LATEST ADVANCES IN THE MANAGEMENT OF DIABETES

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CONFLICT OF INTEREST

- Participated in Research studies funded by the
  - NIH
  - NHLBI
  - VA
  - Kowa Pharmaceuticals
OBJECTIVES

• Describe mechanism, benefits, and side effects of SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists

• Discuss emerging cardiovascular and renal outcomes associated with SGLT2 inhibitors and GLP-1 agonists

• Practice incorporating novel therapeutics for type-2 diabetes into practice
You diagnosed a 66 BM with Type 2 DM. He has no other comorbidity with normal exam and labs. His A1c is 8.1. What medicine would you start along with lifestyle modification and physical activities advices?

1. Glipizide
2. Metformin
3. Pioglitazone
4. Empagliflozin
5. Liraglutide
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Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.

Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin.
68 BM with Type 2 DM comes for routine appointment. He is generally well controlled on Metformin for the last 2 years. Only new complaint is burning feet x 3 months. Exams is unchanged except he has sense of vibration impaired in his feet. A1c is 7.1 What would you do?

1. Order a Nerve Conduction studies
2. Add gabapentin
3. Order vitamin B12 level
4. Educate about feet care & diabetic complications and increase metformin to get better A1c control
5. Refer to neurologist
68 BM with Type 2 DM comes for routine appointment. He is well controlled on Metformin for the last 2 years. Only new complaint is burning feet x 3 months. Exams is unchanged except he has sense of vibration impaired in his feet. What would you do:

1. Order a Nerve Conduction studies
2. Add gabapentin
3. **Order vitamin B12 level**
4. Educate about feet care & diabetic complications
5. Refer to neurologist
• Long-term use of metformin can be associated with vitamin B12 deficiency.

• Periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2019; 41 (Suppl. 1): S75-S84
Which of the following DM medications have been linked to Bladder cancer?

1. Metformin
2. Glipizide
3. Pioglitazone
4. Canagliflozin
5. Exenatide
Which of the following DM medications have been linked to Bladder cancer?

1. Metformin
2. Glipizide
3. Pioglitazone
4. Canagliflozin
5. Exenitide
PIOGLITAZONE AND BLADDER CANCER?

• Pioglitazone, increases the risk of bladder cancer by at least 40% when used for more than a year.

Cancer Risk for Patients Using Thiazolidinediones for Type 2 Diabetes: A Meta-Analysis The Oncologist February 1, 2013 18:148-156
66 years old with insulin dependent brittle DM on 4 medications comes for routine appointment for his uncontrolled Diabetes. He read on internet about wearable “Bionic Pancreas” which automatically detect blood sugars levels and adjust insulin. He would like to get that. You will tell him:

1. There is no such device available at the moment
2. Order the Bionic Pancreas
3. Refer him to a research trial for Bionic Pancreas
4. Suggest dietitian consult for better carb counting
5. Add Semaglutide
66 years old with insulin dependent brittle DM comes for routine appointment for his uncontrolled Diabetes. He read on internet about wearable “Bionic Pancreas” which automatically detect blood sugars levels and adjust insulin. He would like to get that. You will tell him:

1. There is no such device available at the moment
2. Order the Bionic Pancreas
3. Refer him to a research trial for Bionic Pancreas
4. Suggested dietitian consult for better carb counting
5. Add Semaglutide
HYBRID CLOSED-LOOP INSULIN DELIVERY SYSTEM

- Hailed as the world's first artificial pancreas

- A glucose monitoring device and insulin pump to work together to stabilize blood glucose levels.

- It was approved by the FDA in 2016.
58 yo male on atorvastatin, lisinopril and aspirin came to your office worried about the newspaper articles about increase risk of diabetes in patients taking statin medications.

His HTN and LDL are controlled to goal, his previous glucose readings were normal.

What would you like to tell him?

1. Stop atorvastatin
2. Continue atorvastatin and don’t worry
3. Continue atorvastatin with periodic monitoring of blood sugars
4. Tell him to not believe in everything he reads in newspaper.
5. Refer him to endocrinology
58 yo male on atorvastatin, lisinopril and aspirin came to your office worried about the newspaper articles about increase risk of diabetes in patients taking statin medications.

His HTN and LDL are controlled to goal, his previous glucose readings were normal.

What would you like to tell him?

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2. Continue atorvastatin and don’t worry
3. **Continue atorvastatin with periodic monitoring of blood sugars**
4. Tell him to not believe in everything he reads in newspaper.
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INCREASES IN GLYCOSYLATED HEMOGLOBIN (HBA1C) AND FASTING PLASMA GLUCOSE

• In JUPITER trail, a 27% increase in diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients.

• High-dose atorvastatin had also been associated with worsening glycemic control in the PROVE-IT TIMI 22.

• A meta-analysis by Sattar et al. included 13 statin trials with 91,140 participants, reported that statin therapy was associated with a 9% increased risk for incident diabetes (Absolute risk is about 1 in 100-150 patients)
FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks.

Cause and effect has not been established.
WHAT IS THE RECOMMENDED GOAL A1C GOAL?

1. <8
2. <7
3. <6
4. Every patient is different
5. Whatever patient decides
WHAT IS THE RECOMMENDED GOAL A1C GOAL?

1. <8
2. <7
3. <6

4. Every patient is different

5. Whatever patient decides
Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes

- REVIEW AND AGREE ON MANAGEMENT PLAN
- ASSESS KEY PATIENT CHARACTERISTICS
- ONGOING MONITORING AND SUPPORT
- CONSIDER SPECIFIC FACTORS WHICH IMPACT ON CHOICE OF TREATMENT
- IMPLEMENT MANAGEMENT PLAN
- SHARED DECISION-MAKING TO CREATE A MANAGEMENT PLAN
- AGREE ON MANAGEMENT PLAN
- GOALS OF CARE
  - Prevent complications
  - Optimise quality of life

Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019;42(Suppl. 1):S34-S45
### Approach to Individualization of Glycemic Targets

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>A1C 7%</td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>A1C 7%</td>
<td>long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>A1C 7%</td>
<td>short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>A1C 7%</td>
<td>few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>A1C 7%</td>
<td>few / mild</td>
</tr>
<tr>
<td>Patient preference</td>
<td>highly motivated, excellent self-care capabilities</td>
<td>A1C 7%</td>
<td>preference for less burdensome therapy</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>A1C 7%</td>
<td>limited</td>
</tr>
</tbody>
</table>
GLYCEMIC GOALS IN ADULTS

• A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol).

• Consider more stringent goals (e.g. <6.5%) for select patients if achievable without significant hypos or other adverse effects.

• Consider less stringent goals (e.g. <8%) for patients with a history of severe hypoglycemia, limited life expectancy, or other conditions that make <7% difficult to attain.

ANTI-HYPERGLYCEMIC THERAPY: GLYCEMIA TARGETS

• HbA1c < 7.0% (MPG ~150 mg/dL)
• Pre-prandial PG 80-130 mg/dL
• Post-prandial PG <180 mg/dL
• Avoidance of hypoglycemia

• Individualization is key:
  • More stringent (6.0-6.5%) - short disease duration, healthier, no CVD
  • Less stringent (7.5-8.0%+) – comorbidities, complications, hypoglycemias, short life expectancy, limited resources, support or motivation

RELATIVE RISK OF PROGRESSION OF DIABETIC COMPLICATIONS

• 10% reduction in HbA$_1$c

• 43% reduced risk of retinopathy progression

• 18% increased risk of severe hypoglycemia with coma and/or seizure

LIFETIME BENEFITS OF INTENSIVE THERAPY (DCCT)

• Gain of 15.3 years of complication free living compared to conventional therapy

• Gain of 5.1 years of life compared to conventional therapy

**United Kingdom Prospective Diabetes Study (UKPDS)**

*Percent risk reduction per 0.9% decrease in HbA$_{1C}$; UKPDS. Lancet. 1998;352:837-853.*

- **Any diabetes-related endpoint**: -12 (p=0.029)
- **Microvascular endpoint**: -25 (p=0.0099)
- **MI**: -16 (p=0.052)
- **Retinopathy**: -21 (p=0.015)
- **Albuminuria at 12 years**: -34 (p=0.000054)
# IMPACT OF INTENSIVE THERAPY

<table>
<thead>
<tr>
<th>Study</th>
<th>Micro</th>
<th>Macro</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>![Down Arrow]</td>
<td>![Double Arrows]</td>
<td>![Down Arrow]</td>
</tr>
<tr>
<td>DCCT / EDIC</td>
<td>![Down Arrow]</td>
<td>![Double Arrows]</td>
<td>![Double Arrows]</td>
</tr>
<tr>
<td>ACCORD</td>
<td>![Down Arrow]</td>
<td>![Double Arrows]</td>
<td>![Up Arrow]</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>![Down Arrow]</td>
<td>![Double Arrows]</td>
<td>![Double Arrows]</td>
</tr>
<tr>
<td>VADT</td>
<td>![Down Arrow]</td>
<td>![Double Arrows]</td>
<td>![Double Arrows]</td>
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</tbody>
</table>

Initial Trial | Long Term Follow-up

WHAT HAVE WE LEARNED FROM DIABETES TRIALS?

- **DCCT**: Trend toward lower risk of CVD events with intensive control (T1D)
- **EDIC**: 57% reduction in risk of nonfatal MI, stroke, or CVD death (T1D)
- **UKPDS**: nonsignificant reduction in CVD events (T2D).
- **ACCORD, ADVANCE, VADT** suggested no significant reduction in CVD outcomes with intensive glycemic control. (T2D)

Drake TC, Hire D, Rehman SU, O’Connor P. Factors Associated with Failure to Achieve Hemoglobin A1c <8.0% in the Action to Control Cardiovascular Risk in Diabetes Trial. *Diabetes Obes Metab.* 2016 Jan;18(1):92-5
67 year old female with T2DM, HTN, osteopenia, idiopathic pancreatitis, and CAD s/p RCA stent in 2015 is seen in clinic today. Her A1c is 8.5%. Current medications include metformin 1000mg BID, ASA 81mg QD, and Lisinopril 40mg QD. BMI is 27.

What would you add?

1. Canagliflozin
2. Empagliflozin
3. Sitagliptin
4. Liraglutide
5. All of above options are reasonable

Case courtesy of Tanya Nikiforova, MD
• Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% (12.5 mmol/mol) above their glycemic target.

• A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences.
PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

- The early introduction of insulin should be considered
  - if there is evidence of ongoing catabolism (weight loss)
  - if symptoms of hyperglycemia are present
  - or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high.
Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen.

Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium-glucose cotransporter 2 inhibitors are preferred.

For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both.
Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight change</th>
<th>CV effects</th>
<th>Cost</th>
<th>Oral/SQ</th>
<th>Renal effects</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral</td>
<td>Potential benefit</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
<td>Neutral</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Gastrointestinal side effects common (diarrhea, nausea)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Risk of bone fractures (canagliflozin)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>High</td>
<td>No</td>
<td>Loss</td>
<td>Neutral: lixisenatide</td>
<td>Benefit: liraglutide</td>
<td>High</td>
<td>SQ</td>
<td>Benefit: liraglutide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Gastrointestinal side effects common (nausea, vomiting, diarrhea)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral</td>
<td>Potential risk: saxagliptin, alogliptin</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
<td>Neutral</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Caution when initiating or increasing dose due to potential risk of acute kidney injury</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Potential benefit: pioglitazone</td>
<td>Increased risk</td>
<td>Low</td>
<td>Oral</td>
<td>Neutral</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Generally not recommended in renal impairment due to potential for fluid retention</td>
</tr>
<tr>
<td>Sulfonylureas (2nd generation)</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
<td>Neutral</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia</td>
</tr>
<tr>
<td>Insulin</td>
<td>Human Insulin</td>
<td>Highest</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Low</td>
<td>SQ</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Analogues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Injection site reactions</td>
</tr>
</tbody>
</table>

*For agent-specific dosing recommendations, please refer to the manufacturers’ prescribing information. FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium-glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.
If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:

- **ASCVD Predominates:**
  - Add GLP-1 RA with proven CVD benefit, OR
  - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)

- **If HF or CKD Predominates:**
  - Add SGLT-2 inhibitor with evidence of benefit
  - If can’t take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit
Risk of CVD outcomes, CVD-related and all-cause mortality, key side effects, and cost associated with use of listed agents. Data are from the following trials: IRIS (pioglitazone), EMPA-REG OUTCOME (empagliflozin), LEADER (liraglutide), and SUSTAIN-6 (semaglutide). Downward arrows (green) indicate a reduction, and upward arrows (red) indicate an increase; horizontal arrows (yellow) indicate neutral effect. *Denotes major adverse cardiovascular events, most commonly a composite of cardiovascular death, nonfatal MI, and nonfatal stroke. †Denotes hospitalization due to heart failure. ‡Risk for severe hypoglycemia is compared to that observed in patients using sulfonylureas or insulin. §Based on several studies using pioglitazone (excluding IRIS). aCost assumed since drug is not yet marketed.

<table>
<thead>
<tr>
<th>Agent</th>
<th>MACE*</th>
<th>CVD mortality</th>
<th>All-cause mortality</th>
<th>HF admissions†</th>
<th>Hypoglycemia risk‡</th>
<th>Weight change</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↑‡</td>
<td>Low</td>
<td>↑</td>
<td>Low</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Low</td>
<td>↓</td>
<td>High</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
<td>Low</td>
<td>↓</td>
<td>High</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>Low</td>
<td>↓</td>
<td>High</td>
</tr>
</tbody>
</table>

Ismail-Beigi, J GEN INTERN MED (2017) 32: 1044
Indications and CV evidence of glucose-lowering agents in type 2 diabetes. Arrow bar denotes patient category in which the medication class is currently indicated. Green indicates effectiveness (i.e., reduced CV events), yellow indicates CV neutrality, and no color indicates lack of CV data from randomized clinical trials, as interpreted by the authors. For CV effectiveness, the specific types of events reduced are also listed (MACE = major adverse CV events; CVM = CV mortality; HHF = hospitalization for heart failure.) *Metformin effectiveness demonstrated in UKPDS-34 (n = 1704), 1 Kooy et al. (n = 390), 2 and SPREAD-DIMCAD (n = 304). 3 Sulfonylurea safety demonstrated for glibenclamide and chlorpropamide in UKPDS-33 (n = 3867). 4 For thiazolidinediones, safety shown for rosiglitazone for patients with CV risk factors (RECORD, n = 4447) and effectiveness shown for pioglitazone in PROactive (n = 5238) and IRIS (insulin-resistant stroke population with no diabetes, n = 3876). 5 Contraindicated in heart failure. † Dipeptidyl peptidase-4 (DPP-4) inhibitor safety shown for saxagliptin (SAVOR-TIMI 53, n = 16,492), 14 alogliptin (EXAMINE, n = 5380), 15 and sitagliptin (TECOS, n = 14,671). 16 SAVOR found an increased HHF with saxagliptin, with a similar trend in EXAMINE; current guidelines caution the use of saxagliptin and alogliptin in heart failure patients. ‡ SGLT2 inhibitor effectiveness demonstrated for empagliflozin in EMPA-REG OUTCOME (n = 7020); 16 although HHF was reduced in that study, the drug has not yet been tested in a dedicated heart failure study. ¶ Only GLP-1 receptor agonist effectiveness demonstrated for liroaglitide (MACE, CVM) in LEADER (n = 9340) and the investigational semaglutide (MACE only) in SUSTAIN-6 (n = 3297). 21 ** Insulin safety shown in UKPDS-33 (n = 3867) and ORIGIN (n = 12,537). 37 Acute in-hospital studies are not considered.

In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, **empagliflozin** or **canagliflozin** or **liraglutide** should be considered.

These agents have been shown to reduce cardiovascular and all-cause mortality when added to standard care.

American Diabetes Association Standards of Medical Care in Diabetes. Diabetes Care 2019; 41 (Suppl. 1): S74-S85
<table>
<thead>
<tr>
<th>Medication</th>
<th>Population studied</th>
<th>Primary outcome</th>
<th>MACE</th>
<th>CHF Hospitalization</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin (EMPA-REG OUTCOME trial, NEJM 2015)</td>
<td>Known CV disease or at high risk</td>
<td>MACE: CV mortality, nonfatal MI, nonfatal stroke</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Canagliflozin (CANVAS trial, NEJM 2017)</td>
<td></td>
<td></td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Liraglutide (LEADER trial, NEJM 2016)</td>
<td></td>
<td></td>
<td>↓</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Semaglutide (SUSTAIN-6 trial, NEJM 2016)</td>
<td></td>
<td></td>
<td>↓</td>
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</tr>
</tbody>
</table>
ANTI-HYPERGLYCEMIC THERAPY: ORAL AGENTS & NON-INSULIN INJECTABLES

- Biguanides
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- SGLT-2 inhibitors
- Dopamine-2 agonists
- Bile acid sequestrants
- GLP-1 receptor agonists
- Amylinomimetics
<table>
<thead>
<tr>
<th>Drug</th>
<th>A1c Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Secretagog (SFU/Glinide)</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>GLP1RA</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>TZD</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>SGLT2i¹</td>
<td>0.8–1.5</td>
</tr>
<tr>
<td>DPP4i¹</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>α–GI</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Bromocriptine IR²</td>
<td>0.6–0.9</td>
</tr>
<tr>
<td>Amylin²</td>
<td>0.4–0.7</td>
</tr>
<tr>
<td>Colesevelam²</td>
<td>0.3–0.5</td>
</tr>
</tbody>
</table>

Not head to head. Baselines and background therapies differ. Information derived from multiple studies.
Oral Therapy for Type 2 Diabetes: Sites of Action

- **α-Glucosidase inhibitors**
  - Inhibit carbohydrate breakdown

- **TZDs**
  - Glucose intake $\uparrow$
  - FFA output $\downarrow$
  - Adipose tissue

- **SGLT2 Inhibitors**
  - Increase glucose excretion

- **Pancreas**
  - Slow gastric emptying
  - Stimulate insulin secretion
  - SUs (glucose-independent)
  - DPP-4 inhibitors / GLP-1Ra (glucose-dependent)

- **Liver**
  - Upregulate glucose metabolism
  - Suppress glucose production

- **Kidney**
  - Increase glucose excretion

- **Muscle**
  - $\uparrow$ Glucose metabolism

- **Adipose tissue**
  - Adipose tissue

- **Stomach**
  - $\downarrow$ FFA output

GLP-1 AND GIP ARE DEGRADED BY THE DPP-4 ENZYME

Meal

Intestinal GLP-1 and GIP release

DPP-4 enzyme

Active GLP-1 and GIP

Rapid activation

Inactive metabolites

## Glucagon-Like Peptide-1 Agonists

<table>
<thead>
<tr>
<th>GLP-1 Agonists</th>
<th>Daily or BID Injection</th>
<th>Weekly Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td></td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Exenatide</td>
<td></td>
<td>Exenatide ER</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td></td>
<td>Albiglutide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semaglutide</td>
</tr>
</tbody>
</table>
GLP-1

Insulin Secretion

Glucagon

Gastric Emptying

Appetite
GLP-1 AGONISTS: HOW DO THEY WORK?

<table>
<thead>
<tr>
<th>Remember TIDE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAMES</strong> gastric emptying</td>
<td></td>
</tr>
<tr>
<td><strong>INCREASES</strong> insulin secretion</td>
<td></td>
</tr>
<tr>
<td><strong>DECREASES</strong> glucagon</td>
<td></td>
</tr>
<tr>
<td><strong>EATING</strong> effects</td>
<td></td>
</tr>
</tbody>
</table>

Case courtesy of Tanya Nikiforova, MD
<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• High efficacy: A1c reduction 1-1.5%</td>
<td>• Injectable medication: injection site reactions</td>
</tr>
<tr>
<td>• Weight reduction: approved at higher doses</td>
<td>• Pancreatitis: potential risk</td>
</tr>
<tr>
<td>to treat obesity</td>
<td>• GI side effects common: nausea, vomiting, diarrhea in</td>
</tr>
<tr>
<td>• Rare hypoglycemia</td>
<td>10-50%</td>
</tr>
<tr>
<td>• Liraglutide (Victoza): CV benefits in high-risk</td>
<td>• Risk of medullary thyroid cancer (FDA black box warning)</td>
</tr>
<tr>
<td>patients, less progression of nephropathy</td>
<td>• Limited experience with ESRD: CAN be used by increased</td>
</tr>
<tr>
<td></td>
<td>risk of side effects</td>
</tr>
</tbody>
</table>
# SUMMARY OF GLP-1 AGONIST HEAD-TO-HEAD TRIALS

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>TREATMENT</th>
<th>A1c ∆ (%)</th>
<th>WT ∆ (Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARMONY 7</td>
<td>Albiglutide 30 mg, up to 50 mg weekly</td>
<td>Albiglutide: -0.78</td>
<td>Albiglutide: -0.6</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg daily</td>
<td>Liraglutide: -0.99*</td>
<td>Liraglutide: -2.2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWARD-1</td>
<td>Dulaglutide 0.75 mg weekly</td>
<td>Dulaglutide 0.75 mg: -1.3</td>
<td>Dulaglutide 0.75 mg: 0.2</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide 1.5 mg weekly</td>
<td>Dulaglutide 1.5 mg: -1.5</td>
<td>Dulaglutide 1.5 mg: -1.3</td>
</tr>
<tr>
<td></td>
<td>Exenatide 10 mcg BID</td>
<td>Exenatide: -0.99</td>
<td>Exenatide: -1.07</td>
</tr>
<tr>
<td>AWARD-6</td>
<td>Dulaglutide 1.5 mg weekly</td>
<td>Dulaglutide: -1.42</td>
<td>Dulaglutide: -2.9</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg daily</td>
<td>Liraglutide: -1.36</td>
<td>Liraglutide: -3.61</td>
</tr>
<tr>
<td>LEAD-6</td>
<td>Liraglutide 1.8 mg daily</td>
<td>Liraglutide: -1.12*</td>
<td>Liraglutide: -3.24</td>
</tr>
<tr>
<td></td>
<td>Exenatide 10 mcg BID</td>
<td>Exenatide: -0.79</td>
<td>Exenatide: -2.87</td>
</tr>
<tr>
<td>DURATION-1</td>
<td>Exenatide ER 2 mg weekly</td>
<td>Exenatide ER: -1.9*</td>
<td>Exenatide ER: -3.6</td>
</tr>
<tr>
<td></td>
<td>Exenatide 10 mcg BID</td>
<td>Exenatide: -1.5</td>
<td>Exenatide: -3.7</td>
</tr>
<tr>
<td>DURATION-5</td>
<td>Exenatide ER 2 mg weekly</td>
<td>Exenatide ER: -1.6*</td>
<td>Exenatide ER: -2.3</td>
</tr>
<tr>
<td></td>
<td>Exenatide 10 mcg BID</td>
<td>Exenatide: -0.9</td>
<td>Exenatide: -1.4</td>
</tr>
<tr>
<td>DURATION-6</td>
<td>Exenatide ER 2 mg weekly</td>
<td>Exenatide ER: -1.28</td>
<td>Exenatide: -2.68</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg daily</td>
<td>Liraglutide: -1.48*</td>
<td>Liraglutide: -3.57*</td>
</tr>
</tbody>
</table>

*Statistically significant
SAFETY CONCERNS FOR GLP-1 AGONIST

• Most common ADRs: nausea, vomiting, diarrhea, headache, injection site reaction
• Renal impairment
• Severe gastrointestinal disease (gastroparesis)
• Hypoglycemia risk increased when used with insulin or sulfonylurea
• Hypersensitivity reactions
  • angioedema, anaphylaxis, rash, pruritis
• Acute pancreatitis
GLP-1 AGONISTS AND THYROID CARCINOMA

- GLP-1 agonists except exenatide IR/lixisenatide have black box warning for thyroid carcinoma
- Contraindicated with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
- Thyroid C-cell tumors observed in animal studies
- Cases of MTC in humans treated with liraglutide have been reported in post marketing period

DPP-4 Inhibitors

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td></td>
</tr>
</tbody>
</table>
## DPP-4 INHIBITORS

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dosing; pill form</td>
<td>Efficacy: Lower than GLP-1 agonists (A1c reduction 0.4-0.8%)</td>
</tr>
<tr>
<td>Weight neutral</td>
<td>Pancreatitis: Potential risk</td>
</tr>
<tr>
<td>Rare hypoglycemia</td>
<td>Skin reactions: Urticaria, angioedema</td>
</tr>
<tr>
<td>Overall well tolerated</td>
<td>Musculoskeletal: joint pain, muscles aches</td>
</tr>
<tr>
<td>Can be used in CKD/ESRD</td>
<td>Linagliptin – no dose adjustment needed due to hepatic clearance</td>
</tr>
<tr>
<td>Sitagliptin – can be dose adjusted</td>
<td>Sitagliptin – can be dose adjusted</td>
</tr>
</tbody>
</table>

• Linagliptin – no dose adjustment needed due to hepatic clearance
DIPEPTIDYL PEPTIDASE-4 INHIBITORS - DPP4 INHIBITORS

• No significant hypoglycemia or weight gain
• Most common ADRs: URI, nasopharyngitis, headache
• No head-to-head trials
• No clear concern regarding CV outcomes/CHF (saxagliptin)
• Can be used in CKD/ESRD

DPP4 INHIBITORS

• Pancreatitis reports, although no causal relationship has been established
• FDA concluded these drugs may not cause or contribute to the development of pancreatic cancer.”
• Extensive review by FDA (>80,000 patients) has not uncovered reliable evidence of increased pancreatic cancer risk with incretins vs other agents.

Buse JB. Diabetes Care Feb 2017;40(2) 164-170.
SGLT-2 INHIBITORS

Glucose

S1 segment of proximal tubule

SGLT2

Majority glucose reabsorption

Distal S2/S3 segment of proximal tubule

SGLT1

Minority glucose reabsorption

Collecting duct

Negligible glucose in urine

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT-2) INHIBITOR

• Mechanism is not insulin-dependent
• Reduction of weight and BP
• Increased genital mycotic infections
• Cannot be used with reduced eGFR
• Hyperkalemia, renal insufficiency, hypotension and LDL elevation

# Sodium-Glucose Cotransporter-2 Inhibitors

<table>
<thead>
<tr>
<th>SGLT-2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
</tr>
<tr>
<td>Canagliflozin</td>
</tr>
<tr>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>Ertugliflozin</td>
</tr>
</tbody>
</table>
SGLT-2 INHIBITORS

- Euglycemic diabetic ketoacidosis
- Bladder cancer incidence higher with dapagliflozin
- Amputations higher with canagliflozin
- Non significant incidence of bone fx
- CV benefits with empagliflozin in patients with established cv disease

Monotherapy

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes:  - Monitor A1C every 3–6 months

No:  - Assess medication-taking behavior
      - Consider Dual Therapy
<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>
</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>
<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):

**ADA 2019 Guidelines**
Dual Therapy

Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes:  - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)

No:   - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

ADA 2019 Guidelines
CV outcomes

Composite of major adverse cardiac events (MACE), including CV death, nonfatal MI, nonfatal stroke
- Heart failure
- All-cause mortality

- Several medications were found to reduce cardiovascular risk

SGLT-2 inhibitors = Empagliflozin, Canagliflozin

GLP-1 agonists = Liraglutide, Semaglutide
Empagliflozin and CV outcomes

- 7020 patients assigned to receive 10mg/25mg of empagliflozin vs placebo
- All patients had established CV disease
  - history of CAD, prior MI, prior stroke, or PVD
- Most were white men (72%) with mean age 63, BMI 31, A1c 8%

Zinman et al, NEJM, 2015
Empagliflozin and CV outcomes

- Difference in MACE driven by reduced mortality from CV causes
- Fewer hospitalizations for heart failure
- Decreased all-cause mortality
• Canagliflozin 300 mg provided greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea (p<0.05).

• Canagliflozin 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg.

• A mean change in systolic blood pressure from baseline of -5.06 mmHg was observed with Invokana 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.
Canagliflozin 300 mg provided a greater reduction from baseline in HbA1C compared to glimepiride.

Treatment with Canagliflozin 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.
Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor

- Reduce blood glucose levels by increasing the amount of glucose excreted in the urine.
- Monotherapy or added to Metformin
A greater proportion of patients achieving

- an HbA1C less than 7%,
- significant reduction in fasting plasma glucose (FPG),
- improved postprandial glucose (PPG),
- Percent body weight reduction compared to placebo.

• The recommended starting dose of Canagliflozin is 100 mg once daily, taken before the first meal of the day.

• If the eGFR of 60 mL/min/1.73 m² or greater and require additional glycemic control, the dose can be increased to 300 mg once daily.
CANAGLIFLOZIN SIDE EFFECTS

• Female genital mycotic infections
• Urinary tract infection
• Increased urination

ERTUGLIFLOZIN

• 5mg QAM w/o regards to meals up to 15mg/day

• Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor

• Renal impairment: Not recommended if eGFR persistently 30-60 as decreased efficacy & contraindicated if <30
Grade A recommendation: Empagliflozin, Liraglutide

Grade C recommendation: Canagliflozin

**ASCVD?**

**Yes:** Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)

**No:** Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

Semaglutide – FDA approved 12/2017
67 year old female with T2DM, HTN, osteopenia, idiopathic pancreatitis, and CAD s/p RCA stent in 2015 is seen in clinic today. Her A1c is 8.5%. Current medications include metformin 1000mg BID, ASA 81mg QD, and Lisinopril 40mg QD. BMI is 27.

What would you add?

A. Canagliflozin
B. Empagliflozin
C. Sitagliptin
D. Liraglutide
E. All of above options are reasonable
67 year old female an with T2DM, HTN, osteopenia, idiopathic pancreatitis, and CAD s/p RCA stent in 2015 is seen in clinic today. Her A1c is 8.5%. Current medications include metformin 1000mg BID, ASA 81mg QD, and Lisinopril 40mg QD. BMI is 27.

What would you add?

A. Canagliflozin (Bone Fracture Risk)
B. Empagliflozin
C. Sitagliptin (No CV benefit)
D. Liraglutide (Pancreatitis Risk)
E. All of these options are reasonable (Pt has known CAD)

Case courtesy of Tanya Nikiforova, MD
• Individualization of goals and therapy should continue to play a central role in decision-making.

• In choosing a therapeutic regimen, we should continue to consider, in addition to prevalent CVD, each patient’s capabilities, finances, living situation, support systems, cognitive status, other comorbidities, and life expectancy, while implementing shared decision-making.

• Cardiovascular disease (CVD) is the main cause of excess mortality in diabetic patients.

• More intensive glycemic control improves certain microvascular outcomes but has not substantially reduced the risk of cardiovascular (CV) mortality and other adverse CV events such as myocardial infarction and stroke.

• Based on the results of recent trials, the use of medications now proven to reduce CV complications should be prioritized in patients with established CVD, while continuing a multifaceted approach for controlling hypertension and dyslipidemia.
• We anticipate future trials using SGLT2 inhibitors or GLP-1 receptor agonists at earlier stages of type 2 diabetes, especially in those without prevalent CVD.

• Current algorithms for the management of type 2 diabetes based primarily on HbA1c values ought to shift towards a new paradigm that incorporates patients’ CV risk and their likelihood of realizing a CVD benefit into the glucose-lowering drug selection process.
78 year old male with PMHx of obesity, HTN, hyperlipidemia, CKD, and DM2. He had been on glipizide 2.5mg and metformin 500mg bid for years. Six months ago, glipizide was stopped due to frequent hypoglycemia. On return, he has mild leg edema. His creatinine is 2.2, eGFR is 28, and microalbumin to creatinine ratio is 1500. He doesn’t want insulin. A1C is 8.8%.

After stopping metformin, what medication do you start?
1. Add glipizide back at the lowest dose
2. Start pioglitazone
3. Start dapagliflozin
4. Start linagliptin
5. Start insulin

Case courtesy of Tanya Nikiforova, MD
78 year old male with PMHx of obesity, HTN, hyperlipidemia, CKD, and DM2. He had been on glipizide 2.5mg and metformin 500mg bid for years. Six months ago, glipizide was stopped due to frequent hypoglycemia. On return, he has mild leg edema. His creatinine is 2.2, eGFR is 28, and microalbumin to creatinine ratio is 1500. He doesn’t want insulin. A1C is 8.8%.

After stopping metformin, what medication do you start?

1. Add glipizide back at the lowest dose (He has hx of hypoglycemia)
2. Start pioglitazone (Could worsen his edema)
3. Start dapagliflozin (eGFR is too low)
4. **Start linagliptin**
5. Start insulin (Pt does not want)

Case courtesy of Tanya Nikiforova, MD
A 42 year old woman with hypertension, hyperlipidemia, obesity, and recent diagnosis of DM2 presents for follow-up after taking metformin for 4 months. She has been compliant with the medication and been doing her best to exercise and eat well but has not lost any weight. You check her hemoglobin A1c and find that it remains elevated at 7.5. On exam her BP is 135/80 and BMI is 40.

What is the most appropriate next step?
A. Start liraglutide
B. Start linagliptin
C. Start glipizide
D. Start insulin
E. No change in medications
A 42 year old woman with hypertension, hyperlipidemia, obesity, and recent diagnosis of DM2 presents for follow-up after taking metformin for 4 months. She has been compliant with the medication and been doing her best to exercise and eat well but has not lost any weight. You check her hemoglobin A1c and find that it remains elevated at 7.5. On exam her BP is 135/80 and BMI is 40.

What is the most appropriate next step?

A. **Start liraglutide** (Weight loss + CVD Benefits)
B. Start linagliptin (Weight neutral)
C. Start glipizide (Weight gain)
D. Start insulin (Weight gain)
E. No change in medications (DM uncontrolled)

Case courtesy of Tanya Nikiforova, MD
• 58 yo overweight men with diabetes on maximum doses of Metformin, Glipizide and Canagliflozin. Hga1c is 8 now, still refusing insulin but receptive to injectables if he does not have to inject a lot. He is still trying to loose weight.

• Which of the following injectable would you recommend?

  1. Daily Liraglutide (Victoza)
  2. Weekly Liraglutide (Victoza)
  3. Weekly Pramlintide (Symlin)
  4. Weekly Semaglutide (Ozempic)
  5. Daily Semaglutide
• 58 yo overweight men with diabetes on maximum doses of Metformin, Glipizide and Canagliflozin. Hga1c is 8 now, still refusing insulin but receptive to injectables if he does not have to inject a lot. He is still trying to loose weight.

• Which of the following injectable would you recommend?

1. Daily Liraglutide (Victoza)
2. Weekly Liraglutide (Victoza)
3. Weekly Pramlintide (Symlin)
4. **Weekly Semaglutide (Ozempic)**
5. Daily Semaglutide
Semaglutide

- FDA approval in Nov, 2016.
- Longer-acting version of Liraglutide which is once daily.
- Semaglutide once per week.
SEMAGLUTIDIDE

• Convenience

• Excellent efficacy in reducing blood sugar levels

• Helping patients lose weight
SEMAGLUTIDE

• Glucagon-Like Peptide (GLP-1) receptor agonist
• Acting on the same receptor as the endogenous hormone incretin
  • increases glucose-dependent insulin secretion
  • decreases inappropriate glucagon secretion
  • slows gastric emptying.
• Increases first- and second-phase insulin secretion
Semaglutide

- Initial 0.25mg SQ Qwk

- $\rightarrow$ 0.5mg $\rightarrow$ 1mg SQ Qwk

- 0.25mg is only for initiation & not therapeutic
SUMMARY

• Glucose goals & therapies must be individualized
• Diet, exercise & education
• Unless contraindicated, metformin 1st-line drug
• After metformin, data are limited
  • Combination therapy with oral and/or injectables is reasonable
  • Minimize side effects and address patient specific characteristics
• Many patients will require insulin therapy
DM ABC...