Atherosclerotic Cardiovascular Disease (ASVD) in patients with Diabetes

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Macrovascular Complications

Atherosclerotic cardiovascular Disease (ASVD)

Heart
- Coronary artery disease
  - Coronary syndrome
  - Angina
  - MI
  - CHF

Brain
- Cerebrovascular disease
  - TIA
  - Stokes

Extremities
- Peripheral vascular disease
  - Ulceration
  - Gangrene
  - Amputation
Natural History of Type 2 Diabetes

- Years from diagnosis: -10, -5, 0, 5, 10, 15
- Onset
- Diagnosis

Insulin resistance
Insulin secretion
Postprandial glucose
Fasting glucose

Macrovascular complications
Type 2 diabetes
Pre-diabetes


Atherosclerosis Timeline

- Foam cells
- Fatty streak
- Intermediate lesion
- Atheroma
- Fibrous plaque
- Complicated lesion / rupture

- From first decade
  - Growth mainly by lipid accumulation
- From third decade
  - Smooth muscle and collagen
- From fourth decade
  - Thrombosis, hematoma
High Risk of Cardiovascular Events in Type 2 Diabetes

Haffner, NEJM 1998, 229-234
Incidence of Type 2 Diabetes-Related Vascular Disease in Four Ethnic Groups

- Myocardial infarction
- Stroke
- Congestive heart failure

Diabetes and atherosclerosis

- Diabetes ↑ incidence and accelerates course of atherosclerosis
- 2–4× ↑ risk of CAD and stroke
- 2–4× ↑ rate of CHD mortality
- 65% of diabetic mortality is related to atherosclerosis
  - 40% caused by ischemic heart disease
  - 15% caused by other heart disease
  - 10% caused by stroke

Mortality in People with Diabetes

Causes of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>% of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>40</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>15</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
</tr>
<tr>
<td>Cancer</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
</tbody>
</table>


Diabetes and Heart Failure: Current Knowledge

- Numerous trials (e.g., SOLVD, HOPE, and CHS) have identified diabetes as a major risk factor for development of heart failure.
- Diabetes can cause overt heart failure, independent of atherosclerosis or hypertension, via the development of a diabetic cardiomyopathy.
- There is indirect evidence that diabetes frequently causes abnormal heart function, even in the absence of other risk factors.
- Multiple mechanisms have been implicated in the causation of heart failure.

Glycemic Control and Risk of Development of HF in Diabetes


Heart Failure Is More Common in Patients With Type 2 Diabetes

Trends in Attributable CVD Risk in the ARIC Study

- Assessed proportion of CVD risk attributable to traditional risk factors among subjects in the ARIC study
- N=13,541 subjects from ARIC analyzed
  - No known CVD (CHD, heart failure, previous cerebrovascular event)
  - Aged 52-66 years
  - 26% black, 56% women
- Presence of population attributable traditional CVD risk factors assessed at each visit
  - Obesity (BMI ≥30 kg/m²)
  - Hypertension (BP ≥140/90 mm Hg or on antihypertensive medication)
  - Hypercholesterolemia (TC ≥200 mg/dL or on cholesterol-lowering medication)
  - Diabetes (fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or diabetes diagnosis)
  - Smoking status (active smoking within 1 year before exam)
- Subjects assessed for 10-year CVD incidence

ARIC=Atherosclerosis Risk in Communities
BMI=body mass index
BP=blood pressure
CHD=coronary heart disease

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Trends in Attributable CVD Risk in the ARIC Study: Event Rates

- 10-year crude CVD event rate: 1.51 (95% CI, 1.43-1.60)
  - per 100 person-years at first exam (1987-1989)
  - Similar rates seen at subsequent exams

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Crude 10-year event rates (per 100-person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Overall Trends in Attributable CVD Risk Factors in the ARIC Study

- **Hypertension**
  - Largest and most consistent contributor to CVD risk over time
  - No significant differences in risk in visits over time (PAR 0.25 vs 0.25; \( P=0.82 \))

- **Hypercholesterolemia**
  - Major contributor to risk at visit 1; contribution decreased by visit 4
    (PAR 0.18 vs 0.09; \( P=0.08 \))

- **Smoking**
  - Risk did not significantly decrease over time (PAR 0.15 vs 0.13; \( P=0.16 \))
    despite decreased prevalence of smoking

- **Diabetes**
  - Similar risk over time (PAR 0.15 vs 0.17; \( P=0.17 \))

- **Obesity**
  - Similar risk over time (PAR 0.06 vs 0.06; \( P=0.83 \))

\( P \) values are for comparisons between exam 1 and exam 4

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CVD death and number of risk factors

Age-adjusted CVD death rate and number of risk factors (cholesterol, blood pressure, smoking)

- **Death rate per 10,000 person years**
  - **Number of risk factors**: none, one, two, three
  - **Risk factors**: normal, diabetes

MRFIT, Diabetes Care 1993:2:434
Diabetes Is a CV Risk Factor in Framingham Study and Joslin Patients

Risk Factors for Macrovascular Disease

- Not modifiable
  - Genetic factors
  - Family history
- Modifiable
  - Hyperglycemia
  - Hypertension
  - Dyslipidemia
  - Smoking
  - Obesity
  - Physical inactivity
Diabetes and Hyperglycemia Are Associated With Worse CV Outcomes

A Continuum of Glycemia and CV Risk? Evidence for No Glycemic Threshold

- No A1C threshold is apparent
  - Finnish study by Kuusisto et al
  - UKPDS epidemiologic analysis
  - EPIC-Norfolk Study

- Impaired glucose tolerance (IGT) and postprandial hyperglycemia are CV risk factors
  - Funagata Diabetes Study
  - Honolulu Heart Program
  - DECODE Study
  - Rancho Bernardo Study
A1C Predicts CV Risk in Type 2 Diabetes
Kuusisto et al

229 Finnish Patients Followed for 3.5 Years

Incidence (%) over 3.5 years

CHD mortality

All CHD events

A1C tertile

CHD = coronary heart disease
*
P < 0.01 vs lowest tertile;
†P < 0.05 vs lowest tertile


Increased CV Mortality With IGT
Funagata Diabetes Study

2651 Patients Followed for 7 Years

Relative risk

Normal  IGT  Diabetes

1.0  3.0*  4.7*

*P<0.05 vs normal glucose tolerance

Tominaga M et al. Diabetes Care, 1999;22:920-924
Both FPG and 2-h PG Predict Mortality in Persons Not Known to Have Diabetes

DECODE Study


FPG categories
All subjects, n=25,000

2-h PG categories
Subjects with FPG <110, n=20,500

Adjusted hazard ratios

FPG (mg/dL)

<110 110–125 126–139 >140

1.0 1.2 1.7 1.9

2-h PG (mg/dL)

<140 140–200 >200

1.0 1.6 2.0

FPG=fasting plasma glucose

DM and Hypertension
**Antihypertensive treatment**

UK Prospective Diabetes Study (1998)

Intensive blood pressure control policy maintained a lower blood pressure by mean 10/5 mmHg over a median follow-up of 8.4 years in type 2 diabetic patients with relative risk reduction of:

<table>
<thead>
<tr>
<th>Event</th>
<th>RR</th>
<th>p</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>21%</td>
<td>0.005</td>
<td>9</td>
</tr>
<tr>
<td>Diabetes-related deaths</td>
<td>32%</td>
<td>0.02</td>
<td>17</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20%</td>
<td>0.13</td>
<td>23</td>
</tr>
<tr>
<td>Stroke</td>
<td>44%</td>
<td>0.013</td>
<td>12</td>
</tr>
<tr>
<td>Microvascular endpoints</td>
<td>37%</td>
<td>0.01</td>
<td>18</td>
</tr>
</tbody>
</table>

**UKPDS Results: Tight BP Control**

Risk Reduction*

*Compared with less tight control. Captopril and atenolol were equally effective in maintaining tight control of blood pressure in the UKPDS.*

*RR = relative risk; p = p-value; NNT = number needed to treat.*
**Major Outcomes of the Hypertension Optimal Treatment (HOT) Trial: Diabetes Subgroup**

![Graph showing events per 1000 Pt-Years for Major CV Events, MI, and CV Mortality with different diastolic targets and p-values.](image1)


**Heart Outcomes Prevention Evaluation (HOPE) Study**

*Effect of Ramipril on Cardiovascular Events (Myocardial Infarction, Stroke, or CVD Death) ~ 4.5 Yrs*

![Graph showing risk reduction in cardiovascular events with Ramipril compared to Placebo for Diabetic and Nondiabetic patients.](image2)

Diabetic Patients:
- Placebo: 19.8%
- Ramipril: 15.0%
- Risk Reduction: 24%

Nondiabetic Patients:
- Placebo: 16.4%
- Ramipril: 13.0%
- Risk Reduction: 21%

N=3,578, P=<0.001
N=5,719, P=<0.001
MICRO-HOPE: Ramipril Significantly Reduces Cardiovascular Morbidity

Ramipril Effects Beyond Baseline Therapy

- Aspirin
- Other Antiplatelet Agents
- Lipid-Lowering Agents
- Diuretics
- Beta-Blockers
- Calcium-Channel Blockers

Risk Reduction (%)

- Stroke
- Nonfatal MI
- CV Death
- Total Mortality

-35 -30 -25 -20 -15 -10 -5 0

33% * 22% † 37% ‡ 24% §

*P = 0.0074
†P = 0.01
‡P = 0.0001
§P = 0.0004

ONTARGET: Similar CV Outcomes with Ramipril, Telmisartan, and Their Combination

Primary composite outcome:
Death from CV causes, MI, stroke, hospitalization for HF

Risk ratio, 0.99 (95% CI, 0.92-1.07)

Risk ratio, 1.01 (95% CI, 0.94-1.09)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary outcome incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril 10 mg daily (n=8576)</td>
<td>16.5% (n=1412)</td>
</tr>
<tr>
<td>Telmisartan 80 mg daily (n=8542)</td>
<td>16.7% (n=1423)</td>
</tr>
<tr>
<td>Combination therapy (n=8502)</td>
<td>16.3% (n=1386)</td>
</tr>
</tbody>
</table>
ONTARGET: Significantly Increased Risk of Renal Impairment with Combination Therapy

Relative risk, 1.33 (95% CI, 1.22-1.44); P<0.001

Relative risk, 1.04 (95% CI, 0.96-1.14)

- Ramipril 10 mg daily (n=8576)
- Telmisartan 80 mg daily (n=8542)
- Combination therapy (n=8502)

10.2% (n=871)
10.6% (n=906)
13.5% (n=1148)

ONTARGET=The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

ONTARGET: Significantly Increased Potassium Level with Combination Therapy

P<0.001 for comparison

- Ramipril 10 mg daily (n=8576)
- Telmisartan 80 mg daily (n=8542)
- Combination therapy (n=8502)

n=283
n=287
n=480

Data shown for patients with increase in potassium level ≥ 5 mmol/L
ONTARGET=The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
Effects of Intensive Blood Pressure Control on Cardiovascular Events in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

William C. Cushman, MD, FACP, FAHA
Veterans Affairs Medical Center, Memphis, TN

For The ACCORD Study Group
Average: 133.5 Standard vs. 119.3 Intensive, Delta = 14.2

### ACCORD BP

**Trial design:** Half of the diabetic patients within the main ACCORD trial were randomized to a goal systolic blood pressure (BP) <120 mm Hg (n = 2,362) vs. <140 mm Hg (n = 2,371).

**Results**
- Mean systolic BP at 1 year was 119 mm Hg in the intensive group vs. 134 mm Hg in the standard group.
- Mean number of antihypertensives was 3.4 vs. 2.1, respectively.
- Annual rate of cardiovascular mortality, myocardial infarction, or stroke was 1.9% vs. 2.1% (p = 0.20).
- Serious adverse events were 3.3% vs. 1.3% (p < 0.001).

**Conclusions**
- Among patients with type 2 diabetes at high risk for cardiovascular events, a goal systolic BP <120 mm Hg was not superior to a goal <140 mm Hg.

Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive Events (%/yr)</th>
<th>Standard Events (%/yr)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>208 (1.87)</td>
<td>237 (2.09)</td>
<td>0.89 (0.73-1.07)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Total Mortality</strong></td>
<td>150 (1.28)</td>
<td>144 (1.19)</td>
<td>1.07 (0.85-1.35)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Cardiovascular Deaths</strong></td>
<td>60 (0.52)</td>
<td>58 (0.49)</td>
<td>1.06 (0.74-1.52)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Nonfatal MI</strong></td>
<td>126 (1.13)</td>
<td>146 (1.28)</td>
<td>0.87 (0.68-1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Nonfatal Stroke</strong></td>
<td>34 (0.30)</td>
<td>55 (0.47)</td>
<td>0.63 (0.41-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Total Stroke</strong></td>
<td>36 (0.32)</td>
<td>62 (0.53)</td>
<td>0.59 (0.39-0.89)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)

Conclusions

- The ACCORD BP Trial results provide no conclusive evidence that a strategy targeting normal SBP, compared with a standard SBP goal, reduces a composite of major CVD events in high-risk patients with type 2 diabetes, in the setting of good glycemic control.
  - There was a higher risk of SAE in the intensive BP group, but also a 41% lower stroke rate.
  - The stroke effect is consistent with other BP treatment trials.
  - SBP goal <120 mm Hg may reduce strokes in patients with diabetes like those in ACCORD.
Aggressive Blood Pressure Control Increases Coronary Heart Disease Risk Among Diabetic Patients
Diabetes Care 2013 published online May 20, 2013

• LSU Healthcare Services reports the results of a prospective cohort study (2000–2009) on diabetic patients including 17,536 African American and 12,618 white. Cox proportional hazards regression models were used to estimate the association of blood pressure with CHD risk.
• During a mean follow-up of 6.0 years, 7,260 CHD incident cases were identified

CONCLUSIONS:
• “Our study suggests that there is a U-shaped or inverse association between blood pressure and the risk of CHD, and aggressive blood pressure control (blood pressure <120/70 mmHg) is associated with an increased risk of CHD among both African American and white patients with diabetes.”
Aggressive Blood Pressure Control Increases Coronary Heart Disease Risk Among Diabetic Patients
Diabetes Care 2013 published online May 20, 2013

• “For the elder group, the harm is even higher. Since there is currently no robust evidence available for lowering the blood pressure <130/80 mmHg in people with diabetes, it might be advisable to maintain blood pressure between 130–139 and 80–89 mmHg and to recommend less intense goals to elderly patients than to younger ones.”

Stroke
Stroke in a diabetic Patient

- Leading Cause of disability and second most frequent cause of death
- Diabetic patients 1.5-3 times higher risk of stroke sp cerebral infarction as compared to non diabetic (Lacunar, cardioembolic and large vessel stroke)
- Excess risk more pronounced in younger patients and women
- Poorer motor and functional outcomes, higher risk of dementia, recurrent stroke and death

A Public Health Crisis:
Stroke Prevalence is on the Rise


NHLBI Morbidity and Mortality: 1998 Chartbook on Cardiovascular, Lung and Blood Diseases
Modifiable Risk Factors, Population Attributable Risk, and Projected Number of Strokes Prevented

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Exposed</th>
<th>Relative Risk</th>
<th>Population Attributable Risk</th>
<th>Projected Strokes Prevented*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>56%</td>
<td>2.7</td>
<td>49%</td>
<td>360,000</td>
</tr>
<tr>
<td>Smoking</td>
<td>27%</td>
<td>1.5</td>
<td>12%</td>
<td>90,000</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>4%</td>
<td>3.6</td>
<td>9.4%</td>
<td>69,000</td>
</tr>
<tr>
<td>Heavy Alcohol Consumption</td>
<td>75</td>
<td>1.7</td>
<td>4.7%</td>
<td>34,000</td>
</tr>
</tbody>
</table>

*Based on 731,000 strokes
Gorelick PB. Stroke 1994; 25: 220-224

Epidemiological Link Between Blood Pressure and Incidence of Primary Stroke

Result from 7 prospective observational studies (843 strokes)
Stroke and usual diastolic blood pressure (in 5 categories defined by baseline DBP)

Relative risk of stroke by approximate mean usual DBP in over 400,000 individuals without a history of acute myocardial infarction or stroke; 10 yr follow up
MacMahon S et al. Lancet 1990; 335: 765-774
SPARCL: Primary Outcome of Fatal or Nonfatal Stroke

HR, 0.84 (95% CI, 0.71-0.99); P=0.03


SPARCL: First Events

Ischemic Stroke
Hemorrhagic Stroke
Major Coronary Event
Unclassified Stroke

Proteinuria Predicts Stroke and CHD Events in Type 2 Diabetes

![Graph showing survival curves and incidence of CV mortality and stroke/CHD across different proteinuria categories.]

Miettinen et al. Stroke 1996; 27: 2033-2039

Atherosclerotic Peripheral Arterial Disease
Peripheral Arterial Disease: Limb Ischemia

- Claudication
- Rest pain
- Ischemic Ulcers
- Gangrene
### Clinical features to Distinguish Neuropathy and Vascular Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Neuropathy</th>
<th>Vascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of pain</td>
<td>Feet &gt; calves</td>
<td>Calves, thigh, buttocks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; feet</td>
</tr>
<tr>
<td>Quality of pain</td>
<td>Sharp/ Superficial / burning /tingling</td>
<td>Deep ache</td>
</tr>
<tr>
<td>Present at rest</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Effect of walking</td>
<td>Pain improves</td>
<td>Pain worse</td>
</tr>
<tr>
<td>Pain worse in bed</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>Preceded by recent</td>
<td>Sometimes</td>
<td>NO</td>
</tr>
<tr>
<td>BS change</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Peripheral Arterial Disease

**Laboratory Diagnostic Procedure**
- Ankle Brachial Index
- Arterial Pulse Wave Form
- Arterial Oximeter
- Doppler and Ultrasonography
- MRA (Magnetic Resonance Arteriography)
- Aortography and Arteriography
Arterial Doppler Technique

Peripheral arterial analog waveforms:
- Normal
- Progressive disease
- Early disease
- Severe disease

Arterial Doppler Technique

- Dorsal artery of the foot
- Proximal and distal thigh
- Posterior tibial artery
- Popliteal artery
- Proximal and distal calf
- Posterior tibial artery
- Dorsal artery of the foot
- Toe arteries
Segmental Pressure gradient and Ankle Brachial Index (ABI) used as non-invasive test

High compression pressure may indicate medial sclerosis or calcified blood vessels of the extremities
Interventional Trials of Glucose: Effect on CVD

DCCT: Intensive Therapy Significantly Reduces and Maintains HbA$_{1c}$

Predefined CVD outcome = nonfatal MI or stroke; death judged to be due to CVD; subclinical MI; angina, confirmed by ischemic changes on exercise tolerance testing or by clinically significant obstruction on coronary angiography; or the need for revascularization with angioplasty or coronary artery bypass.


Prevalence of Cardiovascular Risk Factors in Diabetic Subjects Relative to Nondiabetics

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Low HDL</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Small, dense LDL</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Increased apo B</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Hyperinsulinemia/insulin resistance</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Central obesity</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Family history of atherosclerosis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = moderately increased compared with nondiabetic population
++ = markedly increased compared with nondiabetic population
- = not different compared with nondiabetic population

**UKPDS**

*Risk Reduction for Key Endpoints with Intensive Therapy*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>% Risk Reduction</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Diabetes-Related Endpoint</td>
<td>12</td>
<td>0.029</td>
</tr>
<tr>
<td>Death Related to Diabetes</td>
<td>10</td>
<td>0.34</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>6</td>
<td>0.44</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>16</td>
<td>0.052</td>
</tr>
<tr>
<td>Microvascular Disease</td>
<td>25</td>
<td>0.0099</td>
</tr>
</tbody>
</table>

**UKPDS = United Kingdom Prospective Diabetes Study.**


Effect of intensified glycemic control on the risk for any type of macrovascular event in patients with type 1 and type 2 DM.
Effect of intensified glycemic control on the risk for any type of macrovascular event and of cardiac, peripheral vascular, and cerebrovascular events in patients with type 1 and type 2 DM.

Megatrials in Type 2 Diabetes: From excitement to frustration?

An Evolving Perspective
Glycemia management and CVD risk in Type 2 Diabetes

- **ACCORD**
  - The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group
  - June 2008 NIH- National Heart Lung and Blood institute halted the intensive glucose treatment arm

- **ADVANCE**
  - The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Collaborative Group
  - June 2008

- **VADT**
  - Veterans Affair Diabetes Trial (VADT)
  - Jan 2009

Each of these trials tested the “Glycemia hypothesis”

- Strategy to reduce glycemia to normal or near normal levels among patients with established type2 DM (about 8-10 yrs duration )
  - Additional risk factors for CVD
  - Documented CVD

- Compared with strategy that uses a more “Standard” approach to management of glycemia, to lowering of CVD events and mortality
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>ADVANCE</td>
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<tr>
<td>VADT</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>


Intensive A1c control

<table>
<thead>
<tr>
<th>Major Trials of Intensive Glycemic Control and CVD Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACCORD</strong></td>
</tr>
<tr>
<td># subjects</td>
</tr>
<tr>
<td>10,281</td>
</tr>
<tr>
<td>11,140</td>
</tr>
<tr>
<td>1,791</td>
</tr>
<tr>
<td>Primary outcome</td>
</tr>
<tr>
<td>HR for primary outcome (95% CI)</td>
</tr>
<tr>
<td>HR for mortality (95% CI)</td>
</tr>
<tr>
<td>Comments</td>
</tr>
</tbody>
</table>
Type 2 Diabetes Therapy and Cardiovascular Events: Comparing VADT With Other Trials

The ACCORD Trial:
Mean A1C Levels at Each Study Visit

Within 4 months after randomization the A1C decreased to 6.4% in the intensive therapy group and to 7.5% in the standard therapy group.

ACCORD=Action to Control Cardiovascular Risk in Diabetes.
ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation.
VADT=Veterans Affairs Diabetes Trial.
*Due to increased mortality in the intensive-therapy group.

In all studies, no decrease in cardiovascular events was observed.

**ACCORD Glucose Arm**

**Trial design:** Type 2 diabetic patients were randomized to intensive therapy (glycated hemoglobin <6%, n = 5,128) versus standard therapy (glycated hemoglobin 7%-7.9%, n = 5,123). Patients were followed for 3.5 years.

**Results**

- CV death, MI, or stroke: 6.9% vs. 7.2% (p = 0.16), respectively
- All-cause mortality: 5.0% vs. 4.0% (p = 0.04), respectively
- CV mortality: 2.6% vs. 1.8% (p = 0.02), respectively

**Conclusions**

- Intensive glucose lowering (mean glycated hemoglobin 6.4%) increased all-cause and CV mortality among type 2 diabetics
- National Heart, Lung, and Blood Institute stopped the trial 17 months early
- Other studies testing intensive glycemic control are ongoing

**Data**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy n=5128</th>
<th>Standard Therapy n=5123</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>257 (5.0)</td>
<td>203 (4.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td>135 (2.6)</td>
<td>94 (1.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>186 (3.6)</td>
<td>235 (4.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>67 (1.3)</td>
<td>61 (1.2)</td>
<td>0.74</td>
</tr>
<tr>
<td>Fatal or nonfatal congestive heart failure</td>
<td>152 (3.0)</td>
<td>124 (2.4)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Data are n (%).

The ACCORD Trial: Summary

- Compared with standard therapy, use of intensive therapy to target normal A1C levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events.
- A higher mortality rate in the intensive-therapy group led to discontinuation of intensive therapy after a mean of 3.5 years of follow-up.
- If there is any benefit associated with intensive glucose lowering, it may take several years to emerge, during which time there is an increased risk of death.

The ADVANCE Trial: Conclusions

- Intensive glucose control lowered A1C value to 6.5% and yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events
- The 10% reduction was primarily a consequence of a 21% relative reduction in nephropathy
- Overall, there was no significant effect of intensive glucose control on the risk of major macrovascular events
- Intensive glucose control was associated with an increased risk of severe hypoglycemia and increased rate of hospitalization
- The main benefit of the intensive treatment regimen was a 1/5th reduction in renal complications

VA Diabetes Trial (VADT)

VADT: Comparing Intensive With Standard Glucose Therapy, Primary Outcome

First Occurrence of a Major Cardiovascular Event*

<table>
<thead>
<tr>
<th>Years</th>
<th>Intensive therapy</th>
<th>Standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.86</td>
<td>0.94</td>
</tr>
<tr>
<td>4</td>
<td>0.74</td>
<td>0.84</td>
</tr>
<tr>
<td>6</td>
<td>0.64</td>
<td>0.74</td>
</tr>
<tr>
<td>8</td>
<td>0.56</td>
<td>0.68</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th>Years</th>
<th>Standard therapy</th>
<th>Intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>899</td>
<td>862</td>
</tr>
<tr>
<td>2</td>
<td>770</td>
<td>774</td>
</tr>
<tr>
<td>4</td>
<td>693</td>
<td>707</td>
</tr>
<tr>
<td>6</td>
<td>637</td>
<td>639</td>
</tr>
<tr>
<td>8</td>
<td>570</td>
<td>610</td>
</tr>
</tbody>
</table>

VADT=Veterans Affairs Diabetes Trial.

*Myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, amputation for ischemic gangrene.

HR= hazard ratio.
CI= confidence interval.

VADT: Comparing Intensive With Standard Glucose Therapy, Secondary Outcomes

Secondary Cardiovascular Outcomes
- New or worsening angina
- New transient ischemic attacks
- New intermittent claudication
- New critical limb ischemia
- Death from any cause

Secondary Microvascular Complications
- Ophthalmologic disorders
  - Cataract surgery
  - Photocoagulation
  - Vitrectomy
  - Retinopathy
- Nephropathy
- Neuropathy

No significant differences were observed between the intensive- and standard-treatment groups for any individual secondary-outcome component.


Insulin Resistance — Hidden Dangers

Type 2 Diabetes
- Hyperinsulinemia
- IGT
- Dyslipidemia
- Hypertension
- Coagulation abnormality

IGT = impaired glucose tolerance
Steno-2: Effect of Multifactorial Intervention on CV Events in Type 2 Diabetes

No. at Risk
Intensive therapy 80 72 65 61 56 50 47 31
Conventional therapy 80 70 60 46 38 29 25 14


Steno-2: Effect of Multifactorial Intervention on Various CV Events in Type 2 Diabetes

No. of CV Events
Intensive therapy Conventional therapy

Death From CV Causes
Stroke
Myocardial Infarction
CABG
PCI
Revascularization
Amputation

Glycemic Control and clinical outcomes

- Proven efficacy for microvascular complications
- Uncertain effects on Cardiovascular outcomes
Recommendations in Type 2 DM

- UKPDS – Newly diagnosed patients with type 2 DM with no prior CVD
  - Reasonable to try to achieve HbA1C ≤ 6.5%
  - May have CV benefits decades later.
- Results of ACCORD, ADVANCE and VADT
  - In older patients with established DM, specifically in presence of macrovascular disease goals need to be individualized.
- While tight BS may lessen microvascular complications, it may increase risk of hypoglycemia and possibly adverse CV events.

Recommendations

- In these patients a prudent Hba1C goal could be ≥ 7%.
- However, a HbA1C of <7% seems reasonable if it can be achieved without the risk of hypoglycemia.
- Smoking cessation, moderate exercise, proper diet, aspirin, lipid lowering agents, BP control should be stressed.
Prevention & Treatment For Macrovascular Complications
“ABCs for Providers and Patients,"

- A: A1c, Aspirin, and Antiplatelet Therapy
- B: Blood Pressure Control
- C: Cholesterol Management
  - Cigarette Smoking Cessation
- D: Diabetes & Pre-Diabetes Lifestyle Management
- E: Exercise
- F: Food Choices
**ADA Guidelines: Glycemic, Blood Pressure, and Lipid Control**

<table>
<thead>
<tr>
<th>A1C</th>
<th>&lt;7.0%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>&lt;140/&lt;80 mm Hg†</td>
</tr>
</tbody>
</table>
| Lipids       | LDL-C: <100 mg/dL (<2.6 mmol/L)‡  
                Statin therapy for patients with MI history or aged >40 years with other risk factors |

*More or less stringent glycemic goals may be appropriate for individual patients. Individualize goals based on diabetes duration, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

†Lower systolic blood pressure goals may be appropriate based on individual patient characteristics and therapeutic response.

‡A lower LDL-C goal of <70 mg/dL, using a high dose of a statin, may be appropriate in persons with overt CVD.

CVD=cardiovascular disease; MI=myocardial infarction

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**“ABCs for Providers and Patients,”**

- A: A1c, Aspirin, and Anti-platelet Therapy
- B: Blood Pressure Control
- C: Cholesterol Management
  - Cigarette Smoking Cessation
- D: Diabetes & Pre-Diabetes Lifestyle Management
- E: Exercise
- F: Food Choices
Recommendations: Antiplatelet Agents (1)

- Consider aspirin therapy (75–162 mg/day) (C)
  - As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%)
  - Includes most men and women >50 years of age who have at least one additional major risk factor
    - Family history of CVD
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria

Recommendations: Antiplatelet Agents (2)

- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk, since potential adverse effects from bleeding likely offset potential benefits (C)
  - 10-year CVD risk <5%: <50 years and with no major additional CVD risk factors
  - In patients in these age groups with multiple other risk factors (10-year risk 5–10%), clinical judgment is required (E)
Recommendations: Antiplatelet Agents (3)

- Use aspirin therapy (75–162 mg/day)
  - Secondary prevention strategy in those with diabetes with a history of CVD (A)
- For patients with CVD and documented aspirin allergy
  - Clopidogrel (75 mg/day) should be used (B)
- Combination therapy with ASA (75–162 mg/day) and clopidogrel (75 mg/day)
  - Reasonable for up to a year after an acute coronary syndrome (B)


“ABCs for Providers and Patients,”

- A: A1c, Aspirin, and Anti-platelet Therapy
- B: Blood Pressure Control
- C: Cholesterol Management
- Cigarette Smoking Cessation
- D: Diabetes & Pre-Diabetes Lifestyle Management
- E: Exercise
- F: Food Choices
BP screening

- Measure BP at all routine visits; confirm elevated BP at separate visit

BP goals

- $<140$ mm Hg systolic for persons with diabetes and hypertension
  - Lower targets (such as $<130$ mm Hg) may be appropriate in certain patients if target can be achieved without treatment burden
- $<80$ mm Hg diastolic for patients with diabetes

Continued on next slide

BP treatment

- BP $\geq 120/80$ mm Hg: Lifestyle changes
- BP $\geq 140/80$ mm Hg
  - Lifestyle changes
  - Pharmacologic therapy
    - ACEI or ARB for persons with diabetes and hypertension
    - $\geq 2$ agents at maximal doses usually required to achieve targets
    - Administer $\geq 1$ agent at bedtime
    - Monitor serum creatinine/eGFR and serum potassium if using ACE inhibitor, ARB, or diuretic

Pregnant women with diabetes and hypertension

- $110–129/65–79$ mm Hg target goal
- ACEI, ARB contraindicated

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension, eGFR = estimated glomerular filtration rate
Hypertension and Diabetes
Pharmacological Treatment

• ACE inhibitors are first line drugs
  – Beneficial effects on kidney- reduce proteinuria
  – Neutral / beneficial effects on glycemic status
  – Reduce cardiovascular events
  – Have anti-atherosclerotic properties
  – Improve endothelial reactivity

• ARB have most of the beneficial effects of ACEI- but are not superior to ACEI.
• ACE plus ARB – Not recommended (OnTarget)

Hypertension and Diabetes
Pharmacological Treatment

• Diuretics- Hydrochlorothiazide (HCTZ)
  – In ALLHAT- chlorthalidone was as effective as Lisinopril and Amlodipine for BP control.
  – Chlorthalidone was better for prevention of CHF
  – Despite slightly worse glycemic status and slightly worse triglyceride status- this did not increase cardiovascular events in the study.
  – HCTZ potentiates the BP lowering effect of ACEI and ARB.
Hypertension and Diabetes
Pharmacological Treatment

• Second or Third line drugs
  – Calcium blockers (Non dihydropyridine)
  – Beta blockers (Carvedilol)

• Other drugs
  – Nitrates
  – Hydralazine
  – Clonidine
  – Alpha blockers

Treatment of Patients with Diabetes and CV Disease

• In patients with a prior MI, beta-blockers should be continued for at least 2 years after the event. B
  – Diabetes Care 2014; 37: suppl 1 pp S 42
“ABCs for Providers and Patients,“

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LDL-C is a predictor of CV mortality in Diabetics
Heart Protection Study: Statin therapy reduces major vascular events in patients with diabetes

![Graph showing major vascular events (%) over years of follow-up for Placebo and Simvastatin with 22% risk reduction and P < 0.0001.]

*Major coronary events, stroke, and revascularizations

ADA Guidelines:
Dyslipidemia and Lipid Management (1 of 2)

Lipid Screening
- Measure fasting lipids at least annually in adults with diabetes
  - Every 2 yrs for adults with low-risk lipid values (LDL-C <100 mg/dL, HDL-C >50 mg/dL, TG <150 mg/dL)

Goals

<table>
<thead>
<tr>
<th>No overt CVD</th>
<th>LDL-C &lt;100 mg/dL (2.6 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt CVD</td>
<td>LDL-C &lt;70 mg/dL (1.8 mmol/L)*</td>
</tr>
<tr>
<td>Alternative goal if goals not achieved on maximal statin therapy</td>
<td>30–40% LDL-C reduction from baseline</td>
</tr>
</tbody>
</table>

*Using high-dose statin therapy; statins contraindicated in pregnancy

Continued on next slide
Ezetimibe ADA 2016

- The addition of ezetimibe (Zetia, Merck) to moderate-intensity statin therapy in select patients with diabetes, based on the recent IMPROVE-IT trial.
  - new recommendations for obtaining a fasting lipid profile in children starting at age 10 years.
Management of lipids in Diabetes

Non-HDL Cholesterol

Calculation of Non-HDL Cholesterol

Non-HDL-C = Total Cholesterol – HDL-C
Elevated triglycerides
Secondary target

Non-HDL: Secondary Target
- Non-HDL = TC − HDL
- Non-HDL: secondary target of therapy when serum triglycerides are ≥200 mg/dL (esp. 200-499 mg/dl)
- Non-HDL goal: LDL goal + 30 mg/dL

Lipid Goals for patients with Diabetes

<table>
<thead>
<tr>
<th>Lipid</th>
<th>ADA 2010¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>&lt;70 highest risk</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Non HDL</td>
<td>&lt;130</td>
</tr>
</tbody>
</table>
# Lipid Lowering Agents

## I. LDL cholesterol lowering
- **Lifestyle interventions**
- **Preferred**
  - HMG CoA reductase inhibitor (statin)
- **Others**
  - Bile acid binding resin (resin), cholesterol absorption inhibitor, (ezetimibe), fenofibrate, or niacin

## II. HDL cholesterol raising
- **Lifestyle interventions**
  - Niacin or fibrates (AIM HIGH DID NOT SHOW BENEFIT)

## III. Triglyceride lowering
- **Lifestyle interventions**
  - Glycemic control
  - Fibrates (gemfibrozil, fenofibrate) (Statin + feno – ACCORD LIPID no benefit)
  - Niacin

## IV. Combined hyperlipidemia
- **First Choice** Improved glycemic control + high-dose statin
- **Second Choice** Improved glycemic control + statin + fibrate
- **Third Choice** Improved glycemic control + statin + niacin ?? AIM High

The combination of statins with niacin, fenofibrate, and especially gemfibrozil may carry an increase risk of myositis

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**FDA Drug Safety Communication Trilipix (fenofibric acid)**

11/9/2011 Trilipix (fenofibric acid) may not lower a patient's risk of having a heart attack or stroke.

- **RECOMMENDATION:** Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in patients in two large randomized controlled trials of patients with type 2 diabetes mellitus (FIELD and ACCORD); healthcare professionals should consider the benefits and risks of Trilipix when deciding to prescribe the drug to patients, and counsel patients about those benefits and risks.
**Recommendations: Dyslipidemia/Lipid Management**

**Treatment recommendations and goals (2)**

- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels
  - with overt CVD (A)
  - without CVD >40 years of age who have one or more other CVD risk factors (A)
- For patients at lower risk (e.g., without overt CVD, <40 years of age) (E)
  - Consider statin therapy in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dL
  - In those with multiple CVD risk factors

**Recommendations: Dyslipidemia/Lipid Management**

**Treatment recommendations and goals (5)**

- If targets are not reached on maximally tolerated doses of statins (E)
- Combination therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended. (A) (added in 2013)
- Statin therapy is contraindicated in pregnancy (B)
Hypertriglyceridemia should be addressed with dietary and lifestyle changes.

Severe hypertriglyceridemia (>1,000 mg/dL) may warrant immediate pharmacological therapy (fibric acid derivative, niacin, or fish oil) to reduce the risk of acute pancreatitis.

Diabetes Care 2014; 37: suppl 1 pp S 40

Recommendations: Dyslipidemia/Lipid Management

- A: A1c, Aspirin, and Antiplatelet Therapy
- B: Blood Pressure Control
- C: Cholesterol Management
  - Cigarette Smoking Cessation
- D: Diabetes & Pre-Diabetes Lifestyle Management
- E: Exercise
- F: Food Choices

“ABCs for Providers and Patients,“
Stop smoking

Physicians Need to Counsel Patients with Diabetes on Non-Glycemic Risk Factors such as Smoking Cessation
“ABCs for Providers and Patients,“

- A: A1c, Aspirin, and Anti-platelet Therapy
- B: Blood Pressure Control
- C: Cholesterol Management
  - Cigarette Smoking Cessation
- D: Diabetes & Pre-Diabetes Lifestyle Management
- E: Exercise
- F: Food Choices

**ADA: Physical Activity/Exercise Recommendations for Patients With Type 2 Diabetes**

- Patients with type 2 diabetes should be evaluated prior to initiation of any exercise program beyond brisk walking
- Exercise program (absent contraindications) should include:
  - \( \geq 150 \text{ min/week moderate-intensity (50\%-70\% max heart rate) aerobic activity, and/or} \)
  - \( \geq 90 \text{ min/week vigorous (>70\% max heart rate) aerobic activity} \)
  - resistance exercise 3 times/week targeting all major muscle groups
- Distribute physical activity over \( \geq 3 \text{ days/week} \) with no more than 2 consecutive days without physical activity

ACC/AHA guidelines

Screening diabetics before exercise program

Noninvasive functional tests (Stress Echo/ Nuclear) can detect CAD earlier and improve assessment of future CAD risk – better than exercise EKG.

Noninvasive Coronary assessment with Calcium scoring and 64 slice CT scans also have better sensitivity for detecting CAD.

However there is NO evidence that such testing in asymptomatic patients (with or without risk factors) improves outcomes or lead to better utilization of treatments.
Strategies for CVD prevention / treatment in diabetes

- Lifestyle changes
- Smoking Cessation
- Lowering of blood pressure
- Lipid lowering
- Aspirin
- Glycaemic control
- Limited salt intake