Antihyperglycemic Agents in the Treatment of Patients with Type 2 Diabetes

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Stanford University School of Medicine
Financial Disclosures

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Unlabeled/Unapproved Uses Disclosure-None
Learning Objectives

1. Understand the rationale for individualizing A1c goals in people with diabetes.
2. Understand the different pathophysiologic defects associated with DM2/ hyperglycemia and how the pharmacologic agents address these defects.
3. Describe the considerations for antihyperglycemic therapy in the patient with type 2 diabetes who has chronic renal disease.
4. Discuss when it may be appropriate for the early use of basal insulin in patients with type 2 DM.
4) Describe recommended therapies and treatment plans from National organizations.
Case Study- Mrs. AA

Med hx: 76 y white woman hx of DM x 10 y but uncontrolled since 2012. PMH: HTN, Dyslipidemia, OSA w BiPAP, hypothyroid and morbid obesity w maintained wt loss of ~ 50 lbs for many yrs. Lifestyle/RF vigilant f/u, no known CVD, F hx of HF, normal LFT’s, eGFR and S Cr 0.8 mg/dL.

Meds: metformin 2500 mg for ~ 10 yrs 1500/1000, Glipizide @ 10 mg 2 x (gradual ↑ in dose) Difficulty w evening DM meds and desserts Sig fear of hypoglycemia Some issues w constipation
HS glucose: ~ 5 hrs post meal: 8 @ 191-220, and 221-250, 3 @ 251-280, 2 @ 181-310,

A1c hx since 2013 7.8-7.9% Initially had decreased to 7.2% in 2012

What to add & why
a) Basil insulin – would offer better control
b) DPP-4 inhibitor - May get to goal wt neutral
c) GLP-1 RA – will get to goal may have wt loss
d) Work on improvement to PM dosing and ↓desserts
Age-adjusted Percentage of U.S. Adults with Obesity or Diagnosed Diabetes

The Diabetes Epidemic: Global Projections, 2010–2030

World
2011 = 366 million
2030 = 552 million
Increase = 51%

- 37.7
- 51.2
- 36%
- 52.8
- 64.2
- 22%
- 71.4
- 120.9
- 69%
- 32.6
- 59.7
- 83%
- 14.7
- 28.0
- 90%
- 25.1
- 39.9
- 59%
- 131.9
- 187.9
- 42%

IDF. Diabetes Atlas 5th Ed. 2011
Criteria for the Diagnosis of Diabetes

- A1C $\geq 6.5\%$
- Fasting plasma glucose (FPG) $\geq 126 \text{ mg/dL} (7.0 \text{ mmol/L})$
- 2-h plasma glucose $\geq 200 \text{ mg/dL} (11.1 \text{ mmol/L})$ during an OGTT
- A random plasma glucose $\geq 200 \text{ mg/dL} (11.1 \text{ mmol/L})$ with sx of hyperglycemia

In absence of unequivocal hypergycemia results should be confirmed by repeat testing

Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S9; Table 2.1
Mean Glucose Levels for Specified A1C Levels

<table>
<thead>
<tr>
<th>A1C%</th>
<th>Mean Plasma Glucose*</th>
<th>Mean Fasting Glucose</th>
<th>Mean Premeal Glucose</th>
<th>Mean Postmeal Glucose</th>
<th>Mean Bedtime Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126 mg/dL 7.0 mmol/L</td>
<td>122 mg/dL 118 mmol/L</td>
<td>144 mg/dL 136 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.5</td>
<td></td>
<td>122 mg/dL 118 mmol/L</td>
<td>144 mg/dL 136 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5-6.99</td>
<td>142 mg/dL 139 mmol/L</td>
<td>164 mg/dL 153 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>154 mg/dL 8.6 mmol/L</td>
<td>152 mg/dL 152 mmol/L</td>
<td>176 mg/dL 177 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0-7.49</td>
<td>152 mg/dL 152 mmol/L</td>
<td>176 mg/dL 177 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5-7.99</td>
<td>167 mg/dL 155 mmol/L</td>
<td>189 mg/dL 175 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>183 mg/dL 10.2 mmol/L</td>
<td>178 mg/dL 179 mmol/L</td>
<td>206 mg/dL 222 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-8.5</td>
<td></td>
<td>178 mg/dL 179 mmol/L</td>
<td>206 mg/dL 222 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>212 mg/dL 11.8 mmol/L</td>
<td>178 mg/dL 179 mmol/L</td>
<td>206 mg/dL 222 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>240 mg/dL 13.4 mmol/L</td>
<td>178 mg/dL 179 mmol/L</td>
<td>206 mg/dL 222 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>269 mg/dL 14.9 mmol/L</td>
<td>178 mg/dL 179 mmol/L</td>
<td>206 mg/dL 222 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>298 mg/dL 16.5 mmol/L</td>
<td>178 mg/dL 179 mmol/L</td>
<td>206 mg/dL 222 mmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92. A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available at [http://professional.diabetes.org/eAG](http://professional.diabetes.org/eAG).

ADA. 6. Glycemic Targets. Diabetes Care. 2015;38(suppl 1):S35; Table 6.1
## Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage* with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

*Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests.

GFR = glomerular filtration rate

ADA. 9. Microvascular Complications and Food Care. Diabetes Care 2015;38(suppl 1):S59; Table 9.2
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care 2015;38:140–149
Diabetologia 2015;58:429–442
ADA-EASD Position Statement Update:
Management of Hyperglycemia in T2DM, 2015

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*Oxford University, Oxford, UK*
1. Patient-Centered Approach

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”


• Gauge patient’s preferred level of involvement.

• Explore, where possible, therapeutic choices. Consider using decision aids (pamphlets, videos, written materials).

• **Shared Decision Making** – a collaborative process between patient and clinician, using best available evidence and taking into account the patient’s preferences and values

• **Final decisions regarding lifestyle choices ultimately lie with the patient.**
Collaborative, Integrated Diabetes Management Team

<table>
<thead>
<tr>
<th>Written DM Management Plan</th>
<th>Include pt, family, Health care team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable Self Management of DM</td>
<td>Education on problem solving for all aspects of DM DSME</td>
</tr>
<tr>
<td>Individualize treatment goals/plans</td>
<td>Consider: Age Physical Activity School/Work Eating pattern Social support Cultural Factors DM complications Health Priorities Co morbidities</td>
</tr>
</tbody>
</table>

DSME – Diabetes Self Management Education

Diabetes Care 2015;38
Q. Diabetes is the leading cause of adult blindness, amputation, and kidney failure.

True or false?
Messages to Our Patients

A. False

• To a large extent, it is poorly controlled diabetes that is the leading cause of adult blindness, amputation and kidney failure.

• Well-controlled diabetes is the leading cause of ..........NOTHING

William H. Polonsky, PhD, CDE
Co Founder and President of Behavioral Diabetes Institute
2. BACKGROUND

- Relationship of glycemic control to microvascular and macrovascular outcomes.
# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

* in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

Meta-Analysis: Effect of Intensive Control on All-cause Mortality

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants, Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UKPDS</strong>47</td>
<td>3071/1549, 539/302</td>
<td>10.1%</td>
<td>0.79 (0.53-1.20)</td>
</tr>
<tr>
<td><strong>PROactive</strong>18-20</td>
<td>2605/2633, 177/186</td>
<td>21.5%</td>
<td>0.96 (0.77-1.19)</td>
</tr>
<tr>
<td><strong>ADVANCE</strong>5</td>
<td>5571/5569, 498/533</td>
<td>29.4%</td>
<td>0.93 (0.82-1.05)</td>
</tr>
<tr>
<td><strong>VADT</strong>21,22</td>
<td>892/899, 102/95</td>
<td>15.5%</td>
<td>1.09 (0.81-1.47)</td>
</tr>
<tr>
<td><strong>ACCORD</strong>8</td>
<td>5128/5123, 257/203</td>
<td>23.6%</td>
<td>1.28 (1.06-1.54)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>17267/15773, 1573/1319</td>
<td>100%</td>
<td>1.02 (0.87-1.19)</td>
</tr>
</tbody>
</table>

Figure 4: Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment

All-cause mortality: Heterogeneity, ACCORD is outlier

2. BACKGROUND

- Overview of the pathogenesis of T2DM
  - Insulin secretory dysfunction
  - Insulin resistance (muscle, fat, liver)
  - Increased endogenous glucose production
  - Decreased incretin effect
  - Deranged adipocyte biology
Natural History of T2D and β-cell Function

Multiple, Complex Pathophysiological Abnormalities in T2DM

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
Multiple, Complex Pathophysiological Abnormalities in T2DM

HYPERGLYCEMIA

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
3. ANTI-HYPERGLYCEMIC THERAPY

• Glycemic targets
  - HbA1c < 7.0% (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l]) reasonable goal for adults.
  - Pre-prandial PG < 130 mg/dl (7.2 mmol/l)
  - Post-prandial PG < 180 mg/dl (10.0 mmol/l)
  - Individualization is key:
    ➢ Tighter targets (6.0 - 6.5%) - younger, healthier
    ➢ Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
    ➢ Avoidance of hypoglycemia

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Approach to the management of hyperglycemia

PATIENT / DISEASE FEATURES

Risks potentially associated with hypoglycemia and other drug adverse effects

Disease duration

Life expectancy

Important comorbidities

Established vascular complications

Patient attitude and expected treatment efforts

Resources and support system

more stringent

HbA1c 7%

less stringent

Usually not modifiable

Potentially modifiable

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
Individualize Glycemic Targets - ADA

- **A1c < 7%** - a reasonable goal for adults
- **A1c < 6-6.5%** - may be appropriate for those with a short duration, long life expectancy, without significant risk of hypoglycemia or other adverse effects of treatment
- **A1c 7.5 8%** - may be appropriate for patients with history of hypoglycemia, limited life expectancy, or those with longstanding diabetes and vascular complications

Diabetes Care 2015;38:140-149;
What Should A1c Goal Be?

31 y Hispanic Male  PMH: Cardiomyopathy, severe improved to moderate, Mar/14 NYHA Class 1, secondary single implantable cardioverter-defibrillator DM2, Hypertriglyceridermia
Meds: carvedilol 25 mg, spironolactone 25 mg Lisinopril, Glargine (Lantus 30 U) – stopped glipizide-sx of hypoglycemia if doesn’t eat w glipizide –
financial issues

**A1c:** 7/2011-12.1%, 9/2011-7.6%, 4/2012-7.5%
9/2012-8.6% 3/10/2014 -9.0%
Normal S Cr & eGFR
What Should A1c Goal Be?

1. < 6.5%
2. < 7%
3. 7-7.5%
4. 7.5-8%
## Treatment Goals for Glycemia in Older Adults

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Rationale</th>
<th>Reasonable A1c Goal</th>
<th>FPG / pre meal glucose mg/dL</th>
<th>Bedtime Glucose mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Few coexisting illness, intact cognitive and functional status</td>
<td>Longer remaining life expectancy</td>
<td>&lt;7.5 % Same as goals for younger adults w/o hypoglycemia or Rx burden</td>
<td>90-130</td>
<td>90-150</td>
</tr>
<tr>
<td>Complex/intermediate Multiple chronic illness / ADL impairments or mild to moderate cognitive impair</td>
<td>Intermediate remaining life expectancy, High Rx burden, hypoglycemia vulnerability fall risk</td>
<td>&lt; 8%</td>
<td>90-150</td>
<td>100-180</td>
</tr>
<tr>
<td>Very Complex</td>
<td>Limited life expectancy benefit uncertain</td>
<td>&lt; 8.5%</td>
<td>100-180</td>
<td>110-200</td>
</tr>
</tbody>
</table>
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: **Lifestyle**
  - Weight optimization
  - Healthy diet
  - Increased activity level


*Diabetes Care 2012;35:1364–1379; Diabetologia 2012;55:1577–1596*
<table>
<thead>
<tr>
<th><strong>Guidelines for Glycemic, BP, &amp; Lipid Control</strong></th>
<th><strong>American Diabetes Assoc. Goals</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1C</strong></td>
<td>&lt; 7.0% <em>(individualization)</em></td>
</tr>
<tr>
<td><strong>Preprandial glucose</strong></td>
<td><em>80-130 mg/dL (3.9-7.2 mmol/l)</em></td>
</tr>
<tr>
<td><strong>Postprandial glucose</strong></td>
<td>&lt; 180 mg/dL</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>&lt; 140/90 mmHg</td>
</tr>
<tr>
<td><strong>Lipids Statin Dose</strong></td>
<td>Overt CVD - High Dose Statin</td>
</tr>
<tr>
<td></td>
<td>CVD Risk Factors – Moderate or High dose Statin</td>
</tr>
<tr>
<td></td>
<td>No Risk Factors</td>
</tr>
<tr>
<td></td>
<td>&lt; 40 years - None</td>
</tr>
<tr>
<td></td>
<td>40-75 Years - Moderate Dose</td>
</tr>
<tr>
<td></td>
<td>&gt; 75 Years – Moderate Dose</td>
</tr>
</tbody>
</table>

ADA. *Diabetes Care*. 2015;38:S49-57
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options:
  
  *Oral agents & non-insulin injectables*

- Metformin
- Sulfonylureas
- Thiazolidinediones
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 receptor agonists
- Meglitinides
- α-glucosidase inhibitors
- Colesevelam
- Dopamine-2 agonists
- Amylin mimetics
Classes of Drugs Available to Treat DM2

History of U.S. Diabetes Therapeutic Advances

- Insulin
- SFU
- 1920
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010

- SGLT-2 inhibitor
- Bromocriptine
- DPP-4 inhibitor
- GLP-1R agonist
- Pramlintide
- Meglitinide
- TZD
- Basal Insulin
- Rapid-acting insulin
- Alpha-glucosidase inhibitor
- Metformin

Notes:
- *Sulfonylureas
- *The first year that the American Diabetes Association published standards of medical care for diabetes.
- *Thiazolidinedione
- *Glucagon-like peptide 1 receptor
- *Dipeptidyl peptidase-4

ADA, Professional Section Quarterly, Summer 2011
<table>
<thead>
<tr>
<th>Oral Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| **Biguanides** | • Activates AMP-kinase (other)  
• ↓ Hepatic glucose production | • Extensive experience  
• No hypoglycemia  
• Weight neutral  
• ? ↓ CVD  
A1c ↓ ~ 1.5% | • Gastrointestinal  
• Lactic acidosis -rare  
• B-12 deficiency  
• Contraindications w ↑ S Creatinine | Low |
| **Sulfonylureas** | • Closes K\textsubscript{ATP} channels  
• ↑ Insulin secretion | • Extensive experience  
• ↓ Microvascular risk  
A1c ↓ ~1.0 to2.0% | • Hypoglycemia  
• ↑ Weight  
• Low durability  
• ? Blunts ischemic preconditioning | Low |
| **Glinides** | • Closes K\textsubscript{ATP} channels  
• ↑ Insulin secretion | • ↓ Postprandial glucose  
• Dosing flexibility  
A1c ↓ ~ 0.5 to1.0% | • Hypoglycemia  
• ↑ Weight  
• ? Blunts ischemic preconditioning  
• Dosing frequency | Mod. |
| **TZDs** | • PPAR-\(\gamma\) activator  
• ↑ Insulin sensitivity | • No hypoglycemia  
• Durability  
• ↓ TGs (pio) ↑ HDL-C  
• ? ↓ CVD events (pio)  
• A1c ↓ ~0.5 to1.4% | • ↑ Weight  
• Edema/heart failure  
• Bone fractures  
• ↑ LDL-C (rosi)  
• ? ↑ MI (rosi) | Low |

Table 1. Properties of anti-hyperglycemic agents
<table>
<thead>
<tr>
<th>Oral Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| α-Glucosidase inhibitors Acarbose-Precose | • Inhibits α-glucosidase  
• Slows carbohydrate digestion / absorption | • No hypoglycemia  
• Nonsystemic  
• ↓ Postprandial glucose  
• ? ↓ CVD events | • Gastrointestinal  
• Dosing frequency  
• Modest ↓ A1c | Mod.    |
| DPP-4 inhibitors                   | • Inhibits DPP-4  
• Increases incretin (GLP-1, GIP) levels | • No hypoglycemia  
• Well tolerated  
• A1C reduction in 0.5-0.8% | • Angioedema / urticaria  
• ? Pancreatitis  
• ? ↑ Heart failure | High    |
| Bile acid sequestrants Colesevelam | • Bind bile acids  
• ? ↓ Hepatic glucose production | • No hypoglycemia  
• ↓ LDL-C | • Gastrointestinal  
• Modest ↓ A1c  
• Dosing frequency | High    |
| Dopamine-2 Agonists Bromocriptine  | • Activates DA receptor  
• Alters hypothalamic control of metabolism  
• ↑ insulin sensitivity | • No hypoglycemia  
• ? ↓ CVD events | • Modest ↓ A1c  
• Dizziness, fatigue  
• Nausea  
• Rhinitis | High    |
| SGLT2 inhibitors                   | • Inhibits SGLT2 in proximal nephron  
• Increases glucosuria | • ↓ Weight 1-3 kg  
• No hypoglycemia  
• ↓ BP  
• Effective at all stages  
• A1C reduction in 0.7-1% range | • GU infections  
• Polyuria  
• Volume depletion  
• ↑ LDL-C  
• ↑Cr (transient) | High    |

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
<table>
<thead>
<tr>
<th>Injectable Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Amylin mimetics  | • Activates amylin receptor  
                 • ↓ glucagon  
                 • ↓ gastric emptying  
                 • ↑ satiety | • ↓ Weight  
                 • ↓ Postprandial glucose | • Gastrointestinal  
                 • Modest ↓ A1c  
                 • Injectable  
                 • Hypo if insulin dose not reduced  
                 • Dosing frequency  
                 • Training requirements | High |
| Pramlintide      |           |            |               |      |
| GLP-1 receptor agonists | • Activates GLP-1 R  
                         • ↑ Insulin, ↓ glucagon  
                         • ↓ gastric emptying  
                         • ↑ satiety | • ↓ Weight  
                         • No hypoglycemia  
                         • ↓ Postprandial glucose  
                         • ↓ Some CV risk factors  
                         • A1C reduction in 0.5-1% range | • Gastrointestinal  
                         • ↑ Heart rate  
                         • Medullary ca (rodents)  
                         • Injectable  
                         • Training requirements | High |
| Insulin          | • Activates insulin receptor  
                 • Myriad | • Universally effective  
                 • Unlimited efficacy  
                 • ↓ Microvascular risk | • Hypoglycemia  
                 • Weight gain  
                 • ↑ Microvascular risk | Variable |

Table 1. Properties of anti-hyperglycemic agents
<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Reduces hepatic glucose output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet (liq)</td>
</tr>
</tbody>
</table>

| Dosage Forms        | 500, 850, 1000; 500, 750, 1000 ER |

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Significant A1C reductions (~1.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Favorable to neutral effects on body weight</td>
</tr>
<tr>
<td></td>
<td>• No hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>• Generic (low cost)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concerns</th>
<th>GI side effects (often dose-related)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contraindicated in chronic renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>S Cr &gt; 1.4 women, &gt; Men in older e GFR &lt; 60</td>
</tr>
<tr>
<td></td>
<td>May impair absorption of Vitamin B12 and folic Acid</td>
</tr>
<tr>
<td></td>
<td>• Potential for lactic acidosis (rare)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Pearls</th>
<th>Drug of choice for initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Start with low dose and up-titrate dose to improve GI tolerance</td>
</tr>
</tbody>
</table>
## Sulfonylureas, Glinides (2nd generation)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dose mg/dL</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glinides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60-120 3x</td>
<td>Starlix</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5, 1, 2, 4</td>
<td>Prandin</td>
</tr>
<tr>
<td></td>
<td>3 x (16 mg)</td>
<td></td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1, 2, 4 qd (8mg)</td>
<td>Amaryl</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5-5 2x (40 mg)</td>
<td>Glucotrol</td>
</tr>
<tr>
<td>Glipizide XL</td>
<td>2.5-5 qd (20 mg)</td>
<td>Glucotrol XL</td>
</tr>
<tr>
<td>Glyburide</td>
<td>1.25-5 qd or 2 x (20 mg)</td>
<td>DiaBeta, Micronase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glynase</td>
</tr>
</tbody>
</table>
# Insulin Secretagogues (sulfonylureas / meglitinides)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Stimulate the pancreas to secret insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>A1C reductions (~1.0 - 2.0%)</td>
</tr>
<tr>
<td></td>
<td>• Quickly lower glucose/A1C</td>
</tr>
<tr>
<td></td>
<td>• Generic (very low cost)</td>
</tr>
<tr>
<td>Concerns</td>
<td>High 2nd failure rate</td>
</tr>
<tr>
<td></td>
<td>• Weight gain</td>
</tr>
<tr>
<td></td>
<td>• Increase risk of hypoglycemia (elderly, CKD, CAD)</td>
</tr>
<tr>
<td>Clinical Pearls</td>
<td>No longer first line therapy</td>
</tr>
<tr>
<td></td>
<td>• Use shorter-acting SFU (e.g., glipizide) to reduce hypoglycemia risk</td>
</tr>
<tr>
<td></td>
<td>• May be more effective in lower doses as an add-on’ medication (combination therapy)</td>
</tr>
</tbody>
</table>
Secondary Failure Rates Greatest with SFU

ADOPT: A Diabetes Outcome Progression Trial

A1C (%)

Number of patients: 4012 3308 2991 2583 2197 822

Treatment Difference at 4 Years
RSG vs. MET - 0.13%, P=0.002
RSG vs. SU - 0.42%, P<0.001

# TZD’s Glitazones (pio-, rosiglitazone)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Insulin Sensitizer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (Generic &amp; Trade Names)</strong></td>
<td>Pio (Actos) 15, 30, 45 mg Rosi (Avandia) - 2, 4 and 8 mg</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>Improve one of the main defects of type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>• No hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>• Durable glycemic control</td>
</tr>
<tr>
<td></td>
<td>• Positive effect on lipids (↑ HDL-C, converts small</td>
</tr>
<tr>
<td></td>
<td>dense to large buoyant LDL-C</td>
</tr>
<tr>
<td></td>
<td>A1c 0.5-1.4 %</td>
</tr>
<tr>
<td><strong>Concerns</strong></td>
<td>Weight gain, edema (precipitating CHF), bone Fractures</td>
</tr>
<tr>
<td></td>
<td>– Use in appropriate people – may need BD scan for</td>
</tr>
<tr>
<td></td>
<td>follow up.</td>
</tr>
<tr>
<td><strong>Clinical Pearls</strong></td>
<td>Effective in prediabetes, best used early in the natural</td>
</tr>
<tr>
<td></td>
<td>history (balance with potential side effects)</td>
</tr>
<tr>
<td></td>
<td>• Be cautious in combo with insulin (fluid retention)</td>
</tr>
</tbody>
</table>
DPP4- Inhibitors

Mechanism of Action of DPP-4 Inhibitors

- Ingestion of food → Release of active incretins (GLP-1 and GIP)
- Pancreas:
  - Glucose dependent → Insulin
  - Glucose uptake by peripheral tissue
  - Fasting and Postprandial Glucose
- DPP-4 enzyme:
  - Inactive GLP-1
  - Inactive GIP
- GLP-1 = glucagon-like peptide-1
- GIP = glucose-dependent insulinotropic polypeptide

References:
# DPP4 Inhibitors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Inhibit the enzyme, DPP-4, that normally inactivates GLP-1 and other incretins within minutes</th>
</tr>
</thead>
</table>
| Benefits            | Once daily oral administration  
• Generally well tolerated  
• Can be added to any diabetes drug Except GLP-1 RAs  
• A1C reduction in 0.5-1% range |
| Concerns            | Dose adjustment with renal insufficiency  
alogliptin, saxagliptin, sitagliptin, not for **linagliptin**  
• Rare reports of hypersensitivity skin reactions ? Pancreatitis ? Heart failure  
• No association or signal for pancreatitis and pancreatic cancer (2013 FDA hearing on pancreatic cancer and incretins |
| Clinical Pearls     | Efficacy of the DPP-4 inhibitors is similar  
• All DPP-4 inhibitors come in combination pill with metformin (Lina- is also combined with Pio) |
**DPP-4 Inhibitors**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Alogliptin</th>
<th>Linagliptin</th>
<th>Saxagliptin</th>
<th>Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Nesina</td>
<td>Tradjenta</td>
<td>Onglyza</td>
<td>Januvia</td>
</tr>
</tbody>
</table>

**Usage and Indications**
- Use with diet and exercise to improve glycemic control in type 2 diabetes
- Combination studies with SFUs, MET, pioglitazone and insulin

**Dosage Administration**
- Alogliptin: Once daily, with or without food. Tablets: 25mg, 12.5mg (CrCl <50 moderate), & 6.25mg (CrCl <30 severe).
- Linagliptin: Once daily, with or without food. Tablets: 5mg. No dose adjustment for renal function.
- Saxagliptin: Once daily, with or without food. Tablets: 5mg & 2.5mg (CrCl <50 moderate or severe) d/c ESRD.
- Sitagliptin: Once daily, with or without food. Tablets: 100mg, 50mg (CrCl <50, moderate), & 25mg (CrCl <30 severe).

**Contraindications**
- Alogliptin: Hypersensitivity
- Linagliptin: Hypersensitivity (urticaria, angioedema, or bronchial hyperreactivity)
- Saxagliptin: Hypersensitivity
- Sitagliptin: Hypersensitivity (anaphylaxis or angioedema)
Renal Handling of Glucose in a Non-Diabetic Individual

- 180 g/day/1.73 m² is filtered glucose load¹
- SGLT-2 transports 90% of filtered glucose out of the tubular lumen¹:⁴

SGLT = sodium-glucose co-transporter.
Renal glucose reabsorption in healthy individuals

~180 g of glucose per day filtered

Glucose

SGLT-2
~90%

SGLT-1
~10%

Gerich JE. Diabetic Medicine. 2010;27:136
Renal Threshold for Glucose

Nair and Wilding. JCEM 2010;95:34
Urinary Glucose Excretion (g/day) vs. Plasma Glucose (mg/dL)

- Normal: $RT_G \sim 180$ mg/dL
- DM2: $\sim 240$

Nair and Wilding. JCEM 2010;95:34
SGLT2 Inhibitors

SGLT2 Inh ~70-90 mg/dL

Nair and Wilding. JCEM 2010;95:34
<table>
<thead>
<tr>
<th>SGLT-2 Inhibitor</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>SGLT-2 Inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Invokana</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Farxiga</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jardiance</td>
<td></td>
</tr>
</tbody>
</table>

**Canagliflozin:**
1. **Suggested starting dose:**
   100 mg daily before first meal of day (eGFR > 45 < 60 mL/min)
   Increase to 300 mg daily if tolerating 100 mg daily and eGFR > 60 mL/min
   Discontinue for eGFR < 45 mL/min/1.73 m²

**Dapagliflozin:**
Starting dose: 5 mg daily in morning with or without food (eGFR for both doses > 60)
Increase to 10 mg daily if tolerating and need additional glycemic control
Discontinue for eGFR < 60 mL/min/1.73 m²

**Empagliflozin:**
Starting dose: 10 mg daily in morning with or without food (eGFR > 45)
Increase to 25 mg daily if tolerating and need additional glycemic control
Discontinue for eGFR < 45 mL/min/1.73 m²
# SGLT-2 Inhibitor

**canagliflozin, dapagliflozin, empagliflozin**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Reduce renal glucose reabsorption and increases urinary glucose excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td>Reduce renal glucose reabsorption and increases urinary glucose excretion • A1C reduction in 0.5-0.8 % range Weight loss 1-3 kg, ↓ BP – SBP4/DBP 2 mm Hg</td>
</tr>
<tr>
<td><strong>Concerns</strong></td>
<td>• UTI&lt; Genital mycotic infections. In women (6 to 12% higher than comparator) and in uncircumcised males (2 to 6% higher than comparator) • Hypotension secondary to volume contracture esp in the elderly, those on loop diruetic use and in patients reduced renal function. Volume depletion, Thirst, Polyuria, Lt headed • Assess renal function (discussed in detail on next slide)</td>
</tr>
<tr>
<td><strong>Clinical Pearls</strong></td>
<td>First oral diabetes medication that leads to statistically significant weight loss. Can be added to any other oral agent or injectable Tell women to practice good hygiene and look out for yeast Infections Physicians’ desk reference (68th ed.). (2014). Montvale, NJ: Physicians’ Desk Reference.</td>
</tr>
</tbody>
</table>
Case Study

Dr. B- 65 Y male PMH: DM 2, premature CAD, proteinuria, HTN, HLD, and fibromyalgia. BMI 28.7 SCr 1.2-1.3 eGFR >60 A1c 6.3% no hypoglycemia

Very well controlled on Metformin 2 GM and pio 30 mg

Bothered by weight gain and news about bladder CA he would like to stop pioglitazone

What would you add?

1) Sulfonylurea
2) GLP 1RA
3) DPP4-Inhibitor
4) Basil Insulin
Injectables
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon ingestion of food

Pancreatic beta cells: Enhanced glucose dependent insulin secretion

Promotes satiety and reduces appetite

Pancreatic alpha cells: ↓ Postprandial glucagon secretion

Liver: Reduced hepatic glucose output

Stomach: Helps regulates gastric emptying

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Approved w Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Bydureon</td>
<td>2 mg, 5 mcg, 10 mcg</td>
<td>Exenatide/Byetta</td>
</tr>
<tr>
<td>Once-weekly</td>
<td>Byetta</td>
<td>0.6, 1.2, 1.8 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Twice-daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>0.75 mg, 1.5 mg</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Once-daily</td>
<td></td>
<td></td>
<td>-Yes</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>0.75 mg, 1.5 mg</td>
<td></td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Tanzeum</td>
<td>30 mg, 50 mg</td>
<td>Albiglutide</td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
<td></td>
<td>-Yes</td>
</tr>
</tbody>
</table>
# GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Mimics the effects of human GLP-1</th>
</tr>
</thead>
</table>
| **Benefits**        | Significant A1C reductions (1.0 to 2.0%)  
|                     | • Statistically significant weight loss  
|                     | • No hypoglycemia                  
|                     | • Once daily and once weekly formulations |
| **Concerns**        | GI side effects (typically nausea)  
|                     | • Contraindicated in patients with a person or family history of MTC or MEN2  
|                     | • Relative contraindication in patients with a history of pancreatitis (important to know the etiology) |
| **Clinical Pearls** | Ideal choice in obese patients with poor control, especially those on large doses of insulin  
|                     | • One of the most powerful agents for type 2 diabetes |

GLP-1 Agonists

• GLP-1 Agonists: Renal Impairment
  Currently limited experience beyond mild-stage renal disease
• Exenatide/Liraglutide
  In patients with stage 1 or 2 chronic kidney disease (CKD), appropriate to administer without dosage adjustment, as tolerated
• Hypoglycemia With GLP-1 Agonists
  Little rise of hypoglycemia except when used with SFUS and or Insulin
Thyroid Tumors With GLP-1 Agonists-Warning: risk of thyroid C-cell tumors in laboratory animals not seen in humans in the post marking period

Incretins and Pancreatitis and Pancreatic Cancer

The conclusions of the June 10, 2013 panel of FDA/NIH indicate that there is insufficient evidence at present to establish an increased risk of pancreatitis or pancreatic cancer with use of Incretin-based therapies in T2DM. There is also no evidence of increased risk of hypoglycemia or any signal of cardiovascular event risk. These findings argue against premature judgments regarding risks of incretin use in the treatment of type 2 diabetes. Reported at recent annual meeting of American Diabetes Association, Chicago, IL, USA, June 23, 2013
Case Study- Mrs. AA

Med hx: 76 y white woman hx of DM x 10 y but uncontrolled since 2012. PMH: HTN, Dyslipidemia, OSA w BiPAP, hypothyroid and morbid obesity w maintained wt loss of ~ 50 lbs for many yrs. Lifestyle/RF vigilant f/U, no known CVD, F hx of HF, normal LFT’s, eGFR and S Cr 0.8 mg/dL.

Meds: metformin 2500 mg for ~ 10 yrs 1500/1000, Glipizide @ 10 mg 2 x (gradual ↑ in dose). Added Sitagliptin 100 mg w some improvement of A1c 7.4% but now back up. Still Difficulty w evening DM meds and desserts Sig fear of hypoglycemia, Some issues w constipation

A1c hx since 2013 7.4-7.9%

What to add & why
a) Basil insulin – would offer better control
b) SGLT2 inhibitor – would offer control wt loss and decr BP
c) GLP-1 RA – will get to goal may have wt loss
d) Work on improvement to PM dosing and ↓desserts
3. ANTI-HYPERGLYCEMIC THERAPY

• Therapeutic options: Insulins

**Human Insulins**
- Neutral protamine Hagedorn (NPH)
- Regular human insulin
- Pre-mixed formulations

**Insulin Analogues**
- Basal analogues (glargine, detemir, degludec)
- Rapid analogues (lispro, aspart, glulisine)
- Pre-mixed formulations
## Generic and Trade Names: Insulin

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast-Acting Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>NovoLog</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra</td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog</td>
</tr>
<tr>
<td><strong>Regular Acting Insulin</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humulin R</td>
</tr>
<tr>
<td><strong>Basal Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>Intermediate-Acting: NPH</td>
<td>Humulin N</td>
</tr>
<tr>
<td>Long-Acting:</td>
<td>Novolin NPH</td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir</td>
</tr>
<tr>
<td>Glargine</td>
<td>Lantus</td>
</tr>
</tbody>
</table>
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: *Insulins*
Appropriate Self-titration is Critical to the Success of Insulin Therapy

- An ADA/EASD consensus algorithm for the initiation and adjustment of basal insulin:

  Start with a long-acting basal insulin
  
  Initiate at 10 units/day or 0.2 units/kg/day
  
  Check fasting glucose daily and increase dose by:
  
  2 units every 3 days until fasting in target range (70 - 130 mg/dL)
Figure 3. Approach to starting & adjusting insulin in T2DM

 Basal Insulin
(usually with metformin +/- other non-insulin agent)

- Start: 10U/day or 0.1-0.2 U/kg/day
- Adjust: 10-15% or 2.4 U once-twice weekly to reach FBG target.
- For hypo: Determine & address cause; ↓ dose by 4 units or 10-20%.

If not controlled after FBG target is reached (or if dose > 0.5 U/kg/day), treat PPG excursions with meal-time insulin. (Consider initial GLP-1-RA trial.)

Add 1 rapid insulin* injections before largest meal

- Start: 4U, 0.1 U/kg, or 10% basal dose. If A1c<8%, consider ↓ basal by same amount.
- Adjust: ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- For hypo: Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

Change to premixed insulin* twice daily

- Start: Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- Adjust: ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- For hypo: Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

Add ≥2 rapid insulin* injections before meals (‘basal-bolus’)

- Start: 4U, 0.1 U/kg, or 10% basal dose/meal. If A1c<8%, consider ↓ basal by same amount.
- Adjust: ↑ dose by 1-2 U or 10-15% once-twice weekly to achieve SMBG target.
- For hypo: Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.
Insulin Pens

- Lilly Pens: Memoir & Kwikpen
- NovoNordisk: NovoPen Echo & FlexTouch
- Sanofi-Aventis: SoloStar

Convenient
Discreet
Protects insulin from light, heat and agitation
Combination Therapy: Adding Basal Insulin to Oral Agents

Only 1 injection per day is typically required
An Effective Strategy to Initiate Insulin Therapy
Convenience (usually given at night or first thing in the morning) but can be taken at lunch – be consistent
Slow, safe, and simple titration
Low dosage compared to a full insulin regimen
Limited weight gain - especially compared to insulin only regimens
Effective improvement in glycemic control by suppressing hepatic glucose production

Ian Blumer, MD, FRCPC
Clinical Pearls: Combination Therapy with Basal Insulin

1. Start with 10 to 15 units (based on FBS, weight)
2. The key to success is frequent follow up after initiation to avoid “failure”
3. Have the patient follow a self-titration regimen and return to clinic or follow up in some other manner (phone, fax, email, EMR i.e. myhealth) within 2 weeks
4. You may be able to limit SMBG to only once or 2 times a day- but alternate checking before bed or in AM on occasion to evaluate need for pre dinner fast acting insulin or additional medications.
Hypoglycemia Treatment

Follow the “Rule of 15” – generally treating a blood glucose < 70 mg/dL
15 grams of fast acting CHO:
4 glucose tablets
½ cup juice or regular soda
Wait 15 minutes, retest glucose
If still < 70 repeat
Once > 70 have a snack or a meal if time.
# Insulins

<table>
<thead>
<tr>
<th>Action</th>
<th>Insulin Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Effective Duration</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus</td>
<td>Aspart (Novolog)</td>
<td>5 - 15 min</td>
<td>30 - 90 min</td>
<td>&lt; 5 hrs</td>
<td><strong>Bolus</strong> insulin lowers after-meal glucose. Efficacy reflected in post-meal BG.</td>
</tr>
<tr>
<td></td>
<td>Lispro (Humalog)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glulisine (Apidra)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular</td>
<td>30 - 60 min</td>
<td>2 - 3 hrs</td>
<td>5 - 8 hrs</td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPH</td>
<td>2 - 4 hrs</td>
<td>4 - 10 hrs</td>
<td>10 - 16 hrs</td>
<td><strong>Basal</strong> insulin controls BG between meals and HS. Efficacy reflected in fasting BG.</td>
</tr>
<tr>
<td></td>
<td>Long Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detemir (Levemir)</td>
<td>3 - 8 hrs</td>
<td>No peak</td>
<td>6 - 24 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glargine (Lantus)</td>
<td>2 - 4 hrs</td>
<td>No peak</td>
<td>20 - 24 hrs</td>
<td></td>
</tr>
<tr>
<td>Bolus + Basal</td>
<td>Intermediate + rapid</td>
<td></td>
<td></td>
<td></td>
<td><strong>Side effects:</strong> hypoglycemia, weight gain.</td>
</tr>
<tr>
<td></td>
<td>Novolog® Mix 70/30</td>
<td>5 - 15 min</td>
<td>Dual peaks</td>
<td>10 - 16 hrs</td>
<td><strong>Typical dosing range:</strong> 0.5–1.0 units/kg body wt/day. Discard opened insulin vials after 28 days.</td>
</tr>
<tr>
<td></td>
<td>70/30 = 70% NPH + 30% aspart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humalog® Mix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75/25 = 75% NPL + 25% lispro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50/50 = 50% NPL + 50% lispro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate + short</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combo of NPH + Reg</td>
<td>30 - 60 min</td>
<td>Dual peaks</td>
<td>10 - 16 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70/30 = 70% NPH + 30% Reg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50/50 = 50% NPH + 50% Reg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from American Association of Clinical Endocrinologists Guidelines 2007. Because insulin action times can vary with each injection, time periods listed here are general guidelines only; please consult prescribing information for details.

Beverly Dyck Thomassian, RN, MPH, BC-ADM, CDE
## Cost Per Vial in Northern CA

<table>
<thead>
<tr>
<th>Per vial cost</th>
<th>Walmart</th>
<th>Walgreens</th>
<th>Costco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular Insulin</td>
<td>$25*</td>
<td>$92</td>
<td>$99</td>
</tr>
<tr>
<td>NPH</td>
<td>$25*</td>
<td>$92</td>
<td>$99</td>
</tr>
<tr>
<td>70/30</td>
<td>$25*</td>
<td>$92</td>
<td>$101</td>
</tr>
<tr>
<td>Humalog</td>
<td>$200</td>
<td>$220</td>
<td>$178</td>
</tr>
<tr>
<td>Novolog</td>
<td>$197</td>
<td>$217</td>
<td>$178</td>
</tr>
<tr>
<td>Apidra</td>
<td>$180</td>
<td>$246</td>
<td>$178</td>
</tr>
<tr>
<td>Levemir</td>
<td>$300</td>
<td>$300</td>
<td>$300</td>
</tr>
<tr>
<td>Lantus</td>
<td>$226</td>
<td>$221</td>
<td>$206</td>
</tr>
</tbody>
</table>

Beverly Dyck Thomassian, RN, MPH, BC-ADM, CDE
Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

- **Monotherapy**
  - Efficacy
  - Hypo risk
  - Weight
  - Side effects
  - Costs

- **Dual therapy**
  - Efficacy
  - Hypo risk
  - Weight
  - Side effects
  - Costs

- **Triple therapy**
  - Efficacy
  - Hypo risk
  - Weight
  - Side effects
  - Costs

---

**Metformin**
- high efficacy
- low risk of hypoglycemia
- neutral/low weight change
- GI/lactic acidosis: low risk

---

**If HbA1c 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- & disease-specific factors):**

- **Metformin +**
  - Sulfonylurea
    - high efficacy
    - moderate risk of hypoglycemia
  - Thiazolidinedione
    - high efficacy
    - low risk of hypoglycemia
  - DPP-4 inhibitor
    - intermediate efficacy
    - low risk of hypoglycemia
  - SGLT2 inhibitor
    - intermediate efficacy
    - low risk of hypoglycemia
  - GLP-1 receptor agonist
    - high efficacy
    - high risk of hypoglycemia
  - Insulin (basal)
    - highest efficacy
    - high risk of hypoglycemia

---

**If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):**

- **Metformin +**
  - Sulfonylurea + TZD
  - Thiazolidinedione + DPP-4-i
  - DPP-4 inhibitor + GLP-1-RA
  - SGLT2 inhibitor + Insulin
  - GLP-1 receptor agonist + Insulin
  - Insulin (basal) + TZD
  - DPP-4-i
  - SGLT2-i

---

**If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:**

- **Metformin +**
  - Basal Insulin + Mealtme Insulin or GLP-1-RA

---

*Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-440*
Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Healthy eating, weight control, increased physical activity & diabetes education

Metformin

- high risk
- neutral/loss
- GI / lactic acidosis
- low

If HbA1c 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- & disease-specific factors):

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

Efficacy
- high
- moderate risk
- high
- intermediate
- high
- highest

Hypo risk
- high
- low risk
- low risk
- low risk
- high
- high

Weight
- gain
- gain
- edema, HF, fxs
- loss
- loss
- gain

Side effects
- low
- hypoglycemia
- rare
- GU, dehydration
- variable
- hypoglycemia

Costs

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

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

Efficacy
- high
- high
- intermediate
- intermediate
- high
- highest

Hypo risk
- moderate risk
- high
- low risk
- low risk
- high
- high

Weight
- gain
- gain
- gain
- gain
- gain
- gain

Side effects
- variable
- variable
- variable
- variable
- variable
- variable

Costs

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
### Healthy eating, weight control, increased physical activity & diabetes education

#### Metformin
- Efficacy: high
- Hypo risk: low risk
- Weight: neutral/loss
- GI / lactic acidosis: low

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (note: not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Sulfonylurea</td>
<td>+ Thiazolidinedione</td>
<td>+ DPP-4 inhibitor</td>
<td>+ SGLT2 inhibitor</td>
<td>+ GLP-1 receptor agonist</td>
<td>+ Insulin (basal)</td>
</tr>
<tr>
<td>Efficacy: high</td>
<td>Efficacy: high</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td>Hypo risk: moderate risk</td>
<td>Hypo risk: low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Weight: gain</td>
<td>Weight: gain</td>
<td>Weight: neutral</td>
<td>Weight: loss</td>
<td>Weight: loss</td>
<td>Weight: gain</td>
</tr>
<tr>
<td>Side effects: edema, HF, fx's</td>
<td>Side effects: lactic acidosis</td>
<td>Side effects: GI, dehydration</td>
<td>Side effects: GI</td>
<td>Side effects: variable</td>
<td>Side effects: hypoglycemia</td>
</tr>
<tr>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (note: not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors):

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

- Metformin + Basal Insulin + Mealtime Insulin or GLP-1-RA
### Metformin

If HbA1c 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- & disease-specific factors):

<table>
<thead>
<tr>
<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></td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td></td>
<td>moderate risk</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>neutral</td>
<td>high</td>
</tr>
<tr>
<td></td>
<td>gain</td>
<td>loss</td>
<td>edema, HF, fxs</td>
<td>loss</td>
<td>GU, dehydration</td>
<td>loss</td>
</tr>
<tr>
<td></td>
<td>hypoglycemia</td>
<td>rare</td>
<td>low</td>
<td>high</td>
<td>variable</td>
<td>gain</td>
</tr>
<tr>
<td></td>
<td>low</td>
<td>high</td>
<td>neutral</td>
<td>high</td>
<td>variable</td>
<td>hypoglycemia</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<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></td>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DPP-4-i</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SGLT2-i</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GLP-1-RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

### Basal Insulin +

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Mealtime Insulin</th>
<th>GLP-1-RA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2A. Anti-hyperglycemic therapy in T2DM: Avoidance of hypoglycemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Efficacy</th>
<th>Hypo Risk</th>
<th>Weight</th>
<th>Side Effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

If HbA1c 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 & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Thiazolidinedione high</th>
<th>low risk</th>
<th>gain</th>
<th>edema, HF, fx</th>
<th>low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>DPP-4 inhibitor intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>rare</td>
<td>high</td>
</tr>
<tr>
<td>Metformin +</td>
<td>SGLT2 inhibitor intermediate</td>
<td>low risk</td>
<td>loss</td>
<td>GU, dehydration</td>
<td>high</td>
</tr>
<tr>
<td>Metformin +</td>
<td>GLP-1 receptor agonist high</td>
<td>low risk</td>
<td>loss</td>
<td>GI</td>
<td>high</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference - choice dependent on a variety of patient & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Thiazolidinedione +</th>
<th>DPP-4-i or SGLT2-i or GLP-1-RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>DPP-4-i or TZD</td>
<td></td>
</tr>
<tr>
<td>Metformin +</td>
<td>SGLT2-i or DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>Metformin +</td>
<td>GLP-1 receptor agonist or TZD</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2B. Anti-hyperglycemic therapy in T2DM: Avoidance of weight gain
Figure 2C. Anti-hyperglycemic therapy in T2DM: Minimization of costs

- **Healthy eating, weight control, increased physical activity & diabetes education**

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

*If HbA1c 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- & disease-specific factors):*

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
</tr>
</tbody>
</table>

*Efficiency: high, moderate risk, gain, hypoglycemia, low*  
*Hypo risk: high, high risk, gain, edema, HF, fx, low*

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

*If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):*

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
</tr>
<tr>
<td>TZD</td>
<td>SU</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

*If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-1:
Rationale and Design of the GlycemiaReduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

OBJECTIVE The epidemic of type 2 diabetes (T2DM) threatens to become the major public health problem of this century. However, a comprehensive comparison of the long-term effects of medications to treat T2DM has not been conducted. GRADE, a pragmatic, unmasked clinical trial, aims to compare commonly used diabetes medications, when combined with metformin, on glycemia-lowering effectiveness and patient-centered outcomes.

RESEARCH DESIGN AND METHODS GRADE was designed with support from a U34 planning grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The consensus protocol was approved by NIDDK and the GRADE Research Group. Eligibility criteria for the 5,000 metformin-treated subjects include ≤5 years’ diabetes duration, >30 years of age at time of diagnosis, and baseline hemoglobin A1c (A1C) of 6.8–8.5% (51–69 mmol/mol). Medications representing four classes (sulfonylureas, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, and insulin) will be randomly assigned and added to metformin (minimum–maximum 1,000–2,000 mg/day). The primary metabolic outcome is the time to primary failure defined as an A1C $7% (53 mmol/mol), subsequently confirmed, over an anticipated mean observation period of 4.8 years (range 4–7 years). Other long-term metabolic outcomes include the need for the addition of basal insulin after a confirmed A1C >7.5% (58 mmol/mol) and, ultimately, the need to implement an intensive basal/bolus insulin regimen. The four drugs will also be compared with respect to selected microvascular complications, cardiovascular disease risk factors, adverse effects, tolerability, quality of life, and cost-effectiveness.

CONCLUSION- GRADE will compare the long-term effectiveness of major glycemia-lowering medications and provide guidance to clinicians about the most appropriate medications to treat T2DM. GRADE begins recruitment at 37 centers in the U.S. in 2013. Diabetes Care 36:2254–2261, 2013
Case Study Glucose Toxicity

67 yr old female: Sent to ER from clinic for sx hyperglycemia > 500 mg/dL in office – glucose 716 mg/dL in ER

Discharged: NPH 20 units 2 x, humalog 5 units AC, (no sliding scale) lisinopril and ASA.

Sig PMH: HTN, hx of pre diabetes, situational depression-no Rx
BP 131/61, P 68, BMI 27 kg/m2 (grad wt gain age 50-60’s of 10lbs)

First apt in clinic ~ 3 weeks later glucose 151 mg/dL
Gl: Brk:100-190 L:131-190 few in 280-300 D:1 @71, 116-170 2 in 200’s

Started on metformin & life style changes very concerned and eager to make changes, met w DM educator
F/U 3 wks w call in between
Case Study Glucose Toxicity

Over 2 months w Close phone f/u and clinic visits steadily decreased NPH and increased metformin. Initially tolerated metformin 500 2 x but then developed diarrhea. Dose decreased to once a day and started on glipizide 2.5 mg 2x.

In two months insulin d/c only on oral meds. Continued w lifestyle changes

Gl: B 94-124, L 72-114, D 87-137
4. OTHER CONSIDERATIONS

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

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- ? SUs & ischemic preconditioning
- ? Pioglitazone & ↓ CVD events
- ? Effects of incretin-based therapies
4. OTHER CONSIDERATIONS

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

➤ Metformin: May use unless condition is unstable or severe
➤ Avoid TZDs
➤ ? Effects of incretin-based therapies
4. OTHER CONSIDERATIONS

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

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: ↓ dose @GFR <45 & stop @GFR <30
- Caution with SUs (esp. glyburide)
- DPP-4-i’s – dose adjust for most
- Avoid exenatide if GFR <30
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 mortality
- Proper drug selection in the hypoglycemia prone

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]
20 Y Tongan female patient. Chief Complaint: Newly diagnoses Uncontrolled Diabetes A1c 14.7% C-Peptide 0.57 w glucose 269 mg/dL, No PMH prior to new dx, BP 124/62 P. 68, BMI 34.7 kg.m2

DX: Type 1 DM vs glucose toxicity

Repeat C-peptide, glucose and anti gad - Increase glyburide to 10 mg 2x Lantus started at 10 units before bedtime (instructed by CDE nurse educator) with titration schedule

Repeat Labs - Results Serum Glucose 324 mg/dL
Hemoglobin A1c Range: <6.5 % - pts value -14.6 % (H)
C-peptide Range: 0.80-4.00 ng/ml - pts value -0.80 ng/ml
Anti Gad 65 - Normal < 0.5 all ages – pts value 17 unit(s) per ml
Latent Autoimmune Diabetes in Adults (LADA)

- The most missed diagnosis in diabetes
- Type 1 diabetes can occur at any age
- Slower beta-cell destruction (may respond briefly to oral agents)
- Positive blood test Anti GAD auto antibodies
- Check a C Peptide with a glucose and can check w after a glucose load.
Key Points - Clinical Pearls

- Glycemic targets & BG-lowering therapies must be individualized, based on a variety of patient and disease characteristics.

- **Diet, exercise, & education**: foundation of any T2DM therapy program.

- Unless contraindicated, metformin remains the optimal first-line drug.

- After metformin, data are limited. **Combination therapy** with 1-2 other oral / injectable agents is reasonable. Try to minimize side effects.

- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain BG control.

- All treatment decisions should be made in conjunction with the patient (focusing on his or her preferences, needs & values.)

- Comprehensive **CV risk reduction** - a major focus of therapy.


*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442