Cardiovascular Risk Reduction and Other Co-Morbidities in Type 2 Diabetes

Following this presentation, you will be able to:

• Describe the relationship between major CV risk factors and CVD outcomes
• Select therapeutic modalities available to practitioners to improve CV risk factors
• Discuss other co-morbid/microvascular conditions seen in patients with type 2 diabetes
• Recognize the implications of recent large trials on guiding clinical decisions and targets for blood pressure and lipid abnormalities
• Explain the role of pharmacologic intervention in the treatment of type 2 diabetes

CV = cardiovascular; CVD = cardiovascular disease.
Type 2 Diabetes and CVD

- Type 2 diabetes is considered a CHD equivalent.
- Atherosclerotic complications are responsible for:
  - 80% of mortality among patients with diabetes
  - More than 75% of all hospitalizations for diabetic complications
- 50% of patients with type 2 diabetes have preexisting CAD
- One-third of patients presenting with MI have undiagnosed diabetes mellitus

CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction.

Compared with Individuals Without Diabetes, Patients with Diabetes Have a 2- to 4-Fold Increased Risk of Developing and Dying of CHD

CVD Mortality Among Participants with and without DM

Note: Bars indicate 95% confidence intervals. Rates are adjusted for age in 10-year intervals.

CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus.

Absolute Risk of MI Is Higher in Patients with DM

DM = diabetes mellitus; MI = myocardial infarction.

T2DM for >15 Years Duration Confers Similar Risk of Fatal CHD as Prior CHD and No Diabetes

20-year Follow-Up of 121,046 Women Aged 30 to 55 Years in Nurses’ Health Study

CHD = coronary heart disease; DM = diabetes mellitus; T2DM = type 2 diabetes mellitus.

How Is CAD Different in Diabetes?

• > CAD extent
  • Multi-vessel disease
  • Distal disease – more difficult to revascularize

• Silent ischemia/MI

• Younger

• Women

• Worse outcomes despite revascularization
  • Increased re-stenosis after PCI even with stents
  • ACB: worse perioperative and long-term outcomes

ACB = aortocoronary bypass; CAD = coronary artery disease; MI = myocardial infarction;
PCI = percutaneous coronary intervention.
Abdominal Obesity and Increased Risk of Cardiovascular Events: HOPE Study


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

*Adjusted for BMI, age, smoking, sex, CVD disease, DM, HDL-cholesterol, total-C

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

Strategies For Reducing Macrovascular Complications

Prevention proven by intervention

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Antiplatelet therapy
- Smoking Cessation
- Exercise
Type 2 Diabetes: A1C Predicts CHD

**CHD Mortality Incidence (%) in 3.5 Years**

- Low <6%
- Middle 6-7.9%
- High >7.9%

*P* < 0.01 vs lowest tertile

**All CHD Events Incidence (%) in 3.5 Years**

- Low <6%
- Middle 6-7.9%
- High >7.9%

**P** < 0.05 vs lowest tertile

A1C = glycated hemoglobin; CHD = coronary heart disease.

**ACCORD: Treatment Effects on Glucose Control**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Standard therapy</th>
<th>Intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.0</td>
<td>6.5</td>
</tr>
<tr>
<td>1</td>
<td>7.5</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>7.0</td>
<td>5.5</td>
</tr>
<tr>
<td>3</td>
<td>6.5</td>
<td>5.0</td>
</tr>
<tr>
<td>4</td>
<td>6.0</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>5.5</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin.

ACCORD: Treatment Effect on Primary Outcome

HR = heart rate.

ADVANCE: Treatment Effect on Glucose Control

A1C = glycated hemoglobin.

ADVANCE: Treatment Effect on Primary Macrovascular Outcome

CV Death, MI, Stroke

Cumulative incidence (%)

Follow-up (months)

CV = cardiovascular; HR = heart rate; MI = myocardial infarction.

VADT-Median A1C +/- IQR

A1C = glycated hemoglobin; INT = intensive control; IQR = interquartile range; STD = standard control; VADT = Veterans Affairs Diabetes Trial.

VADT Primary Outcome

VADT = Veterans Affairs Diabetes Trial.

A1C During DCCT and EDIC Observation

Glycosylated hemoglobin (Percent)

DCCT Intervention

EDIC Observation

Conventional - mean A1C 9.1 %

Training

Conventional - mean A1C 8.2 %

Intensive - mean A1C 8.0 %

Intensive - mean A1C 7.2 %

A1C = glycated hemoglobin; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications.

Cumulative Incidence of the First of Any Predefined Cardiovascular Disease Outcomes

Risk reduction 42%
95% CI: 9, 63
Log-rank $P = 0.016$

Strategies for Reducing Macrovascular Complications

Prevention proven by intervention

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Antiplatelet therapy
- Smoking Cessation
- Exercise
Association of SBP and CV Mortality in Men with T2DM

CV = cardiovascular; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.

Hypertension in Diabetes, UKPDS

BP = blood pressure; UKPDS = United Kingdom Prospective Diabetes Study Group.

Effect of Ramipril on Combined Outcome (MI, Stroke, Death)


MI = myocardial infarction.
Effect of Intensive BP Lowering on Risk of Micro- and Macrovascular Complications: UKPDS

Benefits of 144/82 mmHg vs 154/87 mmHg

- Myocardial infarction: -21%
- Diabetes-related death: -24%
- Retinopathy: -32%
- Renal failure: -34%
- Stroke: -42%
- Vision deterioration: -44%
- Heart failure: -47%
- Diabetes-related endpoint: -56%

BP = blood pressure; UKPDS = United Kingdom Prospective Diabetes Study Group.

# Guideline Recommendations for Uncomplicated and Complicated Hypertension

<table>
<thead>
<tr>
<th>Type of hypertension</th>
<th>BP goal (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Complicated</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>&lt;130/80*</td>
</tr>
<tr>
<td>Other high risk (stroke, MI)</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

*Lower if proteinuria is >1 g/day.

BP = blood pressure; MI = myocardial infarction.

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

HIGH

VERY HIGH

EXTREME

LDL-C (mg/dL)

<100

<70

<55

Non-HDL-C (mg/dL)

<130

<100

<80

TG (mg/dL)

<150

<150

<150

Apo B (mg/dL)

<90

<80

<70

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:**

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 (α-blockers, central agents, vasodilators, aldosterone antagonists)

Achievement of target blood pressure is critical

AACE = American Association of Clinical Endocrinologists

Strategies for Reducing Macrovascular Complications

Prevention proven by intervention

- Hyperglycemia
- Hypertension
- **Dyslipidemia**
- Antiplatelet therapy
- Smoking Cessation
- Exercise
Priorities for Lipid Levels in Adult Patients with Diabetes

- **LDL cholesterol lowering**
  - Statin at maximally tolerated dose

- **HDL cholesterol raising**
  - Behavior: weight loss, physical activity, smoking cessation
  - Glycemic control

- **Triglyceride lowering**
  - Glycemic control first priority
  - Fibric acid derivative (gemfibrozil, fenofibrate)
  - Statins at high dose also have some TG lowering
  - Niacin or high-dose omega-3 fatty acids
  - Triglyceride goal presently <150 mg/dL

HDL = high density lipoprotein; LDL = low density lipoprotein; TG = triglyceride.

### ACC/AHA 2013 Recommendations

#### CVD Primary Prevention – U.S. Adults

<table>
<thead>
<tr>
<th>Group</th>
<th>ACC/AHA 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>All individuals &gt;40 y/o with diabetes are considered high CVD risk</td>
</tr>
<tr>
<td></td>
<td>Rx high-potency statin</td>
</tr>
<tr>
<td></td>
<td>No fixed LDL-C targets</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; LDL-C = low density lipoprotein-cholesterol.

# Statin Therapy in Diabetes

**American Diabetes Association 2016**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Risk Factors</th>
<th>Statin Dose</th>
<th>Lipid Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>None ASCVD risk factor(s)** ASCVD***</td>
<td>No medication Moderate or high High</td>
<td>Yearly or as needed</td>
</tr>
<tr>
<td>40-75</td>
<td>None ASCVD risk factors ASCVD ACS and LDL&gt; 50 mg/dL*</td>
<td>Moderate High High Moderate + Ezetimibe</td>
<td>To monitor adherence</td>
</tr>
<tr>
<td>&gt;75</td>
<td>None CVD risk factors Overt CVD ACS and LDL&gt;50 mg/dL*</td>
<td>Moderate Moderate or high High Moderate + Ezetimibe</td>
<td>To monitor adherence</td>
</tr>
</tbody>
</table>

* On basis of IMPROVE-IT subgroup  
** LDL-C>100 mg/dL, hypertension, smoking, overweight or obesity  
ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL = low density lipoprotein; LDL-C = low density lipoprotein-cholesterol.
### Intensity of Statin Therapy
(Doses in mg/day)

<table>
<thead>
<tr>
<th>Low-intensity daily statin</th>
<th>Moderate-intensity daily statin</th>
<th>High-intensity daily statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce LDL-C &lt;30%</td>
<td>Reduce LDL-C 30% to &lt;50%</td>
<td>Reduce LDL-C &gt;50%</td>
</tr>
<tr>
<td>Simvastatin 10</td>
<td>Atorvastatin 10-20</td>
<td>Atorvastatin (40†)-80</td>
</tr>
<tr>
<td>Pravastatin 10-20</td>
<td>Rosuvastatin 5-10</td>
<td>Rosuvastatin 20-40</td>
</tr>
<tr>
<td>Lovastatin 20</td>
<td>Simvastatin 20-40‡</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 20-40</td>
<td>Pravastatin 40-80</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin 1</td>
<td>Lovastatin 40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4</td>
<td></td>
</tr>
</tbody>
</table>

**Boldface type** indicates specific statins and doses that were evaluated in RCTs included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3. All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

BID indicates twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

Stone NJ et al. *Circulation*. 2014;129[suppl 2]:S1-S45
Cholesterol Lowering in High Risk Patients: The Heart Protection Study

LDL lowering resulted in 22% reduction in CVD events across all LDL categories.

CHD = coronary heart disease; CVD = cardiovascular disease; LDL = low density lipoprotein; MI = myocardial infarction.

AACE Dyslipidemia Management Algorithm

When atherogenic markers are not at goal:

To lower LDL-C:
- Intensify statin and/or,
  - add ezetimibe and/or
  - PCSK9 and/or
colesevelam and/or
niacin

To lower non-HDL-C, TG:
- Intensify statin and/or
  - Rx-grade Omega-3 fatty acid and/or
  - fibrates and/or
  - niacin

To lower APO-B, LDL-P:
- Intensify statin and/or
  - add ezetimibe and/or
  - PCSK9 and/or
colesevelam

AACE = American Association of Clinical Endocrinologists; APO-B = apolipoprotein-B; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; LDL-P = low density lipoprotein-particles; PCSK9 = proprotein convertase subtilisin/kexin type 9; TG = triglyceride.

### PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adjunct to diet and maximally tolerated statin therapy in adults</td>
<td></td>
</tr>
<tr>
<td>• Heterozygous familial hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>• Clinical atherosclerotic CV disease who require additional lowering of LDL-C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIDE EFFECTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions; myalgias; neurocognitive (confusion, impaired memory); nasopharyngitis; upper respiratory tract infection; back pain; influenza.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOSAGE: Alirocumab (Praluent®)</th>
<th>Evolucumab (Repatha®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg/2 weeks or 150 mg/2 weeks</td>
<td>140 mg/2 weeks or 420mg/month</td>
</tr>
</tbody>
</table>

CV = cardiovascular; LDL-C = low density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
Lipid Changes, Baseline To 12 Weeks: Evolocumab vs Ezetimibe or Placebo

HDL=high-density lipoprotein; LDL=low density lipoprotein; Lp (a)=lipoprotein(a) TRIG=triglycerides
Strategies for Reducing Macrovascular Complications

Prevention proven by intervention

- Hyperglycemia
- Hypertension
- Dyslipidemia
- **Antiplatelet therapy**
- Smoking Cessation
- Exercise
What About ASA for 1º Prevention of CVD?

Included: 6 studies, N = 10,117 participants
ASA for 1° Prevention in Diabetes: Meta Analysis of 6 Studies (N=10,117)

No overall benefit for:
- Major CV events
- MI
- Stroke
- CV mortality
- All-cause mortality

ASA = acetylsalicylic acid (aspirin); CV = cardiovascular; ETDRS = Early Treatment Diabetic Retinopathy Study; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI = myocardial infarction; PHS = Physicians’ Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = rate ratio; WHS = Women’s Health Study


<table>
<thead>
<tr>
<th></th>
<th>No. of events/No. in group</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major CV events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Control/placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPAD</td>
<td>68/1262</td>
<td>86/1277</td>
<td>0.80 (0.59-1.09)</td>
</tr>
<tr>
<td>POPADAD</td>
<td>105/638</td>
<td>108/638</td>
<td>0.97 (0.76-1.24)</td>
</tr>
<tr>
<td>WHS</td>
<td>58/514</td>
<td>62/513</td>
<td>0.90 (0.63-1.29)</td>
</tr>
<tr>
<td>PPP</td>
<td>20/519</td>
<td>22/512</td>
<td>0.90 (0.50-1.62)</td>
</tr>
<tr>
<td>ETDRS</td>
<td>350/1856</td>
<td>379/1855</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>Total</td>
<td>601/4789</td>
<td>657/4795</td>
<td>0.90 (0.81-1.00)</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Control/placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPAD</td>
<td>28/1262</td>
<td>14/1277</td>
<td>0.87 (0.40-1.87)</td>
</tr>
<tr>
<td>POPADAD</td>
<td>90/638</td>
<td>82/638</td>
<td>1.10 (0.83-1.45)</td>
</tr>
<tr>
<td>WHS</td>
<td>36/514</td>
<td>24/513</td>
<td>1.48 (0.88-2.49)</td>
</tr>
<tr>
<td>PPP</td>
<td>5/519</td>
<td>10/512</td>
<td>0.49 (0.17-1.43)</td>
</tr>
<tr>
<td>ETDRS</td>
<td>241/1856</td>
<td>283/1855</td>
<td>0.82 (0.69-0.98)</td>
</tr>
<tr>
<td>PHS</td>
<td>11/275</td>
<td>26/258</td>
<td>0.40 (0.20-0.79)</td>
</tr>
<tr>
<td>Total</td>
<td>395/5064</td>
<td>439/5053</td>
<td>0.86 (0.61-1.21)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Control/placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPAD</td>
<td>12/1262</td>
<td>32/1277</td>
<td>0.89 (0.54-1.46)</td>
</tr>
<tr>
<td>POPADAD</td>
<td>37/638</td>
<td>50/638</td>
<td>0.74 (0.49-1.12)</td>
</tr>
<tr>
<td>WHS</td>
<td>15/514</td>
<td>31/513</td>
<td>0.46 (0.25-0.85)</td>
</tr>
<tr>
<td>PPP</td>
<td>9/519</td>
<td>10/512</td>
<td>0.89 (0.36-2.17)</td>
</tr>
<tr>
<td>ETDRS</td>
<td>92/1856</td>
<td>78/1855</td>
<td>1.17 (0.87-1.58)</td>
</tr>
<tr>
<td>Total</td>
<td>181/4789</td>
<td>201/4795</td>
<td>0.83 (0.60-1.14)</td>
</tr>
<tr>
<td><strong>Death from CV causes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Control/placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPAD</td>
<td>1/1262</td>
<td>10/1277</td>
<td>0.10 (0.01-0.79)</td>
</tr>
<tr>
<td>POPADAD</td>
<td>43/638</td>
<td>35/638</td>
<td>1.23 (0.80-1.89)</td>
</tr>
<tr>
<td>PPP</td>
<td>10/519</td>
<td>8/512</td>
<td>1.23 (0.49-3.10)</td>
</tr>
<tr>
<td>ETDRS</td>
<td>244/1856</td>
<td>275/1855</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>Total</td>
<td>298/4275</td>
<td>328/4282</td>
<td>0.94 (0.72-1.23)</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Control/placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPAD</td>
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<tr>
<td>ETDRS</td>
<td>340/1856</td>
<td>366/1855</td>
<td>0.91 (0.78-1.06)</td>
</tr>
<tr>
<td>Total</td>
<td>493/4275</td>
<td>525/4282</td>
<td>0.93 (0.82-1.05)</td>
</tr>
</tbody>
</table>
Primary prevention (75-162 mg/day)
- Type 1 or type 2 diabetes at increased CV risk (10-year risk >10%)
- Men >50 years of age or women >60 years with 1+ additional major risk factor
  - Family history of CVD, HTN, smoking, dyslipidemia, or albuminuria
- Not sufficient evidence to recommend aspirin for primary prevention in lower-risk individuals

Secondary prevention (75-162 mg/day)
- Use aspirin therapy as a secondary prevention strategy in those with diabetes with a history of CVD

CV = cardiovascular; CVD = cardiovascular disease; HTN = hypertension.
ASA Not Routinely Recommended for First-Degree CVD Prevention in Patients with Diabetes

Insufficient evidence to support use of ASA for primary prevention

Risk of bleeding  CVD protection

ASA = acetylsalicylic acid (aspirin); CVD = cardiovascular disease.
Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.
STENO-2: Intensive Group Achieved Targets

BP = blood pressure.

STENO-2: Intensive Group Had Improved CV Outcomes

CV = cardiovascular; NNT = number needed to treat; RRR = relative risk reduction.

STENO 2: Microvascular Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy</td>
<td>0.39 (0.17–0.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.42 (0.21–0.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>0.37 (0.18–0.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1.09 (0.54–2.22)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
STENO 2: 21-Year Follow-up, Death, or CVD Events

Median survival was 7.9 years longer in intensive vs conventional group.

CVD = cardiovascular disease

# Treating the ABCs Reduces Diabetic Complications

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose control (A1C)</strong></td>
<td>▪ Myocardial infarction</td>
<td>☐ 16%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Cardiovascular disease</td>
<td>☐ 51%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Heart failure</td>
<td>☐ 56%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Stroke</td>
<td>☐ 44%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Diabetes-related deaths</td>
<td>☐ 32%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Blood pressure control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipid control (Cardiovascular)</strong></td>
<td>▪ Coronary heart disease mortality</td>
<td>☐ 35%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Major coronary heart disease event</td>
<td>☐ 55%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Any atherosclerotic event</td>
<td>☐ 37%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>▪ Cerebrovascular disease event</td>
<td>☐ 53%&lt;sup&gt;4&lt;/sup&gt;</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 Level</th>
<th>Desirable Levels</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:**
- 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
- ß-blocker
- Thiazide

*If not at goal (2–3 months)*
Add calcium channel blocker, ß-blocker or thiazide diuretic

*If not at goal (2–3 months)*
Add next agent from the above group, repeat

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

*Achievement of target blood pressure is critical*