New Treatment Options for T2D - A Focus on Glycemic Control and Lowering CV Risk

Faculty
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Patients with diabetes are also much more likely to suffer from cardiovascular disease than those without diabetes. In fact, cardiovascular disease is the leading cause of death associated with diabetes – certainly a medical double jeopardy. The American Diabetes Association’s (ADA) recently published the 2017 Standards of Medical Care in Diabetes and included new recommendations on treating both diabetes and cardiovascular disease. Pharmacists are often the medical professional that patients reach out to for guidance and explanation on new pharmaco-therapy and individualized treatment. This program will review the ADA’s latest update to the Standards of Medical Care in Diabetes, review recent outcomes trials of antihyperglycemic therapies in patients with type 2 diabetes (T2D) and outline evidence based treatment strategies to mitigate the risk of cardiovascular disease in patients with T2D.

Learning Objectives

Pharmacist
1. Summarize the ADA and AACE guidelines with respect to efficacy and safety particularly when analyzing cardiovascular and renal outcomes
2. Recognize the drug therapies and show evidence of benefit in improving blood sugars and decreasing risk of cardiovascular and renal events
3. Identify guidelines that are recommended by the ADA and AACE for CV risk reduction and the others in this class

Pharmacy Technician
1. Review how different treatment options work to lower blood sugar levels in patients with diabetes
2. Recognize the effects of diabetes agents on glycosylated hemoglobin levels (A1c)
3. List some common safety concerns about different agents used to treat type 2 diabetes

Nurse
1. Summarize the ADA and AACE guidelines with respect to efficacy and safety particularly when analyzing cardiovascular and renal outcomes
2. Recognize the drug therapies and show evidence of benefit in improving blood sugars and decreasing risk of cardiovascular and renal events
3. Identify guidelines that are recommended by the ADA and AACE for CV risk reduction and the others in this class
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Target Audience
Pharmacists, Pharmacy Technicians, Nurses

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Pharmacy Technician 0798-0000-18-265-L01-T
Nurse 0798-0000-18-265-H01-P

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NEW TREATMENT OPTIONS FOR T2D - A FOCUS ON GLYCEMIC CONTROL AND LOWERING CV RISK

Tamara Goldberg
PharmD, BCPS

OBJECTIVES

Pharmacist
• Summarize the ADA and AACE guidelines with respect to efficacy and safety particularly when analyzing cardiovascular and renal outcomes
• Review pharmacotherapy for the treatment of Type 2 diabetes with respect to efficacy and adverse effects
• Identify treatments that are recommended by the ADA and AACE guidelines for decreasing cardiovascular and renal events

Pharmacy Technician
• Review how different treatment options work to lower blood sugar levels in patients with diabetes type 2
• Recognize the effects of diabetes agents on glycosylated hemoglobin levels (A1c)
• List some common safety concerns about different agents used to treat type 2 diabetes

DIABETES DIAGNOSIS

<table>
<thead>
<tr>
<th>FPG (mg/dl)</th>
<th>HbA1C (%)</th>
<th>OGT (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>≥ 126</td>
<td>≥ 6.5</td>
</tr>
<tr>
<td>Pre-Diabetes</td>
<td>100-125</td>
<td>5.7-6.4</td>
</tr>
<tr>
<td>Normal</td>
<td>70-100</td>
<td>4.5-7.5</td>
</tr>
</tbody>
</table>

* C-peptide level <0.5 ng/ml Dx of type 1 diabetes
* Repeat testing is recommended to confirm diagnosis if diagnosed using fasting BG, OGGT, or HbA1c


CRITERIA FOR TESTING ASYMPTOMATIC ADULT INDIVIDUALS

<table>
<thead>
<tr>
<th>&gt;45 years for all patients</th>
<th>Overweight patients with risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT or IFG on previous testing, A1C ≥6.5%</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;25 or BMI &gt;23 in Asian and 1 or more risk factors</td>
<td></td>
</tr>
<tr>
<td>Children ≥90th percentile for age and sex plus any 2 risk factors</td>
<td></td>
</tr>
<tr>
<td>Test at 3 year intervals in healthy patients (yearly in pre-diabetes)</td>
<td></td>
</tr>
</tbody>
</table>

APPROACH TO MANAGEMENT OF HYPERGLYCEMIA

More Stringent <6.5%  > 7% Less Stringent <7.5-8%

• Short diabetes duration
• Long life expectancy
• Not a lot of comorbidities
• Elderly patient
• Many comorbidities
• History of hypoglycemia
β-CELL FUNCTION DECLINE WITH DM PROGRESSION

β-Cell Function (%)

- IGT
- Postprandial Hyperglycemia

Type 2 Diabetes Phases

- Phase I
- Phase II
- Phase III

Years from Diagnosis

UKPDS 16.
Diabetes.

β-Cell Function Decline with DM Progression

SELECTION OF THERAPY

- HbA1C levels at baseline
  - < 9% - monotherapy
  - > 9% - dual therapy
  - > 10% - insulin
- Medication profile
  - Drug class
  - Adverse effects
  - Efficacy
  - Renal and CV safety outcomes
  - Cost

HYPERCHEMIA: PATHOGENESIS

OMINOUS OCTET

HYPERGLYCEMIA

- Decreased Insulin Secretion
- Increased Glucagon Secretion
- Increased Lipolysis
- Neurotransmitter Dysfunction

HYPGLYCEMIA: PATHOGENESIS

SELECTION OF THERAPY

- HbA1C levels at baseline
  - < 9% - monotherapy
  - > 9% - dual therapy
  - > 10% - insulin
- Medication profile
  - Drug class
  - Adverse effects
  - Efficacy
  - Renal and CV safety outcomes
  - Cost

HYPGLYCEMIA CLASSES

- Sulfonylureas
- TZDs
- DPP-IV inhibitors
- Glibenclamide
- Glucagon like peptides (GLP1)
- SGLT2 inhibitors
- Biguanides
- Alpha-glucosidase inhibitors

BIGUANIDE: METFORMIN (GLUCOPHAGE)

- HbA1C lowering potential: 1.5-2% (High)
- May be used in prediabetes
- Benefits
  - No weight gain
  - Lower risk of hypoglycemia
  - May be used in combination with insulin
  - Favorable lipid profile (CVD benefit)
  - May reduce cardiovascular mortality
  - Used for fertility in polycystic ovary syndrome

Adverse Effects

- GI
  - Diarrhea
  - Abdominal discomfort
  - Nausea/vomiting

Precautions

- B12 deficiency may occur
  - Patients with anemia
  - Peripheral neuropathy
  - Elderly
  - Long term use
**METFORMIN BOXED WARNING**

- Lactic Acidosis
  - Blood lactate levels > 5 mmol/L
  - Non specific symptoms
    - Malaise, myalgias, abdominal pain, somnolence, respiratory distress
  - Metformin decreases liver uptake of lactate
  - Risk Factors
    - Renal impairment
    - Age > 65
    - Excessive alcohol

**METFORMIN AND CONTRAST AGENTS**

- IV iodinated contrast dye
  - STOP metformin at time of test
  - May restart 48 hours after radiographic test with contrast
  - Re-evaluate if to restart based on eGFR after contrast media
    - In patients with CrCl < 60 ml/min

**METFORMIN ADVANTAGES VS DISADVANTAGES**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive experience</td>
<td>Gastrointestinal side effects</td>
</tr>
<tr>
<td></td>
<td>(diarrhea, abdominal cramping, nausea)</td>
</tr>
<tr>
<td>Rare hypoglycemia</td>
<td>Lactic acidosis risk (rare)</td>
</tr>
<tr>
<td>↓ CVD events (UKPDS)</td>
<td>Contraindications: eGFR &lt; 30 ml/min</td>
</tr>
<tr>
<td>Relatively higher A1C efficacy</td>
<td>Vitamin B 12 Deficiency</td>
</tr>
</tbody>
</table>

**METFORMIN DOSING**

- Initial
  - 500 mg daily – BID or 850 mg daily with meals
  - Titrate slow to avoid ADRs (GI)
  - Maximum dose: 2000 mg/day
- If GI adverse effects occur
  - Decrease dose
  - Consider ‘Glucophage’ XR, Fortamet®, Glumetza® with evening meal
  - Long acting products given once a day

**METFORMIN: PRACTICE POINTS FOR PHARMACIST**

- Suggest monitoring of
  - B12 levels, GI ADRs, renal function
- Counseling
  - Tell patients to take with food to reduce GI side effects
  - Metformin may cause a metallic taste and some generics may have an odor
  - Extended-release tablet remnants remain in the stool
  - Do not crush or chew extended release tablets

**DIPEPTIDYL PEPTIDASE INHIBITORS (DPP-4)**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin (Nesina’’) 25 mg</td>
<td>Decrease glucagon secretion</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta’) 5 mg</td>
<td>Increase glucose -dependent insulin secretion</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza’’) 5 mg</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin (Januvia’’) 120 mg</td>
<td></td>
</tr>
</tbody>
</table>
DPP4-INHIBITORS ADVERSE EFFECTS

- Headache
- Upper respiratory tract infections
- Recent FDA alert: Joint pain
  - FDA identified 33 cases with severe arthralgia from Oct 2006 to Dec 2013
  - Pain reported was very intense and debilitating
  - 28/33 cases involved sitagliptin
  - After discontinuation pain goes away within a month

DPP-4 INHIBITORS COUNSELING

- Take with or without meals
- Common side effects
  - Runny/stuffy nose, headache
- Monitor for signs and symptoms of pancreatitis
  - Constant abdominal pain with or without vomiting, loss of appetite, nausea
- Other monitoring parameters
  - Joint Pain
  - Rash
  - Fluid build-up, shortness of breath, trouble breathing, fast weight gain

DPP4-INHIBITORS ADVANTAGES VS DISADVANTAGES

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare hypoglycemia</td>
<td>Angioedema/urticaria and other immune-mediated dermatological effects</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>Pancreatitis risk</td>
</tr>
<tr>
<td>Neutral CVD outcomes</td>
<td>↑ Heart failure hospitalizations (saxagliptin, alogliptin)</td>
</tr>
<tr>
<td>Weight reduction?</td>
<td>All require renal adjustment EXCEPT linagliptin</td>
</tr>
</tbody>
</table>

DPP-4 INHIBITORS PLACE IN THERAPY

- Jenny is a 59 year old female that was diagnosed with DM one year ago. She has a PMH of HTN. Jenny is currently on Metformin 1000 mg PO BID and Enalapril 10 mg po daily. She is complaint with all her medications. Her lab values are as follows: SCr 0.9 mg/dl, A1C 7.4%, K+ 4.3 mg/dl. Her physician would like to optimize her A1C to reach a goal of <7%. What would be the best recommendation for Jenny?
  - DPP-4 Inhibitors - Effective in combination when patient has failed metformin; moderate HbA1c lowering effect (0.5%-0.8%); well tolerated; low incidence of hypoglycemia; can be used as monotherapy

ALPHA-GLUCOSIDASE INHIBITORS

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose (Precose®) 25 mg TID</td>
<td>Delays intestinal absorption of carbohydrates</td>
</tr>
<tr>
<td>Migliitol (Glyset®) 25 mg TID</td>
<td>Works on postprandial blood glucose</td>
</tr>
</tbody>
</table>

ALPHA-GLUCOSIDASE INHIBITORS ADVANTAGES

- Does not cause hypoglycemia as monotherapy
- HbA1c lowering potential
  - Low moderate 0.5-0.8%
- Weight neutral
- Low risk of systemic adverse effects
- Acarbose possible role in prediabetes
**ALPHA-GLUCOSIDASE INHIBITORS**

**Side Effects**
- Abdominal pain
- Flatulence
- Diarrhea

Avoid in patients with GI problems: cirrhosis, IBD, bowel obstruction, digestion or absorption disorders
- Do not use SCr >2.0 mg/dl or CrCl <25 ml/min
- Do not use with advanced liver disease

Hypoglycemia: must use glucose tablets/gel or skim milk to correct
low blood sugar avoid sucrose or complex Carbohydrates

**Monitoring**
- Postprandial Glucose 2 hours after meals
  - Take it with the first bite of a main meal
  - Skip a meal skip a dose

**Counseling**
- Liver function tests (LFTs)
  - Dark urine, pale stools, yellowing of skin and whites of eyes, nausea, vomiting, tiredness, stomach pain, loss of appetite
- SCr and CrCl
  - Educate on signs and symptoms of hypoglycemia
  - Treat ONLY with glucose tablets not juice or soda

**ALPHA-GLUCOSIDASE INHIBITORS PLACE IN THERAPY**

Tom is a 65 year old male patient with PMH of DM x 5 years, hyperlipidemia, stent placement in 2010. His current medication regiment includes: Metformin 1000 mg po BID, empagliflozin10 mg po daily, ramipril 10 mg po daily, plavix 75 mg po daily. At his follow up his labs are as follows: HBA1C 7.3%, fasting plasma glucose 95 mg/dl, Post prandial glucose range 200-250 mg/dl, K+ 4.7 mg/dl, Scr 1.0 mg/dl. His physician would like to optimize Tom’s post prandial glucose levels without an additional risk of hypoglycemia

AACE algorithm recommends these agents to be used in combination with metformin or as monotherapy; low-moderate HbA1c lowering effect; works well on postprandial blood sugars; low incidence of hypoglycemia; acarbose possible role in prediabetes; GI adverse effects may limit use

**SULFONYLUREAS**

**Agents**
- Glyburide (Diabeta®, Micronase®) 2.5-20 mg/day
- Glimepiride (Amaryl®) 1-8 mg/day
- Glipizide (Glucotrol® 5-40 mg/day, Glucotrol XL® 5-20 mg/day)

**Mechanism of action**
- Stimulates the pancreas to secrete insulin

**Advantages and Disadvantages**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long efficacy experience</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>HbA1C lowering effect high 1-2%</td>
<td>Weight Gain</td>
</tr>
<tr>
<td>Effective in combination</td>
<td>Diarrhea, nausea</td>
</tr>
<tr>
<td>Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>
**SULFONYLUREAS PRECAUTIONS**

- Do not use with sulfa allergy
- Associated with secondary failure
  - Pancreas may burn out
- Hypoglycemia risk is high
  - Alcohol increases risk of hypoglycemia
  - Elderly patients
  - Renal/hepatic failure
    - Use glipizide with renal insufficiency
- Risk for cardiovascular mortality

**SULFONYLUREAS**

**Monitoring** | **Counseling**
--- | ---
FPG and HbA1c | Do not skip meals
Take with food or meal
Glipizide 30 minutes prior
Missed dose: Skip dose and take next dose with meal
Renal function
SCr, CrCl | Do not crush or chew extended-release tablets
Part of the extended-release tablet may end up in your stool
Signs and symptoms of Hypoglycemia | Avoid alcohol may cause a low blood sugar
May cause weight gain and GI side effects

**HYPOGLYCEMIA SYMPTOMS**

- Symptoms: shakiness, sweating, hunger, nervousness, palpitations, fatigue
- Consume 15-20 grams of glucose or simple carbohydrates
- Recheck your blood glucose after 15 minutes
- If hypoglycemia continues, repeat
- Once glucose is controlled eat a meal with fat and protein

**SULFONYLUREA PLACE IN THERAPY**

Gale is a 59 year old female with diagnosed with DM 12 months ago. Gale has no PMH. She is on metformin 2g/day and implemented life style changes. Today she is back for follow up with a HbA1c of 8.5%. She has good renal function and is compliant with her medications. What would be a good addition to her therapy?

- Sulfonylureas are effective in combination when patient has failed metformin; They are low in cost. HbA1C lowering effect is 1-2%. May be used as add on or monotherapy. Not the best option for an elderly patients with poor renal function –higher risk of hypoglycemia.

**THIAZOLIDINEDIONE (GLITAZONES)**

- Pioglitazone (Actos®) 15-45 mg/day and rosiglitazone (Avandia®) 4-8 mg/day
- MOA
  - Decreases hepatic glucose output
  - Insulin sensitizer
- Advantages
  - HbA1C lowering potential moderate-high 1-1.5%
  - No risk of hypoglycemia
  - Useful in metabolic syndrome
  - Pioglitazone may prevent a second stroke or TIA
  - Pioglitazone has a favorable lipid profile and may reduce CVD in patients with insulin resistance and cerebrovascular disease
  - Neutral GI adverse effects

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THIAZOLIDINEDIONE (GLITAZONES) ADVERSE EFFECTS

- Weight gain (fluid retention and fat redistribution)
- Peripheral and macular edema
- Increased risk of developing or exacerbating HF
- Increased fracture risk
- Anemia
- Bladder cancer risk
  - With high dose pioglitazone >45 mg or >12 months
- Hepatotoxicity
  - If ALT >3 times ULN and/or bilirubin >2 times ULN STOP the medication

THIAZOLIDINEDIONE (GLITAZONES)

<table>
<thead>
<tr>
<th>Effects on Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>HDL ↑ LDL ↑ Triglycerides</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects on the Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use glitazones in patients with Class III/IV heart failure</td>
</tr>
<tr>
<td>May increase the risk of peripheral edema</td>
</tr>
</tbody>
</table>

May 21, 2007 meta-analysis in NEJM, Rosiglitazone increased the risk of cardiovascular events.

Not restricted as of 2014

THIAZOLIDINEDIONE (GLITAZONES)

Monitoring Counseling

<table>
<thead>
<tr>
<th>HbA1c, FPG</th>
<th>Take with or without food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function tests (LFTs)</td>
<td>Watch for fluid build up</td>
</tr>
<tr>
<td>Urinalysis (blood in urine)</td>
<td>Report painful urination/blood in urine</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>Increases ovulation</td>
</tr>
<tr>
<td>Anemia</td>
<td>May increase the risk of broken bones</td>
</tr>
</tbody>
</table>

THIAZOLIDINEDIONE (GLITAZONES) PLACE IN THERAPY

Tom is a 64 year old male with a PMH of thyroid cancer, Hyperlipidemia, HTN and renal disease (due to excessive NSAID use). He was diagnosed with DM 6 years ago and has been compliant with metformin and glipizide XL. His current A1c is 7.2%. His renal function has been steadily declining with a recent CrCl of 25 ml/min. Tom’s physician would like to discontinue his metformin and is asking for suggestions for alternative oral therapy.

Glitazones are effective in combination when patients failed/cant tolerate metformin; HbA1c lowering effect 1-1.5%; low cost; only anti-diabetic agent to directly reduce insulin resistance; useful in fatty liver patients; low risk of hypoglycemia; pioglitazone also may prevent a second stroke or TIA and CVD (favorable lipid effect); can be used as monotherapy or in combination. Low risk of hypoglycemia.

MEGLITINIDES

- Nateglinide (Starlix™) and repaglinide (Prandin™)
- Dosing
  - Repaglinide 0.5 – 4 mg with each meal (requires dose titration)
  - Take 30 minutes prior to a meal
  - Nateglinide 60-120 mg with each meal
  - Take 1 to 30 minutes prior to a meal
  - Skip a meal? → skip a dose
  - Low carb meal → skip a dose
  - No renal dose adjustment required
- MOA
  - Glucose dependent insulin secretagogue
  - Works on postprandial blood sugars
MEGLITINIDES

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Side effects/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>Hypoglycemia (less than sulfonylureas)</td>
</tr>
<tr>
<td>Short duration of action</td>
<td>Weight gain</td>
</tr>
<tr>
<td>HbA1c lowering effect 0.5-1%</td>
<td>Must take with every meal</td>
</tr>
<tr>
<td>Safe in elderly if taken properly</td>
<td>Low carbohydrate meal skip dose</td>
</tr>
<tr>
<td>Safe in renal impairment</td>
<td>Miss a meal skip the dose</td>
</tr>
<tr>
<td>Synergistic effect with metformin</td>
<td>Drug interactions:</td>
</tr>
<tr>
<td>May be used with glitazones</td>
<td></td>
</tr>
</tbody>
</table>

MEGLITINIDES PLACE IN THERAPY

Tina is a 66 year old female with DM x 10 years. She has been stable on metformin and sitagliptin until recently. Her glucose diary has been trending post prandial glucose levels of about 240 mg/dl. She has no other medical history and her SCr is 1.2. She is determined to continue oral drug therapy and her physician would like to optimize her regimen. She is reluctant to implement life style changes and continues to consume carbs and fats. She also enjoys flexibility with her drug regimen. What would be the best recommendation for Tina?

Effective in combination when patient has failed metformin; moderate effect on HbA1c; Low cost; works BEST on postprandial blood sugars; less hypoglycemia than sulfonylureas if taken properly; safe in elderly and people who have renal impairment; good add on therapy, can be used as monotherapy for patients with postprandial elevated blood sugars; not for those on sulfonylureas.

SGLT2 INHIBITORS

**MOA:** Block 90% of glucose reabsorption in the kidneys and increases glucose excretion into the urine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Renal Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana®)</td>
<td>Start with 100mg/day</td>
<td>May increase to 300 mg/day if eGFR ≥ 60 ml/min</td>
</tr>
<tr>
<td>May increase to 300 mg/day if needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga®)</td>
<td>Start with 5 mg/day</td>
<td>May increase to 10 mg/day</td>
</tr>
<tr>
<td>Empagliflozin (Jardiance®)</td>
<td>Start with 10 mg/day</td>
<td>May increase to 25 mg/day</td>
</tr>
<tr>
<td>Ertugliflozin (Steglatro®)</td>
<td>Start with 5 mg daily</td>
<td>May increase to 15 mg daily</td>
</tr>
</tbody>
</table>

**Side Effects Precautions**

- Urinary tract/fungal infections: Hypotension
- Symptomatic hypotension: Diuretic use
- Euglycemic ketoacidosis: eGFR < 60 avoid dapa and Ertu
- Increase serum creatinine: eGFR < 45 avoid cana and emp 
- Hyperkalemia
- Hypomagnesemia
- Hyperphosphatemia
- Decreased BMD: Risk of bladder cancer with dapagliflozin
- Increased risk of amputations with canagliflozin
- Ketoacidosis
SGLT 2 INHIBITORS: FRACTURE AND AMPUTATION RISK

- **CANVAS trial**
  - Data suggests increase amputation risk
  - Black box warning
  - Fracture risk observed
  - No mechanical explanation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputations (toes, feet or legs)</td>
<td>1.97 (1.41-2.75)</td>
</tr>
<tr>
<td>Fractures</td>
<td>1.26 (1.04-1.52)</td>
</tr>
</tbody>
</table>


SGLT2 INHIBITORS ADVANTAGES

- HbA1c lowering potential moderate 0.8-1.2%
- Weight loss
- Decreases blood pressure
- Low incidence of hypoglycemia
- Empagliflozin and dapagliflozin has potential cardiovascular and renal benefits
- Canagliflozin has potential cardiovascular benefit
- Ertugliflozin unknown if there is cardiovascular benefit

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose regularly and HbA1c</td>
<td>Blood pressure, Kidney function</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>Urine analysis if signs or symptoms of infection</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Urine ketones, CKD signs and symptoms</td>
</tr>
<tr>
<td>Foot exam for signs of infection</td>
<td>Foot exam for signs of infection</td>
</tr>
</tbody>
</table>
| Tidal on the morning | \()
| Hypotension: dizziness, lightheadedness, fainting | Hypertension: muscle weakness, tingling |
| Hyperkalemia: muscle weakness, tingling | Genital yeast infection in females and males |
| Genital yeast infection in females and males | Urinary tract infection: painful urination, difficult |
| Urinary tract infection: painful urination, difficult | urination, increased frequency of urination |
| Diabetic ketoacidosis: abdominal pain, nausea, vomiting, fatigue, problems breathing, sweet smell on breath | Foot infections |

SGLT2 INHIBITORS PLACE IN THERAPY

Don is an overweight 62 year old male with a 5 year history of DM. PMH include HTN (BP 140/87 mmHg) and MI 3 years ago with stent placement. He is currently on metformin 2 g/day and sitagliptin 100 mg daily. He does not watch his diet and mostly eats out. He started to walk more often. He has good renal and liver function. His latest A1c is 7.7%. His physician would like to initiate another oral medication with minimal hypoglycemia risk and with proven cardiovascular safety. What is the best recommendation at this time?

- Effective in combination when patient has failed metformin; HbA1c lowering effect 0.8-1.2%; lowers blood pressure maybe useful in patients with elevated BP; useful in obese patients causes weight loss; low incidence of hypoglycemia; empagliflozin, dapagliflozin, canagliflozin have potential cardiovascular benefit; empag and dapa have renal benefits (slows progression of renal disease)
GLUCAGON LIKE PEPTIDE (GLP-1) AGONISTS

• MOA
  - Decrease postprandial glucagon secretion
  - Increase insulin sensitivity
  - Help regulate gastric emptying
  - Enhance glucose dependent insulin secretion

• FDA Indications
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 DM
  - Liraglutide
    - To reduce the risk of major adverse cardiovascular events in adults with type 2 DM

GLP1: PLEIOTROPIC EFFECTS

- Low risk of hypoglycemia
- Increased incretin effect
- Increased satiety
- Decreased glucagon
- FPG
- PPG

GLP1: DOSING AND A1C DECREASE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Titrate</th>
<th>Dose Adjustments</th>
<th>A1C Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide IR</td>
<td>5 mcg BID in 60 mins of a meal</td>
<td>5 to 10 mcg after 1 month</td>
<td>QID (30/60 mcg/min: use caution; QID &gt; 30 mcg/min: not recommended)</td>
<td>1%</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>2 mg once weekly</td>
<td>N/A</td>
<td>N/A</td>
<td>1.3%</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>0.6 mg once daily</td>
<td>1.2 mg once daily per week</td>
<td>Renal &amp; hepatic impairment: use caution — limited experience</td>
<td>1.5%</td>
</tr>
<tr>
<td>Salmaglutide (Symlin)</td>
<td>0.5 mg</td>
<td>1 mg once weekly</td>
<td>Renal impairment: monitor patients more closely with CrCl 10-30 mL/min, hepatic impairment: not studied</td>
<td>1.6%</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>0.75 mg once weekly</td>
<td>1.5 mg once weekly if inadequate response</td>
<td>Renal impairment: use caution when initiating or escalating dose, hepatic impairment: use with caution</td>
<td>1.5%</td>
</tr>
<tr>
<td>Semaglutide (Ozempic)</td>
<td>0.5 mg</td>
<td>1 mg once weekly</td>
<td>Renal impairment: Monitor renal function in patients with renal impairment</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

GLP 1 AGONISTS

Contraindications
- History of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2*

Black Box Warning
- Medullary thyroid carcinoma and multiple endocrine neoplasia syndrome type 2

Adverse Effects
- Nausea, vomiting, diarrhea, decreased appetite, weight loss, pancytopenia

Monitoring
- FBG, A1C, SCr, BUN

Interactions
- Agents that induce hypoglycemia
- GLP-1 agonists may reduce rate of absorption of orally administered drugs

Clinical pearls
- Low hypoglycemia risk
- Injectable
- Avoid in patients with gastroparesis
- May need to reduce dose of insulin and/or secretagogues
- Can be used in patients with type 2 DM

APPLYING CURRENT GUIDELINES

- Priority for patients requiring a large A1C reduction
- Consider for patients on metformin
- Use in patients with high risk of hypoglycemia
- Overweight patients
  - Semaglutide
  - Liraglutide
  - Liraglutide preferred in patients with established CVD

GLP 1 AGONISTS: SUMMARY OF USE

- Adults with Type 2 Diabetes
  - Avoid History of CVD
  - Pregnant/nursing females

- No restriction in adults > 65 y/o
  - May cause harm to fetus

- Obese/overweight patient
  - Not approved for children at this time

CVD—cardiovascular disease
**COMORBIDITIES IN T2DM**

- All Patients with DM
  - Hypertension: 74%
  - Dyslipidemia: 73%
  - Dyslipidemia and HTN: 56%


**ACC/AHA HYPERTENSION GUIDELINES NOV 2017**

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120–129 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130–139 mm Hg</td>
<td>or 80–89 mm Hg</td>
</tr>
<tr>
<td>Stage 1</td>
<td>≥140 mm Hg</td>
<td>or ≥90 mm Hg</td>
</tr>
</tbody>
</table>

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure, and SBP systolic blood pressure.

**DIABETES AND HYPERTENSION**

- Increased risk of microvascular and macrovascular complications
  - Heart failure
  - Stroke
  - Myocardial infarctions
  - Nephropathy
  - Retinopathy
  - Coronary artery disease (3 fold increase)


**PHARMACOTHERAPY FOR HYPERTENSION**

- ADA
  - ACE-I or ARB is first line therapy
- American Heart Association (AHA)
  - Thiazide
  - ACE-I or ARB
- Patients with diabetes and CKD
- Patients with diabetes are at increased risk of nephropathy, coronary artery disease and heart failure


**SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL (SPRINT)**

Examine effect of intensive high blood pressure treatment vs standard treatment

*Randomized Controlled Trial*
*Target Systolic BP*

**SPRINT OUTCOMES**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Intensive Events</th>
<th>Standard Events</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>243 (1.55)</td>
<td>319 (2.19)</td>
<td>0.75 (0.64, 0.89)</td>
</tr>
<tr>
<td>All MI</td>
<td>97 (0.65)</td>
<td>116 (0.78)</td>
<td>0.83 (0.64, 1.09)</td>
</tr>
<tr>
<td>Non-MI ACS</td>
<td>40 (0.27)</td>
<td>40 (0.27)</td>
<td>1.00 (0.64, 1.55)</td>
</tr>
<tr>
<td>All Stroke</td>
<td>62 (0.41)</td>
<td>70 (0.47)</td>
<td>0.89 (0.63, 1.25)</td>
</tr>
<tr>
<td>All HF</td>
<td>62 (0.41)</td>
<td>100 (0.67)</td>
<td>0.62 (0.45, 0.84)</td>
</tr>
<tr>
<td>CVD Death</td>
<td>37 (0.25)</td>
<td>65 (0.43)</td>
<td>0.57 (0.38, 0.85)</td>
</tr>
</tbody>
</table>
PATIENT CASE: HYPERTENSION

- Patient Name: MT  Sex: M  Age: 61  Height: 5'10”  Weight: 213 lb
- PMH: Diabetes x 5 years  Social Hx: Works as electrician, smokes occasionally
- Ethnicity: Caucasian
- OTC: aspirin 82mg daily, APAP PRN
- Vital signs: BP 154 /92 mmHg, HR: 76, RR 16
- Medication Profile
  - Glipizide XI 10 mg daily
  - Tramadol 50 mg BID
  - Metformin 750 mg BID

What is this patient’s treatment goal?

< 130/80 mmHg

What non pharmacological option should this patient implement?

Decrease salt intake
DASH diet
Exercise
Weight loss

What pharmacologic option would you recommend to treat this patient’s hypertension?

ACEI: class of choice since this patient is diabetic
Obtain K+ levels prior to initiation of therapy

PATIENT CASE

What is this patient’s treatment goal?

< 130/80 mmHg

What non pharmacological option should this patient implement?

Decrease salt intake
DASH diet
Exercise
Weight loss

What pharmacologic option would you recommend to treat this patient’s hypertension?

Nephropathy: Diabetic Kidney Disease

- Diabetes
  - Leading cause of end stage renal disease
  - Affects 20-40% of patients with diabetes
  - Usually asymptomatic for many years
  - Slowly progressive
  - Early indicator
  - Elevated urine albumin-creatinine ratio (UACR)
- Screening for diabetic kidney disease
  - Once yearly
  - All T2DM patients
  - All patients with comorbid HTN

New Treatment Options for T2D - A Focus on Glycemic Control and Lowering CV Risk
**TREATMENT FOR NEPHROPATHY**

- Optimize glucose control
  - Reduces risk and slows progression of nephropathy
- BP Control
  - <130/80 mmHg
  - ACE inhibitors or ARBs except during pregnancy
- No need to reduce dietary protein

**AACE/ACE LIPID TARGETS IN PATIENTS WITH T2DM**

<table>
<thead>
<tr>
<th>HIGH RISK (T2DM, no other risk factors, age &lt;40)</th>
<th>VERY HIGH RISK (T2DM + ASCVD risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dl) &lt;100</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dl) &lt;130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>TG (mg/dl) &lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>TC/HDL-C &lt;3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Apo B (mg/dl) &lt;80</td>
<td>&lt;80</td>
</tr>
<tr>
<td>LDL-P (nmol/L) &lt;1200</td>
<td>&lt;1000</td>
</tr>
</tbody>
</table>


**DYSLIPIDEMIA TREATMENT IN DIABETIC PATIENT**

- Moderate or high intensity statin
- Based on presence of ASCVD risk factor vs overt ASCVD
- ASCVD risk factors include:
  - LDL-C ≥100 mg/dl
  - HTN
  - Smoking
  - Overweight/obese
  - Family history of ASCVD
  - Overt ASCVD
  - Previous CV events or acute coronary syndrome

**APPROACH TO TREATMENT**

- Focus on reduction of cardiovascular risk in 4 statin benefit groups
  - Clinical ASCVD
  - LDL >190 mg/dL
  - Age 40-75 years + diabetes + LDL 70-189 mg/dL
  - Age 40-75 + ASCVD 10 year risk of >7.5%
- A new viewpoint on goals of treatment
  - Global risk assessment for primary prevention
  - Safety recommendations

**STATIN INTENSITY THERAPIES**

**High Intensity (decrease LDL-C ≥50%)**
- Atorvastatin 40-80 mg
- Rosuvastatin 20-40 mg
- Patients with ACS and LDL=50 mg/dL who could not tolerate high dose statins
  - Use moderate intensity statin and ezetimibe

**Moderate Intensity (decrease LDL-C 30-50%)**
- Atorvastatin 10-20 mg
- Rosuvastatin 5-10 mg
- Simvastatin 20-40 mg
- Pravastatin 40-80 mg
- Lovastatin 40 mg
- Fluvastatin XL 80 mg
- Fluvastatin 40 mg Q12
- Pitavastatin 2-4 mg

**STATIN PRACTICE POINTS**

- Statin dose adjustments
  - Change the intensity of statin therapy based on individual response, side effects/tolerability, LDL-C levels
- Monitoring parameters with statins
  - Baseline: 6 weeks after start of therapy
  - Yearly if stable (on an individual basis)
  - Muscle pain, liver function tests, renal function
- Drug interactions with statins
  - Avoid with grapefruit juice
  - Better to take at bedtime
- Contraindications
  - Pregnancy

New Treatment Options for T2D - A Focus on Glycemic Control and Lowering CV Risk
STATINS AND INCREASED RISK OF T2DM

- Risk is dose related
- Finland Study
  - 9000 white males without diabetes followed for 6 years
  - Statin group had 46% increased risk of developing DM
- MOA
  - Can increase insulin resistance
  - Impair the ability of the pancreas to secrete insulin


Should I recommend a statin for my patient?

- If a patient may benefit from a statin start one
- Risk is outweighed by statins' cardiovascular benefits
- Put the risk into a perspective
  - One more case of diabetes compared to about 9 fewer cardiovascular events for every 1000 patients on a statin/year
  - Suggest pravastatin
  - If only moderate LDL lowering is needed and diabetes risk is a concern
  - May DECREASE diabetes risk

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular Disease and Risk management.

ANTIPLATELET THERAPY IN DIABETIC PATIENTS

- Important adjunct to decrease platelet aggregation
- Primary prevention strategy in T2DM patients with increased cardiovascular risk (10 year risk >10%)
- ≥ 50 years old with 1 additional risk factor
  - Hypertension
  - Smoking
  - Hyperlipidemia
  - Family history of premature ASCVD
  - Albuminuria
- Recommend aspirin dose 75-162 mg/day
  - Clopidogrel 75 mg/day if aspirin allergy
- Combination aspirin and clopidogrel for one year after ACS
- Secondary prevention: Hx of CVD regardless of age

DIABETES AND HEART FAILURE

- 50% of patients with type 2 diabetes may develop heart failure
- Medications to avoid in heart failure
  - Thiazolidinedione
  - Saxagliptin may increase hospitalizations
  - Alogliptin and sitagliptin no association with heart failure

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular Disease and Risk management.

DIABETES AND OBESITY

- ~90% of patients with DM are overweight or obese
  - Overweight/obesity associated with poor glycemic control
- Obesity increases risk for:
  - Obstructive sleep apnea (independent risk factor for T2DM)
  - Increases insulin resistance
  - Metabolic syndrome
  - Hypertension
  - Cardiovascular disease

Previous improvements plus:
  - T2DM Prevention
  - With T2DM: better glycemic control and less medication use
  - Improvement in urinary incontinence, mobility and joint pain
  - Improvement in CV risk factors

Previous improvements plus:
  - Reduction in CVD mortality and all cause mortality

≥5% weight loss
≥10% weight loss
≥15% weight loss

DOES GREATER WEIGHT LOSS EQUAL GREATER REDUCTION IN CVD?

- Greater weight loss = greater reduction in CVD?
  - Unclear
  - Large trial that followed patients for 13 years that sustained 6% weight loss did not have better outcomes
  - No mortality benefit
  - BP reduction, control of DM and decrease in lipids = long term benefit
  - Do not discourage pharmacotherapy for weight loss


IMPORTANCE OF CARDIOVASCULAR HEALTH IN T2DM PATIENTS

- Genetics
- Environmental
- Choice
- Adipocyte Phenotype Shift
- Core Defect
- Whole body
- Pancreas
- T2DM
- CV Events
- 1.6% annual CV events
- Risk for CV events starts 10 years before diagnosis of T2DM

CARDIOVASCULAR DISEASE IN DIABETIC PATIENTS

- Leading cause of morbidity and mortality in diabetes
  - CVD is a comorbidity in ~1/3 of patients with diabetes
  - CVD cause of death in 50% of patients with diabetes, versus ~20% without diabetes
- Diabetes is a significant risk factor for CVD
  - Atherosclerosis, angina, MI, stroke
- Common conditions coexisting with type 2 diabetes (HTN, dyslipidemia): risk factors for ASCVD
  - Benefits are observed if you control CVD risk factors

FDA GUIDANCE FOR INDUSTRY: EVALUATING CV RISK FOR NEW DRUGS FOR T2DM 2008

- To demonstrate CV safety for new medications
  - 2/3 of new phase trials should establish an independent committee to blindly adjudicate CV endpoints
  - CV mortality, MI, Stroke, hospitalizations for ACS
  - Include patients in the trials with higher CV risk (advanced disease, elderly, with renal impairment)
  - Provide meta analysis across trials
  - Include sub group assessment (age, sex, race)
  - Longer trial duration

COULD HYPOGLYCEMIC AGENTS ALTER THE RISK OF CARDIOVASCULAR HEALTH IN T2DM PATIENTS?

- Metformin: UKPDS trial
  - Monotherapy usage was shown to have a lower mortality compared to sulfonylureas
- Saxagliptin: SAVOR trial
  - 14000 patients followed for 2 years
  - Neutral results from a cardiovascular events standpoint
  - Increase in heart failure
- Sitagliptin-TECOS trial
  - Stable CHD patients followed for 3 years
  - No increase in HF
  - No benefit from cardiovascular standpoint

CARDIOVASCULAR TRIALS FOR SGLT2 INHIBITORS

- Published Studies
  - EMPA-REG (Empagliflozin)
  - CANVAS (Canagliflozin)
  - DECLARE - TIMI-58 (Dapagliflozin)
- Upcoming Trials
  - VERTIS CV (Ertugliflozin)
  - Cardiovascular outcomes in diabetic patients with vascular disease
  - DAPA-HF (Dapagliflozin)
  - Randomized, placebo-controlled Phase III trial evaluating the effects of dapagliflozin on reducing cardiovascular (CV) death or worsening HF in patients with preserved ejection fraction (HFrEF) with or without diabetes
  - EMPEROR
  - Trial to Evaluate Efficacy and Safety of Olacoxib Daily Dapagliflozin 10 mg Compared to Placebo, in Patients With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF)
EMPA-REG OUTCOME TRIAL
- Randomized, placebo controlled
  - Empagliflozin (10 mg and 25 mg) vs. placebo
  - 42 countries, 590 sites
  - N=7020 adults with T2DM AND established CVD
  - BMI<45 kg/m², eGFR > 30 ml/min
  - Those not on glucose lowering drugs (12 weeks prior to randomization) A1C 7%-9%
  - On glucose lowering agents (12 weeks prior to randomization) A1C 7%-10%
  - Patients were allowed to be on HTN and hyperlipidemia therapy
  - 80% of patients were on statins
  - 70% on ACEI
- Primary endpoint
  - Nonfatal stroke, CV death, nonfatal MI
- Results
  - Hospitalizations for Heart Failure
    - Decreased in empagliflozin arm (HR=0.72)
    - May be due to diuretic properties of this drug
  - Death from any cause
    - 32% risk reduction (P<0.001)
    - Cumulative incidence of primary outcome
      - 34% risk reduction (P<0.04 (superiority))
    - Nephropathy
      - 39% relative risk reduction

CANAGLIFLOZIN CARDIOVASCULAR ASSESSMENT (CANVAS)
- Randomized, placebo controlled
  - N=10,142 patients with T2DM AND high cardiovascular risk
  - Canagliflozin 300 mg or 100 mg
  - Mean follow up-188 days
  - Mean patient age: 63 years
  - Percentage female: 36%
  - Mean duration of diabetes: 13.5 years
  - 65.6% of participants had history of cardiovascular disease
- Results
  - Decreased primary outcome (CV death, nonfatal MI, or nonfatal stroke)-P=0.02
  - Decreased hospitalizations for heart failure
  - Decreased albuminuria progression
  - Amputations 6.3 (cana) vs. 3.4 (placebo)/1000 patient years P<0.05
  - CV death 11.6 (cana) vs. 12.8 (placebo)

DAPAFLIZIN AND CARDIOVASCULAR OUTCOME IN TYPE 2 DIABETES (DECLARE-TIMI-58)
- Randomized, placebo controlled
  - Dapagliflozin 10 mg (n = 8,582); placebo (n = 8,578)
  - Duration of follow-up: 4.2 years
  - 37% female, 79% white, 13.5% Asian
  - Median duration of DM: 10.5 years
  - HbA1c: 8.3%
  - Established atherosclerotic CVD: 40.7%
  - Statins: 75%
- Results
  - Primary outcome of major adverse cardiac events (MACE) for dapagliflozin vs. placebo: 8.8% vs. 9.4%, p < 0.001
  - CV death or heart failure (HF) hospitalization: 4.9% vs. 5.8%, p = 0.005
  - Decrease in end-stage renal disease, or death due to renal or CV causes: 4.3% vs. 5.6%, p = 0.01
  - Amputations: 1.4% vs. 1.3%, p = 0.53

SGLT2 INHIBITORS AND REDUCTION IN CV RISK
- Data from CANVAS and EMPA-REG allay concerns that these drugs worsen diabetic nephropathy
- Small drop in GFR soon after initiation
- Sustained improvement in long term renal outcomes vs

SGLT2 INHIBITORS IN PATIENTS WITH RENAL DISEASE
- Moderate renal impairment and reduced GFR diminish SGLT2 inhibitor efficacy
- May increased adverse effects
- May cause acute renal injury
- ACE inhibitors, NSAID, HF patients

<table>
<thead>
<tr>
<th>SGLT2 Inhibitor</th>
<th>GFR (mL/min)</th>
<th>≥ 60</th>
<th>≥ 45 but &lt; 60</th>
<th>≥ 30 but &lt; 45</th>
<th>&lt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>All doses</td>
<td>100 mg only</td>
<td>Not recommended</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>All doses</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>All doses</td>
<td>All doses</td>
<td>Not recommended</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>All doses</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Contraindicated</td>
<td></td>
</tr>
</tbody>
</table>

SGLT2 INHIBITORS: RENAL BENEFITS?
- Data from CANVAS and EMPA-REG allay concerns that these drugs worsen diabetic nephropathy
- Small drop in GFR soon after initiation
- Sustained improvement in long term renal outcomes vs

<table>
<thead>
<tr>
<th>Study</th>
<th>New/worsening diabetic nephropathy</th>
<th>Albuminuria progression</th>
<th>Composite end point*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG</td>
<td>0.83 (0.73-0.93)</td>
<td>0.62 (0.54-0.70)</td>
<td>0.54 (0.46-0.63)</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Not reported</td>
<td>0.73 (0.67-0.79)</td>
<td>0.60 (0.54-0.77)</td>
</tr>
</tbody>
</table>

* Need for renal replacement, death from renal disease, doubling of serum creatinine with a eGFR ≤ 45 ml/min.
CARDIOVASCULAR TRIALS FOR GLP1 RECEPTOR AGONISTS

- ELIXA (Lixisenatide)
- EXSCEL (Exanitide ER)
- LEADER (Liraglutide)
- SUSTAIN -6 (Semaglutide)

EXSCEL Trial (Exenatide)
- Randomized, Placebo controlled
- N=14,752 followed for 3.2 years
- Primary composite outcome
  - First occurrence of death from cardiovascular causes
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Results
  - Neutral effects

ELIXA (Lixisenatide)
- Objective: evaluate the cardiovascular mortality and morbidity of lixisenatide in patients with type 2 diabetes mellitus at high cardiovascular risk due to a recent acute coronary event
- Placebo N = 3,034, Lixisenatide N = 3,034
- Results
  - Death from cardiovascular causes (P=0.85)
  - Hospitalization for HF (P=0.25)
  - Neutral effects

SUSTAIN -6 (Semaglutide)
- Randomized, placebo controlled
- N=3297 , followed for 104 weeks
- Primary composite outcome
  - First occurrence of death from cardiovascular causes
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Results
  - Less cardiovascular events and death in semaglutide group (P=0.04)
  - Less nephropathy (P=0.02)

LEADER TRIAL
- Randomized, placebo controlled
- CV safety of Liraglutide in T2DM
- Primary outcome
  - Nonfatal stroke, CV death, nonfatal MI
- N=9030 (96.8% of patients completed the trial)
- Inclusion criteria
  - A1C > 7% on oral agents +/- insulin or NO treatment
- Results
  - Primary outcome
    - 13% risk reduction in nonfatal MI, nonfatal stroke, CV death (P=0.01 superiority)

GLP 1 AGONIST: CARDIOVASCULAR OUTCOMES IN TYPE 2 DM PATIENTS

GLP1 RECEPTOR AGONISTS IN PATIENTS WITH RENAL DISEASE

CV RISK REDUCTION: CLASS EFFECT OR AGENT SPECIFIC?

- SGLT2 Inhibitors
  - To date only benefit seen is with empagliflozin, dapagliflozin and canagliflozin
  - Other SGLT2 inhibitors in trials
    - Ertugliflozin
    - Standards of care recommends SGLT2 inhibitor class
- GLP1 agonists
  - Variability among agents in the class
  - Did A1C affect the results?
  - Does not seem to impact cardiovascular outcomes in trials

SEVERE HYPOGLYCEMIA AND MORTALITY

PATHOPHYSIOLOGIC CARDIOVASCULAR CONSEQUENCES OF HYPOGLYCEMIA

Hemodynamic changes
- Heart workload
- Contractility
- Output

Inflammation
- CRP
- VEGF
- IL

Endothelial dysfunction

Rhythm abnormalities
- Heart rate variability

Sympathoadrenal response
- Noradrenaline

Blood Coagulation Abnormality

Factor VIII

Vasodilation

IL

VEGF

CRP

Macrophage activation

Platelet activation

Hypoglycemia


HYPOGLYCEMIA
- Defined as BG < 70 mg/dl
- < 54 mg/dl is defined as clinically important hypoglycemia
- Symptoms
  - Confusion, anxiety
  - Distress, feeling shaky
  - Hunger
  - Headaches
  - Irritability
  - Pounding heart, racing pulse
  - Pale skin
  - Sweating, trembling
  - Weakness

COMPREHENSIVE PATIENT PLAN
- A1c goals
- CV event reduction
- Renal disease prevention
- Low risk of hypoglycemia

QUESTIONS?