. 4.8%, \( P=0.05 \); CVD/MI/stroke: 20.4% vs. 22.2%, \( P=0.003 \)
- Median LDL follow-up average: 53.7 vs. 69.5 mg/dL

**Conclusions**

- In patients with high-risk ACS, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a non-statin agent
- Reaffirms the “lower is better” hypothesis with LDL-C

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.
**Trial design:** Patients with CAD and elevated LDL-C on statin therapy were randomized to SQ evolocumab (n=484) vs SQ placebo (n=486).

**Results**

- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group (P<0.001 for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo (P<0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

**Conclusions**

- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression
FOURIER Trial

- This randomized, double-blind, placebo-controlled trial investigated the effects of adding evolocumab to high-intensity statin therapy compared with high-intensity statins alone.
- Participants were recruited from 12 prior evolocumab trials.
- Median patient follow-up was 2.2 years; study results included data for over 27,500 individuals with clinically evident atherosclerotic disease and baseline LDL-C levels ≥70 mg/dL and HDL-C levels ≥100 mg/dL.
- All study participants were receiving statin therapy with or without ezetimibe, and the evolocumab and placebo groups had the same baseline LDL-C (92 mg/dL).

FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

FOURIER Evolocumab Study

LDL-C Levels Over Time

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Weeks</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>13,779</td>
<td>13,784</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>13,251</td>
<td>13,288</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>13,151</td>
<td>13,144</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>12,954</td>
<td>12,964</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>12,596</td>
<td>12,645</td>
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<tr>
<td></td>
<td>48</td>
<td>12,311</td>
<td>12,359</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>10,812</td>
<td>10,902</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>6926</td>
<td>6958</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>3352</td>
<td>3323</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>790</td>
<td>768</td>
</tr>
<tr>
<td>Absolute difference (mg/dL)</td>
<td>0</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Percentage difference</td>
<td>0</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>P-value</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

FOURIER Primary and Secondary Endpoints

• At 26 months, extremely tight lipid control with evolocumab led to a 15% decrease in risk for the primary composite endpoint and 20% decrease in risk for a secondary composite endpoint
  – The primary endpoint included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina
  – The secondary endpoint included cardiovascular death, MI, or stroke
• Beyond the second year of follow-up, the risk reduction increased to 20% for the primary endpoint and to 25% for the secondary endpoint
• For singular endpoints at 26 months, very tight lipid control reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%

FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.
FOURIER Evolocumab Study Endpoints

Cumulative event rates for the primary efficacy endpoint
(Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.
Effect of Metformin and Lifestyle on Total and LDL-C in Prediabetes

Diabetes Prevention Program
(N=3234)

Baseline (mg/dL) 202

Total Cholesterol

Change in Lipids (%)

Baseline (mg/dL) 127

LDL-C

Lifestyle  Metformin  Placebo

-2.3 -0.9 -1.2

-2.5 -2 -1.5 -1 -0.5 0

-2.5 -2 -1.5 -1 -0.5 0

LDL-C, low-density lipoprotein cholesterol.

Atherogenic Dyslipidemia: The Dyslipidemic Triad

- High TG
- Low HDL-C
- Small, dense LDL particles

↑ Non-HDL-C
Triglycerides
VLDL
Chylomicrons
TG-rich lipoprotein remnants
Small, dense LDL

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglycerides; VLDL, very low-density lipoprotein.

Risk of CHD With Hypertriglyceridemia

Updated Meta-analysis
(N=262,525; 29 Prospective Studies)

CHD, coronary heart disease; HDL, high-density lipoprotein; TG, triglyceride.


CHD, coronary heart disease; HDL, high-density lipoprotein; TG, triglyceride.
Joint Effects of Serum Triglycerides, LDL-C, and HDL-C on CHD Risk

Helsinki Heart Study Analysis: Relative Risk of Cardiac Events Among Placebo Patients

Mean baseline (mg/dL)
TC: 289
TG: 176
HDL-C: 47
LDL-C: 189
Non-HDL-C: 242

CHD, coronary heart disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

The fewest deaths (n=15) occurred in the subgroup with TG <150 and HDL-C >55 mg/dL.

HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.
Fibrate Benefits Are Greatest in Patients with High TG and Low HDL-C

Bezafibrate Infarction Prevention Study

Patients Meeting Primary Endpoint* After 6.5 Years

*Fatal or nonfatal myocardial infarction or sudden death; arrows denote statistically significant differences.

BL, baseline; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Fibrates in HHS and VA-HIT

- HHS showed that fibrates are highly effective at lowering TG, and that reducing TG is associated with fewer ASCVD events and significantly reduces nonfatal MI\(^1\)
- Gemfibrozil use resulted in a 34% reduction in coronary heart disease endpoints (fatal and nonfatal MI or cardiac death)
- An 18-year HHS follow-up showed that TG reduction with fibrates significantly lowered the ASCVD mortality rate\(^2\)
- VA-HIT showed that increasing HDL-C and lowering TG in individuals with ASCVD whose primary lipid abnormality was low HDL-C significantly reduced the rate of coronary events, even without any change in LDL-C levels\(^3\)
- Gemfibrozil use resulted in a 22% reduction in the relative risk for nonfatal MI or coronary death and reduced nonfatal MI, coronary death, or stroke by 24%\(^3\)

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglyceride; VA-HIT, Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial.

Effect of Metformin and Lifestyle on Triglycerides and HDL-C in Prediabetes

Diabetes Prevention Program (N=3234)

<table>
<thead>
<tr>
<th>Change in Lipids (mg/dL)</th>
<th>Triglycerides</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mg/dL)</td>
<td>172</td>
<td>40</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>-25.4</td>
<td>1</td>
</tr>
<tr>
<td>Metformin</td>
<td>-25.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>-25.4</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

Triglycerides: 172 mg/dL (Baseline), -25.4 mg/dL (Lifestyle), -25.4 mg/dL (Metformin), -11.9 mg/dL (Placebo)

HDL-C: 40 mg/dL (Baseline), 1 mg/dL (Lifestyle), 0.3 mg/dL (Metformin), -0.1 mg/dL (Placebo)

HDL-C, high-density lipoprotein cholesterol.

Intensive Lifestyle Intervention Reduces Dyslipidemia

Diabetes Prevention Program (N=3234)


*P<0.001 vs placebo; †P=0.015 vs metformin.
Statins: Primary Metabolic Effects and Main Considerations

**Metabolic Effects**
- Primarily ↓ LDL-C 21%-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors
- Effects on TG and HDL-C are less pronounced (↓ TG 6%-30% and ↑ HDL-C 2%-10%)

**Main Considerations**
- Liver function test prior to therapy and as clinically indicated thereafter
- Myalgias and muscle weakness in some individuals
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors
- Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling)
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for 12 months or more without muscle toxicity
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine
- Plasma elevations of rosvuastatin may be higher among Asian persons than other ethnic groups
- New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with MetS, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.

## Statin Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20 mg</td>
<td>10-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg</td>
<td>10-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-40 mg</td>
<td>5-80 mg*</td>
<td>Oral</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40 mg</td>
<td>20-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-20 mg</td>
<td>10-80 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>5-40 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2 mg</td>
<td>2-4 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

*Simvastatin 80 mg not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.

Crestor (rosuvastatin calcium); [PI]; 2016; Jellinger P, et al. *Endocr Practice*. 2017;23:479-497; Lescol (fluvastatin sodium) [PI]; 2012 Lipitor (atorvastatin calcium) [PI]; 2015; Livalo (pitavastatin) [PI]; 2013; ; Mevacor (lovastatin) [PI]; 2014; Pravachol (pravastatin sodium) [PI]; 2016; Zocor (simvastatin) [PI]; 2015.
Statin Benefits Across a Range of Baseline Levels

Cholesterol Treatment Trialists’ Collaboration

LDL-C 90-130 mg/dL shows same benefit as LDL-C 50-90 mg/dL

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin</td>
</tr>
<tr>
<td>&lt;2 mmol/L (&lt;77 mg/dL)</td>
<td>910 (4.1%)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L (77-96 mg/dL)</td>
<td>1,528 (3.6%)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L (97-116 mg/dL)</td>
<td>1,866 (3.3%)</td>
</tr>
<tr>
<td>≥3.0 to &lt;3.5 mmol/L (117-135 mg/dL)</td>
<td>2,007 (3.2%)</td>
</tr>
<tr>
<td>≥3.5 mmol/L (&gt;136 mg/dL)</td>
<td>4,508 (3.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>10,973 (3.2%)</td>
</tr>
</tbody>
</table>

1 mmol/L = 38.6 mg/dL
LDL-C, low-density lipoprotein cholesterol.
### Effect on CHD and Diabetes Primary Prevention

#### Cholesterol Treatment Trialists’ Collaboration

<table>
<thead>
<tr>
<th>Previous Vascular Disease</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin</td>
<td>Control</td>
</tr>
<tr>
<td>CHD</td>
<td>8,395 (4.5%)</td>
<td>10,123 (5.6%)</td>
</tr>
<tr>
<td>No CHD, vascular</td>
<td>674 (3.1%)</td>
<td>802 (3.7%)</td>
</tr>
<tr>
<td>None</td>
<td>1,904 (1.4%)</td>
<td>2,425 (1.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>145 (4.5%)</td>
<td>192 (6.0%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2,494 (4.2%)</td>
<td>2,920 (5.1%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>8,272 (3.2%)</td>
<td>10,163 (4.0%)</td>
</tr>
</tbody>
</table>

1 mmol/L = 38.6 mg/dL.

CHD: coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RR: relative risk.

Comparison of Statin Effects on Lipids After 6 Weeks of Treatment

Men and Women With LDL-C ≥160 and ≤250 mg/dL (N=2,431)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage range, mg daily</th>
<th>TC (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>20-80</td>
<td>↓ 21 to ↓ 36</td>
<td>↓ 29 to ↓ 48</td>
<td>↑ 4.6 to ↑ 8.0</td>
<td>↓ 12 to ↓ 13</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10-40</td>
<td>↓ 15 to ↓ 22</td>
<td>↓ 20 to ↓ 30</td>
<td>↑ 3.2 to ↑ 5.6</td>
<td>↑ 8 to ↓ 13</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10-80*</td>
<td>↓ 20 to ↓ 33</td>
<td>↓ 28 to ↓ 46</td>
<td>↑ 5.2 to ↑ 6.8</td>
<td>↓ 12 to ↓ 18</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-40</td>
<td>↓ 13 to ↓ 19</td>
<td>↓ 17 to ↓ 23</td>
<td>↑ 0.9 to ↓ 3.0</td>
<td>↓ 5 to ↓ 13</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10-80</td>
<td>↓ 27 to ↓ 39</td>
<td>↓ 37 to ↓ 51</td>
<td>↑ 2.1 to ↑ 5.7</td>
<td>↓ 20 to ↓ 28</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10-40</td>
<td>↓ 33 to ↓ 40</td>
<td>↓ 45 to ↓ 55</td>
<td>↑ 7.7 to ↑ 9.6</td>
<td>↓ 20 to ↓ 26</td>
</tr>
</tbody>
</table>

*Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

# PCSK9 Inhibitor Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>75 mg every 2 weeks</td>
<td>75-150 mg every 2 weeks</td>
<td>SC</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>140 mg every 2 weeks or 420 mg once monthly</td>
<td>Not applicable</td>
<td>SC</td>
</tr>
</tbody>
</table>

**Metabolic Effects**
- ↓LDL-C 48%-71%, ↓non-HDL-C 49%-58%, ↓TC 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels

**Main Considerations**
- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low
- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions with similar rates for drug vs. placebo were:
  - **Alirocumab**: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
  - **Evolocumab**: nasopharyngitis, back pain, and upper respiratory tract infection

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SC, subcutaneous injection; TC, total cholesterol.

Fibrate Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended starting daily dose</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>48-145 mg</td>
<td>48-145 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>1200 mg</td>
<td>1200 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Fenofibric acid</td>
<td>45-135 mg</td>
<td>45-135 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Metabolic Effects**

- Primarily ↓ TG 20%-35%, ↑ HDL-C 6%-18% by stimulating lipoprotein lipase activity
- Fenofibrate may ↓ TC and LDL-C 20%-25%
- Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size
- Fenofibrate ↓ fibrinogen level

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein, LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Fibrates: Main Considerations

- Gemfibrozil may ↑ LDL-C 10%-15%
- GI symptoms, possible cholelithiasis
- May potentiate effects of orally administered anticoagulants
- Gemfibrozil may ↑ fibrinogen level
- Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations
- May cause muscle disorders; myopathy/rhabdomyolysis when used with statin
- Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction
- Fenofibrate dose should be cut by two-thirds and gemfibrozil by one-half when eGFR is 15-60, and fibrates should be avoided when eGFR is <15
- Can improve diabetic retinopathy

eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol.
## Bile Acid Sequestrant Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended daily dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>8-16 g</td>
<td>4-24 g</td>
<td>Oral</td>
</tr>
<tr>
<td>Colestipol</td>
<td>2 g</td>
<td>2-16 g</td>
<td>Oral</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>3.8 g</td>
<td>3.8-4.5 g</td>
<td>Oral</td>
</tr>
</tbody>
</table>

### Metabolic Effects
- Primarily ↓ LDL-C 15%-25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDL-receptor upregulation)
- Colesevelam ↓ glucose and hemoglobin A1C (~0.5%); FDA-approved to treat T2D

### Main Considerations
- May ↑ serum TG
- Frequent constipation and/or bloating, which can reduce adherence
- Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling)
- May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K

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FDA, Food and Drug Administration; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; T2D, type 2 diabetes; TG, triglyceride.

# Cholesterol Absorption Inhibitor Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended daily dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>10 mg</td>
<td>10 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin</td>
<td>10/20 mg</td>
<td>10/10 to 10/80 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

## Metabolic Effects
- Primarily ↓ LDL-C 10%-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors
- ↓ Apo B 11%-16%
- In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%-61%
- In combination with fenofibrate, ↓ LDL-C 20%-22% and ↓ apo B 25%-26% without reducing ↑ HDL-C

## Main Considerations
- Myopathy/rhabdomyolysis (rare)
- When coadministered with statins or fenofibrate, risks associated with those drugs remain (e.g., myopathy/rhabdomyolysis, cholelithiasis)

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Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

# Omega-3 Fatty Acid Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended daily dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3-acid ethyl esters (Lovaza)</td>
<td>4 g</td>
<td>4 g</td>
<td>Oral</td>
</tr>
<tr>
<td>Icosapent ethyl (Vascepa)</td>
<td>4 g</td>
<td>4 g</td>
<td>Oral</td>
</tr>
</tbody>
</table>

## Metabolic Effects
- ↓ TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apo B 4%, and non-HDL-C 8%-14% in individuals with severe hypertriglyceridemia most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased β-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity.
- Icosapent ethyl ↓ LDL-C 5%, whereas, omega-3-acid ethyl esters ↑ LDL-C 45%
Assess TG levels prior to initiating and periodically during therapy

Omega-3-acid ethyl esters can increase LDL-C levels. Monitor LDL-C levels during treatment

May prolong bleeding time. Monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation

Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment. Some patients may experience increases in ALT levels only

Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish

The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia

In patients with paroxysmal or persistent atrial fibrillation, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation

Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). May also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus

Should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm
Niacin Starting Dosages and Dosage Ranges

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended daily dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>250 mg</td>
<td>250-3000 mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Extended release</td>
<td>500 mg</td>
<td>500-2000 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Metabolic Effects**
- ↓ LDL-C 10%-25%, ↓ TG 20%-30%, ↑ HDL-C 10%-35% by decreasing hepatic synthesis of LDL-C and VLDL-C
- ↓ Lipoprotein (a)
- Transforms LDL-C to less atherogenic form by increasing average particle size and also decreases LDL particle concentration

**Main Considerations**
- Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatotoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation
- Deleterious effect on serum glucose at higher dosages
- Increases uric acid levels; may lead to gout

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol.

MTP Inhibitor Starting Dosage and Dosage Range

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommended starting dose</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomitapide</td>
<td>5 mg</td>
<td>5-60 mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Metabolic Effects**

- ↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in individuals with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL

**Main Considerations**

- Can cause increases in transaminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment, is required per FDA REMS
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transaminases, which may be a risk for progressive liver diseases
- Also causes steatosis of the small intestine with resulting abdominal pain and steatorrhea unless a very-low-fat diet is followed; may also cause fat-soluble vitamin deficiency unless vitamin supplements are taken
- Caution should be exercised when used with other drugs with potential hepatotoxicity; because of hepatotoxicity risk, only available through REMS program

ALT, aspartate amino transferase; AST, amino alanine transferase; FDA, Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal transfer protein; REMS, Risk Evaluation and Mitigation Strategy; TG, triglycerides; VLDL, very low-density lipoprotein.

Anti-sense Apolipoprotein B Oligonucleotide Starting Dosage and Dosage Range

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual recommended dosage</th>
<th>Dosage range</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mipomersen</td>
<td>200 mg once weekly</td>
<td>200 mg once weekly</td>
<td>SC</td>
</tr>
</tbody>
</table>

**Metabolic Effects**

- ↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in individuals with HoFH by degrading mRNA for apo B-100, the principal apolipoprotein needed for hepatic synthesis of VLDL (and subsequent intra-plasma production of IDL and LDL)

**Main Considerations**

- Can cause increases in transaminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase, and total bilirubin before initiation, and of ALT and AST during treatment is recommended
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transaminases, which may be a risk for progressive liver diseases
- Caution should be exercised when used with other drugs with potential hepatotoxicity; because of hepatotoxicity risk, only available through REMS program

ALT, aspartate amino transferase; apo, apolipoprotein; AST, amino alanine transferase; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger RNA; SQ, subcutaneous; VLDL, very low-density lipoprotein.