Update in Management of Non-Insulin-Requiring Diabetes: The Case for Combination Therapy

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Disclosures
Advisory Board / Consultant / Speaker
- Boehringer Ingelheim Janssen
- Bristol-Myers Squibb Merck
- Elcelyx Novo Nordisk
- Eli Lilly Receptos
- GlaxoSmithKline Takeda
- Intarcia

"Cellular pathways operate more like webs than superhighways. There are multiple redundancies, or alternate routes, that may be activated in response to the inhibition of a pathway."
"For this reason combination therapies are often needed to effectively treat many tumors and infectious diseases."

- Cancer
- HIV / AIDS
- Hypertension
- Asthma
- Rheumatoid arthritis
- Tuberculosis

Early Use of Combination Therapy is Well Established in Several Therapeutic Areas

Diabetes Awareness, Treatment and Control in Adults: NHANES 2007-2010

Type 2 Diabetes Management: Traditional Stepwise Approach

NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, 2010; World Health Organization HIV/AIDS Prevention, Treatment and Care in the Health Sector 2009
Type 2 Diabetes Management: Proactive Early Combination Approach

- OAD monotherapy
- Diet
- OAD combination
- OAD up titration
- OAD + basal insulin + injections

HbA1c (%)

Duration of Diabetes

The Paradigm Shift in the Management of Type 2 Diabetes

- 1980s – 2000s
  - Lower HbA1c is better
  - Focus on glycemic control and complications

- 2008 and Beyond
  - Attaining individualized HbA1c goals – SAFELY!
  - Focus on tailored therapy
  - Early intervention
  - Select treatments based on patient’s specific needs

2012 ADA/EASD Consensus Algorithm for Type 2 Diabetes Mellitus

Begin with these options if metformin contraindicated

Consider initial dual combination therapy when A1c >9%

Consider initial insulin therapy when A1c >10-12%

Classes of Glucose Lowering Agents for Treating Type 2 Diabetes

Major Organs Regulating Glucose Metabolism

Classical

- SU Glinide
- GLP-1 Ra
- DPP-4i
- Insulin

Less Classical

- Bromocriptine
- AGIs
- Pramlintide
- SGLT2
- Cholesterol
- BR

Effect of Sitagliptin and Metformin on Glucose Control in Type 2 Diabetes

- Placebo
- Sitagliptin 100 qD
- Metformin 500 mg bid
- Sitagliptin 50 mg bid + Metformin 500 mg bid
- Sitagliptin 50 mg bid + Metformin 1000 mg bid

HbA1c (%)
Effect of Sitagliptin and Glipizide Added to Metformin in Type 2 Diabetes Patients

- **Sitagliptin 100 mg qD + metformin ≥1500 mg qD; n=588**
- **Glipizide 5-20 mg qD + metformin ≥1500 mg qD; n=584**

**HbA1c (%)**

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Schernthaner G et al: Diabetes Care 36:2508-2515; 2013

Effect of Sitagliptin and Cangliflozin on Glucose Control in Type 2 Diabetes

- **Sitagliptin 100 mg qD + metformin + SU; n=378 (completed 210)**
- **Canagliflozin 300 mg qD + metformin + SU; n=377 (completed 254)**

**HbA1c (%)**

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Effect of Liraglutide and Glimepiride Added to Metformin in Type 2 Diabetes Patients

- **Placebo**
- **Glimepiride 4 mg qD**
- **Liraglutide 0.6 mg qD**
- **Liraglutide 1.2 mg qD**
- **Liraglutide 1.8 mg qD**

**HbA1c (%)**

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<th>Week</th>
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Comparison of Initial Combination to Sequential Triple Therapy

To compare the efficacy, safety and durability of the approach of initial triple combination therapy (metformin, pioglitazone and exenatide) compared to the more conventional sequential approach to triple therapy (metformin, followed by a sulfonylurea and then basal insulin) to maintain an HbA1c of <6.5%.


LA: Greater Improvement in Glucose Control with ILI

**A1c**

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Main effect: -0.22 (-0.28, -0.15), p<0.05


LA: Greater Use of Medications in DSE

Insulin, Statin and Antihypertensive Use

- **Antihypertensives HR=0.86 (0.75, 0.98), p=0.026**
- **Statins HR=0.96 (0.88, 1.05), p=0.34**
- **Insulin HR=1.11 (1.10, 1.12), p<0.001**

Question

What has been the outcome of and can be the expectations for the cardiovascular outcome trials of incretin-based therapy in type 2 diabetes?

Meta-Analysis Suggests DPP-4 Inhibitors May Reduce Cardiovascular Events

EXAMINE: No Impact of Alogliptin on the Primary Outcome (MACE)

SAVOR-TIMI 53: No Impact of Saxagliptin on the Primary Outcome (MACE)

SAVOR-TIMI 53: Prespecified Clinical End Points

<table>
<thead>
<tr>
<th>Table 1. Prespecified Clinical End Points</th>
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<tbody>
<tr>
<td>End Point</td>
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<td>Cardiac death, myocardial infarction, or stroke (primary composite)</td>
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<tr>
<td>Cardiac death, myocardial infarction, or stroke (composite)</td>
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<td>Death from any cause</td>
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<td>Hospitalization for myocardial infarction</td>
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<td>Hospitalization for stroke</td>
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<td>Hospitalization for unstable angina</td>
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<tr>
<td>Hospitalization for heart failure</td>
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<td>Hospitalization for pneumonia</td>
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Values are percentages of the primary composite events.

[Images and tables as seen in the document]
SAVOR-TIMI 53: Safety End Points


EXAMINE: Other Safety End Points


Incretin Cardiovascular Outcome Trials

EXSCEL - Exenatide LAR n=14,000
LEADER - Liraglutide n=9,340
REWIND - Dulaglutide n=9,622
ELIXA - Lixisenatide n=6,000
CAROLINA (vs SU) - Linagliptin n=6,000
CARMELINA (vs pbo) - Linagliptin n=8,300
TECOS - Sitagliptin n=14,000
SAVOR-TIMI 53 - Saxagliptin n=16,500
EXAMINE - Alogliptin n=5,400
EXCEL - Exenatide n=14,000

Incretin Cardiovascular Outcome Trials

Given that metformin is considered the best initial therapy, what are the relative benefits of other glucose-lowering agents?

A long-term study ...

2012 ADA/EASD Consensus Algorithm for Type 2 Diabetes Mellitus

Begin with these options if metformin contraindicated

Consider initial dual combination therapy when A1c >5%

Consider initial insulin therapy when A1c >10-12%
Future Approaches for Diabetes Therapy

- U300 and U500 insulins
- Glargine + lixisenatide (GLP-1 RA)
- Detemir + liraglutide (GLP-1 RA)
- Liraglutide 3 mg for weight reduction
- Ultra-long acting insulin (LY2605541 or degludec)
  - Once daily but dosing flexibility
  - Less hypoglycemia
  - Less weight gain