Any 1 Care (A1c) about Clinical Outcomes?

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Simplifying Diabetes Management

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Director, PEER
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- Speakers Bureau/Honoraria: ACFP, OCFP, PEICFP, Various Hospitals, University CPD Departments (honorariums and expenses)

- Consulting Fees: N/A

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- Patents: N/A

- Other: CFPC – Employee (MA), University of Alberta (TK)
Making sense of diabetes

Sulfonylureas for Patients with Type 2 Diabetes: Still an Option

**Reasoning:** They lower glucose cheaply and probably not increasing cardiovascular disease
Stories matter, ... what about evidence?

RCT of 1455 Patients x 10 months
On Placebo 3% Died
On Treatment 8% Died

We Killed one in every 21 people going to the CCU for our help.

With the Best Intention & a Great Story

NEJM 1989; 321(6): 406-12
Antioxidant: Story

Oxidative Stress

Antioxidants

We just need more Vitamin A & E!

78 Randomized Trials Studied 296,707

We killed 1 in every ~200 people x3.5 yrs

How much evidence does it take to slay a great theory?

What do Patients Feel or Worry about?

- They might say they are worried about their cholesterol, sugar or maybe A1c”
- For the most part, we had to teach them to fear these.
We have to start distinguishing,

**What we measure,**
- Sugar
- Microalbuminuria
- Lipids
- Blood pressure
- Monofilament
- Diabetic Retinopathy

**What Matters to Patients**
- Survival
- Quality of Life
- Heart Disease & Stroke
- Sensation/Pain
- Vision
- Avoiding Renal Outcomes
What are the bad things that happen?

Average: ~75 y.o. & ~40% male, what happens over 5 years

People without Diabetes

People with Diabetes <10yrs

People with Diabetes ≥10yrs

• The worst to happen is debatable
  • Death vs very low Quality of Life

• Death is bad and the final outcome

~25%  ~35%

What about the other bad things that happen?

1000 People with Diabetes x 10 yrs,
- 50% with micro or macroalbuminuria,
- At 7 yrs, how many need dialysis & how many die

Dialysis

Death [CVD]

Diabetes Care 2003;26:2353-8
What about the other bad things that happen? (2)

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>MI</th>
<th>Stroke</th>
<th>Renal failure (dialysis + Cr&gt;250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Diabetes</td>
<td>18%</td>
<td>14%</td>
<td>5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>(UKPDS 10 Year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Later (66) Diabetes</td>
<td>20%</td>
<td>6.5%</td>
<td>8.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>(Advance 10 Year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What about Amputation varies more with baseline risk (& definition):

- All (≥ toes) can be ~12% x10 yrs in very high risk (with 44% hard CVD)

Other clinical outcomes that are not so good.

<table>
<thead>
<tr>
<th>Glycaemia control</th>
<th>Intensive</th>
<th>Standard</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First composite</td>
<td>556/55119</td>
<td>10.9</td>
<td>586/55115</td>
<td>11.5</td>
<td>0.95 (0.85-1.07)</td>
</tr>
<tr>
<td>Second composite</td>
<td>1956/55119</td>
<td>38.2</td>
<td>2064/55115</td>
<td>40.0</td>
<td>0.95 (0.89-1.01)</td>
</tr>
<tr>
<td>Neph-1: incident microalbuminuria</td>
<td>720/3250</td>
<td>22.2</td>
<td>288/3273</td>
<td>25.3</td>
<td>0.85 (0.77-0.94)</td>
</tr>
<tr>
<td>Neph-2: incident macroalbuminuria</td>
<td>1954/3437</td>
<td>44.4</td>
<td>272/4424</td>
<td>61.1</td>
<td>0.71 (0.59-0.86)</td>
</tr>
<tr>
<td>Neph-3: ESRD</td>
<td>138/5119</td>
<td>2.7</td>
<td>151/5115</td>
<td>3.0</td>
<td>0.92 (0.73-1.16)</td>
</tr>
<tr>
<td>Neph-4: doubling of Scr or &gt;20 UeGFR decrease</td>
<td>2956/5041</td>
<td>58.6</td>
<td>2943/5035</td>
<td>58.5</td>
<td>1.04 (0.99-1.10)</td>
</tr>
<tr>
<td>Neph-5: any of Neph-2, Neph-3, or Neph-4</td>
<td>3056/5119</td>
<td>59.7</td>
<td>207/5115</td>
<td>62.0</td>
<td>1.03 (0.98-1.08)</td>
</tr>
<tr>
<td>Eye-1: photoagulation or vitrectomy</td>
<td>440/4935</td>
<td>9.0</td>
<td>456/4933</td>
<td>9.2</td>
<td>0.97 (0.85-1.10)</td>
</tr>
<tr>
<td>Eye-4: severe loss of vision*</td>
<td>384/4474</td>
<td>8.1</td>
<td>385/4474</td>
<td>8.1</td>
<td>0.89 (0.80-0.99)</td>
</tr>
<tr>
<td>Neuro-1: neuropathy (MNSI score &gt;2.0)</td>
<td>153/2829</td>
<td>55.6</td>
<td>164/2797</td>
<td>58.6</td>
<td>0.92 (0.86-0.99)</td>
</tr>
<tr>
<td>Neuro-2: loss of vibratory sensation</td>
<td>981/4227</td>
<td>23.2</td>
<td>1050/4217</td>
<td>24.9</td>
<td>0.93 (0.85-1.01)</td>
</tr>
</tbody>
</table>

**3 line loss of vision ~20% (aggressive takes off 1.5%)**

**Loss of Light Touch~14% (aggressive takes off 2%)**
Bottom-Line: What are the Patient Oriented Outcomes of Diabetes and Can we Influence them?

Outcomes

- Macrovascular Complications
  - Heart Disease
  - Stroke
- Microvascular
  - Vision
  - Sensory
  - Renal disease

Can we influence them

- Yes:
  - Requires comprehensive approach.
  - Has to balance Quality of Life
  - More to follow
Can we do it with aggressive A1c management?

**E. Cardiovascular Disease Mortality**

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/Total, n/n</th>
<th>Intensive</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early trials</td>
<td></td>
<td>276/2729</td>
<td>126/1138</td>
</tr>
<tr>
<td>UKPDS 33</td>
<td></td>
<td>25/342</td>
<td>53/411</td>
</tr>
<tr>
<td>UKPDS 34</td>
<td></td>
<td>301/3071</td>
<td>179/1549</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>0.75 (0.48 to 1.11)</td>
<td>~15 (~3 to 6)</td>
</tr>
<tr>
<td>Recent trials</td>
<td></td>
<td>235/2008</td>
<td>516/449</td>
</tr>
<tr>
<td>ACCORD</td>
<td></td>
<td>95/5123</td>
<td>49/5123</td>
</tr>
<tr>
<td>ADVANCE</td>
<td></td>
<td>252/5571</td>
<td>244/5568</td>
</tr>
<tr>
<td>VADT</td>
<td></td>
<td>40/902</td>
<td>33/899</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>1.13 (0.79 to 1.63)</td>
<td>4 (-9 to 17)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>729/14162</td>
<td>595/13140</td>
</tr>
<tr>
<td>Heterogeneity P = 0.002; I2 = 76.3%</td>
<td></td>
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**Mortality by A1C**


<table>
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<tr>
<th>Long-term Care Admission</th>
<th>A1C Range</th>
<th>Absolute Risk of Long-term care</th>
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<tbody>
<tr>
<td>80 yo, 67% female</td>
<td>&lt;7%</td>
<td>62%</td>
</tr>
<tr>
<td>Requiring assistance</td>
<td>7.0-7.9%</td>
<td>58%</td>
</tr>
<tr>
<td>(from insulin to no meds)</td>
<td>8.0-8.9%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>≥9.0%</td>
<td>56%</td>
</tr>
</tbody>
</table>

(Lancet 2010; 375: 481-89)
More J-Shaped Curves with A1c

• 6 studies with 7 cohorts examining A1c & survival
  • 147,424 participants followed for 2.4 – 10 years.

• With 7.5% baseline, for every 1% A1c
  – Lower, RR Increases 10%
  – Higher, RR Increases 4%

• **Bottom-Line:** No real change, ~7-7.5 likely best for longevity.

Quality of Life for outcomes in Diabetes?

- Quality of Life in Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>QOL Utility</th>
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<td>Mild Stroke</td>
<td>0.70</td>
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<tr>
<td>Angina</td>
<td>0.64</td>
</tr>
<tr>
<td>Diabetic Neuropathy</td>
<td>0.66</td>
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Diabetes Care 2007;30:2478-83
Quality of Life for outcomes in Diabetes? (2)

- Quality of Life in Diabetes

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<tr>
<td>Diabetic Neuropathy</td>
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<tr>
<td>Comprehensive Diabetes Care</td>
<td>0.64</td>
</tr>
</tbody>
</table>

ACCORD, looking specifically at intense sugar control found mixed results on QoL for different outcomes but overall, no effect. (Diabetes Care 2011;34:807-12.)

Diabetes Care 2007;30:2478-83
Sometimes it can feel discouraging
Managing Diabetes

**STENO:** Small RCT (160 pts x 13 years)
- All DM + microalbuminuria (Danish, white)

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<th>Treatment</th>
<th>Control</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>30%</td>
<td>50%</td>
<td>5</td>
</tr>
<tr>
<td>Mean CVD events</td>
<td>2</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>≥1 CVD events</td>
<td>31%</td>
<td>60%</td>
<td>4</td>
</tr>
<tr>
<td>Treating Retinopathy</td>
<td>18%</td>
<td>34%</td>
<td>7</td>
</tr>
<tr>
<td>Dialysis</td>
<td>1%</td>
<td>7.5%</td>
<td>16</td>
</tr>
</tbody>
</table>

- Tried again: 3057 patients, early DM (age 60) – better by ≤1% any outcome
  - Less risk and most control group also “aggressively” managed

Adjunctive Therapies
Can Lifestyle work in Diabetes?

• RCT 98 Danish DM x5yrs, age 55, 52% male, x1 yr

• Outcome: Intense lifestyle vs standard, similar A1c
  • Reduced DM meds: 74% vs 26%, NNT 3, (Stop NNT 3)
  • Weight: 10% reduced 31% vs 3%, NNT 4 (5% NNT 3)
  • Harms : Mild Hypoglycemia (13% vs 0%),
    • MSK injury (22% vs 0%)

• **Bottom-Line:** Works, 56% vs 15% can actual stop meds plus weight loss. MSK injuries more common.

JAMA. 2017;318(7):637-646.
Can Diabetes be Cured,... Maybe

• RCT of 298 primary care patients: DM <6yrs, no insulin, 7.6%.
  • Diet ~840 kcal/day for 3 months (+ 2 optional) then slow re-intro.

• Results:
  • 1 yr: lost ≥15kg=0 vs 24% (NNT 5), DM remission 4% vs 46% (NNT 3)
    • If Weight loss >15, then 86%
  • Similar but not quite as good the following year.
  • Qol: 6-10 (out of 100) better.

• **Bottom-Line**: Surprise, weight loss can resolve Diabetes.

What if patients help themselves?

The Best NNTs from the Best Treatments

Smoking: NNT for death in high risk = 11
Activity: NNT for any CVD in high risk = 6
Diet (Mediterranean): NNT for CVD in high risk = 12
Is there Better Living through Pharmaceuticals?
Statins (until they’re in the water),…

• 18 RCTs (56,934 patients) – age 57 and 60% male.
  • CVD: RR 0.75 (0.70-0.81). 9% vs 12%, NNT 35
  • Mortality: 4.4% vs 5.2%, NNT 132
  • Others find similar

• **Bottom-Line**: Statins reduce CVD from around 12% to 9%, and slight reduces mortality, over around 4 years.
Primary Prevention: ASA in DM

- 3 RCTs focusing on ASA in Diabetics.
  - 2,500 DM pts, 4.4 yrs: No diff in CVD\(^1\)
  - 1270 DM pts, 6.7 yrs: No Difference in CVD\(^2\)
  - 15480 DM pts, 7.4 yrs: CVD: 8.5% v 9.6% but bleeds up 4.1% v 3.2%

- **Bottom-Line:** Little benefit, if any, seems balanced by the increase in bleeding.

1. JAMA. 2008;300(18):2134-2141.
3. ASCEND study NEJM (epub);
Hypertension

- Regardless of target, Hypertension is the most important risk factor in DM
  - No renal disease: Thiazide, ACE/ARB, Ca+ blocker

Relative risk reductions with different DM interventions

<table>
<thead>
<tr>
<th></th>
<th>BP</th>
<th>Lipid</th>
<th>Sugar</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>~ 50%</td>
<td>~25%</td>
<td>~15%</td>
<td>Unclear?</td>
</tr>
<tr>
<td>Mortality</td>
<td>16%</td>
<td>8%</td>
<td>variable</td>
<td>ns</td>
</tr>
</tbody>
</table>

Glucose Drugs
Drugs that change glucose but NOT hard outcomes.

- **Acarbose**
  - No CVD benefits
  - No Consistent Microvascular

- **DDP-4**

- **TZD**
  - No clear CVD benefits
  - CHF: NNH 100-50
  - Fracture ~NNH 35
  - Bladder Cancer: NNH~4000

- **Insulin**
  - No CVD benefits
  - Weak Microvascular (retinopathy)

- **Sulfonylurea**
  - No CVD benefits
  - (1 RCT – NNH 13 CVD Mortality)
  - Weak Microvascular (retinopathy)
Drugs that change glucose but NOT hard outcomes

- **Acarbose**: $150/3 Months, $300/3 Months
- **DDP-4**:
- **Insulin**: $65-130 / 1500 units
- **TZD**: $250/3 Months, $30/3 Months
- **Sulfonylurea**
Glucose drugs that work: data

**Metformin**
- **Relative Risk Reductions**
  - CVD: ~35%
  - Death: ~35%
  - Micro: Unknown
- **10 year NNT**
  - MI: 16
  - Death: 15

**Relative Risk Reductions**
- CVD: ~15%
- Death: ~30% (or ns-13%)
- Micro: Mixed

**SGLT-2**
- Renal outcomes 27%
- **10 year NNT**
  - MI: 9-34 (or ns)
  - Death: 25-34 (or ns)

**GLP-1**
- **Relative Risk Reductions**
  - CVD: ~10-25% (not lix)
  - Death: ~15% (no sem/lix)
  - Micro: Mixed
- **10 year NNT**
  - MI: 40-72
  - Death: 11 (-45)
Glucose drugs that work: practical

**Metformin**
- No Weight gain
- GI upset.
- $30 / 3 months

**SGLT-2**
- Genital Infections: NNH 6-20
- BP slightly better
- ~$275/3 months

**GLP-1**
- GI upset: NNH 80-8
- Quitting due to AE: NNH ~20
- ? Slight more retinopathy
- Slight better nephropathy/wgt
- ~$600-850/3 months
So, how do we pick,..
# Summary of Glucose Medications

Note: Many Variables here. Example - microvascular hard to prove if looking at Patient Oriented Outcomes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>CVD</th>
<th>Death</th>
<th>Microvascular*</th>
<th>Positive/negative</th>
<th>Drug with Best RCT result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Reduced*</td>
<td>Reduced*</td>
<td>Unclear</td>
<td>+ nil weight</td>
<td>Metformin</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>No</td>
<td>No</td>
<td>Reduced*</td>
<td>- Possible CVD/death</td>
<td>None</td>
</tr>
<tr>
<td>Acarbose</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Insulin</td>
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<td>No</td>
<td>Reduced*</td>
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<tr>
<td>TZD</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>- Fracture/bladder Ca</td>
<td>None</td>
</tr>
<tr>
<td>DPP-4</td>
<td>No</td>
<td>No</td>
<td>No*</td>
<td>None</td>
<td>None</td>
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<tr>
<td>SGLT2</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Mixed¹</td>
<td>+ oral, - genital infections</td>
<td>Empagliflozin</td>
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<td>GLP-1</td>
<td>Reduced</td>
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<td>Mixed²</td>
<td>+ Weight loss, - SQ</td>
<td>Liraglutide</td>
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Footnotes: *Probably; 1) Worse amputation in one; 2) Worse retinopathy
# Summary of Glucose Medications, continued

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Footnotes: *Probably; ¹) Worse amputation in one; ²) Worse retinopathy
Time for
PEER suggested
Diabetes Algorithm
Best Diabetes Algorithm

1. Diabetes Diagnosed (High Glucose)
2. Diet ++
3. Done [& keep off Weight]
Diabetes Algorithm, continued

So you have diabetes (High Glucose)

Stop smoking
Move (30 min on 4 days/week)
Eat Mediterranean

Is there Hypertension (≥140/90)?
Yes
Treat Hypertension
No or treated

Is CVD risk ≥10%?
Yes
Offer a Statin

Metformin
If past CVD (& likely all)

Sugar High

SGLT2 (Empagliflozin)

GLP1 (Liraglutide)
Sugar still not in control

Insulin (hs)
Last Thoughts