RECENT ADVANCES IN PHARMACOTHERAPY OF TYPE 2 DIABETES

Mudit Jain, MD, FACE, CDE
Diabetes & Thyroid Care Center of Excellence, Plantation FL.
Clinical Asst. Professor of Medicine
Nova SE University & Florida Intl. University
DISCLOSURES FOR DR. JAIN

- Speaker’s Bureau: AstraZeneca; Boehringer-Ingelheim; Lilly, Mannkind
Pathophysiology of T2DM

Available Pharmacologic agents

Approach to the Patient with T2DM
Natural History of Type 2 Diabetes

- Impaired glucose tolerance
- Undiagnosed diabetes
- Known diabetes

- Insulin resistance
- Insulin secretion
- Postprandial glucose
- Fasting glucose

Microvascular complications
Macrovascular complications

Adapted from Ramlo-Halsted BA, Edelman SV. *Prim Care.* 1999;26:771-789
The Pathophysiology of Type 2 Diabetes Involves Multiple Dysfunctions

Chronic Hyperglycemia

- Glucose production
- Insulin secretion
- Glucagon secretion
- Glucose uptake
- Lipolysis
- Incretin effect
- Glucose reabsorption
- Neurotransmitter function

Pharmacologic Agents for Type 2 Diabetes

- Biguanides - Metformin
- Sulfonylureas
- Repaglinide & Nateglinide
- Thiazolidinediones
- GLP-1 Receptor Agonists
- DPP-4 Inhibitors
- SGLT-2 Inhibitors
- Alpha Glucosidase Inhibitor - Acarbose
- Bile Acid Sequestrant - Colesevelam
- Amylin Mimetic – Pramlintide
- Dopamine Agonist – Bromocriptine QR
- Insulins
**METFORMIN**

- Initial agent of choice in mild diabetes along with lifestyle

- **Mechanism:**
  - Decreases hepatic glucose production
  - Enhances glucose uptake by muscle

- **Advantages:**
  - Cost-effective
  - Mild weight loss
  - No hypoglycemia
  - Extensive experience
  - Decrease CV events (UKPDS), all cause mortality
  - Effect on lipids, CRP, PAI-1
**METFORMIN**

- **Disadvantages:**
  - GI Side effects - diarrhea, abdominal discomfort
  - Lactic Acidosis – Contraindicated in CKD, liver failure, hypoxia, sepsis, dehydration
  - Vitamin B12 deficiency
SULFONYLUREAS

- Classic insulin secretagogues.
- Second generation - glyburide, glipizide, glimepiride
- Bind to SU receptor on beta cell - cause insulin release, 2\textsuperscript{nd} phase
- Duration of action 16-30 hours – continuous insulin release
SULFONYLUREAS

○ Hypoglycemia – a major concern. Patients need to be educated. Especially in elderly, renal insufficiency

○ Do not alter course of disease progression: 5-7% failure rate annually

○ Weight gain

○ Only advantage – Cost
Repaglinide & Nateglinide

- Repaglinide (Meglinitide)
- Nateglinide (D-Phenylalanine der.)

- Mechanism:
  Stimulate insulin secretion rapidly and for a short period when needed – mealtime
Repaglinide & Naglhinide

- Advantages:
  - Postprandial control
  - Avoidance of continuous insulin secretion/hypoglycemia
  - Dosing flexibility
  - Use in CKD

- Disadvantages:
  - Frequent dosing
  - Hypoglycemia
THIAZOLIDINEDIONES (TZDs)

- Pioglitazone (Actos)
- No longer marketed – rosiglitazone, troglitazone

Mechanism:
- Activation of nuclear PPAR gamma receptor
- Increase in insulin sensitivity – liver and muscle
THIAZOLIDINEDIONES (TZDs)

- Advantages:
  - No Hypoglycemia
  - Durability of control
  - Decrease in CV events (pioglitazone/PROactive)
  - Lipids- inc. HDL, dec. TG

- Disadvantages:
  - Weight gain
  - Edema, CHF
  - Bone fractures
AGENTS USING THE INCRETIN EFFECT

- GLP-1 Agonists
- DPP-IV Inhibitors
The Incretin Effect

Control subjects

- Oral glucose: 50 g dissolved in 400 mL
- Intravenous (IV) glucose: titrated to the same plasma glucose concentration as oral administration

The incretin effect is demonstrated by a potentiated insulin response following oral glucose uptake vs. IV glucose administration

*p≤.05. IR=immunoreactive
Nauck et al. Diabetologia 1986;29:46-52
The Incretin Effect: Diminished in Patients With T2D

Control subjects

Venous Plasma Glucose (mmol/L)

Time (min)

T2D

Venous Plasma Glucose (mmol/L)

Time (min)

IV glucose

Oral glucose

Time of dosing

Incretin effect

The incretin effect is diminished in patients with T2D

*ps ≤ 0.05. IR=immunoreactive; IV=intravenous; T2D=type 2 diabetes
Nauck et al. Diabetologia 1986;29:46-52
Glucoregulatory Role of GLP-1 and GIP Effects in Humans

On ingestion of food:
GLP-1 secreted by L-cells, GIP secreted by K-cells

↓ β-cell workload
Promotes satiety and reduces appetite

α-cells:
↓ Postprandial glucagon secretion

Liver:
↑ Insulin/glucagon:
reduces hepatic glucose output

Stomach:
slows gastric emptying

β-cells: enhance glucose-dependent insulin secretion

β-cell response

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide
GLP-1 Exerts Multiple Actions in Patients With T2D

Administration of GLP-1 to patients with T2D has been associated with:

♦ Reduced fasting hyperglycemia
♦ Normalized postprandial glucose excursions
♦ Suppression of inappropriately high glucagon secretion
♦ Improved β-cell responsiveness and maximal insulin secretory capacity
♦ Reduced food intake and weight loss

GLP-1=glucagon-like peptide-1; T2D=type 2 diabetes
Drucker. Diabetes Care 2003;26:2929-40
Two classes of agents have been developed based on the therapeutic potential of enhancing GLP-1 activity

- GLP-1 receptor agonists: agents that mimic the actions of GLP-1
- Protease DPP-4 inhibitors: agents that prolong the activity of endogenous GLP-1

GLP-1=glucagon-like peptide-1; DPP-4=dipeptidyl peptidase-4

GLP-1 Receptor Agonists

- Exenatide ER, exenatide (Bydureon, Byetta)
- Liraglutide (Victoza)
- Dulaglutide (Trulicity)
- Albiglutide (Tanzeum)

Mechanism:
- Binds to & activates GLP-1 receptors
- Increase insulin secretion - glucose dependent
- Decrease glucagon secretion - glucose dependent
- Decrease gastric emptying
- Decrease appetite
GLP-1 AGONISTS

- Advantages:
  - Weight loss
  - Decrease post-prandial glucose
  - Durability of control
  - Decrease in CV risk
  - No hypoglycemia

- Disadvantages:
  - Injectable
  - GI side effects
## Glucose Control with GLP-1 Receptor Agonists

### Placebo-Adjusted Change from Baseline
(Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb¹</td>
<td>Dul²</td>
<td>Exe³</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.1</td>
<td>7.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo-adjusted</th>
<th>Δ A1C (%)</th>
<th>Placebo-adjusted</th>
<th>Δ A1C (%)</th>
<th>Placebo-adjusted</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline A1C (%)</td>
<td>0</td>
<td>Baseline A1C (%)</td>
<td>0</td>
<td>Baseline A1C (%)</td>
<td>0</td>
</tr>
<tr>
<td>Placebo-adjusted</td>
<td>-1.0</td>
<td>Placebo-adjusted</td>
<td>-0.8†</td>
<td>Placebo-adjusted</td>
<td>-0.7</td>
</tr>
<tr>
<td>Δ A1C (%)</td>
<td>-1.1†</td>
<td>Δ A1C (%)</td>
<td>-1.5†</td>
<td>Δ A1C (%)</td>
<td>-1.5†</td>
</tr>
</tbody>
</table>

*Metformin with or without SU or TZD. ¹Metformin with or without SU. †Absolute change from baseline (active-controlled trial).

**Weight Change with GLP-1 Receptor Agonists**

**Absolute Change from Baseline**  
(Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb¹</td>
<td>Dul²</td>
<td>Exe³</td>
</tr>
<tr>
<td>-0.9</td>
<td>-2.3</td>
<td>-3.1</td>
</tr>
</tbody>
</table>

-0.2

*Metformin with or without SU or TZD. †Metformin with or without SU.*

Clinical Outcomes with Liraglutide

LEADER

Study Design

- N=9340 patients with T2D and high CV risk
- Randomization
  - Liraglutide: n=4672
  - Placebo: n=4668
- Noninferiority study: prespecified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

Key Results

- Median follow-up: 3.5 years
- Difference from placebo at 36 months
  - A1C: −0.40% (95% CI, −0.45% to −0.34%)
  - Weight: −2.3 kg (95% CI, −2.0 to −2.5 kg)
  - SBP: −1.2 mm Hg (95% CI, −0.5 to −1.9 mm Hg)
- CV outcomes
  - Primary: HR 0.87 (95% CI 0.78 to 0.97); \( P=0.01 \) for superiority
  - Secondary HR: 0.88 (95% CI 0.81 to 0.96); \( P=0.005 \) for superiority
- Significantly lower rates of all-cause death and CV death with liraglutide
- Increased rates of gastrointestinal events in liraglutide-treated patients
- Lower numerical incidence of pancreatitis in liraglutide group (not statistically significant)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Clinical Outcomes with Liraglutide

LEADER (N=9340)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67-0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

DPP-IV Inhibitors

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)

Mechanism:

- Prolongation of action of endogenous incretins – GLP-1, GIP
- Increased insulin secretion, suppression of postprandial glucagon - both glucose dependent
The Insulinotropie Actions of GLP-1 Are Glucose Dependent

Pancreatic β-cell

Glucose transporter

GLP-1 receptor

ATP/ADP

cAMP

Insulin granule

Insulin release

K/ATP channel

Ca^{2+} channel

Ca^{2+}

Limited Insulin is Released in Response to GLP-1 Receptor Stimulation in the Absence of Glucose

Pancreatic β-cell

K/ATP channel

Ca\(^{2+}\) channel

Glucose transporter

cAMP

ATP

GLP-1 receptor

Insulin granule

Insulin release

DPP-IV Inhibitors

Advantages:
- No hypoglycemia
- Weight neutral
- Well tolerated

Disadvantages:
- Cost
- Weak
SGLT-2 Inhibitors

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

Mechanism:
Inhibit SGLT2 receptors in proximal tubule-block glucose reabsorption - Glycosuria
The Majority of Filtered Glucose Is Reabsorbed by SGLT2 Transporters\textsuperscript{1,2}

\[ 100 \text{ mg/dL} \times 180 \text{ L/day} = 180 \text{ g glucose/day} \]

- Glucose filtration
- Glucose reabsorption
- SGLT2
- SGLT1
- Loop of Henle
- Collecting duct
- No/minimal glucose excretion

*100 mg/dL = normal glucose concentration; 180 L = volume of plasma the kidneys filter per day; 180 g = glucose filtered per day.*

SGLT = sodium-glucose cotransporter.

SGLT-2 inhibitors

Advantages:
- Weight loss
- BP reduction
- Beta cell independent effect - all stages of T2DM
- EPA-REG study - Decrease in CV event rate & all cause mortality

Disadvantages:
- Genital Mycotic infections, UTI
- Volume depletion
- DKA
- Bone loss - Invokana
Clinical Outcomes with Empagliflozin

Study Design

- N=7020 patients with T2D and CVD
- Randomization
  - Empagliflozin: n=4687
  - Placebo: n=2333
- Noninferiority study: prespecified HR margin = 1.3 for primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina

Key Results

- Median follow-up: 3.1 years
- Week 206 A1C, difference from placebo
  - Empagliflozin 10 mg: -0.24% (95% CI, -0.40% to -0.08%)
  - Empagliflozin 25 mg: -0.36% (95% CI, -0.51% to -0.20%)
- CV outcomes (pooled analysis)
  - Primary: HR 0.86 (95% CI 0.74 to 0.99); P=0.04 for superiority
  - Secondary HR: 0.89 (95% CI 0.78 to 1.01); P<0.001 for noninferiority and P=0.08 for superiority
- Significantly lower rates of all-cause death, CV death, and HF hospitalization with empagliflozin
- Increased rates of genital infections in empagliflozin-treated patients

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

**Clinical Outcomes with Empagliflozin**

**EMPA-REG OUTCOME Pooled Analysis (N=7020)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for HF or CV death</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Insulins

- Short-acting- Regular
- Intermediate-acting- NPH
- Rapid-acting- aspart, lispro, glulisine – Novolog, Humalog, Apidra
- Inhaled Insulin - Afrezza
- Humulin R U500
- Long-acting- glargine, detemir, glargine U-300, deglutec – Lantus, Levemir, Toujeo, Tresiba
- Pre-mixed
Insulin

- **Rapid** (Lispro, Aspart, Glulisine)
- **Short** (Regular)
- **Intermediate** (NPH)
- **Long** (Detemir)
- **Long** (Glargine)

<table>
<thead>
<tr>
<th>Hours after injection</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Basal-Bolus Insulin Absorption Pattern

Pre – mixed Insulins

• Generally taken twice a day before mealtime.
• Combination of regular insulin and an intermediate-acting insulin
• Examples:
  – Humulin 70/30
  – Novolin 70/30
  – Novolog 70/30
  – Humalog Mix 75/25
  – Humalog 50/50
GLYCEMIC TARGETS

- A1c <7.0 ADA
  <6.5 AACE

- Less Stringent target A1c 8.0 or higher – at risk for hypoglycemia, limited life expectancy

- Lower target A1c 6.0-6.5 – select patients, shorter duration of DM, without hypoglycemia

- Preprandial CBG 80-130 mg/dL
  Peak Postprandial CBG <180 mg/dL
Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**
  - low
  - high

- **Disease duration**
  - newly diagnosed
  - long-standing

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few / mild
  - severe

- **Established vascular complications**
  - absent
  - few / mild
  - severe

- **Resources, support system**
  - readily available
  - limited

*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*
ADA/EASD T2D Treatment Algorithm

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

Sulfonylurea
Thiazolidinedione
DPP-4 inhibitor
SGLT2 inhibitor
GLP-1 receptor agonist
Insulin (basal)

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):

Metformin + Thiazolidinedione + DPP-4 inhibitor + SGLT2 inhibitor + GLP-1 receptor agonist + Insulin (basal)

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):

Metformin + Thiazolidinedione + DPP-4 inhibitor + SGLT2 inhibitor + GLP-1 receptor agonist + Insulin (basal)

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-

CHOICE OF ANTI-DIABETIC AGENT

- Affordability
- Complementary mechanism of action
- Beta cell function
- Side effect profile
- Patient preference
- Durability of control
Targets of Antihyperglycemic Agents

Islet α-cell

- Increased glucagon secretion

- Decreased insulin secretion

- Islet β-cell

- Decreased incretin effect

- Increased lipolysis

- Increased glucose reabsorption

- Metformin

- TZDs

- DPP-4i

- GLP-1 RA

- SUs

- Increased hepatic glucose production

- Decreased glucose uptake

*Exogenous insulin does not increase insulin secretion but does act as a substitute for decreased endogenous insulin.

DPP-4i=dipeptidyl peptidase-4 inhibitor; GLP-1 RA=glucagon-like peptide-1 receptor agonist; SGLT-2=sodium-glucose co-transporter-2; SU=sulfonylurea; TZD=thiazolidinedione

1. DeFronzo. Diabetes 2009;58:773-95
ADA/EASD T2D Treatment Algorithm: Sequential Insulin Strategies

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

- **A1C < 8%**
  - TDD 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- **Fixed regimen:** Increase TDD by 2 U
- **Adjustable regimen:**
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

INTENSIFY (Prandial Control)

- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i
- **Add Prandial Insulin**
  - Basal Plus 1, Plus 2, Plus 3
    - Begin prandial insulin before largest meal
    - If not at goal, progress to injections before 2 or 3 meals
    - Start: 10% of basal dose or 5 units
  - Basal Bolus
    - Begin prandial insulin before each meal
    - 50% Basal / 50% Prandial
    - TDD 0.3–0.5 U/kg
    - Start: 50% of TDD in three doses before meals

Glycemic Control Not at Goal*

*Glycemic Goal:

- <7% for most patients with T2D; fasting and premeal
- BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

COPYRIGHT © 2016 AACE MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE.
Common Principles in AACE/ACE and ADA/EASD T2D Treatment Algorithms

- Individualize glycemic goals based on patient characteristics
- Promptly intensify antihyperglycemic therapy to maintain blood glucose at individual targets
  - Combination therapy necessary for most patients
- Insulin eventually necessary for many patients