CV Risk Management in Diabetes Mellitus

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Mr. B
- 40 y/o Latino male c/o fatigue, ED, wants to talk about testosterone
- FH – father died “on insulin” – amputation
- Urine dipstick 3+ glucose

Weight 250#  BP 155/95
HbA1c 9.5%
Fasting labs:
  Glucose 250
  TC 250  TG 250  HDL 35  LDL 165

Bad News
Leading cause of blindness, ESRD, amputation
CV disease
  – Type 2: 2x risk of cardiovascular events, death
  – Type 1: 10 fold increase of age-adjusted risk
Diabetes prevalence (CDC) increasing in the US
  – 9.3% - 28.1 million people – 8.1 million (27.8%) undiagnosed
  – Over 90% type 2 DM (although type 1 also increasing)
More Bad News

At diagnosis of type 2 DM 50% of patients have at least one complication

Diabetes costs in US $245 billion per year – $825 billion worldwide

More Good News –
Glucose control decreases microvascular complications

• In type 1 DM glucose control mitigates risk of all complications

• In type 2 DM:
  – Glucose control decreases microvascular complications
  – Early tight glucose control may improve CV complications

Good News –
CV complications can be decreased in patients with type 2 DM

• Controlling BP conveys greater benefit in DM than almost any other maneuver

And in high risk individuals

• Statins improve outcomes
• ACE inhibitors improve outcomes
• ASA improves outcomes

This can be done and has been done
Disclosures

I have no financial interests in medical or pharmaceutical entities
I do not give lectures for pharmaceutical entities nor do I have research grants associated with PhRMA

References


Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Int Med 3 JANUARY 2017


Objectives

Participants will:
1) understand the need for tight glucose control to prevent microvascular complications and mitigate cardiovascular complications in diabetes
2) feel comfortable discussing the evidence for BP control in diabetes
3) know when to prescribe statins, ACE inhibitors and aspirin for patients with diabetes who have not yet had a vascular event
Type 1 DM

- In type 1 DM glucose control mitigates risk of all complications
  - Glucose control decreases microvascular complications
    - nephropathy
    - Retinopathy
    - neuropathy
  - CV complications can be decreased

Treatment for Type 1 DM is simple
- Insulin Therapy
  “The patient who knows the most lives longest.”
  Elliot P Joslin MD

Excellent evidence –
  avoiding complications and survival directly related to glucose control.
MDI or pump therapy.
It’s not easy
Education is key

In Type 1 Diabetes -
Glycemic control predicts all outcomes

- Insulin
  - basal
  - prandial
  - Corrective
- Glucose monitoring
- Diet – carbohydrate counting
- Exercise
- Encouragement
- Monitor for complications
- Educate - Repeat
Type 1 DM - DCCT

1441 type 1 DM average 26 years old

7 - 9 years of intensive (7%) A1c or conventional (9%) A1c

Intensive control decreased:
- retinopathy 63 - 76%
- microalbuminuria 39 - 54%
- neuropathy 60%
- macrovascular disease 41% (NS)

The Diabetes Control and Complications Trial Research Group.
N Engl J Med 1993; 329:977

Side Effects of Tight Control

Hypoglycemia
- Diet
- Exercise
- Insulin adjustment

Weight gain
- Diet
- Exercise
- Insulin adjustment

DCCT: Risk of Sustained Retinopathy Progression by HbA1c Level and Years of Follow-up

DCCT/EDIC 10 years after DCCT, HbA1c then 8%

10 years after RCT study - DCCT was over – all subjects received usual care.

Despite HbA1c now equal between both groups (intensive vs control), CV outcomes were markedly different


DCCT-EDIC: Long-Term Risk of Macrovascular Complications

![Graph showing long-term risk of macrovascular complications](image1)

![Graph showing any cardiovascular outcome](image2)

Any Cardiovascular Outcome

42% risk reduction

*P* = 0.02

Years Since Entry
Questions about type 1 DM?

But Type 2 Diabetes is Complex

- Some damage occurs before diagnosis
  - associated with insulin resistance
- Early glucose control:
  - Paramount in preventing microvascular complications
  - Likely prevents macrovascular complications
- Blood Pressure and Lipid control are arguably more effective than tight glucose control in reducing cardiovascular risk and macrovascular complications
Mechanisms of Vascular Injury in Type 2 Diabetes

- Metabolic Syndrome
  - Insulin resistance

- Increased Free Fatty Acids cause endothelial dysfunction and are proinflammatory

- Oxidative Stress is increased by multiple cardiovascular risk factors

Resistance to Insulin

Anabolic Effects of Insulin
Patients with DM are more likely to have a greater burden of atherosclerotic risks:

- **CAD**
  - Silent MI, atypical angina
  - Small vessel CAD; Multivessel CAD

- **other CV risks**
  - Hypertension
  - Dyslipidemia
    - Small dense LDL
    - High TG, low HDL
  - Increased fibrinogen, clotting factors, platelet adhesion
  - Endothelial dysfunction

- **Hyperglycemia**

### Myocardial Infarction Stroke CV Death

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic +MI (n=1,304)</th>
<th>Nondiabetic -MI (n=1,344)</th>
<th>Diabetic +MI (n=89)</th>
<th>Diabetic -MI (n=88)</th>
<th>Diabetic +MI (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>P&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>P&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td></td>
<td></td>
<td>P&lt;0.001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For diabetes vs. no diabetes and prior MI vs. no prior MI

Prevention of Complications

- Regular medical care
  - Education
  - Monitoring
    - Glucose (A1c, self monitoring) Goal A1c < 7%
    - Microalbumin
    - Photo or Dilated retinal exam
    - Foot and monofilament testing
- BP control: <139/89 lower is better
- Lipid control
- ASA if needed

High index of suspicion for complications
Educate, Motivate, Intervene - REPEAT

To improve outcomes in diabetes - Remember your ABC’s

- Aspirin: over 50 or risk CV risk
- ACEi or ARB over 50, ↑ BP or microalbuminuria
- Blood Pressure control
- Cholesterol treatment: statins
- Diabetes (glucose) control
- Education (Exercise, Encouragement)

Multiple risk factor intervention

UK Prospective Diabetes Study
5102 newly diagnosed type 2 DM – age 56
An intensive glucose control policy HbA1c
7.0 % vs 7.9 % reduces risk of
any diabetes-related endpoints
  - 12% p=0.030
microvascular endpoints
  - 25% p=0.010
myocardial infarction
  - 16% p=0.052
UKPDS Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA1c by mean 0.9% over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

- 12% for any diabetes related endpoint \( p=0.029 \)
- 25% for microvascular endpoints \( p=0.0099 \)
- 16% for myocardial infarction \( p=0.052 \)
- 24% for cataract extraction \( p=0.046 \)
- 21% for retinopathy at twelve years \( p=0.015 \)
- 33% for albuminuria at twelve years \( p=0.000054 \)

*UKPDS: Metformin Is Associated With a Reduction in Cardiovascular Events*

Mean change in risk vs. conventional therapy in overweight patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metformin</th>
<th>Sulfonylurea/Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-related death</td>
<td>42%</td>
<td>20%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>36%</td>
<td>8%</td>
</tr>
<tr>
<td>Any diabetes-related endpoint</td>
<td>32%</td>
<td>7%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>39%</td>
<td>21%</td>
</tr>
<tr>
<td>Stroke</td>
<td>41%</td>
<td>14%</td>
</tr>
</tbody>
</table>

\( p\) values:

- Diabetes-related death: 0.017
- All-cause mortality: 0.011
- Any diabetes-related endpoint: 0.002
- Myocardial infarction: 0.010
- Stroke: 0.13

*Compared with conventional therapy based on diet/exercise in overweight patients*
### Intensive Glycemic Control in Patients with Lower CVD Risk

<table>
<thead>
<tr>
<th>Randomized controlled trials</th>
<th>DCCT (T1DM)</th>
<th>UKPDS (T2DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>9 vs. 7</td>
<td>8 vs. 7</td>
</tr>
<tr>
<td>Average follow-up (yrs)</td>
<td>6.5</td>
<td>10</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>CVD events</td>
<td>No benefit</td>
<td></td>
</tr>
</tbody>
</table>


### Intensive vs. Standard Glucose Control in T2DM With High CVD Risk

<table>
<thead>
<tr>
<th></th>
<th>ACCORD¹</th>
<th>ADVANCE²</th>
<th>VADT³</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Duration diabetes (yrs)</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.1</td>
<td>7.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Intense A1C goal (%)</td>
<td>&lt;6</td>
<td>≤ 6.5</td>
<td>action &gt;6.5</td>
</tr>
<tr>
<td>CVD risk</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>3.5</td>
<td>5</td>
<td>5.6</td>
</tr>
</tbody>
</table>


### Intensive vs. Standard Glucose Control in T2DM With High CVD Risk

<table>
<thead>
<tr>
<th></th>
<th>ACCORD¹</th>
<th>ADVANCE²</th>
<th>VADT³</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C standard (%)</td>
<td>7.5</td>
<td>7.0</td>
<td>8.5</td>
</tr>
<tr>
<td>A1C intensive (%)</td>
<td>6.4</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Greater with intensive treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD benefit⁵</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death⁶</td>
<td>Increased</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>


⁵ Intensive vs. standard
⁶ Intensive vs. standard
And yet…

UKPDS 10 year follow-up after RCT was completed: Although differences in HbA1c levels lost 1 year after study Between-group relative reductions in risk persisted at 10 years

Holman RR NEJM 2008; 359:1577-1589

<table>
<thead>
<tr>
<th>Sulfonylurea–insulin</th>
<th>Metformin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>any diabetes-related end point</td>
<td>any diabetes-related end point</td>
</tr>
<tr>
<td>– microvascular disease</td>
<td>24% P=0.001</td>
</tr>
<tr>
<td>– myocardial infarction</td>
<td>15% P=0.01</td>
</tr>
<tr>
<td>– death from any cause</td>
<td>13% P=0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sulfonylurea–insulin</th>
<th>Metformin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>any diabetes-related end point</td>
<td>21%, P=0.01</td>
</tr>
<tr>
<td>– myocardial infarction</td>
<td>33%, P=0.005</td>
</tr>
<tr>
<td>– death from any cause</td>
<td>27%, P=0.002</td>
</tr>
</tbody>
</table>

Delayed Benefits in Patients – Younger and Lower CVD risk

<table>
<thead>
<tr>
<th>DCCT – Type 1</th>
<th>UKPDS – Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44</td>
</tr>
<tr>
<td>HbA1c</td>
<td>~ 8%</td>
</tr>
<tr>
<td>Average f/u</td>
<td>6.5 + 9 y</td>
</tr>
<tr>
<td>Microvascular Complications</td>
<td>Decreased</td>
</tr>
<tr>
<td>CVD Events</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Questions about beneficial effects of glucose control in type 1 or type 2 DM?

To improve outcomes in diabetes - Remember your ABC’s

- Aspirin: over 50 or risk CV risk
- ACEi or ARB over 50, ↑ BP or microalbuinuria
- Blood Pressure control
- Cholesterol treatment: statins
- Diabetes (glucose) control
- Education (Exercise, Encouragement)

UK Prospective Diabetes Study
A tight blood pressure control policy
144/82 vs 154/87 mmHg reduces risk of

- any diabetes-related endpoint 24% p=0.005
- microvascular endpoint 37% p=0.009
- stroke 44% p=0.013
BP Goal for Diabetes - 139/89 or less

*major improvement* in CV risk in DM patients:

<table>
<thead>
<tr>
<th>Systolic BP &lt; 145</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;135</td>
<td>UKPDS</td>
</tr>
<tr>
<td>&lt;130</td>
<td>Advance</td>
</tr>
<tr>
<td>Diastolic BP &lt; 80</td>
<td>HOTS</td>
</tr>
</tbody>
</table>

ACCORD trial showed possibly no benefit and more side effects with Systolic < 120

So HEDIS changed BP goal to 139/89, consistent with the JNC 8.

BP control is essential – so is glycemic control

Although benefits of improved BP control were lost 10 years after the UKPDS study

Early tight glucose control resulted in persistent benefits 10 year after

Education

- Glucose, BP and Lipid control
- Safety
- Follow-up
- Self-monitoring glucose
- Symptoms/Treatment of high or low glucose
- Diet
- Exercise
- Smoking cessation

REPEAT

Insulin administration
Mr. B  
5 years later (now 45 years old)  
Followed diet and exercise recommendations  
and weight has plateaued  
No hypoglycemic symptoms  
Meds: metformin 1000 mg bid + NPH 24 U @hs  
lisinopril 20/hctz 25 mg daily  
Weight 225; BP 132/78  
LDL 158, A1c 8.5%, normal Cr and K  
What else?

CV risk management  
• Control glucose  
• Control BP  
• Control lipids  
MONITOR  
REPEAT  
• Diabetes tends to be progressive  
• BP and lipid management tends to be stable

Newer medications associated with decreased CV risk
Liraglutide (GLP-1 agonist) and CV outcomes
Marso et al 2016. NEJM 375:311

Type 2 DM + CV disease
Average 3.8 year follow-up

<table>
<thead>
<tr>
<th></th>
<th>N = 9340</th>
<th>CV events</th>
<th>CV death</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>14.9%</td>
<td>6%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Liraglutide</td>
<td></td>
<td>13%</td>
<td>4.7%</td>
<td>8.2%</td>
</tr>
<tr>
<td><strong>NNT</strong></td>
<td></td>
<td>53</td>
<td>77</td>
<td>71</td>
</tr>
</tbody>
</table>

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
Neal B et al 2017 NEJM. DOI: 10.1056/NEJMoa1611925

<table>
<thead>
<tr>
<th></th>
<th>N &gt; 10,000</th>
<th>Composite CV outcome event per 1000 patient-years</th>
<th>Renal progression</th>
<th>Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>26.9</td>
<td>Decreased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>31.5</td>
<td>DBP and A1c also</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNT</strong></td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGLT-2 Inhibitor
• EMPAG-REG study – high CV risk RCT using Jardiance (empagliflozin)
  – reduced CV related deaths by 2.2% over 3.1 years (3.7% vs 5.9%)
  – 4.5-4.7% increased rate of genital infection
• NNT 45 for 3.1 years to prevent 1 death
• Cost: ~$2000-6000 a year
Degludec v Glargine for 2 years

- 7637 w DM2, 85% with complications
- Age 65, duration of DM 16 years
Similar A1c drop from 8.5% to 7.5%
Less severe hypoglycemia, lower FBS with Degludec
Non-inferiority of Degludec NNT = 120 for 2 years
- 0.8% fewer primary composite outcomes*

*In the time-to-event analysis, the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Mechanisms of Vascular Injury in Type 2 Diabetes

- Metabolic Syndrome
  - Insulin resistance
  - Increased Free Fatty Acids cause endothelial dysfunction and are proinflammatory
  - Oxidative Stress is increased by multiple cardiovascular risk factors

- Dyslipidemia
  - HDL
  - Triglycerides

- Hypertension
- Obesity
- Hyperglycemia

How We EVOLVED
### Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

**Obesity (BMI ≥ 30 kg/m²)**

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;14.0%</th>
<th>14.0%–17.9%</th>
<th>18.0%–21.9%</th>
<th>22.0%–25.9%</th>
<th>&gt;26.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>No Data</td>
<td></td>
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<td></td>
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<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
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</tbody>
</table>

**Diabetes**

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;4.5%</th>
<th>4.5%–5.9%</th>
<th>6.0%–7.4%</th>
<th>7.5%–8.9%</th>
<th>&gt;9.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2000</td>
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<tr>
<td>2014</td>
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</tbody>
</table>


### Type 2 DM – intravascular inflammation

- Hyperglycemia – glycosylation products
- Lipid abnormalities
- Free Fatty Acids
- Bradykinins
- Cytokines
- Increased fibrinogen

### Basement Membrane Damage Is Forever – early tight control
Addressing Intravascular Inflammation

- Evidence:
  - Statins
  - RAS control
    - ACE inhibitors
    - Angiotensin Receptor Blockers
  - ASA
  - BP control
  - Safely lowering glucose in DM
  - Decreasing adiposity
  - Exercise
- Lack of evidence:
  - Vitamins E, C, B12, Folate…
  - "anti-inflammatory diet"

To improve outcomes in diabetes - Remember your ABC’s

- Aspirin: over 50 or risk CV risk
- ACEi or ARB over 50, ↑ BP or microalbuminuria
- Blood Pressure control – use ACEi
- Cholesterol treatment: statins
- Diabetes (glucose) control – insulin early
- Education (Exercise, Encouragement)

<table>
<thead>
<tr>
<th>CHD Prevention Trials with Statins in Diabetic Subjects: Subgroup Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
</tr>
<tr>
<td>Secondary Care</td>
</tr>
<tr>
<td>4S</td>
</tr>
<tr>
<td>LIPID</td>
</tr>
<tr>
<td>4S-Extended</td>
</tr>
</tbody>
</table>

Simvastatin Reduced the Risk of Major Coronary Events
Subgroup Analyses, Scandinavian Simvastatin Survival Study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percent Risk Reduction</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>55%</td>
<td>0.002</td>
</tr>
<tr>
<td>Women</td>
<td>37%</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Older</td>
<td>31%</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Smokers</td>
<td>34%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>n=1814</td>
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<td></td>
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<td>n=407</td>
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</tr>
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<td>n=1156</td>
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<td></td>
</tr>
<tr>
<td>n=542</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=105</td>
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</tbody>
</table>


Simvastatin: Heart Protection Study

After allowance for noncompliance, 40 mg daily simvastatin safely reduces the risk of heart attack, of stroke, and of revascularization by about one third.

5 years of statin typically prevents these major vascular events in:

- 100 of every 1000 people with previous MI NNT= 10
- 80 of every 1000 people with other previous CHD NNT= 12
- 70 of every 1000 people with cerebrovascular disease NNT = 14
- 70 of every 1000 people with other arterial disease
- 70 of every 1000 people with diabetes (age 40+)

irrespective of cholesterol level

(or age, or sex, or other treatments).


Why give statins in diabetes despite ‘normal LDL’?

- Patients with DM have at least twice the CV mortality risk
  This can be considered ‘secondary’ prevention
- HPS, 4S and Steno-2
- Pleotropic effect even with LDL at goal
To improve outcomes in diabetes - Remember your ABC’s

- Aspirin: over 50 or risk CV risk
- ACEi or ARB over 50, ↑ BP or microalbuminuria
- Blood Pressure control – use ACEi
- Cholesterol treatment: statins
- Diabetes (glucose) control – insulin early
- Education (Exercise, Encouragement)

Why give ACE inhibitors in diabetic patients?

- with elevated BP
- with microalbuminuria or higher grade proteinuria
- with ↑ CV risk despite normal BP?

HOPE and Steno-2:
NNT 21-27 over 4 years to prevent CV events and death

Blocking Renin-Angiotensin System forestalls progression of microalbuminuria to proteinuria to ESRD and dialysis

Heart Outcomes Prevention Evaluation (HOPE) Study

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

Table: Effect of Ramipril on Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ramipril</th>
<th>NNT 21</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>18.8</td>
<td>15.0</td>
<td>NNT 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N=3,578</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>16.4</td>
<td>13.0</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N=5,719</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional benefits of ACE inhibitors include:

Maintaining levels of bradykinin, inhibiting platelet aggregation and endothelial apoptosis.

**For Our Patients – Cardiovascular Quality Means Consistency**

- BP and lipid control each associated with better cardiac outcomes.
- Lower HbA1c may.

Aim for excellent control and…
- Any lowering of BP → lower CV risks.
- Any statin → lower CV risks.
- Lower A1c without hypoglycemia → lower CV risks.

Your intervention/intensification is key.

Smoking cessation, ACE inhibitor, statin and ASA ↓ risk.

It works, but it requires everyone participate!

**STENO-2: Risk-Factor Targets Attained at 7.8 Years With Intensive Treatment Program**

<table>
<thead>
<tr>
<th></th>
<th>Intensive Therapy</th>
<th>Conventional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1c &lt;6.5%</td>
<td>38%</td>
<td>26%</td>
</tr>
<tr>
<td>Cholesterol &lt;175 mg/dL</td>
<td>31%</td>
<td>18%</td>
</tr>
<tr>
<td>Triglycerides &lt;150 mg/dL</td>
<td>39%</td>
<td>26%</td>
</tr>
<tr>
<td>Systolic Blood Pressure &lt;130 mm Hg</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>Diastolic Blood Pressure &lt;80 mm Hg</td>
<td>60%</td>
<td>49%</td>
</tr>
</tbody>
</table>

*p = 0.06
*p < .001
*p = 0.001

Copyright 2003 Massachusetts Medical Society, All rights reserved.
Steno-2 Study: Multifactorial Intervention for Type 2 Diabetes: multifactorial, target-driven treatment of type 2 diabetes with microalbuminuria.

– Decreased CV Events

<table>
<thead>
<tr>
<th>Years of Follow-up</th>
<th>Intensive Therapy</th>
<th>Conventional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients at Risk</td>
<td>Patients at Risk</td>
</tr>
<tr>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>14</td>
</tr>
</tbody>
</table>

Cumulative Incidence of Cardiovascular Event (%)


All patients offered intensive management after initial randomized trial - average 7.8 years.

Outcomes

• median of 7.9 years of gain of life.
• 38 intensive-therapy patients vs 55 conventional-therapy patients died during follow-up (HR 0.55 [95% CI 0.36, 0.83], \( p = 0.005 \)).
• hazard for all microvascular complications was decreased in the intensive-therapy group in the range 0.52 to 0.67, except for peripheral neuropathy (HR 1.12).

Steno-2 follow-up over 2 decades:
Early intensive managed type 2 DM vs usual care

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.55 (0.36, 0.82)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.35, 2.7)</td>
</tr>
<tr>
<td>non-CVD death</td>
<td>0.70 (0.41, 1.2)</td>
</tr>
<tr>
<td>Death/CVD state</td>
<td>0.83 (0.54, 1.3)</td>
</tr>
<tr>
<td>CV death/CVD state</td>
<td>0.50 (0.36, 0.77)</td>
</tr>
<tr>
<td>Amputations due to neuropathy</td>
<td>0.67 (0.31, 1.4)</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>0.88 (0.40, 2.0)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1.12 (0.71, 1.7)</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>0.02 (0.01, 0.36)</td>
</tr>
</tbody>
</table>
Although initial Steno-2 trial ended at 7.8 years

A total of 21 years of follow-up with additional intensive management resulted in continued, improved MORTALITY.


Early Glycemic Control and Magnitude of HbA1c Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators

- median age 62.5 years,
- 55% males
- median follow-up of 2.6 years

- A1c attained and amount of improvement both associated with fewer MACE

Svensson E et al 2017. Diabetes Care 40(6); 800

Combined outcome event (acute myocardial infarction, stroke, or death) by achieved early glycemic level.
Adjusted HRs for combined outcome event (acute myocardial infarction, stroke, or death) by achieved HbA1c 6 months after metformin initiation.

Adjusted HRs for combined outcome event (acute myocardial infarction, stroke, or death) by magnitude of HbA1c reduction from baseline to 6 months.

NEJM 2010
And we did it with fewer Caths…

National data for cardiac caths

…And CABG’s

Use of cardioprotective medications increased 2-3 fold

And we did it with generics!
Trend in decreasing MI’s persists

Solomon, M et al. 2016 JACC 68(6), 666.

…and continues to decrease in patients with diabetes

Find your patient’s motivation

- Do not give up
- Escalate and intensify treatment early
- Using insulin and sulfonylureas: educate about hypoglycemia and celebrate success. Allow down-titration to improve self-efficacy
- Adding new meds: look for effect (improved glucose control and/or weight control)
Impact of Improvements in Cardiovascular Care on KPNC Member Mortality: 2000-2008

From 2000-2008:
- 30.4% reduction in mortality from CVD
- 42.2% reduction in mortality from stroke
- 10.9% reduction in mortality from cancer


To improve outcomes in diabetes - Remember your ABC's

• Aspirin: over 50 or risk CV risk
• ACEi or ARB over 50, ↑ BP or microalbuminuria
• Blood Pressure control – use ACEi
• Cholesterol treatment: statins
• Diabetes (glucose) control – insulin early
• Education (Exercise, Encouragement)

You can do it!

Questions?
Comments?