The Diabetes Link to Heart Disease

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Case #1

• 68 yo M with T2DM
• Diagnosed DM for 9 yrs
• No known microvascular complications
• Had lower extremity bypass 3 years ago
• HTN, overweight, hyperlipidemia
  – Metformin, statin, ARB, ASA
• “Feels fine” therefore does not check BG’s
• Moved from Miami to establish care
• Last A1c 11.8% “but I’ve been exercising”
• Today’s A1c =10.9%
Harpo Glycemic
Case #2

• 64 year old with HTN, screening hyperglycemia with FBG 135 mg/dl and 141 mg/dl

• Diagnosed with T2 DM within the last year.
Which of these patients would you screen for CV disease?

- A. Ozzie
- B. Harpo
- C. Both
- D. Neither
REALITY-TV
Impact of Diabetes on Cardiovascular Mortality

* Risk factors analyzed were smoking, dyslipidemia, and hypertension

Diabetes Care 12: 573-579, 1989
CV mortality in DM and non-DM

CV Mortality in Type 1 DM

**FIGURE 1.** Cumulative mortality due to coronary artery disease up to age 55 years in patients with insulin-dependent diabetes mellitus (IDDM) and in the population of the Framingham Heart Study.\textsuperscript{14,20}

Unpublished data courtesy of Adrienne Cupples, PhD.

Extent of CAD

DM  non-DM

HTN
Dyslipidemia
Obesity
Fibrinogen
PAI-1
Dyslipidemia
Endothelial dysfunction
Platelet dysfunction
Renal disease
Plaque composition
Fibrinogen
PAI-1
Hyperhomocysteinemia
Neuropathy
Microalbuminuria
Lipid quality
Coagulopathies
Hyperglycemia
SCREENING
Exercise Stress Testing for CVD


N = 1282 males
Adding Imaging to EST

Task force members *Eur Heart J.* 2013;34:2949.
CAC Screen

Task force members *Eur Heart J.* 2013;34:2949.
Is screening effective?

CVD Screening in DM

• Screening just as sensitive and specific for CVD as in non-DM population
• Imaging increases sensitivity
• Prognostic ability to predict CV event may be shorter in DM than those without DM
• Not effective in asymptomatic individuals if optimal medical therapy used
2015 AHA/ADA Guidelines CVD Screening
Asymptomatic Pts with DM

• Stress testing can be considered in asymptomatic patients at high risk for CVD (strong FHx, PAD, High CAC score) (level C)
• No benefit for CV risk assessment in asymptomatic patients at low to intermediate risk disease (C)
• Consider CAC >40 yr to assess risk (C)

Update on Prevention of Cardiovascular Disease in Adults with type 2 Diabetes Mellitus
Diabetes Care epublish Aug 2015
Trends in age-standardized rates of diabetes-related complications among U.S. adults with diabetes, 1990-2010

The Diabetic Performance Trinity

SUGAR

PRESSURE

LIPIDS
Impact of Glycemic control
on CVD
Glycemia and CVD events

• Direct correlation b/w hyperglycemia and CV events

• However intervention to reduce hyperglycemia not as closely associated with reduction in CV events
T2 DM and CV disease

• What is the impact of glycemic control on CV events?

• ACCORD, ADVANCE, VADT-3 RCTs

• UKPDS- observational data 10 yrs after original trial conclusion
## Differences: ACCORD, ADVANCE, VADT

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Duration DM</td>
<td>10</td>
<td>8</td>
<td>11.1</td>
</tr>
<tr>
<td>Hx Macrovascular dz</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Baseline A1c</td>
<td>8.1%</td>
<td>7.2%</td>
<td>9.4%</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Target A1c</td>
<td>&lt;6%</td>
<td>&lt;6.5</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>Insulin Rx (%)</td>
<td>77 v 55</td>
<td>40 vs 24</td>
<td>89 vs 74</td>
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<tr>
<td><strong>Outcome (Intensive vs Standard)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median A1c @ study end</td>
<td>6.4 vs 7.5%</td>
<td>6.4 vs 7%</td>
<td>6.9 vs 8.5%</td>
</tr>
<tr>
<td>DEATH</td>
<td>5 vs 4%*</td>
<td>8.9 vs 9.6%</td>
<td>11 vs 11%</td>
</tr>
</tbody>
</table>

*p < 0.05  Diabetes Care 32:187, 2009
ACCORD: Treatment Effects on Glucose Control

ACCORD: Treatment Effect on Primary Outcome

Non-fatal MI, Non-fatal Stroke, CVD Death

HR 0.90 (0.78–1.04)  
p=0.16

Standard therapy  2.29%/yr

Intensive therapy  2.11%/yr

MI = myocardial infarction

ACCORD: Treatment Effect on All-cause Mortality

![Graph showing the treatment effect on all-cause mortality. The graph compares standard therapy and intensive therapy over time. The Intensive therapy group has a higher hazard ratio (HR) of 1.22 (1.01–1.46) with a p-value of 0.04, compared to the Standard therapy group, which has an event rate of 1.14%/yr.](ACCORD Study Group. N Engl J Med 2008;358:2545–59)
ADVANCE: Treatment Effect on Primary Macrovascular Outcome

Non-fatal MI, Non-fatal Stroke, CVD Death

Cumulative Incidence (%) vs. Follow-up (Months)

- Standard control
- Intensive control

HR 0.94 (0.84–1.06) p=0.32

VADT: Median HbA1c +/- IQR

No. at risk
Standard therapy     899  811  812  759  760  727  727  707  760  688  667  644  472  329  225
Intensive therapy    892  801  805  763  754  729  706  692  668  661  639  489  340  223

IQR = interquartile range

VADT Primary Outcome

Non-fatal MI, Non-fatal Stroke, CVD Death, Hospitalisation for CHF, Revascularisation

Time to primary outcome

Proportion Free of Primary Outcome

Follow-up Time (Years)

HR 0.88 (0.74–1.05) p=0.14

CHF = congestive heart failure; CL = confidence limits

VADT: Non-fatal CV Events

HR 0.85 (0.70–1.02)  
p=0.0725

Follow-up Time (Years)

Proportion Free of Non-fatal Outcome

Time to Non-fatal Outcome

Intensive

Standard

CV = cardiovascular

UKPDS Intensive Rx (Insulin +SFU)

- Newly Diagnosed T2DM n=3867
- 10 year study
- High risk for MI but little documented CVD
- Microvascular disease reduced 21-34%

UKPDS- Post Treatment Study
10 year post intervention observational study
A1c During UKPDS

Conventional

Intensive therapy

Years from Randomisation

A1c (%)

UKPDS. Lancet 1998;352:837–53
A1c During UKPDS and UKPDS-PTM

**Conventional** vs Intensive therapy

Sulfonylurea/Insulin vs Conventional

Years from Randomisation


UKPDS. Lancet 1998;352:837–53
### Myocardial Infarction Hazard Ratio

*(fatal or non-fatal MI or sudden death)*

#### Intensive (SU/Ins) vs Conventional Glucose Control

<table>
<thead>
<tr>
<th>Year</th>
<th>Con Events</th>
<th>Int Events</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>1997</td>
<td>168</td>
<td>387</td>
<td>HR=0.84, p=0.052</td>
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<tr>
<td>1999</td>
<td>212</td>
<td>450</td>
<td>HR=0.85, p=0.014</td>
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<tr>
<td>2001</td>
<td>239</td>
<td>513</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>271</td>
<td>573</td>
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<tr>
<td>2005</td>
<td>296</td>
<td>636</td>
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<tr>
<td>2007</td>
<td>319</td>
<td>678</td>
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*UKPDS 80. N Eng J Me 2008;359:1577–89*
## Summary of Major Trials T2DM

<table>
<thead>
<tr>
<th>Trial</th>
<th>Micro-v</th>
<th>CVD</th>
<th>Mortality</th>
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<td><strong>VADT</strong></td>
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**Legend:**
- **Initial** (blue down arrow)
- **Follow-up** (orange down arrow)
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators
Cardiovascular Outcomes and Death from Any Cause.

A Primary Outcome

- Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
- P=0.04 for superiority

B Death from Cardiovascular Causes

- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P<0.001

C Death from Any Cause

- Hazard ratio, 0.68 (95% CI, 0.57–0.82)
- P<0.001

D Hospitalization for Heart Failure

- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- P<0.002
Ozzie’s A1c Goal

- Poorly controlled T2DM for 9 years
- High risk for CVD

- A1c b/w 7-8% with “soft landing”

- A1c < 7% if hypoglycemia risk modified
Harpo’s A1c Goal

• Recent onset Type 2 DM
• High risk for CVD

• Goal a1c 6-7% if hypoglycemia can be avoided
Lowering A1c to below or around 7% has been shown to reduce microvascular complication of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long term reduction in macrovascular disease. Therefore a reasonable goal for many non-pregnant adults is < 7% (B)

More stringent A1c goals (< 6.5%) if this can be achieved without significant hypoglycemia or adverse effects. (C)

Less stringent goals (>8%) may be appropriate for patients with severe hypoglycemia, comorbidities, etc. (B)
What about BP?
Major outcomes of the HOT trial

Diabetes subgroup

**Goal of therapy:**
Target diastolic pressure

- < 90 mmHg (n = 501)
- ≤ 85 mmHg (n = 501)
- ≤ 80 mmHg (n = 499)

**Achieved**
- < 90 → 85.2 mm Hg
- ≤ 85 → 83.2 mm Hg
- ≤ 80 → 81.1 mm Hg

**P < 0.005**

ACCORD: Systolic Pressures (Mean ± 95% CI)

Mean # Meds
Intensive: 3.2 3.4 3.5 3.4
Standard: 1.9 2.1 2.2 2.3

Average: 133.5 Standard vs. 119.3 Intensive, Delta = 14.2
Effects of Intensive Blood Pressure Control on CV Events in Type 2 Diabetes in ACCORD

Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD
Death

HR = 0.89
95% CI (0.73-1.07)

Total Mortality

HR = 1.07
95% CI (0.85-1.35)
2014 ADA Treatment Recommendations for Blood Pressure

- People with diabetes and hypertension should be treated to a blood pressure target of < 140/80. (Evidence level B)
- Lower systolic targets, such as < 130, may be appropriate for certain individuals… (C)

SPRINT
Lipids?
Plasma Lipid Levels During Trial

- Total Cholesterol
- LDL Cholesterol
- HDL Cholesterol
- Triglycerides

Fenofibrate vs Placebo

Effects of Combination Lipid Therapy on CV Events in Type 2 Diabetes in ACCORD

**Primary Outcome**
Nonfatal MI, Nonfatal Stroke or CVD Death

HR = 0.92
95% CI (0.79 - 1.08)
p = 0.32

**Total Mortality**

HR = 0.91
95% CI (0.75 - 1.10)
p = 0.33

**Patients with Events (%)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fenofibrate</th>
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</thead>
<tbody>
<tr>
<td>Years Post-Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>7</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>8</td>
<td>0.40</td>
<td>0.40</td>
</tr>
</tbody>
</table>
2015 ADA Treatment Recommendations for Lipids

- **Moderate intensity statin:**
  - 40-75 y.o. with LDL 70-189 (A)

- **High intensity statin:**
  - Those with known CVD (A)
  - Those with >7.5% risk of CVD (B)

- Fasting TG > 500 mg/dl

Standards of Medical Care in Diabetes – 2015. Diabetes Care 38 (Suppl 1): S1-S89. 20145
Steno 2: Percentage of patients achieving treatment goals set for the intensive-therapy group at 7.8 yr

- HbA1c < 6.5%
- Cholesterol < 4.5 mmol/l
- Triglycerides < 1.7 mmol/l
- Systolic BP < 130 mm Hg
- Diastolic BP < 80 mm Hg

STENO-2 - Composite Cardiovascular Endpoint

p < 0.001

Cumulative Incidence of any Cardiovascular event (%)

Follow-up time (years)

Intensive therapy

Conventional therapy

No. at risk

Intensive    80   72  65  61  56  50  47  47  31

Conventional 80   70  60  46  38  29  25  14

STENO 2 - Risk of Death from Any Cause

Cumulative Incidence of death (%)

Follow-up time (years)

No. at risk

Intensive  | 80  | 78  | 75  | 72  | 65  | 62  | 57  | 39

Conventional  | 80  | 80  | 77  | 69  | 63  | 51  | 43  | 30

p = 0.02

Benefit of different interventions per 200 diabetic pts treated for 5 years

- Per 4mmHg lower SBP: -12.5
- Per 1mmol/L lower LDL-C: -8.2
- Per 0.9% lower HbA1c: -2.9

Summary

T2DM- early intensive glycemic control reduces macrovascular complications

- Screening for CVD in asymptomatic individuals not shown to reduce CV events if medical therapy initiated

- T2DM with known CVD or long duration of disease may be harmed by intensive control. Mechanisms are not known.

- After long duration T2DM (or known CVD) BP and cholesterol control more likely to reduce CV events.
Thank you!