DIABETES 2016: UPDATE ON THERAPEUTICS

LORENA A. WRIGHT, MD, FACE

METABOLISM, ENDOCRINOLOGY AND NUTRITION

UNIVERSITY OF WASHINGTON MEDICAL CENTER/ROOSEVELT
In compliance with accrediting board policies, the American Diabetes Association requires the following disclosure to participants:

NAME OF PRESENTER: Lorena A. Wright, MD, FACE

Disclosed no conflict of interest
OBJECTIVES

• Identify the role of new therapeutic agents in the management of diabetes mellitus

• Become familiar with an individualized approach in the management of hyperglycemia in diabetes
CLASSES OF GLUCOSE LOWERING AGENTS FOR TREATING TYPE 2 DIABETES

Modified from Kahn SE et al: Lancet 2014; 383 (9922)
MAIN PATHOPHYSIOLOGICAL DEFECTS IN T2DM

- Hyperglycemia
  - Increased hepatic glucose production
  - Decreased peripheral glucose uptake
  - Increased glucose absorption
  - Decreased pancreatic insulin secretion
  - Increased pancreatic glucagon secretion
  - Decreased incretin effect
  - Decreased gut carbohydrate delivery & absorption

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
MAIN PATHOPHYSIOLOGICAL DEFECTS IN T2DM

HYPERGLYCEMIA

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
CASE 1

- Mrs. Kim is a 33 yo female with h/o T2DM x6 years, on insulin x3 years. Concerned about her weight, which has gradually increased since she was started on Risperdal for bipolar disorder
- Comorbidities: HTN, dislipidemia, obesity: BMI 50.5 and recent h/o pancreatitis
- Meds: metformin 1g BID, Lantus insulin 35u BID + Humalog on average 20-30u QAC, simvastatin 40mg
- HbA1c 8.2%, GFR>60, lipids LDL<100, TGC<200
CASE 2

- Mr. Agewell is a 77yo male with h/o T2DM x12 years, on insulin x3 years.
- He is unable to have his blood sugars under control despite swimming and cutting down on portions.
- Comorbidities include: HTN, dislipidemia, CAD and OA of the knees
- Meds: metformin 1g BID, mixed insulin 70/30- 50u AM and 34u PM
- BMI 35.5, HbA1c 9.2%
### Initial Drug Monotherapy

<table>
<thead>
<tr>
<th>Efficacy (HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side Effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low risk</td>
<td>Neutral/loss</td>
<td>GI / lactic acidosis</td>
<td>Low</td>
</tr>
</tbody>
</table>

#### Healthy eating, weight control, increased physical activity

- **Metformin**
  - Efficacy: High
  - Hypoglycemia: Low risk
  - Weight: Neutral/loss
  - Side Effects: GI / Lactic acidosis
  - Costs: Low
### Table: Comparison of Medications for Diabetes Management

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 inhibitor</th>
<th>SGLT2 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td><strong>Hypo risk</strong></td>
<td>low</td>
<td>moderate risk</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>neutral</td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>neutral</td>
<td>gain</td>
<td>high</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>low</td>
<td>hypoglycemia</td>
<td>edema, HF, fxs</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>GI</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>

### Notes:

- If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors).

### Monotherapy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dual Therapy

| Efficacy | Hypo risk | Weight | Side effects | Costs |}

### References

- Foundation for Care Management
- Center for Learning & Change
- WWW.FCMCME.ORG
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM
### Mono-therapy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low risk</td>
<td>neutral/loss</td>
<td>GI/lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

### Dual therapy

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
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<th>Metformin +</th>
</tr>
</thead>
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<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td>high risk</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>gain</td>
<td>edema, HF, fits</td>
<td>loss</td>
<td>gain</td>
</tr>
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<td>rare</td>
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<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>
## INCRETIN THERAPIES: MAJOR DIFFERENCES

<table>
<thead>
<tr>
<th>Properties/Effect</th>
<th>GLP-1 Receptor Agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Insulin production</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>↑ First-phase insulin response</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>↓ Glucagon</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>↓ Hepatic glucose output</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Delayed</td>
<td>No effect</td>
</tr>
<tr>
<td>Food intake</td>
<td>↓</td>
<td>No effect</td>
</tr>
<tr>
<td>Body weight</td>
<td>↓</td>
<td>No effect</td>
</tr>
<tr>
<td>Hypoglycemia (as monotherapy)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Nausea, vomiting</td>
<td>Minimal</td>
</tr>
<tr>
<td>↓A1c</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Drucker DJ, Nauck MA. Lancet. 2006;368:1696-1705.
DPP-4 Inhibitors

DPP-4 Inh: Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin

1. Weight Neutral
2. No hypoglycemia
3. Ok in CHF or CKD
4. Monotherapy or combo with oral hypoglycemics or insulin

1. Nasopharyngitis, URI
2. Risk of pancreatitis
3. Arthralgias
4. Cost
Recent trials on glucose-lowering agents have been neutral on the primary CV outcome

- **SAVOR-TIMI 53**
  - HR: 1.0
  - (95% CI: 0.89, 1.12)

- **EXAMINE**
  - HR: 0.96
  - (95% CI: UL ≤1.16)

- **TECOS**
  - HR: 0.98
  - (95% CI: 0.88, 1.09)

CV, cardiovascular; HR, hazard ratio; DPP-4, dipeptidyl peptidase-4

*Saxagliptin, alogliptin, sitagliptin

Adapted from Johansen OE. World J Diabetes 2015;6:1092-96
GLP-1 Agonists

Disadvantages
- Cost
- Injectable

Advantages
- Weight loss
- Easy dosing
- Prelude to insulin

GLP-1 agonists: Exenatide, Exenatide ER, Liraglutide, Dulaglutide
Disadvantages:
- GI S/E: Nausea
- Pancreatitis
- Contraindicated in MTC

Advantages:
- Add on to insulin

GLP-1 Agonists:
- GLP-1 agonists: Exenatide
- Exenatide ER
- Liraglutide
- Dulaglutide
Study Overview

• Patients with type 2 diabetes and high cardiovascular risk were assigned to receive either the glucagon-like peptide 1 analogue liraglutide or placebo.
• The rate of first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke was lower with liraglutide.
In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.
<table>
<thead>
<tr>
<th></th>
<th>Metformin +</th>
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<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Weight</td>
<td>neutral/loss</td>
<td>neutral/loss</td>
<td>neutral</td>
<td>neutral/loss</td>
<td>neutral/loss</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>Side effects</td>
<td>GI/lactic acidosis</td>
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<td>GI/lactic acidosis</td>
<td>GI/lactic acidosis</td>
<td>GI/lactic acidosis</td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
<td>low</td>
<td>neutral</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

**Healthy eating, weight control, increased physical activity, and diabetes education**

- Metformin
- Sulfonylurea
- Thiazolidinedione
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 receptor agonist
- Insulin (basal)

**Mono-therapy**
- Efficacy: high
- Hypo risk: low risk
- Weight: neutral/loss
- Side effects: GI/lactic acidosis
- Costs: low

**Dual therapy**
- Efficacy: high
- Hypo risk: moderate risk
- Weight: gain
- Side effects: hypoglycemia
- Costs: low
SGLT-2 INHIBITORS

Canagliflozin (invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)

Glucosuria
Glucose Reduction

SGLT2 Inhibitors Added to Metformin (Absolute Changes from Baseline; Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th></th>
<th>Canaglifozin</th>
<th>Dapaglifozin</th>
<th>Empaglifozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline A1C (%)</td>
<td>7.8</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>-0.93</td>
<td>-0.52</td>
<td>-0.77</td>
</tr>
</tbody>
</table>

SGLT-2 INHIBITORS

- Once daily dosing
  - ↓ A1c ~0.5-0.9%
  - ↓ FPG, PPG
  - ↓ Weight
  - combination with other OA and/or insulin
  - Minimal GI s/e
  - ↓ BP
  - Potential ↓ uric acid

- Polyuria
- Dehydration
- Hypotension
- UTI’s
- Genital infections
- ↑ LDL and non-HDL
- Require near normal GFR
- Cost/Insurance
- Diabetic ketoacidosis
- No long term safety data
DKA develops when insulin levels are too low or during prolonged fasting. DKA most commonly occurs in patients with T1DM, usually accompanied by hyperglycemia. The FAERS cases were somewhat atypical (most had T2DM and their glucose levels, when reported only slightly increased compared to typical cases of DKA).
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Study Overview

- In this study, the addition of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, to standard care reduced cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk.
Glycated Hemoglobin Levels.

Patients with T2D at high risk for CV events who received empagliflozin, vs placebo, had a lower rate of the primary composite CV outcome and of death from any cause when the study drug was added to standard care.
<table>
<thead>
<tr>
<th>Ideal candidates</th>
<th>Do not consider:</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM and HTN</td>
<td>H/o UTI’s or genital infections</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td>Immunocompromised patients: post-transplant, or on immunosuppressant agents</td>
</tr>
<tr>
<td>Patients with frequent hypoglycemia and/or weight gain on other agents (sulfonylureas)</td>
<td>eGFR &lt;45 for Cana &lt;60 for Dapa</td>
</tr>
<tr>
<td>Patients with s/e to other drugs (GI s/e, h/o pancreatitis)</td>
<td>Frailty, elderly prone to falls and/or dehydration</td>
</tr>
<tr>
<td></td>
<td>Caution in advanced diabetes</td>
</tr>
</tbody>
</table>
# GLUCOSE REDUCTION

## DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin
(Absolute Changes from Baseline; Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th></th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
<th>SGLT2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alo¹</td>
<td>Lin²</td>
<td>Sax³</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>7.9</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Δ A1C (%)</td>
<td>-0.6</td>
<td>-0.5</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

WEIGHT REDUCTION

**DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin**

*(Separate Studies; Not Head-to-Head Trials)*

<table>
<thead>
<tr>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
<th>SGLT2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alo¹</td>
<td>Lin²</td>
<td>Sax³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sit⁴</td>
</tr>
<tr>
<td>Alb⁵</td>
<td></td>
<td>Dul⁶</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exe⁷</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exe ER⁸</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lir⁹</td>
</tr>
<tr>
<td>Can¹⁰</td>
<td></td>
<td>Dap¹¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emp¹²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Δ Weight (kg)</th>
<th>0</th>
<th>-1</th>
<th>-2</th>
<th>-3</th>
<th>-4</th>
<th>-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alo¹</td>
<td>-0.3</td>
<td>-0.4</td>
<td>-0.9</td>
<td>-1.2</td>
<td>-2.6</td>
<td>-2.8</td>
</tr>
<tr>
<td>Lin²</td>
<td></td>
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<td></td>
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<tr>
<td>Sax³</td>
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<td>Alb⁵</td>
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<tr>
<td>Exe⁷</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Exe ER⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lir⁹</td>
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<tr>
<td>Can¹⁰</td>
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<td>Dap¹¹</td>
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<tr>
<td>Emp¹²</td>
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<td></td>
</tr>
</tbody>
</table>

NR, not reported.

BACK TO OUR PATIENTS
CASE 1

• Mrs. Kim is a 33 yo female with h/o T2DM x6 years, on insulin x3 years. Concerned about her weight, which has gradually increased since she was started on Risperdal for bipolar disorder

• Comorbidities: HTN, dislipidemia, obesity: BMI 50.5 and recent h/o pancreatitis

• Meds: metformin 1g BID, Lantus insulin 35u BID + Humalog on average 20-30u QAC, simvastatin 40mg

• HbA1c 8.2% , GFR>60, lipids LDL<100, TGC<200
Mrs. Kim’s goals:

1. Glycemic control
2. Weight loss

U300, U500 insulin? GLP-1 based therapy? a SGLT-2 inhibitor?

A GLP-1 receptor agonist? a SGLT-2 inhibitor?
Adapted Recommendations: When Goal is to Avoid Weight Gain

<table>
<thead>
<tr>
<th>Healthy eating, weight control, increased physical activity, and diabetes education</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mono-therapy</strong></td>
</tr>
<tr>
<td>Efficacy: high</td>
</tr>
<tr>
<td>Hypo risk: neutral / loss</td>
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<td>Weight: neutral / loss</td>
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<tr>
<td>Side effects:</td>
</tr>
<tr>
<td>Costs:</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>Metformin + Sulfonylurea</td>
</tr>
<tr>
<td>Metformin + Metformin + Thiazolidinedione</td>
<td></td>
</tr>
<tr>
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<td>Metformin + SGLT2 inhibitor</td>
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<td>Metformin + GLP-1 receptor agonist</td>
<td>Metformin + Insulin (basal)</td>
</tr>
<tr>
<td>Metformin + high</td>
<td>Metformin + intermediate</td>
</tr>
<tr>
<td>Metformin + low risk</td>
<td>Metformin + low risk</td>
</tr>
<tr>
<td>Metformin + neutral</td>
<td>Metformin + low risk</td>
</tr>
<tr>
<td>Metformin + rare</td>
<td>Metformin + loss</td>
</tr>
<tr>
<td>Metformin + high</td>
<td>Metformin + GI, dehydration</td>
</tr>
<tr>
<td>Metformin + high</td>
<td>Metformin + high</td>
</tr>
<tr>
<td>Metformin + high risk</td>
<td>Metformin + gain</td>
</tr>
<tr>
<td>Metformin + hypoglycemia</td>
<td>Metformin + hypoglycemia</td>
</tr>
<tr>
<td>Metformin + variable</td>
<td>Metformin + variable</td>
</tr>
</tbody>
</table>
OTHER CONSIDERATIONS

• **Age: Older adults**
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia

- Less ambitious targets
- HbA1c <7.5–8.0% if tighter targets not easily achieved
- Focus on drug safety
4. OTHER CONSIDERATIONS

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

- Metformin: May use unless condition is unstable or severe
- Avoid TZDs
- Incretin-based-therapies
- SGLT-2 Inh.
4. OTHER CONSIDERATIONS

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

  ➢ Most drugs not tested in advanced liver disease
  ➢ Pioglitazone may help steatosis
  ➢ Insulin best option if disease severe
4. OTHER CONSIDERATIONS

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

- Emerging concerns regarding association with increased morbidity / mortality
- Proper drug selection is key in the hypoglycemia prone
CASE 2

- Mr. Agewell is a 77yo male with h/o T2DM x12 years, on insulin x3 years.
- He is unable to have his blood sugars under control despite swimming and cutting down on portions.
- Comorbidities include: HTN, dislipidemia, **CAD** and OA of the knees
- Meds: metformin 1g BID, mixed insulin 70/30- 50u AM and 34u PM
- **BMI 35.5**, HbA1c 9.2%
• Mr. Agewell’s goals:

1. Glycemic control
2. Avoid hypoglycemia
3. Weight loss
4. Quality of life

“My A1c had always been in the 7’s and now despite my best efforts I do not seem to control my blood sugars at all!... even increasing my insulin doses... this is not working!”

“Sometimes I am not hungry and do not feel like having a full meal... but if I don’t my blood sugars tend to go low”

“I stopped walking with my dog in the morning because my knees hurt... it must be all the weight I have gained in the last months... I am trying to stay active and I joined a swimming class, but I still cannot lose weight...
Adapted Recommendations: When Goal is to Avoid Hypoglycemia

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
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<tbody>
<tr>
<td>Efficacy</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
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<td>low</td>
<td>low</td>
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<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Weight</td>
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<td>neutral</td>
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<td>neutral</td>
<td>neutral</td>
<td>neutral</td>
</tr>
<tr>
<td>Side effects</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
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<tr>
<td>Costs</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>variable</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 inhibitor</th>
<th>SGLT2 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high risk</td>
</tr>
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<td>neutral</td>
<td>loss</td>
<td>loss</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fxS</td>
<td>rare</td>
<td>rare</td>
<td>GI, dehydration</td>
<td>gain</td>
</tr>
<tr>
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<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>hypoglycemia</td>
</tr>
</tbody>
</table>

Healthy eating, weight control, increased physical activity, and diabetes education
## Adapted Recommendations: When Goal is to Avoid Weight Gain

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Healthy eating, weight control, increased physical activity, and diabetes education</th>
<th>Metformin</th>
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<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Weight</td>
<td>Neutral / loss</td>
<td>Low</td>
</tr>
<tr>
<td>Side effects</td>
<td>GI / lactic acidosis</td>
<td>Neutral</td>
</tr>
<tr>
<td>Costs</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Metformin +</th>
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<td>Insulin (basal)</td>
<td></td>
</tr>
<tr>
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<td>intermediate</td>
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<td>high</td>
<td>highest</td>
<td></td>
</tr>
<tr>
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<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
<td></td>
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<tr>
<td>gain</td>
<td>maintenance</td>
<td>maintenance</td>
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<td>maintenance</td>
<td>gain</td>
<td></td>
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<tr>
<td>hypoglycemia</td>
<td>edema, HF, fxS</td>
<td>edema, HF, fxS</td>
<td>GU, dehydration</td>
<td>GI</td>
<td>hypoglycemia</td>
<td></td>
</tr>
<tr>
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<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>variable</td>
<td></td>
</tr>
</tbody>
</table>

Dual therapy:

- **Efficacy**: high
- **Hypo risk**: moderate risk
- **Weight**: gain
- **Side effects**: hypoglycemia
- **Costs**: low
Adapted Recommendations: When Goal is to Avoid Weight Gain

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy*</td>
<td>high</td>
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<tr>
<td>Hypo risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight</td>
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</tr>
<tr>
<td>Side effects</td>
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</tr>
<tr>
<td>Costs</td>
<td>low</td>
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</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

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<tr>
<th>Dual therapy†</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
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</thead>
<tbody>
<tr>
<td>Efficacy*</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td></td>
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<tr>
<td>Hypo risk</td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td></td>
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<td>Weight</td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>low risk</td>
<td></td>
</tr>
<tr>
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<td>edema, HF, fxs</td>
<td>GI, dehydration</td>
<td>GI</td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td></td>
</tr>
</tbody>
</table>

- Sulfonylurea
- Thiazolidinedione
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 receptor agonist

- Insulin (basal)

Order: Metformin + Sulfonylurea
Order: Metformin + Thiazolidinedione
Order: Metformin + DPP-4 inhibitor
Order: Metformin + SGLT2 inhibitor
Order: Metformin + GLP-1 receptor agonist
Order: Metformin + Insulin (basal)
• GLP-1 based therapy: Liraglutide 0.6mg SC → 1.2mg → 1.8mg QD

• ↓ Insulin dose by 20% initially and gradually

• Weight 253.4 lbs. → 234.6 lbs. in 9 months

• Transitioned to basal bolus that allowed him to have more flexibility with meals

• HbA1c 9.2% → 7.5%
UPDATE ON THERAPEUTICS: NEW INSULINS
### Mono-therapy

- **Efficacy**: high
- **Hypo risk**: low risk
- **Weight**: neutral / loss
- **Side effects**: GI / lactic acidosis
- **Costs**: low

---

### Healthy eating, weight control, increased physical activity, and diabetes education

#### Metformin

- **Efficacy**: high
- **Hypo risk**: low risk
- **Weight**: neutral / loss
- **Side effects**: GI / lactic acidosis
- **Costs**: low

---

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choices depend on a variety of patient- and disease-specific factors):

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<thead>
<tr>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

---

### Dual therapy

- **Efficacy**: high
- **Hypo risk**: moderate risk
- **Weight**: low risk
- **Side effects**: edema, HF, fx
- **Costs**: low

---

**Insulin (basal)**

- **Efficacy**: highest
- **Hypo risk**: high risk
- **Weight**: gain
- **Side effects**: hypoglycemia
- **Costs**: variable
Frederick G. Banting

Student Assistant Charles H. Best and Frederick G. Banting are standing on the roof of the medical building with one of the diabetic dogs used in their experiments with insulin.
CHALLENGES WITH LARGE VOLUMES

• Absorption may be impaired
  • Large volume = decreased surface area for absorption

• Discomfort likely with larger volumes

• Practical issues – can’t do more than 100 units per syringe

64 units
0.06 mm²/unit

2 x 32 units
0.08 mm²/unit
CONCENTRATED INSULINS

• No dose adjustment needed
• Patient dials the same dose, pen delivers smaller volume

30 units insulin = 0.3 cc 30 units insulin = 0.1 cc

U-100 U-300
<table>
<thead>
<tr>
<th>PK/PD PARAMETERS</th>
<th>HUMULIN R-U500</th>
<th>DEGLUDEC U200</th>
<th>GLARGINE U300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of action</td>
<td>6-10 hrs</td>
<td>42 hrs</td>
<td>&gt;30 hrs</td>
</tr>
<tr>
<td>Half-life</td>
<td>4 hrs</td>
<td>25 hrs</td>
<td>18-19 hrs</td>
</tr>
<tr>
<td>Steady state</td>
<td>-</td>
<td>2-3 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Concentration (units/mL)</td>
<td>500</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Max, single dose delivery</td>
<td>100</td>
<td>160</td>
<td>80</td>
</tr>
</tbody>
</table>
WHEN TO CONSIDER CONCENTRATED INSULIN?

- Patient on large volume injections causing discomfort
- Those needing to split insulin doses due to large volumes
  - U300 if <80 units per injection
  - U500 if >80 units per injection, >200 units/day
- U500 may allow for fewer injections per day
- Overall glycemic control is the same as U100
CONCENTRATED U-500 INSULIN

- Consider in extreme insulin resistance, pts requiring >200 units insulin per day
  - Improved absorption
  - Fewer daily injections
CONCENTRATED INSULINS

- **Glargine U-300 (Toujeo)**
  - 3-fold concentrated, no dose conversion needed
  - 1.5 ml pens = 450 units per pen
  - Not available in vial form

U-300 glargine
U300 IS NON-INFERIOR TO U100

EDITION 1
U300 vs U100 in basal-bolus insulin

EDITION 2
U300 vs U100 with basal insulin + OADs

EDITION 3
U300 vs U100 insulin naive

Bolli, et al. Diab Obes Metab. 2015;17:386
BENEFITS OF U300?

- Higher insulin dose with U300
  - 9.6 – 13.5% more insulin to achieve same A1C
- Less nocturnal hypoglycemia with U300
  - Rate varied depending on other medications
  - No significant difference for daytime events
- Weight gain
  - Varied between studies, but no significant trend
- Maximum dose per injection is 80 units
DEGLUDEC

New generation ultra-long-acting basal insulin

slow release of IDeg monomers from soluble multihexamers that form after subcutaneous injection, resulting in a long half-life and a smooth and stable pharmacokinetic profile at steady state
THE EFFECT OF VARYING DOSE SCHEDULE

- N=610, 26 week trial
- 1:1:1 ratio to receive Ideg in a flexible once-daily (OD) dosing regimen, prespecified, rotating
- AM and evening schedules; IDeg QD, or Insulin glargine QD
day)

<table>
<thead>
<tr>
<th>Day of the week</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
<th>Mon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing time</td>
<td>AM'</td>
<td>PM'</td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
<td>PM</td>
<td>PM</td>
<td>AM</td>
</tr>
<tr>
<td>Interval between doses (hours)</td>
<td>36–40</td>
<td>8–12</td>
<td>36–40</td>
<td>8–12</td>
<td>36–40</td>
<td>24</td>
<td>8–12</td>
<td></td>
</tr>
</tbody>
</table>
THE EFFECT OF VARYING DOSE SCHEDULE

Equivalent A1C lowering with insulin degludec at varied dosing schedule
Less nocturnal hypoglycemia with degludec vs glargine
STARTING INSULIN DEGLUDEC

- Start at same dose as current basal insulin
- Give once daily at any time of day
- If dose is missed, take next dose as soon as possible (at least 8 hours since last dose)
- Allow 3 days for glucose levels to stabilize between dose adjustments

- Most benefit for shift workers, with variable daily schedules
- May benefit patients who have trouble remembering to take their basal insulin daily
CONCENTRATED PRANDIAL INSULINS

- Lispro U-200 (Humalog)
  - 2-fold concentrated, no dose conversion needed
  - Bioequivalent to U-100, no significant difference
  - More units of insulin per pen
  - Cost approximately the same
# Costs of Insulin

<table>
<thead>
<tr>
<th>Insulin</th>
<th>1 box of pens</th>
<th>1 vial</th>
<th>Cost per unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>$390 (1500 u)</td>
<td>$260 (1000 u)</td>
<td>$0.26</td>
</tr>
<tr>
<td>Glargine U-300</td>
<td>$350 (1300 u)</td>
<td>n/a</td>
<td>$0.27</td>
</tr>
<tr>
<td>Regular U-500</td>
<td>$1600 (3000 u)</td>
<td>$1400 (10,000 u)</td>
<td>$0.14/$0.53</td>
</tr>
<tr>
<td>Degludec</td>
<td>$450 (1500 u)</td>
<td>n/a</td>
<td>$0.30</td>
</tr>
</tbody>
</table>

Data from goodrx.com accessed 8/29/2016
65-year-old woman with a 17-year history of T2DM.
BMI: 35 kg/m²
Difficulty with medication adherence
A1C is 8.1% on 2 g of extended-release metformin daily, 100 mg of sitagliptin daily, and 32 units of detemir twice daily

She refuses additional insulin injections

Recommendation: consideration of degludec U200 or glargine U300 once daily to reduce injection burden to once daily, decrease volume of administered insulin, may improve adherence, and may offer flexible administration timing
• 32-year-old woman with a 20-year history of T1DM.
• Mild nonproliferative diabetic retinopathy and microalbuminuria.
• History of nocturnal hypoglycemia and intentionally prefers to maintain her blood sugars >180 mg/dL
• A1C is 8.4% on 14 units of glargine daily, 1 unit of novolog – 15 g of carbohydrate with a sensitivity of 1 unit Q45 mg/dL >180 mg/dL.
• Recommendation: consideration of degludec U200 or glargine U300 once daily in place of glargine U100 to improve insulin durability and reduce the risk of hypoglycemia. If this reduces fear of hypoglycemia, titration of her regimen to improve glycemic control may be possible
CONCLUSIONS
THANK YOU FOR YOUR INTEREST IN DIABETES

Lorena Alarcon-Casas Wright, MD, FACE
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University of Washington Medical Center/Roosevelt
Harborview Medical Center
Email: LORENAAC@UW.EDU