Non – Insulin Pharmacological Treatment of Type 2 Diabetes

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Disclosure Information

Research Support: American Diabetes Association, AstraZeneca, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, NIH, Novartis, Novo Nordisk, Pfizer, Takeda, sanofi-aventis

Honoraria (Consulting and Lectures): AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Novartis, Novo Nordisk, Takeda, Pan American Laboratories, sanofi-aventis

Clinical Pearls

♦ Prevention of type 2 diabetes is possible
♦ Cardiovascular and microvascular complications of type 2 diabetes begin prior to its clinical diagnosis
♦ Monotherapy fails in the majority of patients with type 2 diabetes
♦ Effective treatment strategies should include reduction in A1C, blood pressure, and cholesterol levels
♦ Improvement in cardiovascular outcomes in patients with type 2 diabetes remains a challenge
DPP: Incidence of Type 2 Diabetes

DPP: Baseline Predictors of Response to Metformin

The ABCs of Diabetes Care

A1C
- ADA recommends < 7% = average glucose of 150 mg/dL
- AACE/IDF recommend ≤ 6.5% = average glucose of 135 mg/dL

Blood pressure
- < 130/80 mm Hg

Cholesterol
- LDL-C: < 100 mg/dL (< 70 mg/dL in very high-risk patients)
- HDL-C: > 40 mg/dL in men and > 50 mg/dL in women
- Non-HDL-C: ≤ 110 mg/dL (< 100 mg/dL in high-risk patients)
- TGs: < 150 mg/dL

Don’t forget aspirin!
Therapy for Type 2 Diabetes:
Sites of Action

- Inhibit carbohydrate breakdown
  - Alpha-glucosidase inhibitors

- Stimulate insulin secretion
  - Secretagogues
  - Incretins
    - Slow gastric emptying
    - ↑ insulin secretion
    - ↓ glucagon secretion


- Metformin
- Thiazolidinediones
  - ↑ glucose metabolism
  - Suppress glucose production
  - ↓ glucose intake
  - ↓ FFA output

OTHER DRUGS
  - Colesevelam
  - Bromocriptine
  - Anti-inflammatory

Updated ADA/EASD Consensus Algorithm

STEP 1

 Tier 1: Well-validated therapies
  - Lifestyle
  - Metformin

 Tier 2: Less well-validated therapies
  - Lifestyle + Metformin + Pioglitazone
  - Lifestyle + Metformin + GLP-1 agonist
  - Lifestyle + Metformin + Basal Insulin
  - Lifestyle + Metformin + Pioglitazone + Sulfonylurea

STEP 2

- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + GLP-1 agonist
- Lifestyle + Metformin + Basal Insulin
- Lifestyle + Metformin + Pioglitazone + Sulfonylurea

STEP 3

- Lifestyle + Metformin + Basal Insulin + Intensive Insulin
- Lifestyle + Metformin + Pioglitazone + Sulfonylurea

Selecting an Individualized Glycemic Regimen From Tier 1 or Tier 2

**Tier 1 Agents**
- When metformin is not tolerated or is contraindicated:
  - Glomerular filtration rate < 30 mL/min
- When a large reduction in A1C is needed:
  - A1C reduction ≥ 1.5%
- When medication cost is a hardship

**Tier 2 Agents**
- When avoidance of hypoglycemia is important:
  - Certain occupations (eg, drivers, heavy equipment operators, using power tools, public safety jobs)
- Certain populations (eg, history of hypoglycemia, alcohol use, elderly patients, renal insufficiency)
- When promotion of weight loss is important

### 13 “Classes” of Agents Currently Available for Controlling Hyperglycemia

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction (%)</th>
<th>Fasting vs PPG</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing (times/day)</th>
<th>Outcome Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Insulin (Long Acting)</td>
<td>1.5-2.5</td>
<td>Fasting</td>
<td>Yes</td>
<td>Gain</td>
<td>1, injected</td>
<td>DIGAMI, UKPDS, (DCCT)</td>
</tr>
<tr>
<td>Insulin (Rapid Acting)</td>
<td>1.5-2.5</td>
<td>PPG</td>
<td>Yes</td>
<td>Gain</td>
<td>1-4 injected</td>
<td>DIGAMI, UKPDS, (DCCT)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Fasting</td>
<td>Yes</td>
<td>Gain</td>
<td>1</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5-1.4</td>
<td>Fasting</td>
<td>No</td>
<td>Gain</td>
<td>1</td>
<td>PROactive, RECORD</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>0.5-1.0</td>
<td>PPG</td>
<td>No</td>
<td>Loss</td>
<td>2, injected</td>
<td>None</td>
</tr>
</tbody>
</table>

**PPG: postprandial glucose**

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### 13 “Classes” of Agents Currently Available for Controlling Hyperglycemia (Cont.)

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction (%)</th>
<th>Fasting vs PPG</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing (times/day)</th>
<th>Outcome Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>1.0-1.5</td>
<td>Both</td>
<td>Yes</td>
<td>Gain</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>0.5-0.8</td>
<td>Both</td>
<td>Rare</td>
<td>Gain</td>
<td>3</td>
<td>NAVIGATOR (pending)</td>
</tr>
<tr>
<td>α-Glucosidase Inhibitor</td>
<td>0.5-0.8</td>
<td>PPG</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>ACE (pending)</td>
</tr>
<tr>
<td>Amylin Mimetics</td>
<td>0.5-1.0</td>
<td>PPG</td>
<td>No</td>
<td>Loss</td>
<td>3, injected</td>
<td>None</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.5-0.8</td>
<td>Both</td>
<td>Yes</td>
<td>Neutral</td>
<td>1</td>
<td>TECOS (pending)</td>
</tr>
<tr>
<td>Bile Acid Sequestrant</td>
<td>0.5</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>1-2</td>
<td>None</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0.1</td>
<td>PPG</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>None</td>
</tr>
</tbody>
</table>

**DPP-4: dipeptidyl peptidase-4**

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### Effect of Antidiabetic Agents on Weight

**Weight Gain**
- Insulin
- Sulfonylureas and other insulin secretagogues
- Thiazolidinediones

**Weight Neutral or Slight Weight Loss**
- α-Glucosidase inhibitors (acarbose, miglitol)
- Metformin
- DPP-IV inhibitors

**Weight Loss**
- GLP-1 mimetics
- Pramlintide
Changing Treatment Paradigm

- Diet & exercise
- Monotherapy
- Combinations of oral agents
- Insulin

Problems:
- Glycemic targets often not met
- Monotherapy not effective long-term
- Treatment fails to address multiple impairments
- Step-wise approach tends to perpetuate “failure”
- Glucose toxicity interferes with treatment response


The Number of Medications Taken Usually Increases With Duration of Disease

- IGT = impaired glucose tolerance

Primary Objectives of Effective Management

- A1C %
- SBP mm Hg
- LDL mg/dL

- Reduction of both micro- and macro-vascular event rates

Primary endpoint: Kaplan-Meier Estimates of the Cumulative Incidence of Monotherapy Failure

- Hazard ratio (95% CI)
  - Rosiglitazone vs metformin, 0.68 (0.55–0.85); \( P < 0.001 \)
  - Rosiglitazone vs glyburide, 0.37 (0.30–0.45); \( P < 0.001 \)


Thiazolidinediones (TZD’s): Pioglitazone and Rosiglitazone

- Mechanism of action
  - Enhance insulin sensitivity in muscle, adipose tissue
  - Inhibit hepatic gluconeogenesis
  - Reduced rate of beta cell dysfunction

- Safety and efficacy
  - Decrease A1C 1-2%
  - Adverse effects: edema, weight gain, anemia; peripheral fractures in women, macular edema, (MIs - rosiglitazone*)

- Dosing
  - Initial dose (monotherapy): 1/2 to 2/3 maximum; dosing 1-2 x/day
  - Maximum effective dose: maximum dose
  - Titration frequency: weeks to month(s)

*Use no longer endorsed by ADA*

PROactive Trial: Adding on Pioglitazone

- Main secondary composite end point: all-cause mortality, nonfatal myocardial infarction, and stroke
  - ARR Pioglitazone 2.1% vs Placebo 2.5%
  - 3-year estimate

- Main primary composite end point: all-cause mortality, nonfatal myocardial infarction (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in coronary or leg arteries, above-ankle amputation


ARR = average risk ratio

PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events
### RECORD Trial

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Rosiglitazone (n = 2220)</th>
<th>Control (n = 2227)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Hospitalization or CV Death</td>
<td>321</td>
<td>323</td>
<td>0.99 (0.85-1.16)</td>
<td>0.930</td>
</tr>
<tr>
<td>All cause</td>
<td>136</td>
<td>157</td>
<td>0.86 (0.69-1.08)</td>
<td>0.190</td>
</tr>
<tr>
<td>CV</td>
<td>60</td>
<td>71</td>
<td>0.84 (0.59-1.18)</td>
<td>0.320</td>
</tr>
<tr>
<td>MI*</td>
<td>64</td>
<td>56</td>
<td>1.14 (0.80-1.63)</td>
<td>0.470</td>
</tr>
<tr>
<td>Stroke*</td>
<td>46</td>
<td>63</td>
<td>0.72 (0.49-1.06)</td>
<td>0.100</td>
</tr>
<tr>
<td>CV Death, MI, or Stroke</td>
<td>154</td>
<td>165</td>
<td>0.93 (0.74-1.15)</td>
<td>0.500</td>
</tr>
<tr>
<td>Heart Failure*</td>
<td>61</td>
<td>29</td>
<td>2.10 (1.35-3.27)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**RECORD:** Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

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### BARI 2D CABG Subgroup: Glycemic Control Reduces Risk of CV Events

- Diabetes patients with coronary artery disease were stratified for either CABG or percutaneous coronary intervention
- Medical therapy: either insulin provision (sulfonylurea/insulin) or insulin sensitization (metformin/thiazolidinediones)
- In the CABG substratum, major CV events after revascularization were significantly lower than after medical therapy
- However, no difference in the overall analysis between prompt revascularization vs medical therapy
- Or between insulin provision vs insulin sensitization

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### Major Pathophysiologic Defects in Type 2 Diabetes

- Insulin resistance
- Glucose uptake
- Hyperglycemia
- Islet-cell dysfunction
- Glucagon
- Pancreas
- Liver
- Insulin (Beta cell)
- Insulin resistance

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Role of Incretins in Glucose Homeostasis

Ingestion of food

- Release of gut hormones — Incretins

- GLP-1 and GIP

Pancreas

- Glucose-dependent insulin from beta cells (GLP-1 and GIP)

- Glucose-dependent glucagon from alpha cells (GIP)

DPP-4 enzyme

- GLP-1 & GIP

Al pha ce ll

Glucose dependent

- Glucagon from alpha cells (GIP)

- Glucose production by liver

GLP–1 Replacement Therapy in T2DM in Development

- Short-acting GLP–1 receptor agonists
  - Exenatide (Amylin/Lilly) - approved
  - Liraglutide (Novo Nordisk) - approved
  - AVE0010 (sanofi-aventis)
  - MKC253 Inhaled (MannKind)

- Long-Acting GLP–1 receptor agonists
  - LAR-exenatide (Amylin/Lilly)
  - Taspoglutide (R1583–Roche)
  - Albiglutide (Syncria®–GSK)
  - Lilly compound
  - Conjuchem compound

Exenatide + Oral Agents

Summary of A1C Changes

- Placebo
- Exenatide 5 μg
- Exenatide 10 μg
**Exenatide + Oral Agents**

**Summary of Weight Changes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide + SU</td>
<td>-1.6</td>
</tr>
<tr>
<td>Exenatide + SU + Met</td>
<td>-1.6</td>
</tr>
<tr>
<td>Exenatide + SU + Met + Insulin</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

*P<0.05 vs placebo

**Exenatide: Potential for Type 2 Diabetes**

**Benefits**
- Beta Cell Effect
  - Restored first-phase insulin
- Three AMIGOS Endpoints
  - A1C ↓ of ~0.8-0.9%
  - A1C ↓ in ~35-65%
  - Weight Loss 1.6-2.8 kg
- Ongoing Open Label Study in Completers/Responders
  - Sustained A1C reductions ~1%
  - Sustained Weight Loss ~3 kg

**Limitations**
- Nausea
  - Mild-Moderate ~40%
  - Severe ~5%
  - Causing Withdrawal ~3%
- Vomiting
  - 13%
  - Causing Withdrawal ~1%
- Twice Daily Injections
- Cost
- No Long-Term Controlled Study

**Exenatide Added to Ongoing Therapy Improves Risk Factors**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change From Baseline</th>
<th>P Value (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>-5.3 ± 0.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>-0.8 ± 0.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>-10.8 ± 3.1</td>
<td>0.0007</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-44.4 ± 12.1</td>
<td>0.0003</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>-11.8 ± 2.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>+8.5 ± 0.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>-3.5 ± 1.2</td>
<td>0.0063</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>-3.3 ± 0.8</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Liraglutide Reduces HbA1c as Monotherapy and in Combination Therapy

LEAD: Weight Reduction With Liraglutide

Comparison of DPP-4 Inhibitors
HbA1c Reductions with Sitagliptin in Monotherapy and Add-on Combination Therapy

Efficacy of Add-on Sitagliptin

Both Sitagliptin and Metformin Increased Active GLP-1 Concentrations
Sitagliptin Provided Weight Reduction (vs. Weight Gain) and a Much Lower Incidence of Hypoglycemia

- Change in body weight over time
- Incidence (%)
- Δ between groups = –2.5 kg (p < 0.001)
- At 52 weeks: Glipizide: +1.2 kg; sitagliptin: –1.3 kg

Saxagliptin Add-on to Metformin

- Reducing in HbA1c in Patients With Inadequately Controlled Type 2 Diabetes on Metformin Alone
- BL A1c (%) Mean Change From Baseline ± SE

Prandial Glucagon After Up To 2 Years Add-on Treatment In T2D Patients inadequately Controlled with Metformin

**ISR/G After Up To 2 Years Add-on Treatment In T2D Patients Inadequately Controlled with Metformin**

![Graph showing ISR/G values with different treatments and significance level.]

- ISR/G (insulin secretory rate relative to glucose) with significance level *p = 0.022*.

**GLP-1 Receptor Agonists vs DPP-4 Inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>GLP-1R Agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Injection</td>
<td>Oral</td>
</tr>
<tr>
<td>GLP-1 concentrations</td>
<td>Pharmacological</td>
<td>Physiological</td>
</tr>
<tr>
<td>Mechanisms of action</td>
<td>GLP-1</td>
<td>GLP-1 + GIP</td>
</tr>
</tbody>
</table>

- Activation of portal glucose sensor
- Insulin secretion: No vs Yes
- Glucagon secretion: No vs Yes
- Gastrointestinal effects: Yes vs No
- Expansion of beta-cell mass: Yes vs Yes
- Nausea and vomiting: Yes vs No
- Potential immunogenicity: Yes vs No

Adapted from Drucker DJ. Cell Metab. 2006;3:153–165.

**Cardiovascular Risk in Saxagliptin Trials**

- MACE: 0.44 (0.24, 0.82)
- ACE: 0.59 (0.35, 1.00)

Data from 8 randomized, double-blind, phase 2b/3 trials.

- MACE = major adverse cardiovascular events
- ACE = acute clinically significant events

- Saxagliptin exposure = 3758 patient-years, comparator exposure = 1293 patient-years.
- Includes revascularization.

Other Considerations: Pancreatitis

Sitagliptin and Sitagliptin/metformin

- FDA Adverse Event Reporting System
  - 88 reports of acute pancreatitis, including 2 cases of hemorrhagic or necrotizing pancreatitis (October 16, 2006-February 9, 2009)
  - 58 (66%) of the patients were hospitalized, 4 of whom were admitted to the intensive care unit
  - 47 (53%) of cases resolved once sitagliptin was discontinued
  - 45 (51%) of cases were associated with at least one other risk factor for developing pancreatitis (diabetes, obesity, high cholesterol, high triglycerides)

- FDA is working with manufacturer to revise prescribing information to include post-marketing reports of acute pancreatitis, and recommendations for healthcare professionals for monitoring patients

DPP-4 Inhibitors: Role in T2DM Therapy

- Oral therapy, once daily
- Endogenous GLP-1 and GIP levels are increased in response to meal and are transient
- Monotherapy, add-on to metformin, TZD, SU, insulin
- Clinically significant A1c reductions
  - Comparable efficacy to rosiglitazone, glipizide

DPP-4 Inhibitors: Safety and Tolerability

- Low risk of hypoglycemia
- No weight gain
- No edema
- No GI effects
- No cardiac issues
- No immunologic effects
- No adverse events attributable to DPP-4 inhibition
- Low risk of drug-drug interactions
- Hypersensitivity reactions with sitagliptin
DPP-4 Inhibitors: Cardiovascular Effects

- Weight neutral
- No effect on BP
- No effect on fasting lipids
- Possible effect on post-prandial lipemia
- Enhance insulin sensitivity
- No CVD signal in clinical trials

Welchol™ Consistently Lowers A1C* by An Additional Mean 0.5%

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Baseline A1C (%)</th>
<th>Change in A1C (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welchol Plus Metformin-Based</td>
<td>8.1</td>
<td>-0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Welchol Plus Sulfonylurea-Based</td>
<td>8.2</td>
<td>-0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Welchol Plus Insulin-Based</td>
<td>8.3</td>
<td>-0.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*From baseline, placebo-adjusted. Data on file, Daiichi Sankyo, Inc.

ITT Population, Last Observation Carried Forward (LOCF): patients on background monotherapy and combination therapy.

FXR: Metabolic Modulator of Post-prandial Hepatic Lipid and Glucose Metabolism
Chronic Subclinical Inflammation: Part of the Insulin Resistance Syndrome

Mean values [SE, log CRP]

Number of metabolic disorders

TINSAL-T2D Stage 1

Changes in circulating metabolic measures, by study group. All data are provided as unadjusted mean changes.

TINSAL-T2D Stage 1: HbA1c (primary endpoint)

Percent HbA1c (change from baseline)

Trial week

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SUMMARY

TYPE 2 DIABETES IS A COMPLEX DISEASE
MULTIPLE NEW TARGETS FOR TYPE 2 DIABETES
WHICH TREATMENT WILL PROVIDE VALUE?