Non Insulin Treatment of Type 2 Diabetes: What the PCP Needs to Know

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What I will cover

• The magnitude of the problem
• Glycemic goals
  – Should we change them in light of newer studies?
• Review ADA and AACE algorithms for the treatment of type 2 diabetes
• Review some of the “older” medications used to treat type 2 diabetes (other than insulin)
• Mention the newer medications
• Provide alternate approach to treatment

Diabetes in the USA today: An epidemic

• 26 million people or just less than 8% of the population
  — 25% undiagnosed
• The number is growing by > 1 million per year
• A major cause of mortality and morbidity
• Cost (direct and indirect) $245 billion per year
  — 1 in 10 US health care dollars spent on diabetes
• And 79 million people at risk for diabetes

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The Diabetes Epidemic: Global Projections, 2010–2030

What percentage of patients with diabetes achieve A1c, lipid and BP goals?

1. 10
2. 20
3. 30
4. 40

Prevalence of Meeting A1c, Blood Pressure and Cholesterol (ABC) Goals in Adults Aged > 20 Years with Diabetes

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Prevalence of Meeting A1c, Blood Pressure and Cholesterol (ABC) Goals in Adults Aged > 20 Years with Diabetes

Casagrande SS et al. Diabetes Care published ahead of print 2/15/13

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>
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<tr>
<td>ACCORD</td>
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<td>←</td>
<td>→</td>
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<tr>
<td>ADVANCE</td>
<td>↓</td>
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<tr>
<td>VADT</td>
<td>↓</td>
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</table>

Summary

• There is benefit in aggressively treating newly diagnosed patients with type 2 diabetes and no complications
• There is a “legacy” effect
• ACCORD, Advance and VADT studies showed no cardiovascular benefit in the populations studied
• ACCORD – intensive therapy was associated with increased mortality, but not other studies
• Advance – intensive control was associated with microvascular benefit

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So what’s the take home message?

• Individualize treatment goals
• For most people getting A1c below 7% is appropriate provided one can do so safely
• In those individuals with established cv disease intensive glucose control may not reduce cv risk but will still reduce microvascular risk
• In all newly diagnosed patients with no cv complications intensive glucose control is beneficial, provided one can achieve this safely

Treatment of Type 2 Diabetes: Factors to Consider

• Diet and exercise form the cornerstone of therapy
• Weight loss for obesity
  – Several pounds may be sufficient to result in improved glucose control
  – Significant weight loss can lead to diabetes remission
• Glucose is toxic to the β cell and worsens insulin resistance

Type 2 Diabetes Management 2013

• Lowering A1c to around 7% especially early after diagnosis can reduce the risk for the development or progression of the long term complications of diabetes
• There are many medications available today to treat type 2 diabetes – if used appropriately this could translate to improved control and less risk for complications
• The challenge for the practicing physician is to know which medications to use and when best to use them
Type 2 Diabetes Management 2013

- There IS consensus that metformin should be first line therapy
- There is NO clear consensus what to add to metformin when A1c goals are not met
  - Few head to head comparator trials
  - Even fewer long term studies evaluating durability of medications on glycemic control, especially when added to metformin

Pathophysiology of Type 2 DM: From the Triumvirate...

To the Ominous Octet

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Non Insulin Medications to Treat Type 2 DM

- TZD
- Metformin
- α cells
- Incretins
- Pramlintide
- β cells
- Sulfonylureas
- Meglitinides
- Incretins
- Pramlintide
- Dopamine receptor agonists
- Serotonin receptor agonists
- Incretins
- SGLT2 Inhibitors
- α glucosidase inhibitors
- Incretins
- Pramlintide
- Colesevelam
- Dopamine receptor agonists
- Serotonin receptor agonists
- Incretins
- SGLT2 Inhibitors

Treatment of Type 2 Diabetes: Key Points

- Individualize targets
- Diet, exercise, education – foundation of any treatment program
- Metformin is first line treatment – unless there is a contraindication
- After metformin, choose drug that is most appropriate for the patient – use additional 1 to 2 oral or injectable agents

Treatment of Type 2 DM: Key Points

- Ultimately many patients will require insulin, alone or in combination with other agents
- Make all treatment decisions with the patient, focusing on her/his preferences, needs and values
- Comprehensive CV risk reduction is vital!
Noninsulin Treatment of Diabetes: What the PCP Needs to Know

Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

Glycemic Control Algorithm

LIFESTYLE MODIFICATION

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Adjustment of Basal Insulin

- For most patients an A1c goal of <7% with a fasting plasma glucose of < 110 mg/dL is appropriate.
- Adjust insulin dose to achieve above goal every 2-3 days as follows:
  - Fasting glucose > 180 mg/dL + 4 units
  - Fasting glucose 140 – 180 mg/dL + 2 units
  - Fasting glucose 110 – 139 mg/dL + 1 unit
- If glucose drops below 70 mg/dL during the night decrease basal insulin dose by 10 – 20%

Choice of drug depends on

- Safety
- Efficacy
- Tolerability/acceptability
- Durability
- Cost

- Phenotypic and genotypic approaches to determine most effective therapy are lacking
Safety

- Hypoglycemia
- Cardiac safety

Hypoglycemia

- Insulin
- Sulfonylureas (SUs)
- NOT (when used alone/without insulin or SUs)
  - Metformin
  - DPP-IV Inhibitors
  - GLP-1 agonists
  - TZD
  - SGLT-2 inhibitors

Hypoglycemia

- Glyburide is associated with more hypoglycemia than other sulfonylureas

Hypoglycemia in ADOPT

- Minor: about 28% had symptoms
- Major: about 0.6% during the 5 years of the study

UKPDS - rates of major hypoglycemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Conventional</th>
<th>Chlorpropamide</th>
<th>Glibenclamide</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>0.7</td>
<td>1.0</td>
<td>1.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>


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What About Ischemic Preconditioning?

- Glyburide may inhibit ischemic preconditioning in people with diabetes, but no evidence that this is the case with glimepiride or glipizide\(^1\)
- NO long term evidence that use of any sulfonylurea is associated with deleterious cardiac events
- Large retrospective studies – patients taking sulfonylureas who were hospitalized with a myocardial infarction showed no tendency to higher morbidity or mortality compared to those not taking sulfonylureas\(^2\)

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UKPDS Long Term Follow Up: Outcomes (Relative Risk Reduction)

<table>
<thead>
<tr>
<th></th>
<th>SU – Insulin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related end point</td>
<td>9% (p = 0.04)</td>
<td>21% (p = 0.01)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>13% (p = 0.007)</td>
<td>27% (p = 0.002)</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>24% (p = 0.001)</td>
<td>33% (p = 0.005)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15% (p = 0.01)</td>
<td>33% (p = 0.005)</td>
</tr>
</tbody>
</table>

Improved outcomes despite no difference in A1c between treatment groups which occurred within a year of study end

“Legacy effect”


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BARI 2D:
No Difference in Survival Between Insulin Sensitizing vs Insulin Providing Therapies


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1. Lee T-M et al. JCEM 2003; 88:531-537

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**Efficacy of Monotherapy in Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Agent</th>
<th>A1C reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin secretagogues</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.5 - 2.0</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.6 - 1.9</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitors</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>DPP-IV Inhibitors</td>
<td>0.6 – 1.0</td>
</tr>
<tr>
<td>GLP-1 receptor analogues</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**TZDs - What’s the take home message?**

- Rosiglitazone use may be associated with increased risk of MI but not CV mortality
- Compared to pioglitazone, rosiglitazone use may be associated with increased risk of stroke, and all cause mortality
- Both TZDs increase risk of CHF
- Pioglitazone may be associated with increased risk of bladder cancer
- TZD use associated with increased risk of long bone fractures

**ADOPT: HbA1c Over Time**

[Graph showing HbA1c over time with comparison between agents]
ADOPT – Blood Glucose Control

<table>
<thead>
<tr>
<th>Year</th>
<th>Glibenclamide</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>6.5</td>
<td>6.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Year 2</td>
<td>6.8</td>
<td>6.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Year 3</td>
<td>7.0</td>
<td>6.9</td>
<td>6.8</td>
</tr>
<tr>
<td>% with A1c &lt; 7% after 4 years</td>
<td>26</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Time to A1c ≥ 7% (yr)</td>
<td>2.75</td>
<td>3.75</td>
<td>4.75</td>
</tr>
</tbody>
</table>

Al-Ozairi E et al Diabetes Care 2007; 30:1677-1680

What Are Some of the “Take Home” Points from ADOPT?

- ADOPT was not a “combination” therapy study
- Average glucose control better with SU during first year of study
- Glucose control really began to diverge at 3 years – average control very similar for 3 groups during first 3 years
- None of the 3 therapies were satisfactory (A1c < 6.5%) as monotherapy
  - Combination therapy is going to be needed earlier on in the natural history of the disease if more people are going to get to goal
- No adverse cardiovascular events with glibenclamide

Bile Acid Sequestrants (BAS): Mechanism of Glucose Lowering Effect

- BAS may alter luminal bile acid composition and affect intestinal glucose absorption
- BAS increase the intestinal release of the incretin cholecystokinin, which results in an increase in pancreatic insulin secretion
- BAS decrease the enterohepatic bile acid pool, decrease FXR activity, and reduce the inhibition of LXR activity

FXR = farnesoid X receptor; LXR = liver X receptor; HNF4α = hepatocyte nuclear factor 4 alpha.
**Joslin Diabetes Center**

**Advances in Diabetes and Thyroid Disease 2013**

Noninsulin Treatment of Diabetes: What the PCP Needs to Know

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**BAS: Mechanisms of Glucose Lowering Effects**

- The ensuing increased LXR activity may
  - Down-regulate enzymes causally related to hepatic insulin resistance and glucose intolerance
  - Suppress hepatic gluconeogenesis
  - Improve hepatic glucose utilization and glucose uptake
- BAS bind bile acids, which may increase HNF4α, an important transcription factor that promotes pancreatic insulin secretion

FXR = farnesoid X receptor; LXR = liver X receptor; HNF4α = hepatocyte nuclear factor 4 alpha.


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**CYCLOSET®**: Proposed mechanism of action

Morning administration (within 2 hours of rising) of CYCLOSET®

- Low dopaminergic tone in hypothalamus & early morning in diabetes
- Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity)

- Decreased postprandial glucose levels
- Reduction in insulin resistance
- Day-time reduction in plasma glucose, TGs and FFAs

Sympathetic tone
HPA axis tone
Hepatic gluconeogenesis
FFA and TG
Insulin resistance
Inflammation/hypercoagulation

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**Diabetes Medications and Body Weight**

<table>
<thead>
<tr>
<th>List A</th>
<th>List B</th>
<th>Continue</th>
<th>Add</th>
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</thead>
<tbody>
<tr>
<td>Weight Gain</td>
<td>Weight Loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preglurin</td>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>GLP-1 Analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>NaGL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-glucosidase inhibitors</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thiazolidinediones</td>
<td></td>
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<tr>
<td>Sulfonylureas</td>
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<td></td>
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<tr>
<td>DPP-4 inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>Sodium-GLucose Cotransporter 2 inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>GLP-1 Analogs</td>
<td></td>
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<tr>
<td>Sodium-GLucose Cotransporter 2 inhibitors</td>
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<tr>
<td>Metformin</td>
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<tr>
<td>Preglurin</td>
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Comparison of Medications that Could be Added to Metformin

<table>
<thead>
<tr>
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<th>SU</th>
<th>TID</th>
<th>DPP-IV</th>
<th>GLP-1</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td><strong>Tolerance</strong></td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Hypoglycemia</td>
<td>Edema/Oedema</td>
<td>Rare pancreatitis</td>
<td>GI Rare pancreatitis</td>
<td>Hypoglycemia Weight gain</td>
</tr>
<tr>
<td><strong>Risk of Hypoglycemia</strong></td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>CV Safety</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>Durability</strong></td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Low</td>
<td>Low – Mod</td>
<td>High</td>
<td>High</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Adapted from Goldfine and Abrahamson, 2013; submitted

What about the “new kid on the block”?

SGLT-2 Inhibitors

SGLT-2 Inhibitor - Canagliflozin

- **Invokana** (Canagliflozin) 1st SGLT-2 inhibitor, approved March 2013
- Once daily dosing before 1st meal of day, 100mg or 300mg tablets
- **MOA**: Inhibition of SGLT2 reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion, with a consequent lowering of plasma glucose levels as well as weight loss.
- Blocks approximately 50-80 grams of glucose per day from being reabsorbed

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SGLT-2 Inhibitor-Canagliflozin

- **Positive effects**
  - Reduction in body weight and systolic blood pressure
- **Side effects**
  - Vaginal yeast infection, urinary tract infection and increased urination
  - Hypoglycemia (<5%), dehydration, dizziness or fainting, hyperkalemia
- **Contraindications**
  - Type 1 diabetes, patients with type 2 diabetes and ketonuria or ketosis
  - Severe renal impairment, end-stage renal disease or patients receiving dialysis

Canagliflozin vs Sitagliptin as Add on to Metformin and Sulfonylurea

Canagliflozin vs Sitagliptin add on to MTF and SU: Change in A1c

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In the UKPDS what percentage of patients required insulin after 6 years of treatment with oral medications?

1. 15
2. 30
3. 50
4. 80
Type 2 diabetes is a progressive disease
Is it because:

1. Insulin resistance gets worse
2. Insulin secretion deteriorates
3. Medications become less effective over time

Decline of β-Cell Function in the UKPDS Illustrates Progressive Nature of Type 2 Diabetes

HOMA=homeostasis model assessment

So what would you add on to metformin if glycemic goals are not being met?
Choose One Only!

1. Sulfonylurea
2. DPP-IV inhibitor
3. GLP-1 receptor agonist
4. TZD
5. Basal Insulin

We need more data!

Glycemia Reduction Approaches in Diabetes (GRADE) Study: Comparative Effectiveness

Screening

T2DM
Treated with metformin alone
A1C 6.0% at screening
+ 5 years duration at screening

Metformin failure
Treat metformin up to 1,000 mg (max) – 2,000 mg/day

Re-randomization
n = 5,000 eligible patients

Sulfonylurea
DPP-IV inhibitor
GLP-1 analog
Insulin


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Cost notwithstanding, is there an alternate approach to treating type 2 diabetes?

- Lifestyle
- Metformin
- GLP-1 analogue or DPP-IV inhibitor
- Insulin
- Bariatric surgery?

Sequential Intensification of Metformin Treatment in Type 2 Diabetes With Liraglutide Followed by Randomized Addition of Basal Insulin Prompted by A1C Targets

Diabetes Care 35:1146–1154, 2012

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A1c Change with Liraglutide followed by Detemir

60% of subjects achieved A1c < 7% with liraglutide alone
43% of the remainder achieved A1c < 7% with additional detemir
Almost 75% of subjects achieved A1c < 7% with GLP-1 RA and detemir

Weight Change with Liraglutide Followed by Detemir

Exenatide Added on to Glargin Treated Subjects Improves A1c

60% achieved A1c < 7% with vs 35% with placebo
Weight Loss Associated with Addition of Exenatide to Glargine

Weekly (QW) Exenatide is More Effective Than Glargine as Add On Treatment in Type 2 DM

Non Glycemic Goals: Treat All Cardiovascular Risk Factors Aggressively

- Smoking cessation
- Hypertension
  - BP less than 130/80 (less than 125/75 if renal disease present)
- Lipids
  - LDL cholesterol ≤ 100 mg/dL (< 70 mg/dL in "high risk" cases)
  - HDL cholesterol ≥ 45 mg/dL
  - Triglycerides ≤ 150 mg/dL
- Aspirin

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To Sum Up

- Type 2 diabetes is a progressive disease
- We need to target primarily insulin resistance and the β cell secretory defect to help patients achieve therapeutic goals
- There are other pathophysiological abnormalities that may need to be addressed in treating patients
- We need to understand the efficacy, mechanism of action, side effects and contraindications of the drugs used to treat type 2 diabetes
- Don’t be afraid to add medications or even start combination therapy simultaneously
- Start insulin earlier if control not possible with oral medications and incretins

Summary

- While more people are reaching therapeutic goals, many more need to get there
- We have many tools available to help patients achieve optimal metabolic control
- The challenge is which ones to use, and when to use them
- We need to treat all cardiovascular risk factors aggressively
- Lifestyle modification remains the cornerstone of therapy