Diabetes Medications: Friend or Foe?
The Evidence is In

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Context of Diabetes Evidence

1930s

• Theories about the role of glucose control

1980s

• A1c developed
• Home glucose monitoring
• Insulin pump
• EBM
Diabetes Complications and Control Trial (DCCT) 1983-93

- N = 1441
- Mean f/u 6.5 years

Intensive
- QID insulin
- A1c = 7.2

Conventional Control
- Daily or BID Insulin
- A1c = 8.9
Risk Reduction in DCCT

Effects of reduction of A1c by 1.9% in intensively treated group

- Retinopathy: 76% (P=0.002)
- Neuropathy: 54% (P=0.002)
- Albuminuria: 60% (P=0.04)
- Microalbuminuria: 54% (P=0.04)
- Macroalbuminuria: 39% (P=0.04)

Epidemiology of Diabetes Intervention and Complications

• EDIC 1993- 2005

• DCCT patients taught intensive control

• Managed by their own providers

• Followed for up to 18 years for MACE
DCCT / EDIC: majority of patients receive intensive therapy and HbA$_{1c}$ levels converge.

Conventional group encouraged to switch to intensive treatment.

DCCT/EDIC: NEJM, 2005;353, No 25: 2643-2653
Lower Glycemia in DM-1 Decreases CVD But Benefits are Delayed (DCCT-EDIC)

UKPDS
United Kingdom Prospective Diabetes Study

- \( N = 5100 \)
- Newly dx’d T2DM
- Compare Sulfs, MFM and Insulin
- Intensive control
- Compare ACE and B Blockers

UKPDS Group, 1998, the Lancet 352: 837-853
UKPDS Data

- Each 1 point drop in A1c  35% non CV risk reduction

- A1c of 7.0 for T2DM

- MI Risk Reduction (p = 0.052)

- MFM: MI Risk Reduction 39% All cause death reduction 36%
UKPDS Data

- MFM, Insulin and Sulfs not atherogenic or cardiotoxic
- Continuous relationship between vascular outcomes and BP
- ACE and B Blockers both safe for
  - BP reduction
  - MI risk reduction
UKPDS at Ten Years

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylurea/Insulin</th>
<th>MFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM Endpoint</td>
<td>9% (p = 0.04)</td>
<td>21% (p = 0.01)</td>
</tr>
<tr>
<td>Microvascular</td>
<td>24% (p=0.001)</td>
<td>26% (p = NS)</td>
</tr>
<tr>
<td>MI</td>
<td>15% (p = 0.01)</td>
<td>33% (p = 0.005)</td>
</tr>
<tr>
<td>Any cause of death</td>
<td>13% (p = 0.007)</td>
<td>27% (p = 0.002)</td>
</tr>
</tbody>
</table>

ADOPT Trial
A Diabetes Outcome Progression Trial

• Newly diagnosed, drug naïve patients
• Time to treatment failure with monotherapy
• 1450 patients randomized to each group:
  • MFM
  • TZD
  • Sulfonylurea
ACCORD TRIAL
Action to Control Cardiac Risk in Diabetes

- NHLBI

- *N* = > 10,200

- Mean age = 62 with PMH of MI or CVA

- Dx of T2DM x 10 years

- Intensive strategy group: Goal of A1c of 6.0

- Standard strategy group: Goal of A1c of < 7.5
ACCORD: Treatment effect on all-cause mortality

CVD Death:
HR 1.35 (1.04–1.76)
P = 0.02

ADVANCE Trial
Action in Diabetes and Vascular Disease

• Repeat of ACCORD

• Goal of intensive control A1c 6.5

• No increase in mortality

• No increase in benefit

Advance Study Group, 2008, NEJM, 3588:2560-2572
DPP
Diabetes Prevention Program

Pre-Diabetes

- Placebo
  - n = 1082

- MFM
  - n = 1073

- Lifestyle
  - n = 1079

NEJM 2002, 346(16) 393-403
The Lancet, 2009(374), 9702, 1677-1686
American Diabetes Association Guidelines 2016

• A1c < 7 for most

• A1c < 6.5 for a few

• A1c < 8 for LLE, advanced micro or macrovascular disease
American Diabetes Association
Prevention Guidelines 2016

- Lose 7% body weight
- 150 minutes physical activity per week
Healthy eating, weight control, increased physical activity & diabetes education

**Mono-therapy**
- Efficacy
- Hypo risk
- Weight
- Side effects
- Costs

**Dual therapy**
- Efficacy
- Hypo risk
- Weight
- Side effects
- Costs

**Triple therapy**
- Efficacy
- Hypo risk
- Weight
- Side effects
- Costs

**Combination injectable therapy**
- Efficacy
- Hypo risk
- Weight
- Side effects
- Costs

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**Metformin**
- high
- low risk
- neutral/loss
- GI/ lactic acidosis
- low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

1. **Metformin +**
   - Sulfonylurea
     - high
     - moderate risk
     - gain
     - hypoglycemia
     - low

2. **Metformin +**
   - Thiazolidinedione
     - high
     - low risk
     - gain
     - edema, HF, fx
     - rare

3. **Metformin +**
   - DPP-4 inhibitor
     - intermediate
     - low risk
     - neutral
     - loss
     - GI, dehydration
     - high

4. **Metformin +**
   - SGLT2 inhibitor
     - intermediate
     - low risk
     - neutral
     - loss
     - GI
     - high

5. **Metformin +**
   - GLP-1 receptor agonist
     - high
     - low risk
     - high
     - gain
     - hypoglycemia
     - variable

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

1. **Metformin +**
   - Sulfonylurea
     - TZD
     - or
     - DPP-4-i
     - or
     - SGLT2-i
     - or
     - GLP-1-RA
     - or
     - Insulin

2. **Metformin +**
   - Thiazolidinedione
     - SU
     - or
     - DPP-4-i
     - or
     - SGLT2-i
     - or
     - GLP-1-RA
     - or
     - Insulin

3. **Metformin +**
   - DPP-4 inhibitor
     - SU
     - or
     - TZD
     - or
     - SGLT2-i
     - or
     - GLP-1-RA
     - or
     - Insulin

4. **Metformin +**
   - SGLT2 inhibitor
     - SU
     - or
     - TZD
     - or
     - DPP-4-i
     - or
     - SGLT2-i
     - or
     - Insulin

5. **Metformin +**
   - GLP-1 receptor agonist
     - SU
     - or
     - TZD
     - or
     - DPP-4-i
     - or
     - SGLT2-i
     - or
     - Insulin

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

**Metformin +**
- Basal Insulin +
- Mealtime Insulin or
- GLP-1-RA
Thiazolidinediones (TZDs)

- Truglitizone (Rezulin) 1997 - 2000
  - Off the market

- Rosiglitazone (Avandia) 2000
  - Black box warning 2010

- Pioglitazone (Actos) 2000
FDA 2008 Proposal

- Non-inferiority studies
- Post marketing cardiovascular outcomes trials
  - Identified endpoints
  - Long term follow up
- Higher risk patients
TZDs
Peroxisome Proliferator Activated Receptors

TZDs and CVD

- Nissen (2007)
  - MA of 42 trials with Rosi
    - N = 27,847
  - OR for MI 1.43 (p = 0.03)
  - OR for death 1.64 (p = 0.06)

- Lincoff (2007)
  - MA of 19 trials with Pio
    - N = 16,390
  - Death, Nonfatal MI or CVA
    - Pio 4.4%
    - Control 5.7%  p = .005
    - HF 2.3% PIO 1.8% control  p = .002

Lincoff, AD et al, 2007, JAMA, 298: 1180-1088
Pioglitazone Meta analysis Lincoff JAMA Death, MI or CVA

TZDs and CVD
Periscope Trial  2008

• Nissen  Pioglitazone vs Glimepiride and Progression of Coronary Atherosclerosis

• N = 543 with CAD
  • Randomized for 18 months

• Then Open label x 18 months

• Compared Percent Atheroma Volume over 18 and 36 months

Nissen S. et al, 2008 JAMA (299)13, 1561 - 1573
## PERISCOPE TRIAL

<table>
<thead>
<tr>
<th></th>
<th>Glimepiride</th>
<th>Pioglitazone</th>
<th>P =</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>4.1 % Increase</td>
<td>16 % Increase</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>.6% decrease</td>
<td>15.3 % decrease</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Atheroma Volume</td>
<td>.73 Increase</td>
<td>.16% decrease</td>
<td>.002</td>
</tr>
</tbody>
</table>

Nissen S. et al, 2008 JAMA (299)13, 1561 - 1573
TZDs: The Good: Periscope Trial

Nissen, S. et al, 2008 JAMA (299)13, 1561-73
TZDs and CVD

• Juurlink, 2009

• Canadian retrospective cohort analysis of Rosi and Pio

• N= 39,763 Age > 65
• Outcome: Death or Hospitalization for MI or HF

• Rosi 6.9% Met the outcome

• Pio 5.3% Met the outcome (Death, HR 0.86 and HF HR 0.83,

• No difference in risk of MI

Juurlink, D. et al, 2009, BMJ; 339;b2942
TZDs and Bladder Ca

- Turner 2013  MA of 18 studies
- Pio: Use vs no use  OR 1.21  p = 0.0005
- Adjusted for tob or COPD  p = 0.003

- Cumulative dose:  > 28 GMS  OR 1.64  p = 0.0001
- Duration:  
  - < 12 months, OR  1.1 p = ns
  - 12 to 24 mon  OR 1.41  p = 0.0006
  - > 24 months  OR 1.51  p = < 0.00001

Rosi: Duration:  2 to 24 months  OR 1.53  p = .01

Turner, R. Et al, 2013 British Journal of Clinical Pharmacology 78-2; 258-273
TZDs and Bladder Ca

- UK data base, Any diabetes drug 2000-2013 f/u through 2014
- N = 145,806 689,616 person years

- Pio
  - 90.2/100,000 or .1% incidence
  - HR 1.63 compared to Pio naïve
  - Cumulative dose >28 GMs HR 1.76
  - Duration:
    - > 12 months HR 1.7  p = <0.01
    - > 24 months HR 1.84  p = < 0.01

- Rosi no association with bladder ca HR 1.1

Tuccori, M. 2016 BMJ, 352; i1541, 1-8
TZDs and Bladder Ca

• Korhonen BMJ 2016

• Data analysis Sweden, Finland and UK

  Two cohorts

  Pio n = 56,337
  Other than Pio n = 317,109

• HR .99 for Pio
  HR 1 for never Pio

• No change in HR with dose or duration
TZDs and NASH

• Cusi et al., 2016 Annals of IM

• Nonalcoholic Steatohepatitis (NASH)

• Insulin resistance, FFAs and high triglycerides contribute

• TZDs target insulin resistance
TZDs and NASH

- N = 101 with T2DM and biopsy proven NASH
- Pio 45 mg or placebo x 36 months and 500 cal hypocaloric diet
- Outcome: 2 point reduction in NAFLD score in 2 categories
  - At 18 months
    - 51% had resolution of NASH
    - 67% of NASH had reduced
    - 58% of Pio had ≥ 2 point reduction in NAFLD score vs
    - 17% in placebo group (p = < 0.001)

Cusi, K et al, 2016 Annals of Internal Medicine online, 21, June 2016
## Improvement in Hepatic Disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pio</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH resolution</td>
<td>51%</td>
<td>19%</td>
<td>P = &lt; .001</td>
</tr>
<tr>
<td>Steatosis</td>
<td>58% reduced score by 2</td>
<td>26</td>
<td>P = &lt; .001</td>
</tr>
<tr>
<td>Inflammation</td>
<td>49</td>
<td>22</td>
<td>P = &lt; .004</td>
</tr>
<tr>
<td>Ballooning</td>
<td>51</td>
<td>24</td>
<td>P = &lt; .004</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>39</td>
<td>25</td>
<td>P = &lt; .130</td>
</tr>
<tr>
<td>Hepatic Triglyceride</td>
<td>12%</td>
<td>4%</td>
<td>P = &lt; .001</td>
</tr>
</tbody>
</table>
GLP1

- Incretin hormone
- Multiple sites of action
- Quickly metabolized
- Promotes weight loss
- Maintains weight loss
Dipeptidyl Peptidase-4 (DPP4) Action

- Enzyme produced in the gut
- Very rapid onset of activity to metabolize GLP1
- Lots of other end targets
Change the Dynamic

- Increase the GLP1 supra physiologic levels

- Decrease the amount of the DPP4 enzyme
Dipeptidyl Peptidase-4 Inhibitor (DPP4)

- DPP4 inhibitors bind with the DPP4 to permit more GLP1 activity
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Linagliptin (Tradjenta)
  - Alogliptin (Nessina)
SAVOR TIMI Trial

• Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53

• Patient with or at risk for cardiovascular events
• Saxagliptin or placebo
• Primary endpoint was CV death, MI or CVA or hospitalization for CV events

• N = 16,492 x 2.1 years

Scirica, B. et al, NEJM, 2013:369-1317-1326
SAVOR TIMI Outcomes

- HR 1.02 for ischemic events  (P = 0.66)

- HR of 1.27 for HF Hospitalization  (p = 0.007)
EXAMINE Trial

• Exploring the Cardiovascular Safety of Therapies for Type 2 Diabetes

• Alogliptin vs. Placebo in patients with ACS in prior 15 to 90 days

• N = 5,380 median of 18 month f/u

• CV Death, Non fatal MI or CVA

White, W. et al, NEJM 2013, 369: 1327-1335;
EXAMINE Trial

- HR for Alogliptin for MACE .98
- HR 1.07 for Hospitalization HF
- No differences in groups
TECOS Study

• Trial Evaluating Cardiovascular Outcomes with Sitagliptin

• N = 14, 671 patients with T2DM and CVD
• Sitagliptin vs Placebo

• CV death, non fatal MI, CVA or hospitalized for Unstable Angina
• HR .98 for CV outcome
• HR 1.0 for hospitalization
• No differences for pancreatitis or ca

Green, J. et al, 2015, NEJM, 373;3, 232-242
SGLT2s

- Sodium-Glucose Co-Transporter 2
- Inhibit glucose reabsorption in the kidney
- **Dapagliflozin** (Forxiga) not approved in 2012, resubmitted in 2013 with more safety data
- **Canagliflozin** (Invokana) FDA Approved in 2013
- **Empagliflozin** (Jardiance)
Site of Action of SGLT2s
SGLT2s

• Reduce A1c in a dose dependent fashion by about 1 point

• FAERS
• 20 cases of DKA in 15 months 2013-2014
• Decreased po intake, major illness Pyelo or urosepsis, heavy ETOH use, reduced insulin use

• AE within 2 weeks of initiating therapy.

• High anion gap metabolic acidosis with BG of ≤ 200
SGLT2s
Acute Kidney Injury

- 101 cases over 18 months
- Within one month of initiation
- Reversible in most cases
  - 11 didn’t recover
  - 4 died from CV causes
- Pts predisposed were hypotensive, dehydrated or taking other renally active (ACE and a diuretics or NSAID)
- Some less than 65 y.o
SGLT2s

• SGLT2s increase fractures in some patients with moderate renal impairment

• Increase PTH which causes increased bone turnover. May impact Vitamin D levels

• Decreased DEXA in total hip and lumbar vertebrae but not wrist or femoral neck

Taylor, S et al, 2015, The Lancet Diabetes and Endocrinology 3, 8-10
SOOOO Diabetes Medications, Friend of Foe?

- Therapy needs to be individualized to the patient
- Family and Social History
- PMH, Ethnic, Cultural Factors
- Patient’s and Provider’s Goals
- Patient Education
- Frequent reassessment and lab work
Contact Information

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