Treatment of Type 1 Diabetes
Goals of T1D Management

- Utilize intensive therapy aimed at near-normal BG and A1C levels
- Prevent diabetic ketoacidosis and severe hypoglycemia
- Achieve the highest quality of life compatible with the daily demands of diabetes management
- In children, achieve normal growth and physical development and psychological maturation
- Establish realistic goals adapted to each individual’s circumstances

T1D, type 1 diabetes.
# Routine Care Recommendations for Patients With T1D

<table>
<thead>
<tr>
<th></th>
<th><strong>Children/Adolescents (0-19 years)</strong></th>
<th><strong>Adults (≥20 years)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height</strong></td>
<td>Every 3 months</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td>Every 3 months</td>
</tr>
<tr>
<td><strong>Nutritionist</strong></td>
<td>Diagnosis, then annually</td>
<td></td>
</tr>
<tr>
<td><strong>Retinal examination</strong></td>
<td>Begin 5 years after diagnosis</td>
<td>Begin 5 years after diagnosis or earlier with visual symptoms or if date of T1D onset is unknown Every 1-2 years thereafter</td>
</tr>
<tr>
<td></td>
<td>Every 1-2 years thereafter</td>
<td></td>
</tr>
<tr>
<td><strong>A1C</strong></td>
<td></td>
<td>Every 3 months</td>
</tr>
<tr>
<td><strong>Lipid profile</strong></td>
<td>Annually, once glycemia is stable</td>
<td>Annually or as needed based on treatment</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td>Every physical examination</td>
</tr>
<tr>
<td><strong>Creatinine clearance, eGFR</strong></td>
<td>At diagnosis, then annually</td>
<td></td>
</tr>
<tr>
<td><strong>ACR</strong></td>
<td>Begin 5 years after diagnosis, then annually</td>
<td>At diagnosis, then annually</td>
</tr>
</tbody>
</table>

ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes.

## AACE Glucose Goals for Nonpregnant Adults with Diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C, %</td>
<td>Individualize on the basis of age, comorbidities, and duration of disease:</td>
</tr>
<tr>
<td></td>
<td>• In general, ≤6.5 for most*</td>
</tr>
<tr>
<td></td>
<td>• Closer to normal for healthy</td>
</tr>
<tr>
<td></td>
<td>• Less stringent for “less healthy”</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>&lt;110</td>
</tr>
<tr>
<td>2-Hour PPG, mg/dL</td>
<td>&lt;140</td>
</tr>
</tbody>
</table>

* Considerations include:

- Residual life expectancy
- Duration of diabetes
- Presence or absence of microvascular and macrovascular complications
- CVD risk factors
- Comorbid conditions
- Risk for severe hypoglycemia
- Patient’s psychological, social, and economic status

CVD, cardiovascular disease; FPG, fasting plasma glucose; PPG, postprandial glucose.

## ADA A1C Goals: Patients with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Age Group</th>
<th>A1C Goal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youth (&lt;18 years)</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Adults</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Older adults</td>
<td></td>
</tr>
<tr>
<td>Healthy†</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>Complex/intermediate health</td>
<td>&lt;8.0%</td>
</tr>
<tr>
<td>Very complex/poor health</td>
<td>&lt;8.5%</td>
</tr>
</tbody>
</table>

*Individualize goal based on patient’s circumstances:
• <6.5% may be appropriate for select patients if achievable without significant hypoglycemia
• <8.5% may be appropriate for patients with history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced complications, or extensive comorbidities

†No comorbidities, long life expectancy.

T1D, type 1 diabetes.
RATIONAL FOR GLYCEMIC CONTROL

Treatment of Type 1 Diabetes
Poor Glycemic Control Among Youth With T1D

SEARCH for Diabetes in Youth (N=3947)

A1C ≥ 9.5%

- African American: 36%
- American Indian: 52%
- Hispanic: 27%
- Asian/Pacific Islander: 26%
- Non-Hispanic white: 12%

Cross-sectional analysis.

T1D, type 1 diabetes.

Suboptimal Glycemic Control in Adults With T1D

CGM, continuous glucose monitoring; EDIC, Epidemiology of Diabetes Interventions and Complications; JDRF, Juvenile Diabetes Research Foundation; Pittsburgh EDC, Pittsburgh Epidemiology of Diabetes Complications; Swedish NDR, Swedish National Diabetes Register; STAR 3, Sensor Augmented Pump Therapy for A1C Reduction; T1D, type 1 diabetes.

Rates of Glycemic Control in T1D by Age Group

T1D, type 1 diabetes.
Predictors of Poor Glycemic Control

- Younger age
- Longer diabetes duration
- Weight <85th percentile
- Not living in a 2-parent household
- Type of diabetes care provider
- Nonwhite race/ethnicity
- Female gender
- Lower parental education
- Poor early glycemic control (2nd year after diagnosis predictive of poor glycemic control later)

Glucose Variability and Health Outcomes: Direct and Indirect Pathways

Glucose variability → Fear of hypoglycemia → Reluctance to intensify therapy → High A1C → Complications, morbidity, mortality

Quality of life

Severe hypoglycemia

(Controversial)

Mortality in Patients With T1D

**Swedish National Diabetes Register**
(n=33,915 with T1D; n=169,249 without diabetes)

Mortality Risk vs Patients Without Diabetes

Mortality Risk by A1C Level

*Adjusted for age, diabetes duration, sex, birthplace, education, CVD status, and cancer status.

T1D, type 1 diabetes.

T1D-Related Mortality

Swedish National Diabetes Register (n=33,915)

Cause of Diabetes-Related Death, All Patients

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKA</td>
<td>14.5%</td>
</tr>
<tr>
<td>Renal</td>
<td>9.2%</td>
</tr>
<tr>
<td>Vascular</td>
<td>9%</td>
</tr>
<tr>
<td>Multiple</td>
<td>67.2%</td>
</tr>
</tbody>
</table>

DKA, diabetic ketoacidosis; T1D, type 1 diabetes.
Rates of DKA Over 12 Month Period in Adults with T1D

T1D Exchange
(N=7012)

1.6
2.7
2.3
4.2
5.5
10.3
21

0
5
10
15
20
25

Patients (%)

<6.5 6.5 - <7.0 7.0 - <7.5 7.5 - <8.0 8.0 - <9.0 9.0 - <10.0 ≥10

Mean A1C in past year (%)

P<0.001

DKA, diabetic ketoacidosis; T1D, type 1 diabetes.
Intensive treatment reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90% compared with conventional treatment.

Absolute risks of retinopathy and nephropathy were proportional to the A1C.

Intensive treatment was most effective when begun early, before complications were detectable.

Risk reductions achieved at a median A1C 7.3% for intensive treatment (vs 9.1% for conventional).

Benefits of 6.5 years of intensive treatment extended well beyond the period of most intensive implementation (“metabolic memory”).

Intensive treatment should be started as soon as is safely possible after the onset of T1D and maintained thereafter.

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes.

Long-Term Benefits of Early Intensive Glycemic Control

DCCT-EDIC (N=1441)

Intensive glycemic control over a mean of 6.5 years reduced CVD complications by 57% after a mean of 17 years of follow-up

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications.
Sustained Effect of Intensive Treatment on Nephropathy in T1D

DCCT-EDIC (N=1349)

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes.

DCCT EDIC. JAMA. 2003;290:2159-2167.
Effect of Intensive Treatment on Retinopathy in T1D

DCCT
(N=1441)

DCCT, Diabetes Control and Complications Trial; T1D, type 1 diabetes.

Severe Hypoglycemia and A1C

DCCT, JDRF, and STAR 3 Studies

- **DCCT (intensive therapy):**
  62 per 100 patient-years;
  A1C: 9.0% → 7.2% (6.5-y F/U)

- **JDRF CGM (adults):**
  20.0 per 100 patient-years;
  A1C: 7.5% → 7.1% (6.0-mo F/U)

- **STAR 3 SAP:**
  13.3 per 100 patient-years;
  A1C: 8.3% → 7.5% (1-y F/U)

Cgm, continuous glucose monitoring; DCCT, Diabetes Control and Complications Trial; JDRF, Juvenile Diabetes Research Foundation; SAP, sensor augmented pump; STAR 3, Sensor Augmented Pump Therapy for A1C Reduction.

Treatment of Type 1 Diabetes

MANAGEMENT OF HYPERGLYCEMIA
Therapeutic Options for Type 1 Diabetes

- Multiple daily injections of rapid acting insulin with meals combined with a daily basal insulin
- Continuous subcutaneous insulin infusion via an insulin pump
- Adjunctive therapy with pramlintide

T1D, type 1 diabetes.
Advances in the Care of Persons With Type 1 Diabetes

- Development of insulin analogues
- Insulin pump therapy
- Home glucose monitoring
- Advent of continuous glucose monitoring (CGM)
Treatment of Type 1 Diabetes

INSULIN OPTIONS
Physiologic Multiple Injection Regimens: The Basal-Bolus Insulin Concept

Basal insulin ~50% TDD
- Controls glucose production between meals and overnight
- Near-constant levels

Bolus insulin ~50% TDD
- Limits hyperglycemia after meals
- Immediate rise and sharp peak at 1 hour post-meal
- 10% to 20% of total daily insulin requirement at each meal

For ideal insulin replacement therapy, each component should come from a different insulin with a specific profile or via an insulin pump (with 1 insulin)

TDD, total daily dose.
Pharmacokinetics of Insulin

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>2-4</td>
<td>4-10</td>
<td>10-16</td>
<td>Greater risk of nocturnal hypoglycemia compared to insulin analogs</td>
</tr>
<tr>
<td>Glargine Detemir</td>
<td>~1-4</td>
<td>No pronounced peak*</td>
<td>Up to 24†</td>
<td>Less nocturnal hypoglycemia compared to NPH</td>
</tr>
<tr>
<td>Degludec</td>
<td>~1</td>
<td>No pronounced peak*</td>
<td>&gt;42</td>
<td>Less nocturnal hypoglycemia compared to NPH</td>
</tr>
<tr>
<td>Regular U-500</td>
<td>≤0.5</td>
<td>~2-3</td>
<td>12-24</td>
<td>• Inject 30 min before a meal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Indicated for highly insulin resistant individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Use caution when measuring dosage to avoid inadvertent overdose</td>
</tr>
<tr>
<td>Regular</td>
<td>~0.5-1</td>
<td>~2-3</td>
<td>Up to 8</td>
<td>• Must be injected 30-45 min before a meal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Injection with or after a meal could increase risk for hypoglycemia</td>
</tr>
<tr>
<td>Aspart</td>
<td>&lt;0.5</td>
<td>~0.5-2.5</td>
<td>~3-5</td>
<td>• Can be administered 0-15 min before a meal</td>
</tr>
<tr>
<td>Glulisine</td>
<td></td>
<td></td>
<td></td>
<td>• Less risk of postprandial hypoglycemia compared to regular insulin</td>
</tr>
<tr>
<td>Lispro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Exhibits a peak at higher dosages.
† Dose-dependent; degl.
NPH, Neutral Protamine Hagedorn.

Principles of Insulin Therapy in Type 1 Diabetes

- Starting dose based on weight
  - Range: 0.4-0.5 units/kg per day
- Daily dosing
  - Basal
    - 40% to 50% TDI
    - Given as single injection of basal analog or 2 injections of NPH per day
  - Prandial
    - 50% to 60% of TDI in divided doses given 15 min before each meal
    - Each dose determined by estimating carbohydrate content of meal
- Higher TDI needed for obese patients, those with sedentary lifestyles, and during puberty

TDD, total daily dose.
Pharmacokinetic Profiles of Insulins

Rapid (lispro, aspart, glulisine, inhaled)

Short (regular)

Intermediate (NPH)

Long (glargine, degludec)

Long (detemir)

Basal/Bolus Treatment

Plasma insulin

Rapid (lispro, aspart, glulisine, inhaled)
Rapid (lispro, aspart, glulisine, inhaled)
Rapid (lispro, aspart, glulisine, inhaled)

Degludec, detemir, or glargine

Breakfast  Lunch  Dinner  Bed
Treatment of Type 1 Diabetes

PRAMLINTIDE
Insulin Replacement Not Always Sufficient for Glucose Control in T1D

• Normal glucose regulation involves multiple hormones (eg, insulin, glucagon, amylin, incretins) and multiple organ systems (eg, pancreas, liver, stomach, brain)
• Insulin replacement therapy does not fully mimic the actions of insulin secreted by the pancreas in a healthy individual
  – Insulin exposure in the liver is lower with replacement therapy than with natural production, resulting in inadequate suppression of endogenous glucose production
  – Higher doses of insulin are required to achieve sufficient suppression of endogenous glucose production, but these are associated with hypoglycemia and weight gain

T1D, type 1 diabetes.
Amylin Is Deficient in Patients with T1D

Normal Diurnal Insulin and Amylin Secretion in Healthy Adults (N=6)

Amylin Secretion in Individuals With and Without T1D

T1D, type 1 diabetes.
Pramlintide

- Human amylin analog with pharmacokinetic and pharmacodynamic properties similar to endogenous hormone
- Mechanism of action
  - Promotes satiety and reduces caloric intake
  - Slows gastric emptying
  - Inhibits inappropriately high postprandial glucagon secretion

Treatment of Type 1 Diabetes

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION
Normal Insulin Secretion

Serum insulin (µU/mL) vs Time

- Basal (background) insulin needs
- Bolus (meal) insulin needs

Meals at 8, 12, and 16 hours, with corresponding insulin spikes.
CSII With Rapid-Acting Analog

CSII, continuous subcutaneous insulin infusion.
Features of Modern Insulin Pumps Not Shared by MDI

- Variable basal and prandial infusion rates
  - Meal profiles (eg, normal and advanced bolus), pre-set basal rate changes, temporary basal rates, etc
- On-board calculators for meal insulin boluses
- Alarms/reminders (eg, missed bolus)
- Ability to download pump data to computer
- Integration with CGM for automatic feedback control and threshold suspend automation (“semi-closed loop”)

CGM, continuous glucose monitoring; MDI, multiple daily injections.
# Technological Features of Insulin Pumps*

| Insulin delivery | • Small bolus increments: 0.05-0.10 units  
|                  | • Extended boluses for delayed digestion or grazing  
|                  | • Multiple insulin-to-carbohydrate ratios, sensitivity factors, BG targets  
|                  | • Bolus calculators (based on BG level and carbohydrate quantity)  
|                  | • Low basal rates: 0.025-0.05 units/h  
|                  | • Multiple basal rates  
|                  | • Temporary basal rates and suspension mode  
| Safety features   | • Alarms for occlusion and low insulin reservoir  
|                  | • Active insulin to prevent insulin stacking  
|                  | • Keypad lock  
|                  | • Waterproof or watertight  
| Miscellaneous     | • Electronic logbook software (insulin doses, BG levels, carbohydrates)  
|                  | • Integrated food databases with customization  
|                  | • Reminder alarms for BG checks, bolus doses  
|                  | • Wireless communication with remote glucose meter  
|                  | • Integration with continuous glucose monitoring technology  

* Will vary by insulin pump make and model.

BG, blood glucose.
Improved Glucose Control with CSII

<table>
<thead>
<tr>
<th>Age group</th>
<th>Baseline (A1C)</th>
<th>12 months (A1C)</th>
<th>≥24 months (A1C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6 years</td>
<td>7.1</td>
<td>6.5</td>
<td>6.6</td>
</tr>
<tr>
<td>7-11 years</td>
<td>7.9</td>
<td>*7.3</td>
<td>7.3</td>
</tr>
<tr>
<td>12-18 years</td>
<td>8.1</td>
<td><strong>7.4</strong></td>
<td>7.6</td>
</tr>
</tbody>
</table>

*P<0.02 vs baseline.

CSII, continuous subcutaneous insulin infusion.

Reduced Risk of Severe Hypoglycemia with CSII


CSII, continuous subcutaneous insulin infusion.
Efficacy of CSII

- Switching to CSII results in
  - Lower A1C, by ~0.5%-0.6%
  - Mean A1C ~7.5%-7.6%
  - Less hypoglycemia
  - Less glucose variability
  - No excessive weight gain
  - Greater patient satisfaction and quality of life

CSII, continuous subcutaneous insulin infusion.
CSII Improves A1C and Hypoglycemia Compared with MDI

Meta-analysis (N=22 studies)

• Rate of severe hypoglycemia T1D was markedly lower during CSII than MDI, with greatest reductions in
  – Patients with most severe hypoglycemia on MDI
  – Patients with longest duration of diabetes

• Greatest improvement in A1C occurred in patients with the highest A1C on MDI

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1D, type 1 diabetes.
CSII Significantly Reduces A1C Compared with MDI

Meta-analysis
(N=22 studies)

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Change in A1C (MDI vs CSII) depends on A1C while on MDI: CSII is most effective in patients with the worst glycemic control on MDI.

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Severe Hypoglycemia with MDI vs CSII

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Rate Ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bode (poor control) (1996)</td>
<td>5.55 (3.57, 8.61)</td>
<td>5.84</td>
</tr>
<tr>
<td>Bode (good control) (1996)</td>
<td>10.50 (4.24, 26.01)</td>
<td>4.66</td>
</tr>
<tr>
<td>Kademman (1999)</td>
<td>6.47 (3.09, 13.55)</td>
<td>5.11</td>
</tr>
<tr>
<td>Maniatis (2001)</td>
<td>1.29 (0.31, 5.42)</td>
<td>3.34</td>
</tr>
<tr>
<td>Rizvi (2001)</td>
<td>8.00 (1.84, 34.79)</td>
<td>3.26</td>
</tr>
<tr>
<td>Litton (2002)</td>
<td>5.75 (0.72, 45.97)</td>
<td>2.19</td>
</tr>
<tr>
<td>Linkeschova (2002)</td>
<td>13.92 (6.95, 27.86)</td>
<td>5.23</td>
</tr>
<tr>
<td>Bruttomesso (2002)</td>
<td>3.44 (1.62, 7.33)</td>
<td>5.07</td>
</tr>
<tr>
<td>Rudolph &amp; Hirsch (2002)</td>
<td>3.81 (2.49, 5.84)</td>
<td>5.87</td>
</tr>
<tr>
<td>Plotnick (2003)</td>
<td>2.18 (1.05, 4.52)</td>
<td>5.13</td>
</tr>
<tr>
<td>Cohen (2003)</td>
<td>4.69 (0.52, 41.98)</td>
<td>2.04</td>
</tr>
<tr>
<td>Hunger-Dathe (2003)</td>
<td>3.62 (2.23, 5.85)</td>
<td>5.75</td>
</tr>
<tr>
<td>Weintrob (2003)</td>
<td>3.00 (0.62, 14.44)</td>
<td>3.04</td>
</tr>
<tr>
<td>Weinzimer (2004)</td>
<td>2.11 (1.50, 2.96)</td>
<td>6.03</td>
</tr>
<tr>
<td>McMahon (2004)</td>
<td>2.89 (1.67, 4.98)</td>
<td>3.13</td>
</tr>
<tr>
<td>Siegel-Czarkowski (2004)</td>
<td>7.07 (0.87, 57.49)</td>
<td>2.17</td>
</tr>
<tr>
<td>Alemzadeh (2004)</td>
<td>2.51 (0.67, 9.47)</td>
<td>3.58</td>
</tr>
<tr>
<td>Mack-Fogg (2005)</td>
<td>2.09 (1.02, 4.22)</td>
<td>5.40</td>
</tr>
<tr>
<td>Sciaffini (2005)</td>
<td>1.19 (0.34, 4.65)</td>
<td>3.61</td>
</tr>
<tr>
<td>Rodrigues (2005)</td>
<td>35.41 (21.94, 57.15)</td>
<td>5.75</td>
</tr>
<tr>
<td>Lepore (2005)</td>
<td>3.50 (2.04, 6.01)</td>
<td>5.61</td>
</tr>
<tr>
<td>Hoogma (2006)</td>
<td>2.50 (1.53, 4.08)</td>
<td>5.73</td>
</tr>
<tr>
<td>Overall (I-squared = 84.2%, p = 0.000)</td>
<td>4.19 (2.86, 6.13)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Severe hypoglycemia reduced by ~75% by switching to pump therapy

No difference between randomized, controlled trials and before/after studies

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

CSII vs MDI

2010 Meta-Analysis
(N=23 studies; 976 participants with T1D)

• Statistically significant difference in A1C favoring CSII
  – Weighted mean difference: -0.3%
    (95% confidence interval -0.1 to -0.4)
• Severe hypoglycemia appeared to be reduced in those using CSII
• Quality of life measures favored CSII

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1D, type 1 diabetes.

Children/adolescents with T1D
- A1C difference: -0.17% (95% CI -0.47 to 0.14%)

Adults with T1D
- A1C difference: -0.01% (95% CI -0.35 to 0.34%)

Adults with T2D
- A1C difference: -0.18% (95% CI -0.43 to 0.08%)

CSII vs MDI
2012 Meta-Analysis

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1D, type 1 diabetes.
The meta-analysis did not demonstrate any improvements in severe hypoglycemia with CSII compared to MDI in children and adolescents.
Almost all pediatric patients with T1D are candidates for CSII

- CSII strongly recommended for children with
  - Recurrent severe hypoglycemia
  - A1C above target range for age
  - Unacceptable fluctuations in blood glucose
  - Microvascular complications
  - Lifestyle compromised by insulin regimen

- CSII may also be beneficial in
  - Very young children
  - Dawn phenomenon
  - Competitive athletes
## Insulin Pump Use in Children

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Improved blood sugar control</td>
<td>• Remembering to give insulin boluses with food intake</td>
</tr>
<tr>
<td>• Insulin availability and convenience</td>
<td>• Ketonuria or ketoacidosis</td>
</tr>
<tr>
<td>• Use of multiple basal rates, temporary basal rates</td>
<td>• Psychological factors</td>
</tr>
<tr>
<td>• Ease of administering multiple boluses</td>
<td>• Expense</td>
</tr>
<tr>
<td>• Reduction of hypoglycemia</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Flexibility and freedom</td>
<td>• Skin infections</td>
</tr>
<tr>
<td>• Control of post-meal blood sugar/CGM values</td>
<td>• Insulin unavailability and instability</td>
</tr>
<tr>
<td>• Ease of adjusting insulin doses with exercise and travel</td>
<td>• Infusion site locations and set changes</td>
</tr>
<tr>
<td></td>
<td>• Physical/logistical considerations</td>
</tr>
</tbody>
</table>

Characteristics of Successful CSII Patients

• Access to diabetes team knowledgeable in CSII, with 24/7 HCP access (physician or RN/CDE)
• Insurance
• Adequate intellectual ability to
  – Understand glycemic trending, even without CGM
  – Master carbohydrate counting or similar system for estimation of prandial insulin dosing (frequent SMBG can make up for poor carb estimation)
  – Understand basics of insulin therapy, including how to correct hyperglycemia before and after meals

CSII, continuous subcutaneous insulin infusion.
Characteristics of Successful CSII Physicians

- Time to spend with the patient
- Consistent philosophy of insulin use among all members of diabetes healthcare team
- Electronic infrastructure in the office or clinic to facilitate downloads and utilize the technology most effectively
- Basic understanding of principles of insulin use (MDI or CSII)

CSII, continuous subcutaneous insulin infusion.
Definitions in the Context of Insulin Pumps

- **Pharmacodynamics vs pharmacokinetics**
  - **Insulin-on-board (IOB)**
    - Amount of insulin from the last bolus that has not yet been absorbed based on pharmacodynamic (not pharmacokinetic) data
  - **Insulin stacking**
    - Correction dose of insulin, used to treat before-meal or between-meal hyperglycemia in a situation when there is still significant IOB

- **Insulin sensitivity factor**
  - Correction factor based on amount of glucose reduction (mg/dL) expected from 1 unit of insulin for the individual patient
CSII: “Smart Pump” Limitations

• All modern pumps include a “bolus calculator” with goal of preventing insulin stacking, but patient must still
  – Check blood glucose
  – Understand “glycemic trends”
  – Estimate carbohydrate content with reasonable accuracy
  – Account for lag time
  – Assume no variability of food or insulin absorption
  – Use appropriate IOB
Not All Patients Have Good Control on CSII

Patients with T1D Switched from MDI to Pump Therapy (N=104)

![Bar chart showing A1C levels on CSII]

- <7.0%: 17%
- 7.0-8.4%: 56%
- ≥8.5%: 27%

A1C on CSII significantly correlated with prior A1C on MDI (r=0.66; P<0.001)

CSII, continuous subcutaneous insulin infusion; T1D, type 1 diabetes.
Treatment of Type 1 Diabetes

CONTINUOUS GLUCOSE MONITORING
Definitions

- Professional CGM
  - Equipment owned by the provider
  - CGM Data may be blinded or visible to patient

- Personal CGM
  - Device owned by patient
  - Blood glucose data visible, able to be seen continuously
Continuous Glucose Monitoring in Type 1 Diabetes

JDRF Sensor Trial

• Patients
  – Baseline A1C >7.0%
  – Age cohorts
    • 8-14 years (n=114)
    • 15-24 years (n=110)
    • ≥25 years (n=98)
• Improvement sustained for 12 months in patients aged ≥25 years
• No significant difference between CGM and control group among patients <25 years of age

JDRF, Juvenile Diabetes Research Foundation.
Change in A1C Over Time

JDRF Sensor Trial
(N=322)
Patients ≥25 Years of Age

CGM, continuous glucose monitoring; JDRF, Juvenile Diabetes Research Foundation.
Relationship Between Frequency of CGM Use and Change in A1C

JDRF Sensor Trial (N=232)

CGM, continuous glucose monitoring.

A1C Goal Attainment

JDRF Sensor Trial
(N=232)

Patients Achieving A1C <7%

CGM, continuous glucose monitoring.

Optimal vs Poor Glucose Control With CGM

Patients With Baseline A1C >9%

-55 55-80 81-140 141-240 >240

<table>
<thead>
<tr>
<th>Blood glucose (mg/dL)</th>
<th>Median % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>-31.1</td>
</tr>
<tr>
<td>55-80</td>
<td>27.4</td>
</tr>
<tr>
<td>81-140</td>
<td>94.6</td>
</tr>
<tr>
<td>141-240</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;240</td>
<td>-36.4</td>
</tr>
</tbody>
</table>

Patients With Baseline A1C ≤7%

-55 55-80 81-140 141-240 >240

<table>
<thead>
<tr>
<th>Blood glucose (mg/dL)</th>
<th>Median % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>-46.4</td>
</tr>
<tr>
<td>55-80</td>
<td>-14.5</td>
</tr>
<tr>
<td>81-140</td>
<td>8.8</td>
</tr>
<tr>
<td>141-240</td>
<td>-8.5</td>
</tr>
<tr>
<td>&gt;240</td>
<td>-14.2</td>
</tr>
</tbody>
</table>

CGM, continuous glucose monitoring.
Mean A1C and Change From Baseline with CGM

*P <0.05 vs baseline; †P<0.001 vs baseline.

CGM, continuous glucose monitoring.

CGM Use with Either CSII or MDI Improves Glycemic Control

Patients with T1D (N=34, Per Protocol Population)

Time Spent in Different Glucose Ranges

Glucose range (mg/dL)

- *P < 0.01 vs baseline; †P < 0.001 vs baseline.
- **Baseline value determined after 4 weeks of blinded CGM use.

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; T1D, type 1 diabetes.

CGM vs SMBG: Meta-analysis of Randomized Controlled Trials

• CGM associated with significant reduction in A1C, with greatest reductions in patients
  – With highest A1C at baseline
  – Who most frequently used sensors
• CGM reduced hypoglycemia

“The most cost effective or appropriate use of continuous glucose monitoring is likely to be when targeted at people with T1D who have continued poor control during intensified insulin therapy and who frequently use continuous glucose monitoring.”
CGM vs SMBG

2012 Meta-Analysis

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; SMBG, self-monitoring of blood glucose.

CGM Adherence and A1C

2012 Meta-Analysis

CGM, continuous glucose monitoring.

CSII + CGM vs MDI + SMBG

STAR 3

CSII + CGM (n=244) vs MDI + SMBG (n=241)

A1C (%) vs Months

0 3 6 9 12

7 7.2 7.4 7.6 7.8 8 8.2 8.4 8.6

8.3 8.0 8.3 8.0 8.1 8.1 7.5 7.5

P<0.001 P<0.001 P<0.001 P<0.001

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; SMBG, self-monitoring of blood glucose STAR, Sensor-Augmented Pump Therapy for A1C Reduction.

Effect of 1 Year of CGM Usage on A1C

STAR 3

Rate of Sensor Use

<table>
<thead>
<tr>
<th>Rate of Sensor Use</th>
<th>Baseline A1C</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20% (n=7)</td>
<td>7.9</td>
<td>-0.43</td>
</tr>
<tr>
<td>20%-40% (n=27)</td>
<td>8.2</td>
<td>-0.19</td>
</tr>
<tr>
<td>41%-60% (n=46)</td>
<td>8.4</td>
<td>-0.64</td>
</tr>
<tr>
<td>61%-80% (n=108)</td>
<td>8.25</td>
<td>-0.79</td>
</tr>
<tr>
<td>&gt;80% (n=56)</td>
<td>8.3</td>
<td>-1.21</td>
</tr>
</tbody>
</table>

Increased frequency of sensor use was associated with greater reductions in A1C ($P=0.003$ with adjustment for baseline A1C)

CGM, continuous glucose monitoring; STAR, Sensor-Augmented Pump Therapy for A1C Reduction.
CGM Over 18 Months

STAR 3 Continuation Study

A1C (%)

Study Phase

Continuation Phase

* P<0.001 for between-groups comparison.
† P<0.001 for within-group comparison using crossover group’s 12-month A1C value as comparator.

CSII + CGM (n=244)

Crossover (MDI to SAPT)

CGM, continuous glucose monitoring; STAR, Sensor-Augmented Pump Therapy for A1C Reduction.

Pediatric Diabetes Consensus Conference: Use of CGM

• Frequent, nearly daily use of CGM
  – Can lower A1C levels in children and adolescents who are not well-controlled, irrespective of the treatment regimen
  – Can reduce exposure to hypoglycemia and maintain target A1C levels in well-controlled patients

• Intermittent use of CGM
  – May be of use to detect postmeal hyperglycemia, nocturnal hypoglycemia, and the dawn phenomenon

• Development of smaller, more accurate, and easier-to-use devices is needed to enhance CGM utilization in youth with T1D

CGM, continuous glucose monitoring; T1D, type 1 diabetes.
AACE Recommendations for Personal CGM

Evidence-Based Recommendations

• Use in adults and children with T1D
  – Real-time glucose management by patient
  – Retrospective adjustments to diabetes management

• CGM with CSII or MDI: significant improvements in A1C without increased hypoglycemia

• Threshold suspend integrated CGM + CSII: significant improvements in A1C and reduction in hypoglycemia

• Improved reliability and accuracy with newer devices

Areas for Further Research or Development

• Standardized data reporting across all devices

• Benefits in insulin-using patients with T2D

• Benefits in pregnant women with diabetes

• Cost reductions with CGM vs SMBG

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injections; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

Personal CGM defined as CGM owned by the patient and used on daily basis.

AACE Recommendations: CGM in Pregnancy

- Macrosomia is common due to inability to identify hyperglycemic spikes
- SMBG misses both hyper- and hypoglycemic events
- All CGM-in-pregnancy studies are positive
- Based on the frequency of hyperglycemia, AACE recommends that all pregnant women with T1D receive personal CGM

CGM, continuous glucose monitoring; T1D, type 1 diabetes.
Treatment of Type 1 Diabetes

CLOSED LOOP SYSTEMS: ARTIFICIAL PANCREAS
Effectiveness and Safety of an Artificial Pancreas

- Study comparing 2 systems in patients with T1D
  - Age 5-18 years (N=17)
  - Closed loop “artificial pancreas” linking CSII insulin delivery with CGM (33 nights)
  - Standard CSII (21 nights)
- No significant difference in glycemic outcomes in primary analysis

Secondary analysis of pooled data

<table>
<thead>
<tr>
<th></th>
<th>Closed loop</th>
<th>CSII</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in target BG range (%)</td>
<td>60 (51-88)</td>
<td>40 (18-61)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Time BG ≤70 mg/dL (%)</td>
<td>2.1 (0.0-10.0)</td>
<td>4.1 (0.0-42.0)</td>
<td>0.0304</td>
</tr>
<tr>
<td>BG &lt;54 mg/dL (no. events)</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

BG, blood glucose; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; T1D, type 1 diabetes.
Emerging Options: CSII with “Low Glucose Suspend” Feature

- **LGS Start (0 minutes):** Insulin infusion stops; alarm sounds
- **LGS End (2 hours):** Insulin infusion resumes
- **Emergency Alarm (2 minutes):** If user does not respond, siren turns on and pump displays emergency message
- **Re-suspend (6 hours):** Insulin infusion suspends again if cycle is not interrupted and sensor glucose is still below the preset threshold value

**Sensor Glucose**

**LGS Threshold Setting**
Low Glucose Suspend Feature Reduces Hypoglycemic Exposure

Threshold Suspend Reduces Nocturnal Hypoglycemia Without Increasing Hyperglycemia

Patients Randomized to Sensor-Augmented Pump with or Without Threshold-Suspend for 3 Months (N=247)

A1C (%)

<table>
<thead>
<tr>
<th></th>
<th>At randomization</th>
<th>At 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold-suspend</td>
<td>7.26</td>
<td>7.24</td>
</tr>
<tr>
<td>No threshold-suspend</td>
<td>7.21</td>
<td>7.14</td>
</tr>
</tbody>
</table>

No change in A1C

Threshold Suspend Reduces Nocturnal Hypoglycemic Exposure

Mean AUC for Nocturnal Hypoglycemic Events

- **Threshold-suspend**
  - Run-in phase: 1547
  - Study phase: 980

- **No threshold-suspend**
  - Run-in phase: 1406
  - Study phase: 1568

38% reduction in AUC

**AUC**, area under the curve.

Threshold Suspend Reduces Both Nocturnal and Daytime Hypoglycemia

Sensor Glucose <70 mg/dL

<table>
<thead>
<tr>
<th>Percent</th>
<th>Threshold-suspend</th>
<th>No threshold-suspend</th>
<th>Threshold-suspend</th>
<th>No threshold-suspend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 to &lt;70 mg/dL</td>
<td>1.8</td>
<td>2.8</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>50 to &lt;60 mg/dL</td>
<td>3</td>
<td>3.1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>&lt;50 mg/dL</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day and night combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 to &lt;70 mg/dL</td>
<td>3</td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>50 to &lt;60 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Closed-Loop Studies Result in Less Nocturnal Hypoglycemia at Diabetes Camp

• MD-Logic: a fully automated closed-loop system

• Study participants
  – Children, mean age 14 years (N=54)
  – Randomized to 1 night on closed-loop, then 1 night on sensor augmented pump (or vice versa)

• Results
  – Nocturnal hypoglycemia (glucose <63 mg/dL)
    • Closed-loop system: 7 episodes
    • Control: 22 episodes
  – Less glucose variability with closed-loop system

Nocturnal Glycemia With Closed-Loop vs Sensor-Augmented Pump

Artificial Pancreas Nights

Control Nights

Bionic Pancreas

- Bihormonal secretion
  - Insulin
  - Glucagon
- Integrated continuous glucose monitor
- Fully automated
  - Control algorithm run on smart phone
  - Insulin and glucagon secreted in response to CGM data every 5 minutes
- Insulin bolus priming based on qualitative assessment of meal type and size
- Type
  - Breakfast
  - Lunch
  - Dinner
- Size
  - Typical
  - More than usual
  - Less than usual
  - Small bite
Effect of Bionic Pancreas on Glycemic Control

Mean Blood Glucose

- Adults (n=20)
  - Bionic pancreas: 133 mg/dL
  - CSII (control): 159 mg/dL
  - P<0.001

- Adolescents (n=32)
  - Bionic pancreas: 138 mg/dL
  - CSII (control): 157 mg/dL
  - P=0.004

Time Spent with BG <70 mg/dL

- Adults (n=20)
  - Bionic pancreas: 7.3%
  - CSII (control): 7.7%
  - P=0.23

- Adolescents (n=32)
  - Bionic pancreas: 4.1%
  - CSII (control): 8.7%
  - P=0.01

Treatment of Type 1 Diabetes

HYPOGLYCEMIA
Rates of Severe Hypoglycemia Over 12 Month Period in Adults with T1D

T1D Exchange (N=7012)

<table>
<thead>
<tr>
<th>Mean A1C in past year (%)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.5</td>
<td>13.9</td>
</tr>
<tr>
<td>6.5 - &lt;7.0</td>
<td>12.5</td>
</tr>
<tr>
<td>7.0 - &lt;7.5</td>
<td>8.3</td>
</tr>
<tr>
<td>7.5 - &lt;8.0</td>
<td>12.4</td>
</tr>
<tr>
<td>8.0 - &lt;9.0</td>
<td>13.7</td>
</tr>
<tr>
<td>9.0 - &lt;10.0</td>
<td>9.4</td>
</tr>
<tr>
<td>≥10</td>
<td>12.1</td>
</tr>
</tbody>
</table>

NS, not significant; T1D, type 1 diabetes.

Incidence of Severe Hypoglycemia Increases with T1D Duration but Not Age

T1D Exchange (N=7012)

Multivariate Regression Model

Data from the T1D Exchange study shows that the incidence of severe hypoglycemia increases with the duration of T1D. The association is statistically significant ($P<0.001$), with a higher incidence observed in participants with a duration of T1D of 20 or more years compared to those with a duration of 20 years or less.

NS, not significant; T1D, type 1 diabetes.

## Hypoglycemia: Risk Factors

### Patient Characteristics
- Older age
- Female gender
- African American ethnicity
- Longer duration of diabetes
- Neuropathy
- Renal impairment
- Previous hypoglycemia

### Behavioral and Treatment Factors
- Missed meals
- Elevated A1C

---

Pathophysiology of Glucose Counterregulation in T1D


T1D, type 1 diabetes.
Defective Glucose Counterregulation and Hypoglycemia Unawareness

T1D, type 1 diabetes.
Causes of Hypoglycemia in Toddlers and Preschoolers

- Unpredictable food intake and physical activity
- Imprecise administration of low doses of insulin
- Frequent viral infections
- Inability to convey the symptoms of low blood sugar
Consequences of Hypoglycemia

- Cognitive, psychological changes (e.g., confusion, irritability)
- Accidents
- Falls
- Recurrent hypoglycemia and hypoglycemia unawareness
- Refractory diabetes
- Dementia (elderly)
- CV events
  - Cardiac autonomic neuropathy
  - Cardiac ischemia
  - Angina
  - Fatal arrhythmia

Cognitive Effects of Hypoglycemia in Children With T1D

- Repeated severe hypoglycemia reduces long-term spatial memory in children with type 1 diabetes.
- Early exposure to hypoglycemia may be more damaging to cognitive function than later exposure.

## Symptoms of Hypoglycemia

<table>
<thead>
<tr>
<th>Classification</th>
<th>Blood Glucose Level (mg/dL)</th>
<th>Typical Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild hypoglycemia</td>
<td>~50-70</td>
<td>• Neurogenic: palpitations, tremor, hunger, sweating, anxiety, paresthesia</td>
</tr>
<tr>
<td>Moderate hypoglycemia</td>
<td>~50-70</td>
<td>• Neuroglycopenic: behavioral changes, emotional lability, difficulty thinking, confusion</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>&lt;50*</td>
<td>• Severe confusion, unconsciousness, seizure, coma, death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Requires help from another individual</td>
</tr>
</tbody>
</table>

*Severe hypoglycemia symptoms should be treated regardless of blood glucose level.*

Treatment Challenges in the Elderly With Type 1 Diabetes

• Lack of thirst perception predisposes to hyperosmolar state
• Confusion of polyuria with urinary incontinence or bladder dysfunction
• Increased risk of and from hypoglycemia
  – Altered perception of hypoglycemic symptoms
  – Susceptibility to serious injury from falls or accidents
• Compounding of diabetic complications by effects of aging
• Frequent concurrent illnesses and/or medications
• More frequent and severe foot problems
Special Considerations in the Elderly With Type 1 Diabetes

- Intensive therapy/tight control for otherwise healthy elderly patients
- Less strict glycemic goals for elderly patients with severe complications or comorbidities or with cognitive impairment
  - FPG <140 mg/dL
  - PPG <220 mg/dL

FPG, fasting plasma glucose; PPG, postprandial glucose.

Treatment of Hypoglycemia

Hypoglycemia symptoms (BG < 70 mg/dL)

Patient conscious and alert
- Consume glucose-containing foods (fruit juice, soft drink, crackers, milk, glucose tablets); avoid foods also containing fat
- Repeat glucose intake if SMBG result remains low after 15 minutes
- Consume meal or snack after SMBG has returned to normal to avoid recurrence

Patient severely confused or unconscious (requires help)
- Glucagon injection, delivered by another person
- Patient should be taken to hospital for evaluation and treatment after any severe episode

BG = blood glucose; SMBG = self-monitoring of blood glucose.
Fear of Hypoglycemia

- Hypoglycemia-associated anxiety, depression, and fear are common among patients with T1D and their caregivers
- Hypoglycemia avoidance behaviors may adversely affect glycemic control

T1D, type 1 diabetes.
Treatment of Type 1 Diabetes

MANAGEMENT OF COMORBIDITIES—DYSLIPIDEMIA IN T1D
Factors That May Increase Risk for Ischemic ASCVD in Patients With T1D

Individuals with T1D for >15 years or with ≥2 CV risk factors should be treated as if they had T2D. Given the risks associated with T1D, dyslipidemia in this population must not be overlooked and should be treated aggressively.

- Albuminuria
- Late-onset T1D (>30 years of age) without nephropathy, but with:
  - Initiation of intensive control more than 5 years after diagnosis
  - Duration of disease greater than 15 years
- Previous history of MI or poorly controlled A1C
- Insulin resistance or MetS and an hsCRP concentration >3.0 mg/L

ASCVD, atherosclerotic cardiovascular disease; CV, cerebrovascular; hsCRP, highly sensitive C-reactive protein; MetS, metabolic syndrome; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes.
## Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th>Major</th>
<th>Additional</th>
<th>Nontraditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Advancing age</td>
<td>• Obesity or abdominal obesity</td>
<td>• Increased lipoprotein (a)</td>
</tr>
<tr>
<td>• High total serum cholesterol level</td>
<td>• Family history of hyperlipidemia</td>
<td>• Elevated clotting factors</td>
</tr>
<tr>
<td>• High non–HDL-C</td>
<td>• Small, dense LDL-C</td>
<td>• Inflammation markers (hsCRP; Lp-PLA₂)</td>
</tr>
<tr>
<td>• High LDL-C</td>
<td>• Increased Apo B</td>
<td>• Elevated homocysteine levels</td>
</tr>
<tr>
<td>• Low HDL-C</td>
<td>• Increased LDL particle concentration</td>
<td>• Apo E4 isoform</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>• Fasting/postprandial hypertriglyceridemia</td>
<td>• Elevated uric acid</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• PCOS</td>
<td>• Increased triglyceride-rich remnants</td>
</tr>
<tr>
<td>• Cigarette smoking</td>
<td>• Dyslipidemic triad*</td>
<td></td>
</tr>
<tr>
<td>• Family history of ASCVD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hypertriglyceridemia; low HDL-C; and small, dense LDL-C.

Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA₂, lipoprotein-associated phospholipase A₂; PCOS, polycystic ovary syndrome.

Baseline Proteinuria Increases Cardiovascular Risk

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

<table>
<thead>
<tr>
<th>Event Type</th>
<th>No Proteinuria</th>
<th>Mixed Trials</th>
<th>All Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Death</td>
<td>6.3</td>
<td>18.6</td>
<td>39.9</td>
</tr>
<tr>
<td>CVD Death</td>
<td>1.2</td>
<td>9.3</td>
<td>18.7</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>11.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>7.5</td>
<td>12.4</td>
</tr>
</tbody>
</table>

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.
AACE ASCVD Risk Categories

**Low risk:**
- No risk factors

**Moderate risk:**
- 2 or fewer risk factors and a calculated 10-year risk of less than 10%

**High risk:**
- 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%

**Very high risk:**
- 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

**Extreme risk:**
- 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 (<55 years of age for males or <65 years of age for females)
- 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.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPG, clinical practice guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

# AACE ASCVD Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk factors*/10-year risk†</th>
<th>Treatment goals (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C</td>
</tr>
</tbody>
</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.

Comprehensive Management of Cardiovascular Risk

• Manage CV risk factors
  – Weight loss
  – Smoking cessation
  – Optimal glucose, blood pressure, and lipid control

• Use low-dose aspirin for secondary prevention of CV events in patients with existing CVD
  – May consider low-dose aspirin for primary prevention of CV events in patients with 10-year CV risk >10%

• Measure coronary artery calcification or use coronary imaging to determine whether glucose, lipid, or blood pressure control efforts should be intensified

CV, cardiovascular; CVD, cardiovascular disease.
Statin Use in Patients with Diabetes

- Majority of patients with T2D have a high cardiovascular risk
- People with T1D are at elevated cardiovascular risk
- LDL-C target: <70 mg/dL—for the majority of patients with diabetes who are determined to have a high risk

- Use a statin regardless of LDL-C level in patients with diabetes who meet the following criteria:
  - >40 years of age
  - ≥1 major ASCVD risk factor
    - Hypertension
    - Family history of CVD
    - Low HDL-C
    - Smoking

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

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>HIGH</th>
<th>VERY HIGH</th>
<th>EXTREME</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:
TO LOWER Non-HDL-C, TG:
TO LOWER Apo B, LDL-P:
TO LOWER LDL-C in FH:**

Intensity statin, add ezetimibe, PCSK9i, colesevelam, or niacin
Intensity statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
Intensity 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

ACEi or ARB
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 (a-blockers, central agents, vasodilators, aldosterone antagonist)
Achievement of target blood pressure is critical

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# CVD Risk Factors: AACE Targets

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommended Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Individualize, but generally:</td>
</tr>
<tr>
<td></td>
<td>Systolic &lt;130</td>
</tr>
<tr>
<td></td>
<td>Diastolic &lt;80</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Very high CV risk</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Extreme CV risk</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Very high CV risk</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Extreme CV risk</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Very high CV risk</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Extreme CV risk</td>
<td></td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Very high CV risk</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Extreme CV risk</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

## Lipid Management in Diabetes

### Elevated LDL-C, non-HDL-C, TG, TC/HDL-C ratio, ApoB, LDL particles
- Statin = treatment of choice
- Add bile acid sequestrant, niacin, and/or cholesterol absorption inhibitor if target not met on maximum-tolerated dose of statin
- Use bile acid sequestrant, niacin, or cholesterol absorption inhibitor instead of statin if contraindicated or not tolerated

### LDL-C at goal but non-HDL-C not at goal (TG ≥200 mg/dL and/or low HDL-C)
- May use fibrate, niacin, or high-dose omega-3 fatty acid to achieve non-HDL-C goal

### TG ≥500 mg/dL
- Use high-dose omega-3 fatty acid, fibrate, or niacin to reduce TG and risk of pancreatitis

---

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HDL-C, high density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC = total cholesterol.

## Dyslipidemia Treatment Options

<table>
<thead>
<tr>
<th>Class MOA</th>
<th>Efficacy</th>
<th>Main Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG CoA reductase inhibitors (statins)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competitively inhibit rate-limiting step of cholesterol synthesis, slowing production in liver</td>
<td>↓ 21-55%</td>
<td>• Risk of myopathy, increased liver transaminases</td>
</tr>
<tr>
<td></td>
<td>↑ 2-10%</td>
<td>• Contraindicated in liver disease</td>
</tr>
<tr>
<td></td>
<td>↓ 6-30%</td>
<td>• Liver enzyme monitoring required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk of new-onset diabetes</td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibit intestinal absorption of cholesterol</td>
<td>↓ 10-18% (monotherapy) ↓ 34-61% (add-on to statins)</td>
<td>• Risk of myopathy</td>
</tr>
<tr>
<td><strong>PCSK9 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibit PCSK9 binding to LDL receptors, increasing availability of receptors for LDL clearance</td>
<td>↓ 48-71% (add-on to statins)</td>
<td>• Injection</td>
</tr>
<tr>
<td><strong>Fibric acid derivatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulate lipoprotein lipase activity</td>
<td>↓ VLDL Fenofibrate may ↓ LDL-C 20-25%</td>
<td>• GI symptoms, possible cholelithiasis</td>
</tr>
<tr>
<td></td>
<td>↑ 6-18%</td>
<td>• Gemfibrozil may ↑ LDL-C</td>
</tr>
<tr>
<td></td>
<td>↓ 20-35%</td>
<td>• Myopathy risk increased when used with statins</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein cholesterol; HMG-CoA, hydroxymethylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL-C, very low density lipoprotein cholesterol.

# Dyslipidemia Treatment Options

<table>
<thead>
<tr>
<th>Class MOA</th>
<th>Efficacy</th>
<th>Main Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin/nicotinic acid <strong>Reduce hepatic synthesis of LDL-C and VLDL-C</strong></td>
<td>↓ 10-25%</td>
<td>• Skin flushed, pruritus, GI symptoms, potential increases in blood glucose and uric acid</td>
</tr>
<tr>
<td>Bile acid sequestrants <strong>Bind bile acids in the intestine</strong></td>
<td>↓ 15-25%</td>
<td>• GI symptoms</td>
</tr>
<tr>
<td>MTP inhibitor <strong>Inhibit synthesis of chylomicrons and VLDL</strong></td>
<td>↓ Up to 40%</td>
<td>• Liver enzyme monitoring required&lt;br&gt;• Steatosis of liver and small intestine</td>
</tr>
<tr>
<td>Anti-sense ApoB oligonucleotide <strong>Degrade mRNA for apoB-100, which is needed for synthesis of LDL</strong></td>
<td>↓ 21%</td>
<td>• Liver enzyme monitoring required&lt;br&gt;• Steatosis of liver and small intestine</td>
</tr>
<tr>
<td>Omega-3 fatty acids <strong>Reduce hepatic synthesis of VLDL-triglycerides and/or enhancing triglyceride clearance</strong></td>
<td>VLDL-C ↓ 20-42%</td>
<td>• Increase LDL-C levels&lt;br&gt;• Monitor coagulation status&lt;br&gt;• Increased frequency of symptomatic AF</td>
</tr>
</tbody>
</table>

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTP, microsomal transfer triglyceride; VLDL-C, very low density lipoprotein cholesterol.
# 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.
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 rosuvastatin 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.

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

---

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 gemofibrozil 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

---

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)

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%

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

Omega-3 Fatty Acids: Main Considerations

- 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

AF, atrial fibrillation.
# 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 transminases (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 transminases, 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.

# Benefits of Aggressive LDL-C Lowering in Diabetes

## Primary event rate (%) vs Aggressive Lipid Lowering

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Better</th>
<th>Worse</th>
<th>P value</th>
<th>Difference in LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT Diabetes, CHD</td>
<td>13.8</td>
<td>17.9</td>
<td></td>
<td>0.026</td>
<td>22*</td>
</tr>
<tr>
<td>ASCOT-LLA Diabetes, HTN</td>
<td>9.2</td>
<td>11.9</td>
<td></td>
<td>0.036</td>
<td>35†</td>
</tr>
<tr>
<td>CARDS Diabetes, no CVD</td>
<td>5.8</td>
<td>9.0</td>
<td></td>
<td>0.001</td>
<td>46†</td>
</tr>
<tr>
<td>HPS All diabetes</td>
<td>9.4</td>
<td>12.6</td>
<td></td>
<td>&lt;0.0001</td>
<td>39†</td>
</tr>
<tr>
<td>HPS Diabetes, no CVD</td>
<td>9.3</td>
<td>13.5</td>
<td></td>
<td>0.0003</td>
<td>39†</td>
</tr>
</tbody>
</table>

*Atorvastatin 10 vs 80 mg/day.
†Statin vs placebo.

Randomized Trials of Statins: A Meta-Analysis of CV Events

Patients with Diabetes
(N=18,686; 14 RCTs)

Risk Reduction in Major Vascular Events per mmol/L Decrease in LDL-C

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (CI)</th>
<th>Test for heterogeneity or trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of diabetes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>147 (20.5%)</td>
<td>196 (26.2%)</td>
<td>0.79 (0.62-1.01)</td>
<td>$\chi^2_{1}=0.0; p=1.0$</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1318 (15.2%)</td>
<td>1586 (18.5%)</td>
<td>0.79 (0.72-0.87)</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1082 (17.2%)</td>
<td>1332 (21.4%)</td>
<td>0.78 (0.71-0.86)</td>
<td>$\chi^2_{1}=0.0; p=0.7$</td>
</tr>
<tr>
<td>Women</td>
<td>383 (12.4%)</td>
<td>450 (14.6%)</td>
<td>0.81 (0.67-0.97)</td>
<td></td>
</tr>
<tr>
<td>All diabetes</td>
<td>1465 (15.6%)</td>
<td>1782 (19.2%)</td>
<td>0.79 (0.74-0.84)</td>
<td></td>
</tr>
</tbody>
</table>

Global test for heterogeneity within subtotals: $\chi^2_{13}=13.9; p=0.4$

- ■ RR (99% CI)
- ○ RR (95% CI)

Treat Patients With the Greatest Absolute Risk the Most Aggressively

### 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>LDL-C Range</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mmol/L (&lt;77 mg/dL)</td>
<td>Statin: 910 (4.1%) Control: 1,012 (4.6%)</td>
<td>0.78 (0.61-0.99)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L (77-96 mg/dL)</td>
<td>Statin: 1,528 (3.6%) Control: 1,729 (4.2%)</td>
<td>0.77 (0.67-0.89)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L (97-116 mg/dL)</td>
<td>Statin: 1,866 (3.3%) Control: 2,225 (4.0%)</td>
<td>0.77 (0.70-0.85) P=0.3</td>
</tr>
<tr>
<td>≥3.0 to &lt;3.5 mmol/L (117-135 mg/dL)</td>
<td>Statin: 2,007 (3.2%) Control: 2,454 (4.0%)</td>
<td>0.76 (0.70-0.82)</td>
</tr>
<tr>
<td>≥3.5 mmol/L (&gt;136 mg/dL)</td>
<td>Statin: 4,508 (3.0%) Control: 5,736 (3.9%)</td>
<td>0.80 (0.76-0.83)</td>
</tr>
<tr>
<td>Total</td>
<td>Statin: 10,973 (3.2%) Control: 13,350 (4.0%)</td>
<td>0.78 (0.76-0.80)</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.

Residual Cardiovascular Risk in Major Statin Trials

CHD events still occur in patients treated with statins

<table>
<thead>
<tr>
<th></th>
<th>Secondary</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LIPID</td>
<td>CARE</td>
</tr>
<tr>
<td>Total Pop. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C N (Δ)</td>
<td>9014 (-25%)</td>
<td>4159 (-28%)</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>15.9</td>
<td>12.3</td>
</tr>
<tr>
<td>LDL-C N (Δ)</td>
<td>782</td>
<td>586</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>23.0</td>
<td>19.0</td>
</tr>
</tbody>
</table>

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.

**Primary composite CV endpoint**

<table>
<thead>
<tr>
<th>Percent reduction</th>
<th>Ezetimibe/simvastatin (n = 9,067)</th>
<th>(P=0.016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>32.7%</td>
<td>34.7%</td>
</tr>
<tr>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.
## IMPROVE-IT

### Major Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Simvastatin (BL LDL-C: 69.5 mg/dL)</th>
<th>EZE/Simvastatin (BL LDL-C: 53.7 mg/dL)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34.9</td>
<td>33.2</td>
<td>0.267</td>
</tr>
<tr>
<td>Female</td>
<td>34.0</td>
<td>31.0</td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>30.8</td>
<td>29.9</td>
<td>0.098</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>39.9</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>30.8</td>
<td>30.2</td>
<td>0.023</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.5</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Prior LLT</td>
<td>43.4</td>
<td>40.7</td>
<td>0.272</td>
</tr>
<tr>
<td>No prior LLT</td>
<td>30.0</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>LDL-C &gt;95 mg/dL</td>
<td>31.2</td>
<td>29.6</td>
<td>0.670</td>
</tr>
<tr>
<td>LDL-C ≤95 mg/dL</td>
<td>38.4</td>
<td>36.0</td>
<td></td>
</tr>
</tbody>
</table>

EZE, ezetimibe; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

Lipid Effects of Adding a Fenofibrate to a Statin in Patients With T2D

Action to Control Cardiovascular Risk in Diabetes (N=5518)

Effect of Fenofibrate Plus Statin on CV Events in Patients With T2D

Action to Control Cardiovascular Risk in Diabetes (N=5518)
Benefits of Fenofibrate Plus Statin in Patients With T2D

Action to Control Cardiovascular Risk in Diabetes (N=5518)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.52 (2765)</td>
<td>11.26 (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤34 mg/dl</td>
<td>12.24 (964)</td>
<td>15.56 (906)</td>
<td>1.03 (0.95-1.12)</td>
<td>0.24</td>
</tr>
<tr>
<td>35–40 mg/dl</td>
<td>10.12 (860)</td>
<td>9.47 (866)</td>
<td>1.10 (0.98-1.22)</td>
<td></td>
</tr>
<tr>
<td>≥41 mg/dl</td>
<td>9.08 (925)</td>
<td>8.99 (968)</td>
<td>1.01 (0.91-1.12)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤128 mg/dl</td>
<td>9.88 (891)</td>
<td>11.29 (939)</td>
<td>1.14 (1.04-1.25)</td>
<td>0.64</td>
</tr>
<tr>
<td>129–203 mg/dl</td>
<td>10.50 (924)</td>
<td>9.86 (913)</td>
<td>1.09 (0.98-1.21)</td>
<td></td>
</tr>
<tr>
<td>≥204 mg/dl</td>
<td>11.13 (934)</td>
<td>12.84 (888)</td>
<td>1.16 (1.04-1.29)</td>
<td></td>
</tr>
<tr>
<td>Triglyceride–HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All others</td>
<td>10.11 (2264)</td>
<td>10.11 (2284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.0%</td>
<td>8.69 (1324)</td>
<td>10.56 (1335)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8.1%</td>
<td>12.20 (1435)</td>
<td>11.94 (1415)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fenofibrate Benefits Most Likely in Patients with High TG and Low HDL-C

Action to Control Cardiovascular Risk in Diabetes (N=5518)

The benefit associated with fenofibrate treatment was confined to the high TG/low HDL-C subgroup (<18% of ACCORD-LIPID trial population).

CV, cerebrovascular; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; RR, risk reduction; TG, triglycerides.

Effect of Fenofibrate on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

Diabetes Atherosclerosis Intervention Study

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.59</td>
<td>2.42</td>
</tr>
<tr>
<td>Endpoint</td>
<td>-29%</td>
<td>+1%</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.01</td>
<td>1.05</td>
</tr>
<tr>
<td>Endpoint</td>
<td>+7%</td>
<td>+2%</td>
</tr>
</tbody>
</table>

Quantitative Coronary Angiography

*P=0.02 vs placebo

FIELD: Fenofibrate Intervention in Event Lowering in Diabetes

Multinational, randomized controlled trial (N=9,795) of patients with T2D currently taking statin therapy assigned to add-on treatment with fenofibrate or placebo.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fenofibrate % (n)</th>
<th>Placebo % (n)</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary events</td>
<td>5% (256)</td>
<td>6% (288)</td>
<td>0.89</td>
<td>0.75-1.05</td>
<td>0.16</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>2% (110)</td>
<td>2% (93)</td>
<td>1.19</td>
<td>0.90-1.57</td>
<td>0.22</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>3% (158)</td>
<td>4% (207)</td>
<td>0.76</td>
<td>0.62-0.94</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; MI, myocardial infarction; T2D, type 2 diabetes.
Fenofibrate and CV Events

FIELD (N=9795 Patients With T2D)

Baseline cholesterol (mg/dL): TC 194; TG 154; HDL-C 42; LDL-C 119; Non-HDL-C 152

- **CHD Events** (Primary Endpoint)
  - Placebo: 5.9, Reduction: 11%, P=0.16
  - Fenofibrate 200 mg: 5.2

- **Nonfatal MI**
  - Placebo: 4.2, Reduction: 24%, P=0.01
  - Fenofibrate 200 mg: 3.2

- **CHD Death**
  - Placebo: 1.9
  - Fenofibrate 200 mg: 2.2, Increase: 19%, P=0.22

- **Total CVD Events** (Secondary Endpoint)
  - Placebo: 13.9
  - Fenofibrate 200 mg: 12.5, Reduction: 11%, P=0.035

- **Coronary Revascularization**
  - Placebo: 7.4
  - Fenofibrate 200 mg: 5.9, Reduction: 21%, P=0.003

* Not corrected for large placebo-group statin drop-in rate.

** Nonfatal MI and CHD death.

† CHD events, stroke, CVD death, revascularizations.

CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides.

Greatest Benefit of Fenofibrate Seen in Patients With Elevated TG and Low HDL-C

FIELD

Hazard ratio
95% CI
P value

Any MetS Criteria
13.9
0.89
0.80-0.99
<0.01

Low HDL-C**
15.1
0.86
0.75-0.99
<0.01

TG >200 mg/dL
17.2
0.77
0.63-0.94
<0.01

Low HDL-C + TG >200 mg/dL
17.8
0.73
0.58-0.91
<0.05

*Not corrected for large placebo group statin drop-in rate

**HDL-C <40 mg/dL (men) and <50 mg/dL (women).

CI, confidence interval; CV, cerebrovascular; FIELD, Secondary Endpoints from the Fenofibrate Intervention and Event Lowering in Diabetes trial; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, risk reduction; TG, triglycerides.

Coronary Drug Project: 15-Year Follow-up

Event Rate (%)

Total Mortality

CHD Mortality

Placebo (n = 2008)

Niacin (n = 827)

11% Reduction

$P < 0.0004$

12% Reduction

$P < 0.05$
Dyslipidemia Summary

- Patients with diabetes and insulin resistance syndrome have atherogenic dyslipidemia and an increased risk for CVD
- Although statin therapy is effective in lowering LDL-C, residual CVD risk remains after statin therapy
- To reduce residual CVD risk, lipid abnormalities beyond LDL-C (non-HDL-C, triglycerides, HDL-C) should be intensively treated

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.