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

• Recognize the implications of recent large trials on clinical decisions guiding choice and targets for blood pressure and lipid abnormalities

• Discuss other co-morbid/microvascular conditions seen in patients with type 2 diabetes

• Explain the role of pharmacologic intervention in the treatment of type 2 diabetes

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CV = cardiovascular; CVD = cardiovascular disease
### CVD Risk Factor Modifications Algorithm

#### Dyslipidemia

**Therapeutic Lifestyle Changes (See Obesity Algorithm)**

**LIPID PANEL: Assess CVD Risk**

- **Statin Therapy**
  - If statin-intolerant:
    - Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C-lowering therapies
  - Repeat lipid panel; assess adequacy, tolerance of therapy
  - If TG > 500 mg/dL, fibrates, omega-3 ethyl esters, niacin

**Risk Levels**

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>MODERATE (DM but no other major risk and/or age &lt;40)</th>
<th>HIGH (DM + major CVD risk(s) [HTN, Fam Hx, low HDL-C, smoking] or CVD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;120</td>
<td>&lt;100</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>&lt;3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
</tr>
<tr>
<td>LDL-P (nmol/L)</td>
<td>&lt;1200</td>
<td>&lt;1000</td>
</tr>
</tbody>
</table>

- **Desirable Levels**

- **If not at desirable levels:**
  - Intensify TLC (weight loss, physical activity, dietary changes) and glycemic control; Consider additional therapy

- **To lower LDL-C:**
  - Intensify statin, add ezetimibe &/or coleselam &/or niacin
  - To lower Non-HDL-C, TG:
    - Intensify statin &/or add OM3EE &/or fibrates &/or niacin
  - To lower Apo B, LDL-P:
    - Intensify statin &/or ezetimibe &/or coleselam &/or niacin
  - Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* even more intensive therapy might be warranted

### Hypertension

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

- **ACEI or ARB**
  - For initial blood pressure >150/100 mm Hg: Dual therapy
    - Thiazide
    - Calcium Channel Blocker
    - ß-blocker

- If not at goal (2–3 months):
  - Add ß-blocker or calcium channel 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 (ß-blockers, central agents, vasodilators, spironolactone)

- Achievement of target blood pressure is critical

---

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Vascular Disease Events in Patients with Diabetes (Age 35-64): Framingham Heart Study, 30-year Follow-up

Risk Ratio

(Relative to subjects without diabetes

†P<0.001

*P<0.05)

Age-adjusted annual rate/1,000

Men | Women

CHD

20† | 19†

Stroke

6† | 3*

Intermittent claudication

9† | 9†

Cardiac failure

11† | 10†

Total CVD

38† | 30†

Diabetes is a Vascular Disease

Visceral vs Subcutaneous Adiposity

CT scans matched for BMI and total body fat

Visceral obesity
Fat mass: 19.8 kg
VFA: 155 cm²

Subcutaneous (sc) obesity
Fat mass: 19.8 kg
VFA: 96 cm²

BMI = body mass index; CT = computerized tomography; VFA = visceral fat area

Abdominal Obesity and Increased Risk of Cardiovascular Events: HOPE Study

Adjusted Relative Risk

Waist circumference (in):

- Tertile 1: <37.4
- Tertile 2: 37.4–40.5
- Tertile 3: >40.5

Men:
- CVD death: 1
- MI: 1
- All-cause deaths: 1

Women:
- CVD death: <34.3
- MI: 34.3–38.5
- All-cause deaths: >38.5

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

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

Metabolic Markers to Identify Overweight Individuals Sufficiently Insulin-resistant To Be at Increased Risk for CV Disease

Sensitivity (true-positive)

Receiver-operating Characteristic (ROC) curve analysis

TG, TG/HDL, & insulin most useful metabolic markers in identifying insulin resistance

Optimal cut-points: TG (≥130 mg/dL), TG/HDL( ≥3.0), and Insulin ( ≥109 pmol/L)

Syndrome X (1988)

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

- Resistance to insulin-stimulated glucose uptake
- Hyperinsulinemia
- Hypertension
- Glucose intolerance
- Increased VLDL-triglycerides
- Decreased HDL-cholesterol

- Resistance to Insulin-stimulated suppression of adipose tissue lipolysis $\rightarrow$ free fatty acids
- And, while not required, ‘Syndrome X’ was more common in overweight or obese individuals

HDL = high density lipoprotein; VLDL = very low-density lipoprotein

Reaven, GM. Diabetes. 1988;37:1595-1607
NCEP-ATP III 2001 Guidelines: Clinical Identification of the Metabolic Syndrome

≥3 of the following are needed for diagnosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>- men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>- women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>150 mg/dL</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
</tr>
<tr>
<td>- men</td>
<td>&lt;40 mg/dl</td>
</tr>
<tr>
<td>- women</td>
<td>&lt;50 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>130/85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>110 mg/dL → 100 mg/dL</td>
</tr>
</tbody>
</table>

HDL = high density lipoprotein cholesterol; NCEP ATP III = Third Nation Cholesterol Education Program Adult Treatment Panel
Metabolic Syndrome and Risk of Incident Cardiovascular Events and Death: A Systematic Review and Meta-Analysis of Longitudinal Studies

37 eligible studies including 43 cohorts (inception 1971 to 1997; N=172,573), utilizing either the NCEP, WHO, or modified versions

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

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

Collaborative Atorvastatin Diabetes Study (CARDS)
Consistent Statin Effects on Primary Endpoint Components

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Atorvastatin</th>
<th>Risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>127 (9.0)</td>
<td>83 (5.8)</td>
<td>37% (17–52) p = 0.001</td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>77 (5.5)</td>
<td>51 (3.6)</td>
<td>36% (9–55)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>34 (2.4)</td>
<td>24 (1.7)</td>
<td>31% (−16–59)</td>
</tr>
<tr>
<td>Stroke</td>
<td>39 (2.8)</td>
<td>21 (1.5)</td>
<td>48% (11–69)</td>
</tr>
</tbody>
</table>

Favors Atorvastatin: Hazard ratio
Favors Placebo: Hazard ratio

Residual Cardiovascular Risk, Even After Treatment With Statins

• Despite high-dose statin therapy, there is high residual risk in patients with diabetes, low HDL, elevated triglycerides, and other risk factors

• Therefore, these other risk factors should be addressed

HDL = high density lipoprotein cholesterol

PROVE-IT TIMI 22, Primary Endpoint

All-cause Death or Major Cardiovascular Events

% with event

Months of follow-up

Pravastatin 40mg (26.3%)

Atorvastatin 80mg (22.4%)

16% RRR (P = 0.005)

Residual Risk

AACE 2013 Dyslipidemia Management Algorithm

When Atherogenic Markers not at goal:

To Lower LDL-C:
- Intensify statin and/or
- add ezetimibe and/or colesevelam and/or niacin

To Lower Non-HDL-C, TG:
- Intensify statin and/or
- Rx-grade omega-3 ethyl esters and/or fibrates and/or niacin

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

Apo B = apolipoprotein B; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglyceride

Niacin

• Despite high-dose statin therapy, there is high residual risk in patients with diabetes, low HDL, elevated triglycerides, and other risk factors

• Although niacin, or nicotinic acid (vitamin B₃) has been shown to increase HDL cholesterol, the results of recent large clinical trials have shown little cardiovascular protection for patients with diabetes

• Outcomes indicate that while low HDL is associated with poor outcomes, increasing HDL does not appear to be protective for major vascular events.

HDL = high density lipoprotein cholesterol

## ADA/ACC Consensus Statement: Treatment Goals

### Treatment Goals in Patients with Cardiometabolic Risk and Lipoprotein Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>LDL-C (mg/dL)</th>
<th>Non–HDL-C (mg/dL)</th>
<th>Apo B (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest-risk patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Known CVD or</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>– Diabetes plus ≥1 additional major CVD risk factor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High-risk patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– No diabetes or known CVD but ≥2 major CVD risk factors* or</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>– Diabetes but no other major CVD risk factors*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Major risk factors beyond dyslipidemia include smoking, hypertension, and family history or premature CHD.

ACC = American College of Cardiology; ADA = American Diabetes Association; Apo B = apolipoprotein B; CHD = coronary heart disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Proprotein convertase
Proprotein convertase
Subtilisin kexitin

• Proprotein convertase family consists of at least 9 endoprotease enzymes
Proprotein convertase subtilisin-kexin 9

- PCSK9 is widely distributed in Liver, Intestine, kidneys and CNS
- Regulates plasma LDL-C levels through increased degradation of LDL receptor proteins
- Overexpression of PCSK9 results in increased circulating levels of LDL-C
- Single point mutations associated with increased proprotein convertase function may result in familial autosomal dominant hyperlipidemia and increased risk of early MI and stroke

New Eng J Med 2011;365:2507-2518
PCSK9 Inhibitors

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

New Eng J Med 2015;372:1489-1499
New Eng J Med 2015;372 1500-1509
# PCSK9 inhibitors

| Indications                                                                 | Adjunct to diet and maximally tolerated statin therapy in adults  
| Heterozygous familial hypercholesterolemia  
| Clinical atherosclerotic CV disease who require additional lowering of LDL-C |
| Side effects                                                               | Injection site reactions  
| Myalgias                      
| Neurocognitive (confusion, impaired memory)                                 |
| Dosage: Alirocumab (Praluent)                                               | 75 mg/2 weeks or 150 mg/2 weeks |
| Evolucumab (Repatha)                                                       | 140 mg/2 weeks or 420 mg/month |
ACCORD-LIPID: Primary Outcomes Possible Benefit Confined to the High Triglycerides/Low HDL-C Subgroup

Analysis of fenofibrate benefit in pre-specified high TG/low HDL subgroup vs. all others

CV = cardiovascular; Fen = fenofibrate; HDL-C = high-density lipoprotein cholesterol; Simva = simvastatin; TG = triglyceride
The Framingham Heart Study

Risk of CHD by Triglyceride Level

N = 5127

Relative CHD Risk

CHD = coronary heart disease

Castelli WP. Am J Cardiol. 1992;70:3H-9H.
Algorithm for Managing Severe Hypertriglyceridemia (SH)

**Acute management SH +/- pancreatitis**
- Dietary measures: NPO; I.V. fluids; Insulin, if diabetes
  - Add Rx-grade Omega-3 fatty acids
  - Add fibrates to OM-3 fatty acids
  - Add niacin to fibrates and OM-3 fatty acids
  - Consider medium chain TG
  - If poorly responsive, apheresis (plasmapheresis) until TG <1000 mg/dL

**Chronic management SH**
- Dietary measures: Low carbohydrate, low-fat <20 g LC-FA/day, MCT, abstinence from alcohol

If TG not at desirable level

When TGs are lowered to <500 mg/dL, secondary targets become non-HDL-C, LDL-C, LDL-P; begin statin therapy

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
Hypertension

**Goal:**
- Systolic ~130 mmHg
- Diastolic ~80 mmHg

- **ACEi** or **ARB**
  - For initial blood pressure >150/100
  - If not at goal (2-3 months)
    - Add beta-blocker or calcium channel blocker or thiazide diuretic
  - Add next agent from the above group, repeat
    - If not at goal (2-3 months)
      - Additional choices
        - (alpha-blockers, central agents, vasodilators, spironolactone)
      - Achievement of target blood pressure is critical

# 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.
ADVANCE & ACCORD BP Reduction in Context – UKPDS

Incidence of MI and microvascular endpoints by mean systolic BP, adjusted for age, sex, and ethnic group, for white men aged 50-54 years at diagnosis (mean diabetes duration 10 years)

Incidence per 1000 patient-years (%)

Mean systolic BP (mmHg)

Myocardial Infarction

Microvascular Endpoints

BP = blood pressure
MI = myocardial infarction

2024-patient study (340 had diabetes [DM] and 281 survived hospitalization for acute MI); of the 127 patients with diabetes taking β-blockers, 80% received propranolol and 20% received other β-blockers.
Beta-Blocker Recommendations for T2DM

- Recommend the use of beta-blocker in type 2 diabetes patients with heart failure and/or history of myocardial infarction
- Beta-blockers may be used safely in patients using blood pressure control
- Early trials indicated that glucose metabolism may be adversely affected by some beta-blockers; however, newer agents such as bisoprolol and carvedilol have not been shown to have this effect
- Beta-blockers may mask some signs and symptoms of hypoglycemia in patients with longstanding diabetes, particularly patients on insulin

## UKPDS “Legacy Effect” of Earlier Glucose Control with Insulin or Sulfonylurea

Total number of patients with clinical outcomes evaluated during 30 years follow-up: 2,729 from intensive treatment group vs 1,138 from conventional treatment group

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Interv.</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregate endpoint</td>
<td>-1997</td>
<td>-2007</td>
</tr>
<tr>
<td>Any diabetes-related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>P: 0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>P: 0.0099</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>P: 0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>P: 0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, P = Log Rank

UKPDS: “Legacy Effect” of Earlier Glucose Control with Metformin in Overweight Patients

Total number of patients with clinical outcomes evaluated during 30-years follow-up: 342 from intensive treatment group vs 411 from conventional treatment group

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Interv.</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregate endpoint</td>
<td>-1997</td>
<td>-2007</td>
</tr>
<tr>
<td>Any diabetes-related endpoint</td>
<td>RRR: 32%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>P: 0.0023</td>
<td>0.013</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 29%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>P: 0.19</td>
<td>0.31</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 39%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>P: 0.010</td>
<td>0.005</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 36%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>P: 0.011</td>
<td>0.002</td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, P = Log Rank

STENO-2: Total Mortality by Treatment Arm Over Time

Total mortality decreased by 50% with intensive treatment, seen only after >10 years follow-up (mean 13.3 years)

- Intensive vs. Conventional HR:
  - Year 4: 2.0
  - Year 8: 1.0
  - Year 13: 0.54

- End of multifactorial intervention: 46%

HR = hazard ratio

Time-Course of CVD Prevention by Glycemia Control in DM: Summary

• **Microvascular benefits**
  — Accrue early (≤6 years in DCCT, UKPDS, Kumamoto, ADVANCE, STENO-2)

• **Macrovascular benefits:**
  — Are **not** seen in trials of ≤10-years’ treatment (with A1C diff. 0.8%-1.8%; ACCORD, ADVANCE, VADT, DCCT, UKPDS)
  — Were seen in the Kumamoto trial, with A1C diff. 2.3% at 10 years
  — Are seen at ≥10 years, even when glycemic difference lost – so-called “Legacy Effect” (STENO-2, UKPDS-metformin, UKPDS 17-year follow-up)
  — Total mortality was increased at <5 y (STENO-2, ACCORD)
    • But at 13.3 years, total mortality was reduced (STENO-2)

A1C = glycated hemoglobin; CVD = cardiovascular disease; DM = diabetes mellitus; MI = myocardial infarction

Still a long way to go

A1C = glycated hemoglobin; BP = blood pressure; LDL/LDL-C = low density lipoprotein cholesterol

Casagrande SS, Fradkin JE, Saydah SH, Rust KF, Cowie CC. Diabetes Care 2013;36:2271-2279
### ABCs of CVD Risk Management (1)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-platelets/anticoagulants</td>
<td>Treat all high-risk patients with one of these</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>Optimize BP especially if CVD, type 2 diabetes, or low EF present</td>
</tr>
<tr>
<td>Anti-anginals</td>
<td>Relieve anginal symptoms, allow patient to exercise</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
</tr>
<tr>
<td>BP control</td>
<td>Aim for BP &lt;130/85 mm Hg, or &lt;130/80 mm Hg for type 2 diabetes</td>
</tr>
<tr>
<td>b-blockers</td>
<td>Post MI or low EF</td>
</tr>
</tbody>
</table>

CVD=cardiovascular disease; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; BP=blood pressure; EF=ejection fraction; MI=myocardial infarction

# ABCs of CVD Risk Management (2)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Cholesterol management</td>
<td>➢ LDL-C targets, NCEP ATP III guidelines</td>
</tr>
<tr>
<td></td>
<td>➢ CHD, CHD risk equivalents: &lt;100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>➢ &gt;2 RF: &lt;130 mg/dL</td>
</tr>
<tr>
<td></td>
<td>➢ 0-1 RF: &lt;160 mg/dL</td>
</tr>
<tr>
<td></td>
<td>➢ HDL-C: &gt;40 mg/dL (men)</td>
</tr>
<tr>
<td></td>
<td>➢ &gt;50 mg/dL (women)</td>
</tr>
<tr>
<td>➢ Cigarette-smoking cessation</td>
<td>➢ TG: &lt;150 mg/dL</td>
</tr>
<tr>
<td></td>
<td>➢ Long-term smoking cessation</td>
</tr>
</tbody>
</table>

LDL-C = low density lipoprotein cholesterol; CHD = coronary heart disease; HDL-C = high density lipoprotein cholesterol; RF = risk factor; TG = triglycerides

## ABCs of CVD Risk Management (3)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D</strong></td>
<td></td>
</tr>
<tr>
<td>Dietary/weight counseling</td>
<td>➢ Achieve optimal BMI</td>
</tr>
<tr>
<td>Diabetes management</td>
<td>➢ ↓ saturated fats; ↑ fruits, vegetables, fiber</td>
</tr>
<tr>
<td></td>
<td>➢ Achieve A1C &lt;7%</td>
</tr>
<tr>
<td><strong>E</strong></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>➢ Improve physical fitness (aim for 30 min/days on most days of week)</td>
</tr>
<tr>
<td>Education of patients and families</td>
<td>➢ Optimize awareness of CAD risk factors</td>
</tr>
</tbody>
</table>

BMI=body mass index; A1C=glycated hemoglobin; CAD=coronary artery 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>Blood glucose control</td>
<td>▪ Myocardial infarction</td>
<td>↓ 16%¹</td>
</tr>
<tr>
<td></td>
<td>▪ Cardiovascular disease</td>
<td>↓ 51%²</td>
</tr>
<tr>
<td></td>
<td>▪ Heart failure</td>
<td>↓ 56%³</td>
</tr>
<tr>
<td></td>
<td>▪ Stroke</td>
<td>↓ 44%³</td>
</tr>
<tr>
<td></td>
<td>▪ Diabetes-related deaths</td>
<td>↓ 32%³</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>▪ Coronary heart disease mortality</td>
<td>↓ 35%⁴</td>
</tr>
<tr>
<td></td>
<td>▪ Major coronary heart disease event</td>
<td>↓ 55%⁵</td>
</tr>
<tr>
<td></td>
<td>▪ Any atherosclerotic event</td>
<td>↓ 37%⁵</td>
</tr>
<tr>
<td></td>
<td>▪ Cerebrovascular disease event</td>
<td>↓ 53%⁴</td>
</tr>
</tbody>
</table>

Two-Track Approach to Reduce Risk

**Track 1**
Lower glucose to prevent microvascular complications and progression to diabetes

- Lifestyle intervention
- Pharmacotherapy in high risk patients

**Track 2**
Address cardiovascular disease risk factors

- Lifestyle intervention
- Blood pressure goals: <130/80 mm Hg
- LDL goal: <100 mg/dL
Effect of Intensive BP Lowering on Risk of Micro- and Macrovascular Complications: UKPDS

Benefits of 144/82 mm/HG vs 154/87 mm/HG

HDL’s Complexity: Anti-Atherogenic Actions

- Reverse Cholesterol Transport
  - Cellular Cholesterol Efflux
- Anti-infectious
- Anti-inflammatorv
- Anti-oxidative
- Anti-apoptotic
- Vasodilatory
- Endothelial Repair

HDL-C
Apo A-I / II

ADA Recommendations for Aspirin Therapy in Diabetes

• Aspirin 75-162 mg/day recommended as
  – Secondary prevention in patients with diabetes and history of CVD
  – Primary prevention for patients with diabetes and 10-year CVD risk >10%
    • Do not use for primary prevention in patients with lower CVD risk because potential adverse effects (eg, bleeding) are likely to offset potential benefits

• Use clopidogrel 75 mg/day for those with CVD and documented aspirin allergy

• Combination therapy with aspirin and clopidigrel is reasonable for ≤1 year after ACS
Intensive Glycemic Control and Long-term Macrovascular Risk in Younger Patients With Shorter Duration of Disease

DCCT
T1DM, 5-6 years duration
(N=1441)

UKPDS
T2DM, newly diagnosed
(N=4209)

CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.

Epidemiologic Relationships Between A1C and All-cause Mortality in the ACCORD Trial

Does A1C achieved predict a risk for all-cause mortality?

Adjusted (Model 3) Relationships


## Glucose Control and CHD Events

<table>
<thead>
<tr>
<th>Study</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>UKPDS(^4,7)</td>
<td>3071/1549 426/259</td>
<td>8.6%</td>
<td>0.75 (0.54-1.04)</td>
<td></td>
</tr>
<tr>
<td>PROactive(^18-20)</td>
<td>2605/2633 164/202</td>
<td>20.2%</td>
<td>0.81 (0.65-1.00)</td>
<td></td>
</tr>
<tr>
<td>ADVANCE(^5)</td>
<td>5571/5569 310/337</td>
<td>36.5%</td>
<td>0.92 (0.78-1.07)</td>
<td></td>
</tr>
<tr>
<td>VADT(^21,22)</td>
<td>892/899 77/90</td>
<td>9.0%</td>
<td>0.85 (0.62-1.17)</td>
<td></td>
</tr>
<tr>
<td>ACCORD(^8)</td>
<td>5128/5123 205/248</td>
<td>25.7%</td>
<td>0.82 (0.68-0.99)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773 1182/1136</td>
<td>100%</td>
<td>0.85 (0.77-0.93)</td>
<td></td>
</tr>
</tbody>
</table>

- Intensive treatment better
- Standard treatment better
DYSLIPIDEMIA

THERAPEUTIC LIFESTYLE CHANGES
(See Obesity Algorithm)

If not at desirable levels:
Intensify TLC (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:
Intensify statin, add ezetimibe &/or colesevelam &/or niacin
Intensify statin &/or add OM3EE &/or fibrates &/or niacin
Intensify statin &/or ezetimibe &/or colesevelam &/or niacin

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up
**Benefits of Aggressive LDL-C Lowering in Diabetes (and Residual Risk)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Event Rate, %</th>
<th>Aggressive Lipid-lowering</th>
<th>Aggressive Lipid-lowering</th>
<th>Difference in LDL-C, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td><strong>TNT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, CHD</td>
<td>13.8</td>
<td>17.9</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td><strong>ASCOT-LLA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, HTN</td>
<td>9.2</td>
<td>11.9</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td><strong>CARDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, no CVD</td>
<td>5.8</td>
<td>9.0</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td><strong>HPS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All diabetes</td>
<td>9.4</td>
<td>12.6</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Diabetes, no CVD</td>
<td>9.3</td>
<td>13.5</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

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

• Major CV risk factors and CVD outcomes
• Therapeutic modalities available to clinicians to improve CV risk factors
• Implications of recent large trials on clinical decisions guiding choice and targets for blood pressure and lipid abnormalities
• Additional co-morbid/microvascular conditions seen in patients with T2DM
• Role of pharmacologic intervention in the treatment of type 2 diabetes