What to do after metformin? 2nd line therapies for DM-2

KM Pantalone
Director of Clinical Research
Department of Endocrinology

Disclosures

• Speaker Bureau:
  – Bristol-Myers Squibb, AstraZeneca, Eli Lilly

• Consultant:
  – Novo Nordisk, Eli Lilly, Sanofi, Merck
A1C Goal Achievement

• The scope of the problem:
  – Studies have demonstrated that nearly 50% of patients with DM-2 are not at A1C goal of <7%

Why is this really so difficult?

![Chart showing patients (%) at A1C<7% over two time periods]


2nd Line Therapy

• Metformin, in the absence of contraindications, or intolerability, is the preferred 1st line agent to manage glycemia in patients with DM-2

• In patients who require additional glycemic control, what medication should they receive?
Two Decisions

1. Determine individualized glycemic target (A1C)

2. Decide which medication is the best option to assist in meeting the individualized glycemic target

Individualized Goals

Medication Choice

- Efficacy (↓ HbA1C)
- Hypoglycemia
- Weight
- Side Effects
- Cost


Options
Available Medications

Timeline of Anti-diabetic Approvals

SGLT-2 inhibitors
2012 ADA/EASD Position Statement


Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(INCLUDING MEDICALLY ASSISTED WEIGHT LOSS)

ENTRY A1C < 7.5%
ENTRY A1C ≥ 7.5%
ENTRY A1C ≥ 9.0%

NO SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY
INSULIN OR OTHER AGENTS

ADD OR INTENSIFY INSULIN

LEGEND

Progression of Disease

https://www.aace.com/publications/algorith
Options

- Besides metformin, 8 additional oral and 3 injectable anti-diabetic therapy classes are available.
- Now that we have therapies that are weight neutral, or assist with weight loss, and do not increase the risk of hypoglycemia, why are we still using agents that cause weight gain and hypoglycemia?
We will discuss the most commonly utilized anti-diabetic drugs as 2\textsuperscript{nd} line options:
-\textbf{Sulfonylureas}
-\textbf{TZDs}
-\textbf{DPP-4 inhibitors}
-\textbf{GLP-1 receptor agonists}
-\textbf{SGLT-2 inhibitors}

-The patient’s A1C at the time a 2\textsuperscript{nd} line therapy is initiated may necessitate the addition of insulin therapy.

-Depending on specific circumstances or patient-related issues, one of the less common classes may need to be utilized as a 2\textsuperscript{nd} line therapy.

\textbf{Sulfonylureas (SFUs)}

- \textbf{Insulin secretagogue}
  - glyburide, glimepiride, glipizide

- \textbf{Good drugs, fallen out of favor in recent years}

- \textbf{Contraindications/Concerns:}
  - Use in elderly
  - Caution should be used in patients with liver or kidney dysfunction or in patients who often delay or skip meals.
SFUs
Advantages vs. Disadvantages

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive experience</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>↓ Microvascular risk (UKPDS)</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Low Cost</td>
<td>↓ Blunts myocardial IP</td>
</tr>
<tr>
<td></td>
<td>Low durability</td>
</tr>
</tbody>
</table>

SFUs, Low Cost?

• From 2007-2009, in U.S. adults ≥ 65 years of age, oral hypoglycemic agents (i.e. insulin secretagogues) were implicated in 10.7% of hospitalizations related to adverse drug events

• Mean costs for hypoglycemia visits:
  – $17,564 for an inpatient admission
  – $1,387 for an ED visit
  – $394 for an outpatient visit


SFUs

• University Group Diabetes Program (UGDP) 1975
  – Sulfonylurea (tolbutamide) may increase the risk of cardiovascular death
  – FDA mandated warning labels regarding an increased risk of cardiovascular-related mortality be added to all sulfonylureas
  – Currently all sulfonylureas approved for use within the United States are accompanied with this warning

NOT supported by the UKPDS which followed University Group Diabetes Program (UGDP), Diabetes. 1970; 19(Suppl 2):747-830.

Thiazolidinediones (TZDs)

• TZDs are agonists of peroxisome proliferator-activated receptor gamma (PPARγ)
  – Pioglitazone
  – Rosiglitazone

• Primarily enhance insulin sensitivity of muscle and fat, and mildly of the liver
TZDs

- Contraindications/Concerns include:
  - These agents should be avoided in patients with functional class III or IV heart failure

- Common side effects:
  - Weight gain, with an increase in subcutaneous adiposity
  - Fluid retention, which typically manifests as peripheral edema, but heart failure has been shown to occur on occasion

- No Hypoglycemia

---

Pioglitazone

- Has favorable effect on lipids: lowering triglycerides, increasing HDL, and increasing the LDL particle size

In August 2011, the FDA approved an update to the pioglitazone warning label to publicize the possible link between extended use of pioglitazone (12 months or more) and an increased risk of developing bladder cancer.

  - Increased risk of bladder cancer in patients exposed to pioglitazone
  - Risk may be increased with duration of use

Rosiglitazone

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

FDA NEWS RELEASE

For Immediate Release: Nov. 29, 2011
Media Inquiries: Morgan Liscinsky, 301-766-0167, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 1-888-INFO-FDA, druginfo@fda.hhs.gov

Preliminary analysis of a large diabetes trial has indicated that rosiglitazone, a thiazolidinedione (TZD) class of oral antidiabetic medication, is associated with an increased risk of myocardial infarction and all-cause mortality. This analysis is consistent with recent results of the RECORD trial, a randomized, placebo-controlled trial of rosiglitazone in patients with type 2 diabetes. The RECORD trial showed an increased risk of myocardial infarction and death from cardiovascular causes in patients treated with rosiglitazone compared to placebo. These findings, which are preliminary and based on the analysis of a smaller subset of patients, suggest that rosiglitazone may pose a greater risk than currently recognized, and the available evidence supports caution in the use of these medications. The European Medicines Agency (EMA) has recommended that rosiglitazone be withdrawn from the market in Europe.

Dipeptidyl Peptidase-4 inhibitors (DPP-4)

Mechanism of Action

Oral intake

Glucose

Small intestine brush border

GLP-1

DPP-4 inhibitors

Rapidly inactivated to GLP-1 (9-36) and GIP (3-42)

Pancreas

β cells

Glucose uptake

Insulin

Glucagon

Liver

Fat

Muscle

β cells

Glucose production
Incretin Effect

The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose
Crossover of Healthy Subjects (n = 6)
- Oral Glucose
- Intravenous (IV) Glucose

DPP-4 Inhibitors

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin
DPP-4 inhibitors

- Generally well tolerated
  - Most common side effect is headache
  - An increase in nasopharyngitis has also been reported
- Weight neutral
- No hypoglycemia
- Some require renal dose adjustment

DPP-4 inhibitors, concerns

- ? Increase risk of acute pancreatitis
- ? Increase risk of pancreatic cancer
• 16,492 patients, randomized, followed for median 2.1 years

• Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups:
  – acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group
  – chronic pancreatitis, <0.1% in both groups

• Pancreatic cancer—there were 5 cases in the saxagliptin group vs. 12 in the placebo group (P=0.095)


• 5,380 patients, randomized, followed for median 1.5 years

• The incidences of acute and chronic pancreatitis were similar in the alogliptin and placebo groups; no cases were fatal

• No reports of pancreatic cancer

Cardiovascular Risk

- SAVOR-TIMI 53: The primary outcome from the study showed no statistically significant difference in the combined rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke between the saxagliptin and placebo arms.

- EXAMINE: Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.

CHF, the new controversy?

**Saxagliptin**

- More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure:
  - 3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007
    - A 0.7% absolute increased risk
    - A 27% increase in relative risk

- The largest number of increased hospitalizations occurred among the quartile of patients enrolled in the trial with baseline blood levels of NT-pro-brain natriuretic peptide of at least 333 pg/mL.

- The greatest excess rate of hospitalization for heart failure occurred within the first 6 months of treatment:
  - After the first 6 months, hospitalization rates for this reason were virtually identical in the two treatment arms of the study.
CHF, the new controversy? Alogliptin

- An absolute 0.6% higher rate of hospitalizations for heart failure
  - An 18% relative increase

- NOT statistically significant

TECOS

- Trial Evaluating Cardiovascular Outcomes With Sitagliptin
- Began in 2008
- Recruitment is now complete
- Over 14,700 people with DM-2, aged 50 years or older, who have heart and circulatory disease and whose blood glucose is not being controlled well, are taking part
- Each participant will receive either sitagliptin or a placebo and will be followed for three to five years
- Results anticipated to be available in 2015
GLP-1 Analogues

• GLP-1 agonists
  – Increase glucose-dependent insulin secretion
  – Decrease inappropriate glucagon secretion
  – Slow gastric emptying
  – Suppress appetite (weight loss)
• Available agents
  – Exenatide (BID), Liraglutide (QD)
  – Once weekly (QW): Exenatide, Albiglutide, Dulaglutide

GLP-1 Agonists

• Benefits
  – Weight loss
  – Low (no) risk of hypoglycemia
  – Improved Glycemic control
  – Reduction in systolic BP
  – ? In-vivo increase B-cell growth/replication
  – ? Reduce CV risk

• Side Effects/Adverse Reactions
  – Nausea, vomiting, diarrhea, injection site reactions
Warnings

• Thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), were noted in rats, but human relevance remains uncertain

• Contraindicated in patients with a personal or family history of MTC and in patients with MEN2

• Routine serum calcitonin measurements, or thyroid ultrasounds, are of uncertain value, and not recommended

Warnings

• Pancreatitis: In clinical trials, there were more cases of pancreatitis among GLP-1-treated patients than among comparator-treated patients

• If pancreatitis is suspected, GLP-1 therapies and other potentially suspect drugs should be discontinued
  – GLP-1 agonists should not be restarted if pancreatitis is confirmed
  – Use with caution in patients with a history of pancreatitis
Sodium-glucose co-transporter 2 (SGLT2) inhibitor

• Dapagliflozin, Canagliflozin, Empagliflozin

• Block the glucose reabsorption function of the kidney, resulting in the excretion of excess glucose—up to 10% of daily calorific intake—in patients' urine


Glucose reabsorption by the proximal convoluted tubule

Copyright © 2011 American Diabetes Association, Inc.
SGLT-2 inhibitors

• Benefits
  – Weight loss
  – Low (no) risk of hypoglycemia
  – Improved Glycemic control
  – Reduction in systolic BP (~ 5 mmHg)

• Risks/Negatives
  – Slight increase in LDL cholesterol
  – Hypotension
    • Intravascular volume contraction
  – UTIs, genital mycotic infections
  – Bladder Cancer (???) Breast Cancer (???)
  – Increase risk of CVA (???)

Conclusions

• Utilize 2nd line medications that have multiple benefits, in addition to their ability to improve glycemia
  – Low risk of hypoglycemia
  – Weight neutral or loss
  – Improvements in other clinical parameters, such as systolic BP
  – Better glycemic durability