Pharmacotherapy of Type 2 Diabetes
Disclosures

I am a member of a Biodel, Lilly, Metavention, NovoNordisk, and VTech Pharma Advisory Boards and have served as a consultant for Merck and Takeda.
Effects of Type 2 Diabetes on Glucose Metabolism

Liver
- Glycogenolysis
- Gluconeogenesis
- Glycogen

Brain
- Glycogen
- Lactate
- FFA
- CO₂

Muscle
- FFA
- CO₂
- Lactate

Fat
- Glycerol
- Lactate
- Alanine
- Glutamine

Kidney
- Glycogen

Gut

CP1048009-11
The Ideal Therapy

Glucocentric:
• Normalize preprandial, postprandial, and intraprandial glucose concentrations

Holistic:
• Normalize everything

In a manner that is convenient, comfortable, and affordable
Premise for Intensive Management of Type 2 Diabetes

Appropriate use of agents whose mechanism(s) of action are complimentary and suitable for a given individual is required to achieve optimal glycemic control in people with type 2 diabetes.
Lifestyle Modification

Not only may improve survival, but also

- Improves insulin secretion and action
- Lowers glucose concentrations
- Lowers blood pressure
- Lowers lipids
- Improves sleep quality

And it makes you feel better
Metformin

- Epidemiologic studies suggest that it decreases both micro- and macrovascular complications.
- One randomized controlled trial (UKPDS) indicates it reduces both microvascular and macrovascular complications in obese people with short duration of diabetes.
- However, in that study, addition of metformin to a sulfonylurea resulted in an increase in mortality in obese individuals.
How Does Metformin Lower Glucose Concentrations?

Effect on HbA1c: -1.0 to -1.5%

• In rodents,
  • Improves insulin action
  • increases AMPK
  • Antagonizes glucagon
  • Inhibits mitochondrial glycerophosphate dehydroygenase

• In humans,
  • Lowers fasting insulin
  • Lowers glucose production
  • Decreases gluconeogenesis
  • Increases GLP-1
Effects Metformin on Glucose Tolerance

**Glucose**

- Time (min)
- Pre-Metformin
- Post-Metformin

**Insulin**

- Time (min)
- Pre-Metformin
- Post-Metformin

DeFronzo R, JCEM 1991
Sulfonylureas

- Many retrospective epidemiologic studies suggest use associated with increased CVD and/or mortality.
- Nurses Health Study noted use increased risk of cardiovascular heart disease compared to non-users (mostly metformin alone).
- However, reduced overall mortality over the long term in the follow up of the UKPDS.
- Implications of selectivity for pancreatic and extra-pancreatic channels unclear.
- Long-term effects on beta cell mass and function not known.
How do Sulfonylureas Lower Glucose Concentrations?

**Effect on HbA1c: -1.0 to -1.5%**

- Stimulate insulin secretion in a non-glucose dependent manner
- Increase overall insulin availability but do not restore early postprandial insulin secretion
- Do not directly alter insulin action
- Do not directly suppress glucagon
Effects of Tolazamide Glucose Tolerance and Insulin Secretin

Firth R et al: Diabetes, 1987
GLP-1 Agonists

- No long term outcome studies showing reduced micro- or macrovascular events
- Consistently results in modest weight loss
- Short term studies indicate GLP-1 agonist may have a favorable effect on endothelial function but no effect on heart failure
- May increase the risk of pancreatitis. If so, effect appears to be small. Long term effect on cancer (e.g. pancreas, thyroid, colon, and breast) uncertain
How do GLP-1 Agonists Lower Glucose Concentrations?

<table>
<thead>
<tr>
<th>Effect on HbA1c: -1.0 to -1.5%</th>
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<tbody>
<tr>
<td>• Stimulate insulin secretion in a glucose dependent manner</td>
</tr>
<tr>
<td>• Suppresses glucagon</td>
</tr>
<tr>
<td>• Increases satiety</td>
</tr>
<tr>
<td>• May improve hepatic insulin action either directly or via CNS</td>
</tr>
</tbody>
</table>
Effects of GLP-1 On Insulin and Glucagon Secretion in Type 2 Diabetes

Nauck M, Diabetologia 1993
Does inhibition of glucagon reduce postprandial glucose concentrations control?
Insulin

Non-Diabetic Insulin Profile

Diabetic Insulin Profile

Shah P: AJP, 1999
Glucagon

Non-Diabetic Insulin Profile

Diabetic Insulin Profile

Shah P: AJP, 1999
**Glucose**

*Non-Diabetic Insulin Profile*

*Diabetic Insulin Profile*

- Suppressed glucagon
- Non-suppressed glucagon

Minutes

Shah P: AJP, 1999
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<th>DPP-4 Inhibitors</th>
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<td>• No long term outcome studies showing reduced micro- or macrovascular events</td>
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<td>• Do not alter weight</td>
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<td>• Do not have an effect on endothelial function</td>
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<tr>
<td>• May increase the risk of heart failure and pancreatitis</td>
</tr>
<tr>
<td>• May modulate immune function and inflammation</td>
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How do DPP-4 Inhibitors Lower Glucose Concentrations?

**Effect on HbA1c: -0.7 to -0.9%**

- Stimulate insulin secretion in a glucose dependent manner
- Minimal suppression of glucagon
- Do not alter satiety
Effects DPIV Inhibitors on Glucagon Secretion in Type 2 Diabetes

Vella A, Diabetes, 2007
Thiazolidiones

- May decrease cardiovascular events
- Increases body fat
- Increases risk of congested heart failure
- Decreases bone density and increases risk of fractures
- May increase risk of bladder cancer
How Do Thiazolindiones Lower Glucose Concentrations?

Effect on HbA1c: -0.7 to -0.9%

- Improves hepatic insulin action primarily by increasing insulin induced suppression of gluconeogenesis
- Effects on extra-hepatic insulin action (at physiologic insulin concentrations) is less clear
- Increases insulin secretion
- Does not alter glucagon secretion
Effects Three Months of Treatment With Either Pioglitazone or Glipizide on Insulin Secretion

**Pioglitazone**

- **Insulin**
  - Pre-treatment
  - Post-treatment
  - Nondiabetic

**Glipizide**

- **Insulin**
  - Pre-treatment
  - Post-treatment
  - Nondiabetic

Basu, A, (unpublished)
SGLT 2 Inhibitors

- People with SGLT 2 mutations live normal lives despite extensive glycosuria
- SGLT 2 present in the kidney and perhaps in alpha cells; SGLT 1 present in many tissues (e.g. intestine, brain)
- SGLT 2 inhibitors decrease both weight (glycosuria) and blood pressure (volume)
- May increase risk of falls and CV events particularly in the elderly and/or in the presence of volume depletion
- May increase glucagon and glucose production
How Do SGLT 2 Inhibitors Lower Glucose Concentrations?

Effect on HbA1c: -1.0 to -1.2%

- Lowers glucose by increasing glucose disappearance via a non-insulin dependent process (i.e. glycosuria)
- Effectiveness decreases as renal function decreases
- Glucose level achieved and risk of hypoglycemia likely will depend on $K_m$
- Increases risk of urinary and genital infections
- Lowers overall mortality in high risk subjects
Cardiovascular Outcomes and Death from Any Cause

**Primary Outcome**

- **Placebo**
- **Empagliflozin**

**Death from CV Causes**

- **Placebo**
- **Empagliflozin**

**Death from Any Cause**

- **Placebo**
- **Empagliflozin**

**Hospitalization for HF**

- **Placebo**
- **Empagliflozin**

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*Zinman et al: NEJM, 2015*
Do SGLT 2 Inhibitors Alter Insulin or Glucagon Secretion?

Glucose

Insulin

Glucagon

Ferrannini E: JCI, 2014
<table>
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<td>• Epidemiologic studies suggest use associated with increased mortality</td>
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<tr>
<td>• Results in systemic hyperinsulinemia</td>
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<td>• Increases the risk of hypoglycemia</td>
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Goals for Exogenous Insulin

**Prandial**
- Increase rate of absorption
- Decrease intra-individual variability
- Make relatively hepatic specific

**Basal**
- Prolong duration of action
- Decrease intra-individual variability
- Make relatively hepatic specific
New Basal Insulins

- U-300 glargine
- Degludec
U-100 Glargine
Insulin Glargine

A-Chain

1  5  10  15  20Asn

B-Chain

1  5  10  15  20  25  30

Substitution

Gly

Extension

Arg Arg
Intra-subject Variability With Glargine

Concentrations (µIU/mL)

Subject 2
Subject 3
Subject 7
Subject 9

Subject 14
Subject 18
Subject 19
Subject 22

Subject 27
Subject 28
Subject 34
Subject 35

Hours

Scholtz et al: Diabetes 48(suppl 1):A97, 1999
U-300 Glargine
(Toujeo)
Reduction of Depot Surface

Steinstraesser et al. Diabetes Obes Metab. 2014;16:873-6
Glucose Infusion Rates

T1/2 = 17-19 hours vs. 13 hours glargine
Within subject variability: 34%

Outcomes U-300 Glargine

Type 1 Diabetes (Edition 4)
- Comparable HbA1c vs. Glargine U-100
- Decreased nocturnal hypoglycemia first 8 weeks; no difference in confirmed, severe, or nocturnal hypoglycemia thereafter

Type 2 Diabetes (Edition 1, 2 and 3)
- Comparable HbA1c vs. Glargine U-100
- No difference in confirmed or severe but lower or same nocturnal hypoglycemia
Insulin Degludec
(Tresiba)
Insulin degludec

Identical to human insulin except for removal of threonine at B30

Multi-hexamer chains self-assemble to form subcutaneous depot

Hexamers disassemble, releasing monomers which absorbs to the circulation

Insulin Degludec Pharmacodynamic Profile

Glucose Infusion Rates

T1/2 = 25 hours
Within subject CV:
20% degludec vs 82% glargine

Heise T et al. Diabetes, Obesity, Metabolism 14:944, 2012
Outcomes Insulin Degludec

Type 1 Diabetes (Begin Basal Bolus, Begin Flex)
- Comparable HbA1c vs. Glargine U-100
- Lower or same overall, nocturnal, or severe hypoglycemia

Type 2 Diabetes (Begin Long, Asia, Basal Bolus, Flex)
- Comparable HbA1c vs. Glargine U-100
- Lower or same overall, nocturnal, or severe hypoglycemia

- Lower mean and SD of fasting glucose but no difference in CV
The “Ideal” Prandial Insulin

- Absorbed sufficiently rapidly to mimic the post-prandial pattern of change in insulin concentrations that occur in non-diabetic humans
- Safe
- Reproducible
- Appropriate balance (both biologic and temporal) of effects on the liver and extra-hepatic tissues
New Prandial Insulins

• Afrezza (Technospheres Insulin)
• Faster Aspart
Nondiabetic

“Late” type-2

“Early” type-2

Glucose

mmol/l

0

10

20

Insulin

μU/mL

0

65

130

Minutes

0

60

120

180

240

300

Nondiabetic

“Early” type-2

“Late” type-2
Structure of a Technosphere® Particle

HO₂C-CH=CH-CONH₃-NHCO₂H

Afrezza

- Forms microparticles under acidic conditions that can be dried to powder.
- Dissolves in the presence of neutral or basic conditions
- Absorbed after inhalation
- Intravenous dose: 97% cleared by the kidney
- PO dose: 95% excreted in feces
- Clearance decreased with renal or liver disease
Insulin Concentrations Following Inhalation of Afrezza Compared to Injection of Lispro

Insulin

- 20 units Technosphere
- 8 units Lispro

FOA: Briefing Document, 2014
Outcomes Afrezza

Type 1 and Type 2 Diabetes

- Inferior or same reduction of HbA1c vs. aspart
- Lower severe hypoglycemia
- Lost weight or less weight gain
- More DKA
- Two fold higher drop out rate
- Cough and reversible decrease in FEV$_1$

Fast Aspart

- Insulin aspart formulated with nicotinamide (vitamin B3), arginine and zinc
- Nicotinamide increases the rate of absorption by enhancing rate of disassociation to monomers
- Arginine improves stability
- Zinc stabilizes insulin hexamer
Insulin Concentrations After Injection of Faster Aspart Versus Aspart

Heise: Diabetes, Obesity and Metabolism 17:682, 2015
Effects of Faster Aspart Versus Aspart on Postprandial Glucose Concentrations

Press release from NovoNordisk announced that compared to insulin aspart, faster aspart resulted in:

- A significantly greater reduction in HbA1c with no difference in hypoglycemia in people with type 1 diabetes
- Comparable reduction in HbA1c and comparable rates of hypoglycemia in patients with type 2 diabetes.
Faster Aspart

- Is it “fast” enough to make a difference in clinical use?
- Can it be used in insulin pumps and if so, does it lower HbA1c and reduce hypoglycemia?
- Is it safe with repeated injections or long term infusion?
How to Successfully Implement Intensive Management of Type 2 Diabetes

In order to achieve optimal glycemic control in people with type 2 diabetes:

• Use agents whose mechanism(s) of action are complimentary
• That are given at the appropriate time and in an appropriate doses
• Whose benefits outweigh risks in the individual in whom they are being used
Questions & Discussion