New Agents and Technologies in the Pipeline for the Treatment of Patients with Diabetes

Peter Stein, MD
Janssen Research and Development
Agents in Phase 3 Development for T2DM

• Long-acting GLP-1 analogues – including once-weekly exenatide, albiglutide, dulaglutide

• SGLT2 inhibitors - including canagliflozin, dapagliflozin, empagliflozin

• GPR40 agonists - TAK875

• Dual PPAR α/γ agents: aleglitazar (Phase 3 studies for post-MI use)

• Insulins
  – Inhaled - Afrezza®
  – Long-acting – Insulin degludec; LY2605541 (Lilly)
AHAs Sites of Action

- Glucose reabsorption
- Kidney
- SGLT2 inhibitors
- SU, meglitinid es
- DPP-4
- GLP-1 agents

↓ Glucagon

Liver

Adipose

Kidney

Muscle

Pancreas

Insulin secretagogue

Glucose reabsorption

Defective insulin secretion

Insulin release

Glucagon release

FFA release

Impaired glucose uptake

Glucose uptake

Carbohydrates

Intestines

AGI

SGLT2 inhibitors

GLP-1

DPP-4

TZD

Biguanide

FFA absorption

Insulin release

Defective insulin secretion

Insulin secretion
Sodium-glucose Transporter-2 (SGLT2): Key Renal Transporter Reabsorbing Filtered Glucose Back into Systemic Circulation

SGLT2
- Primarily expressed in kidney
- Responsible for majority of renal glucose reabsorption

SGLT1
- Responsible for small portion of renal glucose reabsorption
- Prominent role in intestinal glucose absorption
SGLT2 Inhibition Leads to Improved Glucose Control in T2DM

- Inhibition of SGLT2 increases urinary glucose excretion (UGE)
- Directly reduces plasma glucose concentrations
- Increased UGE is loss of calories (4 kcal per gram of carbohydrate)
Dapagliflozin: Comparator Study to Glipizide in Add-on to Metformin

Nauck et al Diabetes Care 2011
### Dapagliflozin: Comparator Study to Glipizide in Add-on to Metformin

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin + metformin n = 406</th>
<th>Glipizide + metformin n = 408</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall summary of patients with an AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>318 (78.3)</td>
<td>318 (77.9)</td>
</tr>
<tr>
<td>≥ 1 related to study treatment</td>
<td>110 (27.1)</td>
<td>110 (27.0)</td>
</tr>
<tr>
<td>Leading to discontinuation*</td>
<td>37 (9.1)</td>
<td>24 (5.9)</td>
</tr>
<tr>
<td>Patients with SAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>35 (8.6)</td>
<td>46 (11.3)</td>
</tr>
<tr>
<td>≥ 1 related to study treatment</td>
<td>6 (1.5)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>9 (2.2)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Patients with special interest AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemic events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14 (3.4)§</td>
<td>162 (39.7)§</td>
</tr>
<tr>
<td>Major episode</td>
<td>0</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Minor episode</td>
<td>7 (1.7)</td>
<td>147 (36.0)</td>
</tr>
<tr>
<td>Signs and symptoms suggestive of genital infections‖</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50/406 (12.3)</td>
<td>11/408 (2.7)</td>
</tr>
<tr>
<td>Male</td>
<td>12/226 (5.3)</td>
<td>1/223 (0.4)</td>
</tr>
<tr>
<td>Female</td>
<td>38/180 (21.1)</td>
<td>10/185 (5.4)</td>
</tr>
<tr>
<td>Signs and symptoms suggestive of UTI‖</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44/406 (10.8)§</td>
<td>26/408 (6.4)</td>
</tr>
<tr>
<td>Pyelonephritis/pyelocystitis</td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

Safety table results extracted from Nauck et al Diabetes Care 2011 (see publication for complete results)
Canagliflozin Active-comparator (Glimepiride) Add-on to Metformin
Change in A1C (LOCF)

LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

Hypoglycemia Event Incidence:
- CANA 100 mg: 5.6%
- CANA 300 mg: 4.9%
- GLIM: 34.2%

Cefulu et al ADA2012
Canagliflozin Active-comparator (Glimepiride) Add-on to Metformin

Percent Change in Body Weight (LOCF)

LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin; LS, least squares; SE, standard error.

Cefalu et al ADA2012
## Canagliflozin Active-comparator (Glimepiride) Add-on to Metformin

### Summary of Overall Safety and Selected AEs

<table>
<thead>
<tr>
<th></th>
<th>Subjects, n (%)</th>
<th>GLIM (n = 482)</th>
<th>CANA 100 mg (n = 483)</th>
<th>CANA 300 mg (n = 485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td>330 (68.5)</td>
<td>311 (64.4)</td>
<td>332 (68.5)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td></td>
<td>28 (5.8)</td>
<td>25 (5.2)</td>
<td>32 (6.6)</td>
</tr>
<tr>
<td>AEs related to study drug*</td>
<td></td>
<td>113 (23.4)</td>
<td>118 (24.4)</td>
<td>145 (29.9)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
<td>39 (8.1)</td>
<td>24 (5.0)</td>
<td>26 (5.4)</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td>2 (0.4)</td>
<td>0</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Genital mycotic infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male†</td>
<td></td>
<td>3 (1.1)</td>
<td>17 (6.7)</td>
<td>20 (8.3)</td>
</tr>
<tr>
<td>Female‡§</td>
<td></td>
<td>5 (2.3)</td>
<td>26 (11.3)</td>
<td>34 (13.9)</td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td>22 (4.6)</td>
<td>31 (6.4)</td>
<td>31 (6.4)</td>
</tr>
<tr>
<td>Osmotic diuresis-related AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollakiuria (increased frequency)</td>
<td></td>
<td>1 (0.2)</td>
<td>12 (2.5)</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>Polyuria</td>
<td></td>
<td>2 (0.4)</td>
<td>4 (0.8)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Volume-related AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural dizziness</td>
<td></td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

AE, adverse event; GLIM, glimepiride; CANA, canagliflozin; UTI, urinary tract infection.

*Possibly, probably, or very likely related to study drug, as assessed by investigators.

†GLIM, n = 263; CANA 100 mg, n = 252; CANA 300 mg, n = 241.

‡GLIM, n = 219; CANA 100 mg, n = 231; CANA 300 mg, n = 244.

§Including vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
SGLT2 Inhibitors – Reported Profile

Efficacy
• Glucose-lowering
  – HbA$_{1c}$, FPG, PPG
• Decreases body weight
• Lowers blood pressure

Safety
• Genital infections (vulvovaginitis, balanitis)
• UTIs
• Adverse events related to diuretic response (osmotic diuresis)
• Other reported adverse effects
GPR40 – a new target for the treatment of patients with T2DM

- GPR40 – a G-protein coupled receptor (GPCR) – with endogenous ligands including free fatty acids
- On pancreatic islet beta-cells and on gut incretin secreting cells (GLP-1)
- Stimulates glucose-dependent release of insulin

Araki DOM 2012
GPR40 Agonist: TAK875
Dose-Range Finding Study Results

Burant et al Lancet 2012
Glucose Monitoring: Closing the Loop

JDRF CGM Study Group
Diabetes Care 2009
Glucose monitoring: Closing the Loop

- **Glucose Target**
- **CGM Reading**
- **Controller-Determined Insulin Dose**
- **Glucose**
- **Insulin Dose**

![Graph showing glucose concentration over time with meal and snack events.
Blue line represents closed-loop delivery, and orange line represents control.
Haidar CMAJ 2013]
Stem Cell-Based Therapeutics

• Stem cell based therapies – differentiating into insulin-secreting cells ex-vivo and transplanting SC

• Rejection as the key limitation (xeno- or allo-transplantation)

• One approach: encapsulation
Immunoprotection Strategy Using an Encapsulation Device

- Loading Port
- Oxygen, Nutrients & Glucose
- Insulin
- Outer Cell Vascularizing Membrane
- Pancreatic Precursor Cells
- Inner Cell Isolation Membrane
- Immune Cell Barrier
“Game Changers” in the Care of Patients with Diabetes

• Near term – new classes of agents that add to our treatment options

• “Mid-term” – CV outcome studies for recent / new classes (DPP-4, GLP-1, SGLT2 inhibitors)

• Long-term - transforming how we care of patients
  – Closing the loop (artificial pancreas)
  – Stem cell approaches
  – Agents that restore / expand beta-cell functional mass
CV Outcome Study Results from New Agent Classes

• GLP-1 receptor agonists
  – LEADER (liraglutide)
  – EXSCEL (once-weekly exenatide)
  – REWIND (Dulaglutide)
  – ELIXA (Lixisenatide)

• DPP-4
  – TECOS (Sitagliptin)
  – SAVOR (Saxagliptin)
  – EXAMINE (Alogliptin)
  – CAROLINA (Linagliptin)

• SGLT2
  – DECLARE (Dapagliflozin)
  – CANVAS (Canagliflozin)
  – Empagliflozin

Study Results 2013-2019
Current US Diabetes Control: NHANES

53% in 2007-2010 vs 44% in 1999-2003

Survey Participants (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>≥10</th>
<th>9.0–9.9</th>
<th>8.0–8.9</th>
<th>7.0–7.9</th>
<th>6.0–6.9</th>
<th>&lt;6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999–2002</td>
<td>12.6</td>
<td>6.3</td>
<td>14.9</td>
<td>22.1</td>
<td>27.3</td>
<td>16.9</td>
</tr>
<tr>
<td>2003–2006</td>
<td>7.3</td>
<td>6.1</td>
<td>9.6</td>
<td>20.2</td>
<td>34.3</td>
<td>22.5</td>
</tr>
<tr>
<td>2007–2010</td>
<td>6.8</td>
<td>5.9</td>
<td>9.4</td>
<td>25.4</td>
<td>34.9</td>
<td>17.6</td>
</tr>
</tbody>
</table>

Insulin use†

- 1999–2002: 26.6±2.7
- 2003–2006: 26.5±1.4
- 2007–2010: 30.3±1.8

Any diabetes medication†‡§¶

- 1999–2002: 82.6±2.1
- 2003–2006: 83.6±1.8
- 2007–2010: 89.0±1.3

P=0.009

Ali NEJM 2013
At diagnosis of type 2 diabetes

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

- If A1C < 8.5%
  - If not at glycemic target (2-3 mos)
    - Start / Increase metformin
  - If not at glycemic targets
- If A1C ≥ 8.5%
  - Start metformin immediately
    - Consider initial combination with another antihyperglycemic agent
  - If not at glycemic targets
  - Symptomatic hyperglycemia with metabolic decompensation
    - Initiate insulin +/- metformin

Add an agent best suited to the individual:

Patient Characteristics
- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- Comorbidities (renal, cardiac, hepatic)
- Preferences & access to treatment
- Other

Agent Characteristics
- BG lowering efficacy and durability
- Risk of inducing hypoglycemia
- Effect on weight
- Contraindications & side-effects
- Cost and coverage
- Other

See next page…

Canadian Diabetes Association Guidelines 2013
If not at glycemic target

- Add another agent from a different class
- Add/Intensify insulin regimen

Make timely adjustments to attain target A1C within 3-6 months

### Add an agent best suited to the individual (agents listed in alphabetical order):

<table>
<thead>
<tr>
<th>Class</th>
<th>Relative A1C lowering</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Other therapeutic considerations</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitor (acarbose)</td>
<td>↓</td>
<td>Rare</td>
<td>neutral to ↓</td>
<td>Improved postprandial control, GI side-effects</td>
<td>$$</td>
</tr>
<tr>
<td>Incretin agents: DPP-4 Inhibitors GLP-1 receptor agonists</td>
<td>↓↓ to ↓↓↓</td>
<td>Rare</td>
<td>neutral to ↓</td>
<td>GI side-effects</td>
<td>$$$</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓↓↓</td>
<td>Yes</td>
<td>↑↑</td>
<td>No dose ceiling, flexible regimens</td>
<td>$-$$$$</td>
</tr>
<tr>
<td>Insulin secretagogue: Meglitinide</td>
<td>↓↓</td>
<td>Yes</td>
<td>↑</td>
<td>Less hypoglycemia in context of missed meals but usually requires TID to QID dosing</td>
<td>$$</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>↓↓</td>
<td>Yes</td>
<td>↑</td>
<td>Gliclazide and glimepiride associated with less hypoglycemia than glyburide</td>
<td>$</td>
</tr>
<tr>
<td>TZD</td>
<td>↓↓</td>
<td>Rare</td>
<td>↑↑</td>
<td>CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect</td>
<td>$$</td>
</tr>
<tr>
<td>Weight loss agent (orlistat)</td>
<td>↓</td>
<td>None</td>
<td>↓</td>
<td>GI side effects</td>
<td>$$$</td>
</tr>
</tbody>
</table>
**Current ADA/EASD Guidelines: Stepwise, Individualized Therapy**

The ADA / EASD treatment algorithm:

**Stepwise individualized patient therapy – weighing benefits and risks**

### Initial drug monotherapy
- **Efficacy** (↓ HbA1c)
- **Hypoglycemia**
- **Weight**
- **Side effects**
- **Costs**

### Two drug combinations*
- **Efficacy** (↓ HbA1c)
- **Hypoglycemia**
- **Weight**
- **Major side effect(s)**
- **Costs**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Sulfonlurea†</td>
<td>high</td>
<td>moderate risk</td>
</tr>
<tr>
<td>Metformin + Thiazolidinedione</td>
<td>high</td>
<td>low risk</td>
</tr>
<tr>
<td>Metformin + DPP-4 Inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
</tr>
<tr>
<td>Metformin + GLP-1 receptor agonist</td>
<td>high</td>
<td>low risk</td>
</tr>
</tbody>
</table>

*If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):*

### Three drug combinations

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Sulfonlurea† + TZD</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Metformin + Sulfonlurea† + DPP-4-i</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Metformin + GLP-1 RA + DPP-4-i</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

*If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):*

### If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

*Diabetes Care* 2012;35:1364–1379
*Diabetologia* 2012;55:1577–1596
There is a Threshold Relationship Between Plasma Glucose and UGE

There is a Threshold Relationship Between Plasma Glucose and UGE

Healthy Subjects
RTG*\sim 180 \text{ mg/dL}

*Renal threshold for glucose
Renal Glucose Reabsorption and RT\textsubscript{G} are Elevated in T2DM

*Renal threshold for glucose

FDA Advisory Committee Sponsor Slide Presentation 10Jan2013
SGLT2 Inhibition Lowers $RT_g$ Increasing UGE

*Renal threshold for glucose*
Low Glucose Suspend  
(Reactive Shut-Off)

Reactive suspension of insulin delivery at hypoglycemia with predefined period until resumed.

Hypo Minimizer  
(Predictive Hypo Control)

Predictive suspension or reduction of insulin before hypoglycemia occurs. User interaction required for Hyper region.

Hypo / Hyper Minimizer  
(Predictive Zone Control)

Predictive modulation of insulin delivery when outside target range to limit hypo/hyper excursions.

Hybrid Closed-loop  
(Predictive Target Control)

Predictive modulation of insulin to target with user interaction required to announce meals/activity to algorithm.

Automatic Closed-Loop  
(Automated Predictive Target Control)

Predictive modulation of insulin delivery to target with the ability at all times with no user interaction.

Automatic Closed-Loop  
(Automated Dual Hormone Target Control)

Predictive modulation of insulin and glucagon delivery to target at all times with no user interaction.

Sources: Close Concerns, JDRF, Internal Assessment, Closed-loop insulin delivery for treatment of type 1 diabetes, BMC Medicine, Nov. 2011