Disclosures

- Betsy and Zach work for Rocky Mountain Health Plans.
- We do not have any financial interest in the medications we are discussing today.
- We have no intention to malign any person, business or product.
There is an new generic to Advair

1. True
2. False
3. Unsure
Which is the preferred second line therapy for T2DM after metformin?

1. Sulfonylureas
2. SGLT2 inhibitors
3. TZD
4. DPP-4 inhibitors
5. GLP-1 agonist
6. None of the above
AirDuo and the Authorized Generic

A breath of generic air
What is AirDuo and the AG?

- Fluticasone/salmeterol combination
- Brand (AirDuo) and authorized generic (AG) released the same day
- Comes in Respiclick inhaler
- 3 strengths of ICS with fixed dose LABA
  - Fluticasone 55mcg/salmeterol 14mcg
  - Fluticasone 113mcg/salmeterol 14mcg
  - Fluticasone 232mcg/salmeterol 14 mcg
# Dose Comparison

**How Supplied:**

<table>
<thead>
<tr>
<th>Fluticasone/Salmeterol Products</th>
<th>Authorized Generic of AirDuo</th>
<th>Advair Diskus</th>
<th>Advair HFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>55mcg/14mcg</td>
<td>100mcg/50mcg</td>
<td>45mcg/21mcg</td>
</tr>
<tr>
<td>Medium</td>
<td>113mcg/14mcg</td>
<td>250mcg/50mcg</td>
<td>115mcg/21mcg</td>
</tr>
<tr>
<td>High</td>
<td>232mcg/14mcg</td>
<td>500mcg/50mcg</td>
<td>230mcg/21mcg</td>
</tr>
</tbody>
</table>

**Total Daily Dosing Comparison:**

<table>
<thead>
<tr>
<th></th>
<th>Authorized Generic</th>
<th>Advair Diskus</th>
<th>Advair HFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>1 puff PO BID</td>
<td>1 puff PO BID</td>
<td>2 puff PO BID</td>
</tr>
<tr>
<td>Total Daily Dose</td>
<td>110 – 464mcg</td>
<td>200 – 1000mcg</td>
<td>180 – 920mcg</td>
</tr>
</tbody>
</table>
# Cost – All Asthma Inhalers (AWP)

<table>
<thead>
<tr>
<th>AirDuo</th>
<th>AG of AirDuo (generic)</th>
<th>Advair Diskus</th>
<th>Advair HFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$342 (all strengths)</td>
<td>$112 (all strengths)</td>
<td>$349 (100/50 mcg)</td>
<td>$349 (100/50 mcg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$434 (250/50 mcg)</td>
<td>$434 (250/50 mcg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$570 (500/50 mcg)</td>
<td>$570 (500/50 mcg)</td>
</tr>
</tbody>
</table>

Not Covered  Tier 1 – generic  Tier 2  Tier 2

<table>
<thead>
<tr>
<th>Breo Ellipta</th>
<th>Symbicort</th>
<th>Dulera</th>
</tr>
</thead>
<tbody>
<tr>
<td>$386 (all strengths)</td>
<td>$324 (80/4.5 mcg)</td>
<td>$349 (all strengths)</td>
</tr>
<tr>
<td></td>
<td>$370 (160/4.5 mcg)</td>
<td></td>
</tr>
</tbody>
</table>

Tier 2  Tier 2  Tier 2
Type 2 Diabetes
Metformin

The Sheriff
Metformin “The Sheriff”
Metformin

- Cardiovascular risk reduction with UKPDS study
- Lowers A1c 1-2%
- Weight Neutral
- Usual effective dose = 1500 - 2000 mg/day
- Adverse effects
  - GI upset (take with food), vitamin B12 deficiency (long term), and lactic acidosis
The Wild West of Options

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

If A1C 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- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>highest</td>
</tr>
<tr>
<td>high risk</td>
</tr>
<tr>
<td>gain</td>
</tr>
<tr>
<td>hypoglycemia</td>
</tr>
<tr>
<td>variable</td>
</tr>
</tbody>
</table>
Sulfonylureas "Beta Cell Rustlers"
Sulfonylureas

The 2nd generation of putting the squeeze on beta cells in the pancreas

- No conclusive CV data
- A1c reduction 1-2%
- Decreased microvascular complication per the UKPDS
- Adverse effects
  - Glucose independent
    - High risk of hypoglycemia
    - Glyburide has an active metabolite that increases risk of hypoglycemia more than the other two
  - Weight gain
Thiazolidinedione “The Lone Rangers”

- Liver
  - (Direct activation of PPARγ?)
  - Thiazolidinedione
  - Adipose
    - Activation of PPARγ
    - Modification of gene expression/transcription
      - ↓ Lipolysis
        - ↓ Free fatty acids
      - ↓ TNF-α
        - ↓ Leptin
        - ↑ Adiponectin
    - Muscle
      - (Direct activation of PPARγ?)
- Improved insulin sensitivity
TZD

pioglitazone (Actos)
rosiglitazone (Avandia)

- No conclusive CV data
- A1c reduction 0.5 – 1.4%
- May take up to 12 weeks to see efficacy
- Increase HDL and lower triglycerides (pioglitazone)

BBW
- Exacerbating congestive heart failure
- Contraindicated in NYHA class III/IV

Adverse effects
- Increased risk of bone fractures, edema, and weight gain
DPP-4 inhibitors “The Towns Folk”

* Physiological $t_{1/2} = 2$ mins due to rapid inactivation by DPP-IV
DPP-4 inhibitors

Nesina (alogliptin)
Tradjenta (linagliptin)
Onglyza (saxagliptin)
Januvia (sitagliptin)

- No conclusive CV data
- A1c reduction 0.4 – 0.8%
- No hypoglycemia risk when used as monotherapy
- Weight neutral
- Generally well tolerate
- No renal adjustment for Tradjenta
- Adverse effects
  - Associated with acute pancreatitis and may worsen heart failure
GLP-1 “High Society”
GLP-1 agonist

- Victoza (liraglutide)
- Adlyxin (lixisenatide)
- Byetta (exenatide)
- Bydureon (exenatide LAR)
- Trulicity (dulaglutide)
- Tanzeum (albiglutide)

- Victoza has CV reduction data (NNT = 98)
- HbA1c reduction 0.5 – 1.5%
- Less hypoglycemia risk when used as monotherapy
- Weight loss (4 – 9 lbs)
- Injection only = high cost
- Contraindication for medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Adverse effects:
  - GI upset, nausea, pancreatitis, may develop antibodies over time
SGLT2 “The Outlaws”

- **a Normal TGF**
  - Afferent arteriole
  - Efferent arteriole
  - SGLT2
  - No glucose

- **b Diabetes**
  - Afferent arteriole vasodilation
  - Efferent arteriole vasoconstriction
  - SGLT2
  - Intraglomerular pressure
  - GFR
  - Renin
  - Angiotensin
  - SGLT2
  - Na+ reabsorption
  - JGA
  - Na+ delivery to JGA

- **c Diabetes and SGLT2-inhibition**
  - Afferent arteriole
  - Efferent arteriole unaffected
  - SGLT2
  - Intraglomerular pressure and normalization of GFR
  - Glucose excretion
  - JGA
  - Na+ delivery to JGA

*Nature Reviews | Nephrology*
SGLT2

Invokana (canagliflozin)
Farxiga (dapagliflozin)
Jardiance (empagliflozin)

- Jardiance has CV reduction data (NNT = 45), Invokana coming soon (Canvas trial)
- A1c reduction 0.5 – 1%
- No hypoglycemia risk when used as monotherapy
- Weight Loss (4-9 lbs)
- Decrease blood pressure (3 – 5 mm Hg)
- Take with first meal of the day
- Adverse effects:
  - Volume depletion, increased urination and LDL-C, increased genitourinary infections, transient increase SCr, diabetic ketoacidosis
How do I lower your blood sugar?--let me count the ways....

The explosion of oral hypoglycemics for type II DM

June 22, 2017
Betsy Longenecker MD
Which of the following is NOT a class of drug used to lower blood sugar in type 2 DM?

1. TZDs
2. PCSK-9 inhibitors
3. DPP-4 inhibitors
4. GLP-1 receptor agonists
5. SGLT2 inhibitors
Mechanisms for lowering blood sugar

- Oral
  - Decreasing appetite
- Intestinal
  - Slowing down gastric emptying
  - Increasing the effective concentration of gut hormones--- decreasing glucagon and stimulating pancreas to secrete more insulin,
  - Decrease rate of intestinal carbohydrate absorption
- Peripheral: increasing insulin sensitivity at cell level
- Liver:—decreasing glucose production
• Liver
  • Decreases hepatic glucose production
• Pancreas
  • Increases insulin secretion
• Kidney
  • Blocks glucose reabsorption by kidney
• Peripheral: Increases insulin sensitivity in cells
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2017
## Dual Therapy

### Metformin + Lifestyle

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 inhibitor</th>
<th>SGLT2 inhibitor</th>
<th>GLP-1 receptor agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td><strong>Hypo Risk</strong></td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>hypoglycemia</td>
<td>edema, HF, fxS</td>
<td>rare</td>
<td>GU, dehydration, fxS</td>
<td>GI</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>
### Summary of glucose-lowering interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected decrease in A1C with monotherapy, %</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 1: Well-validated core</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 1: Initial therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle to decrease weight and increase activity</td>
<td>1.0 to 2.0</td>
<td>Broad benefits</td>
<td>Insufficient for most within first year</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0 to 2.0</td>
<td>Weight neutral</td>
<td>GI side effects, contraindicated with renal insufficiency</td>
</tr>
<tr>
<td><strong>Step 2: Additional therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5 to 3.5</td>
<td>No dose limit, rapidly effective, improved lipid profile</td>
<td>One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1.0 to 2.0</td>
<td>Rapidly effective</td>
<td>Weight gain, hypoglycemia (especially with gliburide or chlorpropamide)</td>
</tr>
<tr>
<td><strong>Tier 2: Less well validated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>0.5 to 1.4</td>
<td>Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)</td>
<td>Fluid retention, HF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>0.5 to 1.0</td>
<td>Weight loss</td>
<td>Requires injection, frequent GI side effects, long-term safety not established, expensive</td>
</tr>
<tr>
<td><strong>Other therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>0.5 to 0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side effects, three times/day dosing, expensive</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>0.5 to 1.5*</td>
<td>Rapidly effective</td>
<td>Weight gain, three times/day dosing, hypoglycemia, expensive</td>
</tr>
<tr>
<td>Framintide</td>
<td>0.5 to 1.0</td>
<td>Weight loss</td>
<td>Three injections daily, frequent GI side effects, long-term safety not established, expensive</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>0.5 to 0.8</td>
<td>Weight neutral</td>
<td>Long-term safety not established, expensive, possible increased risk of HF with saxagliptin</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>0.5 to 0.7</td>
<td>Weight loss, reduction in systolic blood pressure</td>
<td>Vulvovaginal candidiasis, urinary tract infections, long-term safety not established</td>
</tr>
</tbody>
</table>


*Repaglinide more effective in lowering A1C than nateglinide.

The ADA recommendations 2017

- Metformin should be first line agent for most type 2 DM patients without contraindications.
- If you need to add a second agent, and you want a non insulin agent, there is no real preference between the TZDs, SUs, SGLT2s, DPP-4s, GLP-1s
- How to decide—think of side effect, efficacy, cost
Metformin has been associated with all of the following side effects except:

- Abdominal bloating
- Hair loss
- B 12 deficiency
- Lactic acidosis
Case 1: What to add?

- 78 yo female with COPD, obesity, HTN, macular degeneration, and DM, and some mild to moderate cognitive impairment, maintained on Metformin 500 BID, and glipizide 5 mg BID.
- She has home health nurses twice a week.
- Nurses report HgbA1C of 8%. And BGs post prandial in the 130 range.
- She has had 2 falls in the last month and seems more confused at times.
- Should you change her DM meds? How and why?
• Avoid hypoglycemia especially in cognitively impaired adults.
• Hypoglycemia can of course contribute to confusion
• Both repeated hypoglycemic events and also significant duration of moderate hyperglycemia increase the risk of cognitive dysfunction
• Recommendations, ADA:
<table>
<thead>
<tr>
<th>Patient characteristics/health status</th>
<th>Rationale</th>
<th>Reasonable A1C goal#</th>
<th>Fasting or preprandial glucose</th>
<th>Bedtime glucose</th>
<th>Blood pressure</th>
<th>Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few coexisting chronic illnesses, intact cognitive and functional status)</td>
<td>Longer remaining life expectancy</td>
<td>&lt;7.5% (58 mmol/mol)</td>
<td>90–130 mg/dL (5.0–7.2 mmol/L)</td>
<td>90–150 mg/dL (5.0–8.3 mmol/L)</td>
<td>&lt;140/90 mmHg</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td>Complex/Intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)</td>
<td>Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk</td>
<td>&lt;8.0% (64 mmol/mol)</td>
<td>90–150 mg/dL (5.0–8.3 mmol/L)</td>
<td>100–180 mg/dL (5.6–10.0 mmol/L)</td>
<td>&lt;140/90 mmHg</td>
<td>Statin unless contraindicated or not tolerated</td>
</tr>
<tr>
<td>Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)</td>
<td>Limited remaining life expectancy makes benefit uncertain</td>
<td>&lt;8.5%* (69 mmol/mol)</td>
<td>100–180 mg/dL (5.6–10.0 mmol/L)</td>
<td>110–200 mg/dL (6.1–11.1 mmol/L)</td>
<td>&lt;150/90 mmHg</td>
<td>Consider likelihood of benefit with statin (secondary prevention more so than primary)</td>
</tr>
</tbody>
</table>
Back to our patient

- maintained on Metformin 500 BID, and glipizide 5 mg BID.
- She has home health nurses twice a week.
- Nurses report HgbA1C of 8%. And BGs post prandial in the 130 range.
- She has had 2 falls in the last month and seems more confused at times.
- ?changes in meds
<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>moderate risk</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>gain</td>
<td>gain</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>hypoglycemia</td>
<td>edema, HF, fxS</td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>
Treatment of older diabetics with end-organ disease.

- Take home messages from studies of older diabetics: the longer you have had DM, the more likely you are to have both cardiovascular complications AND hypoglycemia.
- There is not good quality evidence that tight (<7% HgbA1C) control in older diabetics, certainly >70 years old, will significantly reduce mortality, as compared to “moderate control”, (7-8.9%)

- Published online January 12, 2015.
- Published online December 9, 2013.
But what about those darn quality measures if I don’t tightly control DM?

- How are you being graded?
- In all RMHP programs, there are 2 diabetes related clinical quality measures (Hemoglobin A1c Poor Control and LDL Management):

- **Measure:** Diabetes Hemoglobin A1c Poor Control - Percentage of patients 18-75 years of age with diabetes who had hemoglobin A1c > 9.0% during the measurement period (a lower rate indicates better control).
  - **Numerator:** Patients whose most recent HbA1c level (performed during the measurement period) is > 9.0% (greater than 9.0%).
  - **Denominator:** Patients 18-75 years of age with diabetes with a visit during the measurement period.
  - Measurement Period = 1/1/xx – 12/31/xx

- **Measure:** Diabetes LDL Management - Percentage of patients 18-75 years of age with diabetes whose LDL-C was adequately controlled (<100 mg/dL) during the measurement period.
  - **Numerator:** Patients whose most recent LDL-C level performed during the measurement period is <100 mg/dL.
  - **Denominator:** Patients 18-75 years of age with diabetes with a visit during the measurement period.
  - Measurement Period = 1/1/xx – 12/31/xx
In the CPC+ Program, there are also 2 diabetes related measures (Hemoglobin A1c as listed above and also the Diabetes Eye Exam measure):

**Measure:** Diabetes Eye Exam - Percentage of patients 18-75 years of age with diabetes who had a retinal or dilated eye exam by an eye care professional during the measurement period or a negative retinal exam (no evidence of retinopathy) in the 12 months prior to the measurement period.

**Numerator:** Patients with an eye screening for diabetic retinal disease. This includes diabetics who had one of the following: A retinal or dilated eye exam by an eye care professional in the measurement period or a negative retinal exam (no evidence of retinopathy) by an eye care professional in the year prior to the measurement period.

**Denominator:** Patients 18-75 years of age with diabetes with a visit during the measurement period.
Speaking of monitoring BGs

- JAMA article 6/10/17

Glucose Self-Monitoring in Non-Insulin-Treated Patients With Type 2 Diabetes in Primary Care Settings: A Randomized Trial

Laura A. Young, MD, PhD; John D. Buse, MD, PhD; Mark A. Weaver, PhD; Mahan D. Wu, Dr PH, MPH; C. Madeline Mitchell, MURP; Tamara Blaierney, BS; Kimberlea Grimm, BBS; Jennifer Rees, RN, CPF; Franklin Niblock, BS; Katrina E. Donahue, MD, MPH; for the Moni t Trial Group
For patients on oral hypoglycemics only, with HgbA1C 6.5%-9.5%

• CONCLUSIONS:

**CONCLUSIONS AND RELEVANCE** In patients with non-insulin-treated type 2 diabetes, we observed no clinically or statistically significant differences at 1 year in glycemic control or HRQOL between patients who performed SMBG compared with those who did not perform SMBG. The addition of this type of tailored feedback provided through messaging via a meter did not provide any advantage in glycemic control.
Case 2: 48 yo female with DM, knee OA and BMI of 40. On metformin and glipizide, HgbA1C 8.2%
Patient is needle phobic

- **What might be a logical choice for third oral agent?**

### Table: Triple Therapy

<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>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or</td>
<td>DPP-4-i</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>or</td>
<td>SGLT2-i</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>DPP-4-i</td>
</tr>
<tr>
<td>or</td>
<td>GLP-1-RA</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>SGLT2-i</td>
</tr>
<tr>
<td>or</td>
<td>Insulin⁶</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>GLP-1-RA</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

- **Combination Injectable Therapy** *(See Figure 8.2)*
### Dual Therapy  Metformin +  Lifestyle Management

<table>
<thead>
<tr>
<th></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>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td>gain</td>
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<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>hypoglycemia</td>
<td>edema, HF, fx</td>
<td>rare</td>
<td>GU, dehydration, fx</td>
<td>GI</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>COSTS</strong>*</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 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):
48 yo female with DM, knee OA and BMI of 40. On metformin and glipizide, HgbA1C 8.2% 
Patient is needle phobic

- GLP-1 vs SGLT2 vs DPP4 (but weight “neutral”)
- GLP-1= sub Q injectable
- One GLP1 is actually FDA approved for weight loss= Saxenda, AWP for one month=$1385.00, per ADA document (usually not covered by insurance)
- An SGLT2 is an option
- Other non-injectable possibility which might provide weight loss advantage: acarbose, (only modest efficacy and frequent GI side effects including diarrhea)
63 yo obese male, self-employed truck driver, type 2 DM on metformin at max dose x 6 mos with Hgb A1C of 9.8%...

- Thoughts on drugs to add:
  - Sulfonylurea?
    - + on $, efficacy.... ---but ?hypoglycemia
  - His sister is on “jardiance”—she likes it
    - An SGLT2 inhibitor
    - Positives: intermediate efficacy,
    - negatives? Urinary frequency, cost
## Dual Therapy - Metformin + Lifestyle Management

<table>
<thead>
<tr>
<th></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>
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</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
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<tr>
<td><strong>Hypo Risk</strong></td>
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<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
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<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td>gain</td>
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<tr>
<td><strong>Side Effects</strong></td>
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<td>edema, HF, fxs</td>
<td>rare</td>
<td>GU, dehydration, fxs</td>
<td>GI</td>
<td>hypoglycemia</td>
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<td>low</td>
<td>low</td>
<td>high</td>
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</tbody>
</table>

If A1C target not achieved after approximately 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):
72 yo retired male with type DM and hx of CAD sp CABG 3 years ago, creat 1.5...Hgb A1C of 8.3 on sulfonylurea only and dietary management. Other meds include ASA, ACE inhibitor, and beta blocker

- BGs from home monitoring show range from 140-300 in general. No low BGs or syx.
- What drug or drug combinations might be advantageous/disadvantageous for this patient?
Any contraindication to metformin?

- Calculated creatinine clearance = 46 ml/min

Cut-offs and contraindications for metformin?

- Impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min)
- Concurrent active or progressive liver disease
- Active alcohol abuse
- Unstable or acute heart failure at risk of hypoperfusion and hypoxemia
- Past history of lactic acidosis during metformin therapy
- Decreased tissue perfusion or hemodynamic instability due to infection or other causes
Renal threshold cutoffs for metformin

On the basis of these and other studies, the US Food and Drug Administration (FDA) revised its labeling of metformin, which previously had identified metformin as contraindicated in women and men with serum creatinine levels $\geq 1.4$ mg/dL (124 micromol/L) and $\geq 1.5$ mg/dL (133 micromol/L), respectively [72]. The use of metformin is contraindicated in patients with an eGFR $< 30$ mL/min, and the initiation of metformin is not recommended in patients with an eGFR between 30 and 45 mL/min. For patients taking metformin whose eGFR falls below 45 mL/min, the benefits and risk of continuing treatment should be assessed, whereas metformin should be discontinued if the eGFR falls below 30 mL/min.

Up to Date 6/2017
The following is our approach to the administration of metformin:

- For patients with an eGFR <30 mL/min, we do not prescribe metformin.
- For patients with an eGFR ≥45 mL/min, we prescribe full dose.
- For patients with an eGFR of 30 to 44 mL/min and in the absence of active kidney disease (e.g., glomerulonephritis), some UpToDate authors and editors would not initiate metformin, whereas others would reduce the metformin dose by half (no more than 1000 mg per day) and increase the frequency of kidney function monitoring, although there are little or no data to support the glycemic efficacy [71,80] and safety of the latter approach. Lower doses of metformin may not produce the desired lowering of glycemia and may not be safer.
- For patients taking metformin whose eGFR falls below 45 mL/min, we reduce the metformin dose by half (no more than 1000 mg per day) with more frequent testing of eGFR, although there are few data to support the efficacy and safety of this approach.
- For patients taking metformin whose eGFR falls below 30 mL/min, we discontinue metformin.

Up to Date 6/2017
If you are going to add the metformin, either stop the sulfonylurea, or reduce dose, or monitor carefully!

Will metformin decrease his risk of stroke, MI and CV mortality?...probably
**EMPA- REG OUTCOME study and LEADER study**

- Empagliflozin in DM with established CV disease decreased composite outcome of MI, stroke, and CV death by 14% (absolute rate 10.5% vs 12.1%)—vs. placebo and standard care.

- LEADER study for liraglutide similar—with a rate in composite outcomes of stroke, MI, and CV death of 13% compared to 14.9% placebo after FU of 3.8 years.

- True effect? Class effect?, no effect?
Consider initiating insulin first line in newly diagnosed diabetics whose HGbA1C is

1. > 9%
2. >10%
3. > 8.5%
Figure 8.2—Combination injectable therapy for type 2 diabetes. FBG, fasting blood glucose; GLP-1 RA, GLP-1 receptor agonist; hypo, hypoglycemia. Adapted with permission from Inzucchi et al. [21].