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.
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.

Rates of diabetes-related complications declined between 1990 and 2010 (relative risk reductions):

- Myocardial infarction: -68.8%
- Death from hyperglycemic crisis: -64.4%
- End-stage renal disease: -28.3%
- Stroke and amputation: ~50%

ESRD = end-stage renal disease.

### Event Rates/10,000 Adults/Year

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Overall</th>
<th>Fold Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>45.5</td>
<td>5.7</td>
<td>8</td>
</tr>
<tr>
<td>Stroke</td>
<td>52.9</td>
<td>7.9</td>
<td>7</td>
</tr>
<tr>
<td>Amputation</td>
<td>28.4</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>ESRD</td>
<td>20</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

ESRD = end-stage renal disease.

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.
Adipose Tissue in Obesity

Lean

Obese

Després J-P. Eur Heart J Suppl. 8(suppl B):B4-12, 2006.
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
Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association

Jay S. Skyler, MD, MACP; Richard Bergenstal, MD; Robert O. Bonow, MD, MACC, FAHA; John Buse, MD, PhD; Prakash Deedwania, MD, FACC, FAHA; Edwin A.M. Gale, MD; Barbara V. Howard, PhD; M. Sue Kirkman, MD; Mikhail Kosiborod, MD, FACC; Peter Reaven, MD; Robert S. Sherwin, MD
Glucose Control and CHD Events

<table>
<thead>
<tr>
<th></th>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS4,7</td>
<td>3071/1549 426/259</td>
<td>8.6%</td>
<td></td>
<td>0.75 (0.54-1.04)</td>
</tr>
<tr>
<td>PROactive18-20</td>
<td>2605/2633 164/202</td>
<td>20.2%</td>
<td></td>
<td>0.81 (0.65-1.00)</td>
</tr>
<tr>
<td>ADVANCE5</td>
<td>5571/5569 310/337</td>
<td>36.5%</td>
<td></td>
<td>0.92 (0.78-1.07)</td>
</tr>
<tr>
<td>VADT21,22</td>
<td>892/899 77/90</td>
<td>9.0%</td>
<td></td>
<td>0.85 (0.62-1.17)</td>
</tr>
<tr>
<td>ACCORD8</td>
<td>5128/5123 205/248</td>
<td>25.7%</td>
<td></td>
<td>0.82 (0.68-0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773 1182/1136</td>
<td>100%</td>
<td></td>
<td>0.85 (0.77-0.93)</td>
</tr>
</tbody>
</table>

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CHD = coronary heart disease; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; UKPDS = United Kingdom Prospective Diabetes Study Group; VADT = Veterans Affairs Diabetes Trial.
A1C During DCCT and EDIC Observation

Glycosylated hemoglobin (Percent)

DCCT Intervention

Conventional - mean A1C 9.1 %

Intensive - mean A1C 7.2 %

Training

Conventional - mean A1C 8.2 %

Intensive - mean A1C 8.0 %

EDIC Observation

Study year

0 1 2 3 4 5 6 7 8 9

Intensive mean A1C 8.0 %

Conventional mean A1C 8.2 %

Study year

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 mortality rate per 10,000 person-years

SBP (mmHg)

No diabetes
Diabetes

No diabetes
Diabetes

<120
120-139
140-159
160-179
180-199
≥200

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

Effect of Intensive BP Lowering on Risk of Micro- and Macrovascular Complications: UKPDS

Benefits of 144/82 mmHG vs 154/87 mmHG

-21 -24 -32 -34 -42 -44 -47 -56

Myocardial infarction Any diabetes-related endpoint Diabetes-related death Retinopathy Renal failure Stroke Vision deterioration Heart failure

Risk Reduction (%)
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.

AACE = American Association of Clinical Endocrinologists

Garber AJ et al. *Endocr Pract.* 2015;21(No. 4)
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.
# Cholesterol Lowering in High Risk Patients: The Heart Protection Study

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

<table>
<thead>
<tr>
<th>Prior disease category</th>
<th>Simvastatin-allocated</th>
<th>Placebo-allocated</th>
<th>Event rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior MI or other CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Cerebrovascular</td>
<td>234/723 (32.4%)</td>
<td>276/737 (37.4%)</td>
<td></td>
</tr>
<tr>
<td>+ Peripheral vascular</td>
<td>568/2059 (27.6%)</td>
<td>681/1988 (34.3%)</td>
<td></td>
</tr>
<tr>
<td>+ Diabetes mellitus</td>
<td>325/972 (33.4%)</td>
<td>381/1009 (37.6%)</td>
<td></td>
</tr>
<tr>
<td>+ None of above</td>
<td>617/3674 (16.8%)</td>
<td>840/3740 (22.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal: any CHD</strong></td>
<td>1459/6694 (21.8%)</td>
<td>1841/6892 (27.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>No prior CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Cerebrovascular</td>
<td>172/922 (18.7%)</td>
<td>212/898 (23.6%)</td>
<td></td>
</tr>
<tr>
<td>+ Peripheral vascular</td>
<td>327/1325 (24.7%)</td>
<td>420/1376 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>+ Diabetes mellitus</td>
<td>276/2006 (13.8%)</td>
<td>367/1976 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>+ None of above</td>
<td>574/3575 (16.1%)</td>
<td>744/3575 (20.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal: no CHD</strong></td>
<td>574/3575 (16.1%)</td>
<td>744/3575 (20.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>CHD or no prior CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Cerebrovascular</td>
<td>406/1645 (24.7%)</td>
<td>488/1635 (29.8%)</td>
<td></td>
</tr>
<tr>
<td>+ Peripheral vascular</td>
<td>895/3384 (26.4%)</td>
<td>1101/3364 (32.7%)</td>
<td></td>
</tr>
<tr>
<td>+ Diabetes mellitus</td>
<td>601/2978 (20.2%)</td>
<td>748/2985 (25.1%)</td>
<td></td>
</tr>
<tr>
<td>+ None of above</td>
<td>628/3794 (16.8%)</td>
<td>855/3858 (22.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>2033/10269 (19.8%)</td>
<td>2585/10267 (25.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity $\chi^2$ for “Any CHD” vs “No CHD”=0.1

Simvastatin better Placebo better

0.76 (0.71–0.82) p<0.0001

0.75 (0.67–0.84) p<0.0001

0.76 (0.72–0.81) p<0.0001

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

Statins and CVD in Patients with Diabetes: CTT Meta-analysis

<table>
<thead>
<tr>
<th>Major vascular event and prior diabetes</th>
<th>Events (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>Major coronary event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>776 (8.3%)</td>
<td>979 (10.5%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2561 (7.2%)</td>
<td>3441 (9.6%)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7.4%)</td>
<td>4420 (9.8%)</td>
</tr>
</tbody>
</table>

Test for heterogeneity within subgroup: $\chi^2 = 0.1; p = 0.8$

CTT = Cholesterol Trialists Collaboration; CVD = cardiovascular disease; RR = rate ratio.

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)**</td>
<td>No medication</td>
<td>Yearly or as needed</td>
</tr>
<tr>
<td></td>
<td>ASCVD***</td>
<td>Moderate or high High</td>
<td></td>
</tr>
<tr>
<td>40-75</td>
<td>None ASCVD risk factors</td>
<td>Moderate</td>
<td>To monitor adherence</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS and LDL&gt; 50 mg/dL*</td>
<td>High Moderate + Ezetimibe</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>None CVD risk factors</td>
<td>Moderate</td>
<td>To monitor adherence</td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>Moderate or high High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS and LDL&gt;50 mg/dL*</td>
<td>Moderate + Ezetimibe</td>
<td></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</td>
<td>Reduce LDL-C</td>
<td>Reduce LDL-C</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>30% to &lt;50%</td>
<td>&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.
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

- Reduce LDL-C levels
- Have been shown to reduce cardiovascular endpoints

LDL-C = low density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

The Role of PCSK9 in the Regulation of LDL Receptor Expression

LDL = low density lipoprotein; LDL-R = low density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9; SREBP = sterol response element binding protein.

## 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>• Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>• Heterozygous familial hypercholesterolemia</td>
<td>• Clinical atherosclerotic CV disease who require additional lowering of LDL-C</td>
</tr>
</tbody>
</table>

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

| DOSAGE: Alirocumab (Praluent®) | 75 mg/2 weeks or 150 mg/2 weeks                                                     |
| Evolucumab (Repatha®)           | 140 mg/2 weeks or 420mg/month                                                        |

CV = cardiovascular; LDL-C = low density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
Alirocumab in Individuals with and without Diabetes: ODYSSEY Study

HeFH or high CV risk patients on maximally tolerated statin ± other LLT, with LDL >70 mg/dL

Least-squares mean difference, baseline to week 24

Apo B=apolipoprotein B; CV=cardiovascular; DM=diabetes mellitus; HeFH=heterozygous familial hypercholesterolemia; Lp(a)=lipoprotein(a); LDL=low density lipoprotein; LLT=lipid-lowering therapy

LDL-C
Non-HDL-C
Apo B
Lp(a)

### 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

<table>
<thead>
<tr>
<th>RISK LEVELS</th>
<th>DESIRABLE LEVELS</th>
<th>HIGH</th>
<th>VERY HIGH</th>
<th>EXTREME</th>
<th>RISK LEVELS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td>&lt;55</td>
<td>HIGH: DM but no other major risk and/or age &lt;40</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;80</td>
<td>VERY HIGH: DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CHD, TIA)</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>EXTREME: DM plus established clinical CVD</td>
<td></td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
<td>&lt;70</td>
<td></td>
<td></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, colesuevelam, 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, colesuevelam, 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
- ACEi or ARB + β-blocker
- ACEi or ARB + 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 (β-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical
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 = acetylsalicylic acid (aspirin); CVD = cardiovascular disease.

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.
Antiplatelet Agents in Diabetes: 2013

• **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.

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

- Glycosylated Hemoglobin <6.5%: P=0.06
- Cholesterol <175 mg/dl: P<0.001
- Triglycerides <150 mg/dl: P=0.19
- Systolic BP <130 mm Hg: P=0.001
- Diastolic BP <80 mm Hg: P=0.21

BP = blood pressure.

STENO-2: Intensive Group Had Improved CV Outcomes

Any CV event

NNT = 5

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>

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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


Percent (%)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C&lt;7.0%</td>
<td>43.1</td>
<td>44.1</td>
<td>52.5</td>
<td>56.2</td>
</tr>
<tr>
<td>BP&lt;130/80</td>
<td>33.2</td>
<td>38.1</td>
<td>44.2</td>
<td>48</td>
</tr>
<tr>
<td>LDL&lt;100mg/dL</td>
<td>9.9</td>
<td>35.3</td>
<td>51.1</td>
<td>12</td>
</tr>
<tr>
<td>All 3 at Goal</td>
<td>4.5</td>
<td>7</td>
<td>18.8</td>
<td>18.8</td>
</tr>
</tbody>
</table>

Still a long way to go

A1C = glycated hemoglobin; BP = blood pressure; LDL = low density lipoprotein; LDL-C = low density lipoprotein-cholesterol; NHANES = National Health and Nutrition Examination Survey.