Endocrine and Metabolism PRN Focus Session—Updates in Treatment Options for Diabetes
Activity No. 0217-0000-14-122-L01-P, 2.0 contact hours; Knowledge-based activity.

Tuesday, October 14
1:15 p.m.–3:15 p.m.
Convention Center:
Grand Ballroom G

Moderator: Jessica Trompeter, Pharm.D.
Assistant Professor, Bernard J. Dunn School of Pharmacy, Winchester, Virginia

Agenda

1:15 p.m. Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors: Clinical Use in Diabetes
Matthew W. Strum, Pharm.D., BCACP, CDE
Clinical Assistant Professor, University of Mississippi School of Pharmacy, University, Mississippi

1:45 p.m. Glucagon-like Peptide 1 Receptor Agonists: Beyond Endocrine
Krystal L. Edwards, Pharm.D., FCCP, BCPS
Associate Professor, Texas Tech School of Pharmacy, Dallas, Texas

2:15 p.m. Basal Insulin: A Look Ahead
Robin L. Koffarnus, Pharm.D., BCACP
Assistant Professor, Department of Pharmacy Practice – Ambulatory Care Division, Texas Tech School of Pharmacy – Dallas/Fort Worth Campus, Dallas, Texas

2:45 p.m. Treatment of Diabetes: A Review of Cardiovascular Outcomes
Craig D. Williams, Pharm.D.
Clinical Professor, Department of Pharmacy Practice OSU/OHSU College of Pharmacy; Clinical Associate Professor of Medicine, Oregon Health & Science University School of Medicine, Portland, Oregon

Conflict of Interest Disclosures

Krystal L. Edwards: no conflicts to disclose.
Robin L. Koffarnus: no conflicts to disclose.
Learning Objectives

1. Review the pharmacology of SGLT2 Inhibitors.
2. Evaluate the clinical evidence and place in therapy of SGLT2 Inhibitors in the treatment of diabetes.
3. Compare SGLT2 Inhibitors to current diabetes treatment options.
5. Examine the endocrine and exocrine effects of GLP1 receptor antagonists.
6. Discuss the evidence and implications for the evolving role of GLP1 receptor antagonists in the treatment of diabetes.
7. Discuss new options in basal insulin therapy.
8. Compare and contrast the ultra long acting insulin with current insulin options.
9. Evaluate the benefits and limitations of basal insulin therapy.
10. Interpret current evidence for cardiovascular risk with treatment options for diabetes.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors: Use in Clinical Practice
Matthew Strum, Pharm.D., BCACP, CDE
October 14, 2014

Learning Objectives
- Review the pharmacology of SGLT2 Inhibitors (SGLT2-I’s)
- Evaluate the clinical evidence and place in therapy of SGLT2-I’s in the treatment of diabetes
- Compare SGLT2-I’s to current diabetes treatment options
- Evaluate the benefits and limitations of using SGLT2-I’s in the treatment of diabetes

Pharmacology of SGLT2-I’s

Glucose Homeostasis
- Body glucose stores ≈ 450 g
- Daily glucose turnover ≈ 250 g
- Typical Western diet ≈ 180 g/day
- Gluconeogenesis (liver & kidney) bridges gap
- Brain consumes ≈ 125 g/day
- Kidneys assist in homeostasis by reabsorbing glucose

Kidney: Glucose Control
Normal Renal Glucose Physiology
- 180 g of glucose is filtered each day
- Virtually all glucose reabsorbed in the proximal tubules & reenters the circulation
- SGLT2 reabsorbs ≈ 90% of the glucose
- SGLT1 reabsorbs ≈ 10% of the glucose
- Virtually no glucose excreted in urine

Conflict of Interests
- Speakers Bureau:
  - Janssen
- Consultant (Insulin Pump Trainer):
  - Medtronic
  - Tandem
  - Insulet

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Glucose/Na Transport Genes

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Distribution</th>
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<tbody>
<tr>
<td>SGLT1 (SLC5A1)</td>
<td>Intestine, trachea, kidney, heart, brain, testis, prostate</td>
</tr>
<tr>
<td>SGLT2 (SLC5A2)</td>
<td>Kidney, brain, liver, thyroid, muscle, heart</td>
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<tr>
<td>SGLT4 (SLC5A9)</td>
<td>Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas</td>
</tr>
<tr>
<td>SGLT5 (SLC5A10)</td>
<td>Kidney</td>
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<tr>
<td>SGLT6 (SMIT2, SLC5A11)</td>
<td>Brain, kidney, intestine</td>
</tr>
<tr>
<td>SMIT1 (SLC5A3)</td>
<td>Brain, heart, kidney, lung</td>
</tr>
</tbody>
</table>


Normal Renal Physiology


Renal Glucose Transport


Renal Targeting


Renal Threshold for Glucose Excretion

Adapted from Nair S, Wilding JP. JCEM. 2010;95:34-42.
Mather A, Pollack C. Kid. Int. 2011;79(suppl 120);S1-S6.

Effects of SGLT2-1’s

Inhibition of renal tubular Na⁺-glucose cotransporter
reversal of hyperglycemia
reversal of “glucotoxicity”

- Insulin sensitivity in muscle
- GLUT4 translocation
- Insulin signaling
- Insulin sensitivity in liver
  - Glucose-6-phosphatase
- Gluconeogenesis
  - Decreased Cori Cycle
- FEP carboxylase
- Improved beta cell function


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Rationale for SGLT2 Inhibition

SGLT2 is a low-affinity, high capacity glucose transporter in the proximal tubule responsible for 90% of glucose reabsorption. Mutation in SGLT2 transporter linked to hereditary renal glycosuria, a relatively benign condition in humans. Selective SGLT2-I’s have a novel & unique MOA, reducing blood glucose concentrations by increasing renal excretion of glucose. Decreased glycemia will decrease glucose toxicity leading to further improvements in glucose control. Selective SGLT2 inhibition, would also cause urine loss of the calories from glucose, potentially leading to weight loss.

Clinical Evidence: FDA Approved SGLT-2 I’s

- Canagliflozin
- Dapagliflozin
- Empagliflozin

Canagliflozin Studies

- vs diet and exercise
- vs glimeperide add on metformin background therapy
- vs sitagliptin with metformin background therapy
- vs placebo add on to metformin/pioglitazone

Canagliflozin Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Compare</th>
<th>Meds</th>
<th>A1C (%)</th>
<th>FPG (mg/dL)</th>
<th>Wt (kg)</th>
<th>BP (mmHg)</th>
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Canagliflozin

- Canagliflozin added to metformin significantly improved glycemic control in T2DM
- Low incidence of hypoglycemia
- Significant weight loss

Dapagliflozin Studies

- vs Placebo and metformin background therapy
- vs glipizide add on metformin background therapy
- vs glimeperide with metformin background therapy
- vs Placebo add on to pioglitazone
### Empagliflozin Studies

- Approved 8/1/2014
- vs Placebo add on to metformin
- vs glimeperide with metformin background therapy
- vs sitagliptin add on to metformin
- vs Placebo as add on to pioglitazone or pio + metformin

### Meta-Analysis of Double-Blind Controlled Trials

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### A1C Reduction from Baseline

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<td>0.3</td>
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### Change in Body Weight (Kg) from Baseline

- Adapted from Diabetes Care: [2014;37:1650-1659.]
- © American College of Clinical Pharmacy
SGLT-2 Inhibitors Compared to Traditional Treatment Options

Glucose Lowering Agents

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>DPP-4 Inhib.</th>
<th>GLP-1 Agonist</th>
<th>SU</th>
<th>Glinide</th>
<th>TZD</th>
<th>Colesevelam</th>
<th>AG</th>
<th>Insulin</th>
<th>Pramlintide</th>
<th>SGLT2-I's</th>
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</thead>
<tbody>
<tr>
<td><strong>FPG lowering</strong></td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
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<td>Mild</td>
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<td>Mild</td>
<td>Neutral</td>
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<td><strong>Risks</strong></td>
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<td><strong>Weight Gain</strong></td>
<td>Neutral</td>
<td>Mild</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Mild</td>
<td>Neutral</td>
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<td><strong>Hypoglycemia</strong></td>
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<td>Neutral</td>
<td>Mild</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Benefit</td>
<td>Benefit</td>
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<tr>
<td><strong>Average A1C Reduction</strong></td>
<td>1.2%</td>
<td>0.1%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>1%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>Variable</td>
<td>0.5%</td>
<td>0.7-1.03%</td>
<td>Variable</td>
</tr>
</tbody>
</table>


Benefits and Limitations of SGLT-2 Inhibitors

Benefits
- Insulin independence
- Weight reduction
  - Avg **kg**
- Low risk of hypoglycemia
- Blood pressure reductions

Limitations/concerns
- Polyuria
- Electrolytes
- Urinary tract infections
  - Bacterial
  - Fungal
- Genital fungal infections
  - Vulvovaginitis
  - Balanitis
- Malignancies??
- Hypotension??

SGLT2 Perspective

SGLT2: Blood Pressure

- Meta-analysis 27 RCT's (Baker et al)
  - SBP reduction 4 mmHg
  - DBP reduction 1.6 mmHg
- No significant effect on orthostatic hypotension
- Meta-analysis 17 RCT's (Berhan & Barker)
  - Treatment with SGLT2-I's resulted in significant decrease in SBP & DBP from baseline

Adverse Events

SGLT2 Perspective

- Glucose will be in the urine
  - Commercial Driver’s License (CDL)
- Prospective prescription for antifungal?
  - Vulvovaginitis
- Medwatch

SGLT2 Inhibitors

- Canagliflozin (Invokana®): 100mg & 300mg tablets
  - Metformin IR + canagliflozin (Invokamet™)
- Dapagliflozin (Farxiga™): 5mg & 10mg tablets
  - Metformin XR + dapagliflozin (Xigduo™) [PDUFA – 10/29/2014]
- Empagliflozin (Jardiance®): 10mg & 25mg tablets
- In Development:
  - Ertugliflozin – Phase II
  - Ipragliflozin – Phase III (approved in Japan 01/2014)
  - Luseogliflozin - (approved in Japan 03/2014)
  - Remogliflozin – Phase IIb
  - Sergliflozin – (halted after Phase II)
  - Tofogliflozin – Phase III (approved in Japan 03/2014)

QUESTIONS?
GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS: BEYOND ENDOCRINE

Krystal L Edwards, Pharm.D., FCCP, BCPS
Texas Tech UHSC School of Pharmacy – DFW Campus
Associate Professor
Pharmacy Practice Department - Ambulatory Care Division

CONFLICTS OF INTEREST
- None to disclose

LEARNING OBJECTIVES
1. Examine the endocrine and exocrine effects of Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs)
2. Discuss the evidence and implications for the evolving role of GLP-1 RAs in the treatment of diabetes

Focus on:
Benefits Beyond Blood Glucose Lowering

OUTLINE
- Weight reduction
- Cardiovascular (CV) benefits
- Other potential future uses

- BASIC REVIEW -
GLP-1 RAs: MOA
- Incretin hormone → stimulates post-prandial insulin secretion
- Other pancreatic effects:
  - Increases insulin production
  - Decreases glucagon secretion
  - Increases β-cell glucose sensitivity
- Extra-pancreatic effects → receptors located in the brain, heart, kidney, lung, & GI tract

Gallwitz B. Endocrine. 2014 [epub Mar 2014]

USE IN OBESITY / WEIGHT REDUCTION
USE IN OBESITY / WEIGHT REDUCTION:
PROPOSED BENEFIT
- Average of 1.5-4 kg weight loss sustained over 6-18 months in pts with DM
- Studies with exenatide & liraglutide in obese non-DM pts showed weight loss of 2-7 kg

Madsbad S. Diabetes Obes Metab. 2014;16:9-21
Rosenstock J et al. Diabetes Care. 2010;33:1173-75

USE IN OBESITY / WEIGHT REDUCTION:
MOA
- GLP-1 secretion may be lower in obese patients (decreased incretin effect)
- GI tract: slows gastric emptying leading to sensations of fullness up to transient nausea & vomiting
- CNS:
  - Receptors in hypothalamus & brain stem → regulation of food intake & sends satiety signal
  - Increases adiponectin & leptin levels

Gallwitz B. Endocrine. 2014 [epub Mar 2014].

USE IN OBESITY / WEIGHT REDUCTION:
CLINICAL EVIDENCE

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 RA</th>
<th>Baseline BMI (kg/m²)</th>
<th>Ave Weight Loss</th>
<th>≥5% Weight Loss</th>
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</thead>
<tbody>
<tr>
<td>Rosenstock</td>
<td>Exenatide 10 mcg BID (vs. placebo)</td>
<td>39.6</td>
<td>5.1 kg</td>
<td>32% (p = 0.039)</td>
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<tr>
<td>Dushay (n=41, 35 wk)</td>
<td>Exenatide 10 mcg BID (vs. placebo)</td>
<td>33.1</td>
<td>2.5 kg</td>
<td>30% (NR)</td>
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<tr>
<td>Astrup (n=564, 20 wk)</td>
<td>Liraglutide 1.2mg, 1.8 mg, 2.4 mg, &amp; 3 mg Qdaily (vs. placebo &amp; orlistat)</td>
<td>34.1 - 35</td>
<td>6.7, 7.1, 7.9, &amp; 9.1 kg</td>
<td>61% (p&lt;0.002)</td>
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<tr>
<td>Astrup (n=398, 1-2 yr)</td>
<td>Liraglutide, 2.4-3* mg Qdaily (vs. placebo &amp; orlistat)</td>
<td>34.1 - 35</td>
<td>5.8 kg - 1 yr*, 7.8 kg - 2 yr*</td>
<td>64% - 1 yr* (p&lt;0.02), 52% - 2 yr* (p=0.001)</td>
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</table>


USE IN OBESITY / WEIGHT REDUCTION:
LINK TO GUIDELINES
- FDA approval for weight loss agent recommends at 1 year:
  - ≥5% weight loss w/statistically significant results
  - Proportion with ≥5% weight loss in at least 35% of pts is double the proportion in placebo-tx group w/statistically significant results
- Only liraglutide 2.4-3 mg has met criteria


CARDIOVASCULAR BENEFITS

- CV Risk Factors and Cardiac Function
  - Blood Pressure & Heart Rate effects
  - Lipid benefits
- Endothelial dysfunction benefits
- Clinical Effects
  - s/p myocardial infarction (MI)
  - Left ventricular (LV) dysfunction
  - Cardiovascular outcomes in clinical trials

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CARDIOVASCULAR BENEFITS:
BLOOD PRESSURE & HEART RATE

- Effect in DM pts:
  - ↓ SBP & ↓ DBP ~3.5 mmHg
  - ↑ HR 2-5 bpm

- MOA:
  - BP: weight loss; natriuresis/diuresis; endothelium vasodilation
  - HR: compensatory due to BP change; vasodilation


CARDIOVASCULAR BENEFITS:
LIPIDS

- Effect in DM pts:
  - ↓ total cholesterol up to 14%
  - ↓ LDL up to 16%
  - ↓ TGs up to 18%
  - ↓ apoB levels
  - ↑ HDL up to 3.1%

- MOA:
  - Reduction in post-prandial TGs along with apoB & non-esterified fatty acids due to delayed gastric emptying


CARDIOVASCULAR BENEFITS:
ENDOTHELIAL DYSFUNCTION BENEFITS

- Induced endothelial-dependent relaxation of pulmonary artery vessels
- ↑ nitric oxide (NO) production
- ↓ carotid artery intima:media ratio

- ↓ reactive oxygen species (ROS)
- ↓ tumor necrosis factor (TNF)-α
- Induced plasminogen activator inhibitor (PAI)-1
- ↓ vascular cell adhesion molecule-1 (VCAM-1)
- ↑ adiponectin & leptin
- Improved interleukin 6 (IL-6)
- ↓ hsCRP

* Results controversial and not consistent


CARDIOVASCULAR BENEFITS:
THE CLINICAL BENEFITS

- s/p Myocardial Infarctions*
  - ↓ infarct size & improves survival
  - Improves cardiac output

* In animals & animal models


CARDIOVASCULAR BENEFITS:
THE CLINICAL BENEFITS

- Left Ventricle function
  - Improves LV function & systemic hemodynamics w/ advanced dilated cardiomyopathy*
  - HF pts w/ LV dysfunction:
    - Potential ↓ resting HR & ↓ SBP
    - Improves regional & global LV function
    - Improves QOL
    - ↓ in-hospital mortality rate (27% vs. 10% placebo)
    - No benefit in recent study of HF & IHD pts

* In animals & animal models


CARDIOVASCULAR BENEFITS:
THE CLINICAL BENEFITS

Meta-analysis of 33 trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Cardiovascular</td>
<td>0.78</td>
<td>0.51-1.13, p=0.18</td>
</tr>
<tr>
<td>Events (MACE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.89</td>
<td>0.46-1.70, p=0.81</td>
</tr>
<tr>
<td>MI (n=29)</td>
<td>0.87</td>
<td>0.48-1.56, p=0.63</td>
</tr>
<tr>
<td>CVA (n=11)</td>
<td>0.87</td>
<td>0.37-2.05, p=0.75</td>
</tr>
</tbody>
</table>

Compared to placebo “trend” towards benefit with MACE, MI, & all-cause mortality

### Cardiovascular Benefits: Summary

- Decrease surrogate markers for CVD protection
  - BP, HR, endothelial benefits
- Limited and/or controversial human studies for clinical relationship
  - Myocardial infarctions & LV dysfunction
- No increased risk for CVD in pts treated with GLP-1 RAs in clinical trials

### Other Benefits / Uses

#### Neurological Disorders

- Potential use:
  - Alzheimer’s & Parkinson’s disease (PD) and strokes
    - Possible relationship between neuronal cell death & insulin dysfunction → hippocampal atrophy
    - PD study: improvement in movement scale
- MOA*:
  - Protected hippocampal neurons from glutamate- & amyloid-β peptide-induced cell death
  - Protected against impairment of spacial memory & cognitive dysfunction
  - Beneficial effects on DM polyneuropathy & peripheral nerve degeneration
  - Prevented degenerative process

  * In animals & animal models

#### Hepatic Steatosis

- Potential use:
  - Fatty liver disease
    - Improvement in LFTs
    - Decreased hepatic fat
    - LEAN study: goal to show improvement in liver disease (liver fat, inflammation & scarring) and related metabolic parameters in overweight nonalcoholic steatohepatitis patients
- MOA:
  - Decrease in weight?
  - Other?

### Psoriasis

- Potential use:
  - Possible link with increased psoriasis and T2DM
  - Case reports of improvements with psoriasis with liraglutide and exenatide in T2DM pts
- MOA:
  - Anti-inflammatory: ↓ TNF-α, ↓ pro-inflammatory response, & ↓ ROS

### Summary
GLP-1 RAs: Benefits Beyond Blood Glucose Lowering

- Benefits outside of T2DM
  - Decrease weight
  - Cardiovascular protection/benefits
  - Anti-inflammatory effects
  - Fatty liver disease

- Clinical human trials:
  - Weight loss independent of T2DM
  - No increased risk of CVD in T2DM
2014 ACCP Annual Meeting

Basal Insulin: A Look Ahead
Robin L. Koffarnus, Pharm.D., BACAP
October 14, 2014

Conflicts of Interest

- I have no conflicts of interest to disclose.

Learning Objectives

- Discuss new options in basal insulin therapy
- Compare and contrast the ultra long acting insulins with current insulin options
- Evaluate the benefits and limitations of basal insulin therapy

Audience Poll

- How often do you manage diabetes in your current practice?
  a. Daily
  b. A few times per week
  c. A few times per month
  d. Less than once per month

Current Options in Therapy

- Neutral Protamine Haegedorn (NPH) – intermediate acting
- Detemir – long acting
- Glargine – long acting
Basal Insulin Comparison

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Peak Duration</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH Isophane/zinc</td>
<td>4-8 hours</td>
<td>8-12 hours</td>
</tr>
<tr>
<td>Detemir Analog (increased albumin binding)</td>
<td>Minimal</td>
<td>16-24 hours</td>
</tr>
<tr>
<td>Glargine Analog (proinsulin)</td>
<td>Minimal to none</td>
<td>16-24 hours</td>
</tr>
</tbody>
</table>

Pros and Cons

**NPH**
- **Pros**: Can be combined with regular and rapid-acting insulin
- **Cons**: Twice daily dosing

**Detemir**
- **Pros**: Decreased hypoglycemia compared to NPH
- **Cons**: Cannot mix

**Glargine**
- **Pros**: Decreased hypoglycemia compared to NPH and detemir
- **Cons**: Cannot mix

New Options

- Insulin degludec
- PEGylated insulin lispro
- Insulin glargine U300

Insulin Degludec

- Unique mechanism of action:
  - Formulation with phenol and zinc creates stable dihexamer
  - After injection, multihexamer chains form as phenol diffuses, creating a depot
  - Zinc diffuses, multihexamer chains disassemble, insulin degludec monomers release into blood stream

- Duration of action >42 hours
- No peak
- Can be combined in solution with rapid-acting insulin

BEGIN Basal-Bolus Type 1

- 52 wk, phase 3, randomized, open label, target-to-treat, non-inferiority trial
- Adults, Type 1 DM >1 year, basal:bolus therapy >1 year, and A1c ≤10%
  - Once daily degludec with PM meal
  - Insulin glargine given anytime (consistent schedule)
  - Bolus mealtime aspart for each group
- Basal insulin titrated to blood glucose (BG) level of 70-90 mg/dL pre-breakfast
- Bolus insulin titrated to BG of 70-90 mg/dL pre-prandial and bedtime

Safety and Efficacy at 1 Year

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Insulin Units/kg/day</th>
<th>A1C %</th>
<th>Overall Hypoglycemia*</th>
<th>Nocturnal Hypoglycemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degludec (n=472)</td>
<td>0.75</td>
<td>-0.4</td>
<td>42.54</td>
<td>4.41</td>
</tr>
<tr>
<td>Glargine (n=157)</td>
<td>0.82</td>
<td>-0.39</td>
<td>40.18</td>
<td>5.86</td>
</tr>
</tbody>
</table>

| p value, 95% CI | p=0.0001 | -0.14 – 0.11 | p=0.48 | p=0.021 |

*Episodes per patient-year of exposure
Conclusion

- Once daily degludec + aspart required less total daily insulin to lower A1c compared to once daily glargine + aspart
- Degludec had decreased nocturnal hypoglycemia compared to glargine


BEGIN Basal-Bolus Type 2

- 52 wk, phase 3, randomized, open label, target-to-treat, non-inferiority trial
- Adults, Type 2 DM ≥6 months, insulin therapy ≥3 months, A1c 7-10%, and BMI ≤40 kg/m²
  - Once daily degludec with PM meal
  - Insulin glargine given anytime (consistent schedule)
  - Bolus mealtime aspart for each group
  - Metformin and pioglitazone permitted (consistent doses)
  - Excluded GLP-1 or rosiglitazone used for ≥3 months
- Basal insulin titrated to BG level of 70-90 mg/dL pre-breakfast
- Bolus insulin titrated after basal insulin


Safety and Efficacy at 1 Year

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Insulin Units/kg/day</th>
<th>A1c %</th>
<th>Overall Hypoglycemia*</th>
<th>Nocturnal Hypoglycemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degludec (n=755)</td>
<td>1.46</td>
<td>-1.1</td>
<td>11.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Glargine (n=211)</td>
<td>1.42</td>
<td>-1.2</td>
<td>13.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

95% CI; p value

-0.04 – 0.22 p=0.106 p=0.038

*Episodes per patient-year of exposure


BEGIN Once Long

- 1 year, phase 3, parallel group, randomized, open label, target-to-treat, non-inferiority trial
- Adults, Type 2 DM ≥6 months, insulin naive, on oral antidiabetics, A1c 7-10%, and BMI ≤40 kg/m²
  - Once daily degludec with PM meal
  - Insulin glargine given anytime (consistent schedule)
  - Metformin + DPP-4 continued
  - Excluded GLP-1 or TZD used within 3 months
- Insulin initiated at 10 units and titrated to BG level of ~70-90 mg/dL (3.9-4.9 mmol/L) pre-breakfast


Safety and Efficacy at 1 Year

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Insulin Units/kg/day</th>
<th>A1c %</th>
<th>Overall Hypoglycemia*</th>
<th>Nocturnal Hypoglycemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degludec (n=773)</td>
<td>0.59</td>
<td>-1.06</td>
<td>1.52</td>
<td>0.25</td>
</tr>
<tr>
<td>Glargine (n=257)</td>
<td>0.6</td>
<td>-1.19</td>
<td>1.85</td>
<td>0.39</td>
</tr>
</tbody>
</table>

95% CI; p value

-0.04 – 0.22 p=0.106 p=0.038

*Episodes per patient-year of exposure

Conclusion

- Degludec + oral agents was non-inferior to glargine + oral agents in A1c lowering
- No difference in total daily insulin dose
- Degludec had less nocturnal hypoglycemia compared to glargine


Two 26-week, phase 3, parallel group, randomized, open label, non-inferiority trials

- Adults, Type 2 DM, A1c 7-10%, and BMI <45 kg/m²
  - Three times weekly degludec (MWF) with AM or PM meal
  - Insulin glargine given anytime (consistent schedule)
  - Metformin + DPP-4 continued


Conclusion

- Degludec 3 times weekly was not shown to be non-inferior to glargine once daily in A1c lowering
- Rates of hypoglycemia varied by type and trial

Safety and Efficacy at 26 Weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>AM Degludec (n=230)</th>
<th>AM Glargine (n=230)</th>
<th>PM Degludec (n=233)</th>
<th>PM Glargine (n=234)</th>
<th>95% CI; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c %</td>
<td>-0.9</td>
<td>-1.3</td>
<td>-1.1</td>
<td>-1.4</td>
<td>0.18 – 0.51</td>
</tr>
</tbody>
</table>

95% CI -0.12 – 0.02 0.75 – 1.40 0.44–1.35

*Episodes per patient-year of exposure

BEGIN FLEX

- 26 week, phase 3, parallel group, randomized, open label, target-to-treat, non-inferiority trial
- Adults, Type 2 DM >6 months, insulin naive on oral antidiabetics or basal insulin plus oral medications, A1c 7-11%, and BMI <40 kg/m²
  - Once daily degludec given on pre-specified schedule (8-40 hr intervals)
  - Once daily degludec with PM meal
  - Insulin glargine given anytime (consistent schedule)
  - Oral agents continued
  - Excluded GLP-1, TZD, DPP-4, or alpha-glucosidase inhibitor used within 3 months
  - Insulin titrated to BG level of ~70-90 mg/dL (3.9-4.9 mmol/L) pre-breakfast


Safety and Efficacy at 26 Weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>A1c %</th>
<th>Overall Hypoglycaemia*</th>
<th>Nocturnal Hypoglycaemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degludec</td>
<td>-1.26</td>
<td>3.6</td>
<td>0.6</td>
</tr>
<tr>
<td>(n=229)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>-1.26</td>
<td>3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>(n=230)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.12 – 0.02</td>
<td>0.75 – 1.40</td>
<td>0.44-1.35</td>
</tr>
</tbody>
</table>

*Episodes per patient-year of exposure
Conclusion

- Degludec given on a predetermined flex schedule with intervals of 8-40 hours was non-inferior to once daily glargine in A1c lowering
- Degludec had similar rates of hypoglycemia compared to glargine

Summary: Insulin Degludec

- Novel basal insulin
- Similar results for type 1 and type 2 diabetes
- Similar A1c lowering compared to glargine
- Can be combined with rapid-acting insulin or oral agents
- May require lower total daily insulin dose compared to glargine
- Less overall hypoglycemia and nocturnal hypoglycemia compared to glargine
- May be given on a flex schedule with intervals ranging from 8-40 hours

PEGylated Insulin Lispro

- Novel method to extend insulin half-life:
  - Polyethylene glycol polymer chain covalently attached to insulin
  - Increases molecule size to reduce renal clearance and delay subcutaneous absorption
- Duration of action >36 hours
- May have increased hepatic effects resulting in increased action in peripheral tissues

Safety and Efficacy at 12 Weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>A1c (%)</th>
<th>FPG (mg/dL)</th>
<th>Intraday BG Variability (mg/dL)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-Lispro (n=195)</td>
<td>7.0 ± 0.1</td>
<td>118.2 ± 2.0</td>
<td>34.4</td>
<td>-0.6 ± 0.2</td>
</tr>
<tr>
<td>Glargine (n=95)</td>
<td>7.2 ± 0.1</td>
<td>116.9 ± 2.7</td>
<td>39.1</td>
<td>0.3 ± 0.2</td>
</tr>
</tbody>
</table>

p value: p=0.279, p=0.433, p=0.031, p<0.001

Bergenstal, et al.

- 12 week, phase 2, parallel group, randomized, open label, non-inferiority trial
- 18-65 yrs, Type 2 DM ≥1 year, on metformin + sulfonylurea + daily glargine or NPH (<1 unit/kg/day) for ≥3 months, A1c ≤10.5%, and BMI 19-45 kg/m²
  - Once daily PEG-lispro (LY2605541) in the AM
  - Once daily glargine in the AM
  - Metformin ± sulfonylurea continued
- Insulin titrated to fasting plasma glucose (FPG) level of ≤100 mg/dL

Conclusion

- Peg-Lispro given once daily demonstrated comparable glucose control compared to once daily glargine
- Peg-Lispro had lower intraday blood glucose variability and decreased weight compared to glargine
Insulin Glargine U300

- More concentrated form of currently available glargine
- Smaller depot surface area may extend Tmax to reduce peak
- Hypothesized that higher concentration may result in fewer injections for patients with insulin resistance


EDITION 1

- 6 month, parallel group, randomized, open label, non-inferiority trial
- Adults, A1c 7-10%
  - Once daily glargine U100 or glargine U300
- Dose titration to FPG ~80 – 100 mg/dL (4.4-5.6 mmol/L)

Riddle MC. Diabetes Care. 2014 July 30. [Epub ahead of print]

Study Participants
- N=807
  - Mean Age = 60 years
  - Diabetes duration = 16 years
  - BMI = 36.6 kg/m²
  - Baseline A1c = 8.15%
- Results at 6 months
  - No difference in A1c lowering
    - Least squares mean difference -0.00% (95% CI -0.11 – 0.11)
  - Fewer participants with confirmed/severe hypoglycemic events in glargine U300 group compared to glargine U100
    - 36% vs. 44%, RR 0.79, (95% CI 0.67-0.93), p< 0.005

Riddle MC. Diabetes Care. 2014 July 30. [Epub ahead of print]

EDITION 2

- 6 month, randomized, open label, non-inferiority trial
- Adults, Type 2 DM, basal insulin (>42 units/day) + oral agents
  - Once daily glargine U100 or glargine U300

Yki-Jarvinen H. Diabetes Care. 2014 Sep 5. [Epub ahead of print]

Study Participants
- N=811
  - BMI = 34.8 kg/m²
  - Baseline A1c = 8.24%
- Results at 6 months
  - No difference in A1c lowering in glargine U300 vs. glargine U100
    - -0.57% vs. -0.56%, (95% CI -0.14 – 0.12)
  - Fewer participants with nocturnal confirmed (70 mg/dL) or severe hypoglycemic events in glargine U300 group compared to glargine U100
    - RR 0.77, (95% CI 0.61-0.99), p=0.038

Yki-Jarvinen H. Diabetes Care. 2014 Sep 5. [Epub ahead of print]

Conclusion

- Glargine U300 given once daily demonstrated comparable glucose control compared to once daily glargine U100
- Glargine U300 had decreased nocturnal and severe hypoglycemia compared to glargine U100

Riddle MC. Diabetes Care. 2014 July 30. [Epub ahead of print]

Yki-Jarvinen H. Diabetes Care. 2014 Sep 5. [Epub ahead of print]
Future Research and Applications

- Comparison of new basal insulins to detemir
- Combination products
  - 70/30 insulin degludec/aspart
  - Insulin degludec/liraglutide 1 unit/0.036 mg
- Larger trials on PEG-Lispro and Glargine U300
- Investigation into potential weight loss benefits of PEG-Lispro
- Head-to-head trials of ultra-long-acting agents

Garber AJ. Diabetes Obes Metab. 2014;16:483-491. 37

2014 ACCP Annual Meeting
Basal Insulin: A Look Ahead
Robin L. Koffarnus, Pharm.D., BACAP
October 14, 2014
VI. Prevention and management of complications
A. Cardiovascular disease
   1. HTN control
   2. Dyslipidemia management
   3. Anti-platelet
   4. Smoking cessation

VI. Prevention and management of complications
A. Cardiovascular disease
   1. HTN control
      a. systolic BP < 140 rather than < 130
   2. Dyslipidemia management
      a. LDLc targets (<70 w/ CVD, < 100 w/o CVD) still but may change in 2015
   3. Anti-platelet
   4. Smoking cessation
   5. Hyperglycemia?
2012 ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

A pre-supposition: Insulin itself is neither CV protective nor CV toxic - ORIGIN trial. NEJM;367:319-28.

Sulfonylureas and pre-conditioning/CVD events

- Interesting data from in vitro models and some animal data
- Not a cause of CVD but may worsen outcomes in case of event
- Comparative effectiveness of sulfonylurea and metformin monotherapy on CV events in T2DM. Roumie, CL, et al.
- Effects of sulfonylureas on mitochondrial ATP-sensitive K+ channels in cardiac myocytes: implications for sulfonylurea controversy. Sato T, Nishida H, Miyazaki M, Nakaya H.

BARI-2D findings same as Cochrane: 2013

Cochrane: Sulfonylurea monotherapy for patients with diabetes mellitus

Data: 72 randomized controlled trials (RCTs) met inclusion criteria with 22,589 participants; 9,707 randomized to SU and 12,805 to non-SU therapies

Comparator agents included insulin, meglitinides, incretins, metformin and TZDs

Findings: No significant differences for mortality, CV mortality or a composite of CVD events between SU monotherapy and any other class of agents

Author’s Conclusions: Insufficient data from RCTs to recommend for or against SU monotherapy compared to other agents.

Conclusion, SUs: Agree with ADA/EASD

4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

What about Metformin? 2005

Cochrane: Metformin monotherapy for patients with diabetes mellitus

Data: 29 randomized controlled trials (RCTs) met inclusion criteria with 5,259 participants. Four trials powered for M+M

Comparator agents included placebo, diet, insulin, meglitinides, metformin, TZDs and alpha glucosidase inhibitors

Findings: “Obese participants assigned to intensive blood glucose control with metformin showed a greater benefit than overweight patients on conventional treatment for any diabetes-related outcomes…and myocardial infarction.”

Author’s Conclusions: Metformin may be the first therapeutic option in overweight or obesity as it may prevent some vascular complications
What about Metformin?

2005

Cochrane: Metformin monotherapy for patients with diabetes mellitus

Myocardial infarction from UKPDS: 22% RRR (p=NS)

<table>
<thead>
<tr>
<th>Subgroup (95% CI)</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifluralin 500 (SU) &amp; tolbutamide</td>
<td>0.73</td>
<td>0.55, 0.98</td>
<td>0.02</td>
</tr>
</tbody>
</table>

So the metformin “signal” comes mostly from UKPDS as the 2012 ADA/EASD statement indicates

Background: Remember that in the University Group Diabetes Program (UGDP) trial, phenformin exhibited unexpected INCREASE in CV mortality.

JAMA: Aug 9, 1971

UKPDS was a complicated trial design with contradictory findings:

- Patients randomized in the metformin trial (UKPDS 34) were all overweight and comparison was both to diet (“conventional”) as well as an intensive “add-on” arm
- Not all centers were used for the metformin arm and numbers were limited (~ 1,700 of the > 4,000 patients in UKPDS)
- When the intensive “add-on” arm was analyzed:
  - Compared to 269 patients on SU monotherapy, 268 patients on SU+Met had a 60% increased risk for death from any cause (p=0.041) including a 79% increased risk for fatal MI (17 vs. 10 deaths; p=NS)

What is the positive vascular data for metformin?

39% RRR in myocardial infarction with metformin monotherapy compared to conventional group:

Lancet, Sept. 12, 1998

<table>
<thead>
<tr>
<th>Aggregate endpoint</th>
<th>Metformin Intensive</th>
<th>Metformin Conventional</th>
<th>Placebo Intensive</th>
<th>Placebo Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident MI</td>
<td>269</td>
<td>268</td>
<td>269</td>
<td>268</td>
</tr>
<tr>
<td>p=0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

But, there was no difference in MI between intensive treatment with metformin (A1C 7.4%) and intensive treatment with SU or insulin (A1C “similar”)

Additionally, since metformin therapy was “intensive” there was an A1C difference between conventional (8.0%) and metformin groups (7.4%) with a Fu of 10.7 years AND Since 44% of conventional group could not achieve A1C goal with diet alone, SU or insulin therapies were used which resulted in rate of “major hypoglycemic” attacks of 0.7% per year vs. 0% in metformin arm

Conclusions for metformin:

Positive effects in very complicated UKPDS which were likely partly an artifact of trial design which have not been replicated outside of UKPDS

A suitable first choice for hyperglycemic therapy but no CVD mandate

The “glitazones” or TZDs

Rosiglitazone never as bad as purported and FDA reversed earlier position in 2013:

FDA letter to GSK dated May, 2014

We have also determined that elements to assure safe use that require that healthcare providers who prescribe rosiglitazone for outpatient or long-term care use are specially certified, that rosiglitazone be dispensed only by specially certified pharmacies, and that rosiglitazone be dispensed only to patients with evidence or other documentation of safe use conditions are no longer necessary to ensure the benefits of the drug outweigh the risks.
However, 2014 Package Insert for rosiglitazone still mentions CVD warning……

**WARNINGS and PRECAUTIONS**
- Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure (NYHA Class III or IV) may increase risk of heart failure exacerbation.
- Do not use in patients with severe renal impairment (Ccr 30–50 mL/min).
- Insulin has been documented to cause an adverse effect on cardiac contractility.
- Do not use in significant hypotension (5% to 10% increase in systolic pressure, 5% to 10% increase in diastolic pressure).
- Increased incidence of bone fracture (5.7)

……so choice among TZD class likely to remain pioglitazone.

But, should pioglitazone be a preferred choice for CVD?

2012 ADA/EASD statement cites reduction in CVD with pioglitazone but fails to make it a “preferred” agent in this population due to single trial evidence and concerns about concomitant CHF:

Single trial: PROactive: 5,238 patients saw a 13.4% RRR in combined CVD endpoint of death, non-fatal MI and stroke (10.4% vs. 11.9%) but individual event rates low:

Non-fatal MI: 85 events vs. 95 events over nearly 3 years of follow-up. 
*Lancet* 2005;366:1279-1288

In data not published in trial but presented at AHA and formerly posted on trial website (proactive-results.com)……

Glitzones: Conclusions

Concern about rosiglitazone overblown and from a very different population (low-risk, primary prevention CVD trials) than the small benefit which was found for pioglitzone (secondary CVD prevention)

But, pioglitzone is generic, does appear to have small benefit in patients with established CVD and does not contribute significantly to hypoglycemic episodes.

If we have a patient with CHD and with low risk for CHF (how many diabetics is that?) then could maybe make a case for pioglitzone but no preference for choice in absence of CHD

What about hypoglycemia?

Degree of glycemic control in ACCORD did not account for adverse effects

Epidemiologic Relationships Between A1C and All-Cause Mortality During a Median 3.4-year Follow-up of Glycemic Treatment in the ACCORD Trial

Matthew Riddle, Valerie Ambrosius, David Brillen, John Buse, Robert Byington, et al.

Results: “Higher A1C was associated with greater risk of death. The risk of death with the intensive strategy increased approximately linearly from 6-9%.”

Diabetes Care 2010;33:983-990

In the 3 large RCTs examining glycemia and CVD: all showed trends for reductions in events.


Non-fatal MI significantly reduced 24% (p<0.001)

So, better average glycemic control improves CVD outcomes but not by a lot. The problem though may be episodes of hypoglycemia….
Influence of severe hypoglycemia on events in ADVANCE

<table>
<thead>
<tr>
<th>Events</th>
<th>Sv. Hypo: Yes (n=231)</th>
<th>Sv. Hypo: No (n=10909)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major macrovascular events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td>33 (15.9%)</td>
<td>1114 (10.2%)</td>
<td>3.53 (2.41–5.17)</td>
</tr>
<tr>
<td>Major microvascular events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td>24 (11.5%)</td>
<td>1107 (10.1%)</td>
<td>2.19 (1.40–3.45)</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td>45 (19.0%)</td>
<td>986 (9.0%)</td>
<td>3.27 (2.29–4.85)</td>
</tr>
<tr>
<td>CVD deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td>22 (9.5%)</td>
<td>520 (4.8%)</td>
<td>3.79 (2.36–6.08)</td>
</tr>
<tr>
<td>Non-CVD deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td>23 (10.0%)</td>
<td>466 (4.3%)</td>
<td>2.80 (1.84–4.79)</td>
</tr>
</tbody>
</table>

By what mechanism(s) could hypoglycemia increase CVD risk?

- Cardiac arrhythmias due to abnormal cardiac repolarisation in high-risk patients (IHD, cardiac autonomic neuropathy)
- Increased thrombotic tendency/decreased thrombolysis
- Cardiovascular changes induced by catecholamines
  - Increased heart rate
  - Silent myocardial ischaemia
  - Angina and myocardial infarction

4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

Conclusion:
ADA/EASD got it about right. While there are several things to consider in regards to diabetic therapies and CVD, aside from metformin being a reasonable first choice, there is no mandate to elevate any given therapy over another for CVD benefit.