

**Main Line Health Physician Partners**

# **Type 2 Diabetes Mellitus Treatment Guidelines**

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## **FIRST-LINE THERAPY (NON-PHARMACOLOGIC)**

### **1) Lifestyle Management should be advocated at:**

- a) time of diagnosis
- b) at the time of each visit until adequately controlled and then annually
- c) addition of new complicating factors
- d) at times of transition of care
- e) when treatment regimen is adjusted.

### **2) Diabetes Education:**

- a) Offer referral to a comprehensive diabetic education program provided by a diabetic nurse educator and nutritionist.
- b) Emphasis on healthful eating. The Mediterranean Diet, DASH diet and predominately plant-based diets have demonstrated effectiveness.

### **3) Physical Activity Recommendations:**

- a) Pertains to most adults approved to engage in physical activity
- b) Moderate to vigorous aerobic physical activity of 150 minutes or more per week spread over at least 3 days per week with no more than 2 consecutive days without activity.
- c) Two to three sessions of resistance exercise per week on nonconsecutive days.

### **4) Smoking Cessation:**

- a) Includes smoking, e-cigarettes and smokeless tobacco
- b) Advise all patients not to use cigarettes, other tobacco products or e-cigarettes.
- c) Consider referral for smoking cessation classes and/or MLHS cessation resources.

### **5) Alcohol Consumption**

- a) Instruct to minimize frequency of use and volume.
- b) Advise not to consume alcohol beyond moderation as defined by current standards.

**If A1c Remains Above Goal**



## **METFORMIN (FIRST LINE PHARMACOLOGIC THERAPY)**

- 1) Initial pharmacologic choice for T2DM**
- 2) Immediate Release OR Extended Release can be utilized (avoid Glumetza or its generic form).**
- 3) ER formulation especially useful when patients experience GI intolerance.**
- 4) Contraindications & Precautions**
  - a) GFR <30 metformin needs to be stopped
  - b) Don't initiate metformin if GFR <45
  - c) Assess risk/benefit of continuing metformin if GFR moves to <45 while on therapy and consider a 50% dose decrease.
- 5) Dosing**
  - a) Immediate Release metformin (500 mg, 850 mg, 1,000 mg)
    - i) If GFR >45 AND a1c <8.0%: initiate IR metformin 500 mg PO with dinner; in 2 weeks titrate to 500 mg PO BID with meals, then recheck a1c 8-12 weeks later
    - ii) If GFR >45 AND a1c >8.0% OR GFR >45 and a1c not controlled on 500 mg PO BID titrate to 500 mg PO am and 1,000 mg PO pm; in 2 weeks titrate to 1,000 mg PO BID with meals and recheck a1c 8-12 weeks later.
  - b) Extended Release metformin (500 mg, 750 mg) (avoid Glumetza or its generic form)
    - i) If GFR >45 AND a1c <8.0%: initiate 500 mg PO with dinner and slowly titrate to 2,000 mg if a1c >8.0%
- 6) Monitoring**
  - a) Check a1c at least twice per year if <8.0% and Q 3 months if a1c >8.0%
  - b) Serum creatinine annually
  - c) Vitamin B12 annually (5-10% of patients receiving metformin develop B12 def. within 5 years).
- 7) Iodinated Contrast Material Protocol**
  - a) Hold metformin in patients with a GFR <60 and are about to receive iodinated IV contrast (not gadolinium) anytime within the next two days. Prescribers are encouraged to recheck the GFR 48 hours post procedure and resume if GFR is stable and >30.
- 8) Strategies to Consider for Patients Experiencing Metformin Intolerance**
  - a) Utilize a low starting dose of 250 mg PO daily with largest meal

- b) Titrate the dosage in the lowest possible amount (250 mg instead of 500 mg)
- c) Slow down the rate of dose titration
- d) Return to the last tolerated dose for at least 2 weeks and then gradually advance.
- e) Consider allowing the patient to titrate at their own pace with careful monitoring
- f) Consider changing to ER formulation (often added cost; avoid Glumetza or its generic form)
- g) Consider checking for *H. pylori* infection (results in higher rates of GI intolerance)

**If A1c Remains Above Goal**



**Select from the following the most appropriate treatment plan**

## **T2DM WITH ASCVD PREDOMINATING**

- a) Unless contraindicated, choose GLP-1 RA OR SGLT2i**
- b) Optimize First Line Non-Pharmacologic Therapy & Metformin**
- c) GLP-1 RA**
  - i) Can be added to existing regimen of lifestyle modification and metformin OR utilized as 3<sup>rd</sup> pharmacologic agent with an SGLT2i, metformin and lifestyle modification**
  - ii) Contraindications & Precautions**
    - (1) Not to be used if history of pancreatitis
    - (2) Not to be used in patients with history of medullary thyroid cancer
    - (3) Not to be used in patients with history of multiple endocrine neoplasia 2 (MEN-2)
    - (4) Exercise caution when using GLP-1 RA class in patients with familial thyroid cancer
  - iii) ASCVD Usage Preference & Initial Dosing**
    - (1) liraglutide > semaglutide > dulaglutide > exenatide\* or lixisenatide\*
    - (2) liraglutide (Victoza): 0.6 mg SC daily x 7 days then titrate 1.2 mg SC daily (a lower starting dose of 0.3 mg with a slower titration schedule can be considered if GI intolerance is a concern)
    - (3) semaglutide (Ozempic): 0.25 mg SC weekly x 4 wks. then titrate 0.5 mg SC weekly
    - (4) dulaglutide (Trulicity): 0.75 mg SC weekly
    - (5) \*exenatide (Bydureon/Byetta) & lixisenatide (Adlyxin): given their comparative lack of efficacy with CVD and weight loss, it is appropriate not to consider exenatide or lixisenatide unless formulary requires.
- d) SGLT2i**
  - i) Can be added to existing regimen of lifestyle modification and metformin OR utilized as 3<sup>rd</sup> pharmacologic agent with a GLP-1 RA, metformin and lifestyle modification**
  - ii) Contraindications & Precautions**
    - (1) Ketoacidosis concerns: assess risk of ketoacidosis (alcoholism, calorie restriction and pancreatic disease) and discontinue the drug in situations known to

predispose to ketoacidosis (e.g. prolonged fasting due to illness or surgery)

- (2) Exercise caution when using SGLT2i class in high fall risk patients with known low bone mass; patients with history of frequent UTI's
- (3) Caution with NSAIDs, ACEIs, ARBs, diuretics due to dehydration risk and hypotension or kidney injury.
- (4) SGLT2i class not recommended if GFR <45
- (5) FDA Canagliflozin (Invokana) warning for lower limb amputation exists in patients with established CVD or at risk of CVD. Before starting assess for risk (prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers). Discontinue if these occur.
- (6) Canagliflozin (Invokana) max dose = 100 mg when GFR 45-59.

iii) **ASCVD Usage & Initial Dosing**

- (1) Canagliflozin or Empagliflozin
- (2) Canagliflozin (Invokana): 100 mg PO once daily
- (3) Empagliflozin (Jardiance): 10 mg PO once daily

iv) **Basal Insulin OR TZD**

- (1) Consider when patient intolerance for GLP-1 RA and/or SGLT2i exists OR when patient requires additional pharmacological treatment to control a1c.

**e) Basal Insulin**

**f) TZD**

i) **Contraindications & Precautions**

- (1) Contraindicated in patients with NYHA Class I-IV Heart Failure, active bladder cancer or a history of bladder cancer.

ii) **Initial Dosing**

- (1) Pioglitazone can be initiated in patients without history of heart failure at 15mg or 30 mg PO once daily.

**g) SU**

i) **Usage Preference**

- (1) Usually recommended as last option for treatment of T2DM
- (2) If utilized, glimepiride or glipizide are suggested

ii) **Contraindications & Precautions**

- (1) Risk of hypoglycemia exists
- (2) Contraindicated in patients with history of DKA

iii) **Initial Dosing**

- (1) The usual starting dose of glimepiride is 1-2 mg PO once daily, administered with breakfast or the first main meal.
- (2) The recommended starting dose of glipizide is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.



## **T2DM WITH HF OR CKD PREDOMINATING**

- a) Unless contraindicated, choose SGLT2i > GLP-1 RA**
- b) Optimize First Line Non-Pharmacologic Therapy & Metformin**
- c) SGLT2i**
  - i) 1<sup>st</sup> choice to add to metformin if no contraindications exist**
  - ii) Contraindications & Precautions**
    - (1) Ketoacidosis concerns: assess risk of ketoacidosis (alcoholism, calorie restriction and pancreatic disease) and discontinue the drug in situations known to predispose to ketoacidosis (e.g. prolonged fasting due to illness or surgery)
    - (2) Exercise caution when using SGLT2i class in high fall risk patients with known low bone mass; patients with history of frequent UTI's
    - (3) Caution with NSAIDs, ACEIs, ARBs, diuretics due to dehydration risk and hypotension or kidney injury.
    - (4) SGLT2i class not recommended if GFR <45
    - (5) FDA Canagliflozin (Invokana) warning for lower limb amputation exists in patients with established CVD or at risk of CVD. Before starting assess for risk (prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers). Discontinue if these occur.
    - (6) Canagliflozin (Invokana) max dose = 100 mg when GFR 45-59.
  - iii) CKD or HF Usage & Initial Dosing**
    - (1) Canagliflozin or Dapagliflozin or Empagliflozin
    - (2) Canagliflozin (Invokana): 100 mg PO once daily
    - (3) Dapagliflozin (Farxiga): 5 mg PO once daily in am
    - (4) Empagliflozin (Jardiance): 10 mg PO once daily
- d) GLP-1 RA**
  - i) Recommended as add on to the dual therapy of a SGLT2i class medication plus metformin OR with metformin if SGLT2i class is not tolerated or contraindicated.**
  - ii) Contraindications & Precautions**
    - (1) Not to be used if history of pancreatitis
    - (2) Not to be used in patients with history of medullary thyroid cancer

- (3) Not to be used in patients with history of multiple endocrine neoplasia 2 (MEN-2)
- (4) Exercise caution when using GLP-1 RA class in patients with familial thyroid cancer

**iii) ASCVD Usage Preference & Initial Dosing**

- (1) liraglutide > semaglutide > dulaglutide > exenatide\* or lixisenatide\*
- (2) liraglutide (Victoza): 0.6 mg SC daily x 7 days then titrate 1.2 mg SC daily (a lower starting dose of 0.3 mg with a slower titration schedule can be considered if GI intolerance is a concern)
- (3) semaglutide (Ozempic): 0.25 mg SC weekly x 4 wks. then titrate 0.5 mg SC weekly
- (4) dulaglutide (Trulicity): 0.75 mg SC weekly
- (5) \*exenatide (Bydureon/Byetta) & lixisenatide (Adlyxin): given their comparative lack of efficacy with CVD and weight loss, it is appropriate not to consider exenatide or lixisenatide unless formulary requires.

**e) Basal Insulin**

- i) Consider when patient intolerance for GLP-1 RA and/or SGLT2i exists OR when patient requires additional pharmacological treatment to control a1c.

**f) TZD**

**i) Contraindications & Precautions**

- (1) Contraindicated in patients with NYHA Class I-IV Heart Failure, active bladder cancer or a history of bladder cancer.

**ii) Initial Dosing**

- (1) Pioglitazone can be initiated in patients without history of heart failure at 15mg or 30 mg PO once daily.

**g) SU**

**i) Usage Preference**

- (1) Usually recommended as last option for treatment of T2DM
- (2) If utilized, glimepiride or glipizide are suggested

**ii) Contraindications & Precautions**

- (1) Risk of hypoglycemia exists
- (2) Contraindicated in patients with history of DKA

**iii) Initial Dosing**

- (1) The usual starting dose of glimepiride is 1-2 mg PO once daily, administered with breakfast or the first main meal.
- (2) The recommended starting dose of glipizide is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

## COMPELLING NEED FOR WEIGHT LOSS

- a) **Optimize First Line Non-Pharmacologic Therapy & Metformin**
- b) **Either GLP-1 RA OR SGLT2i can be considered as second pharmacologic agent**
- c) **GLP-1 RA**
  - i) **Contraindications & Precautions**
    - (1) Not to be used if history of pancreatitis
    - (2) Not to be used in patients with history of medullary thyroid cancer
    - (3) Not to be used in patients with history of multiple endocrine neoplasia 2 (MEN-2)
    - (4) Exercise caution when using GLP-1 RA class in patients with familial thyroid cancer
  - ii) **Usage Preference & Initial Dosing**
    - (1) liraglutide > semaglutide > dulaglutide > exenatide\* or lixisenatide\*
    - (2) liraglutide (Victoza): 0.6 mg SC daily x 7 days then titrate 1.2 mg SC daily (a lower starting dose of 0.3 mg with a slower titration schedule can be considered if GI intolerance is a concern)
    - (3) semaglutide (Ozempic): 0.25 mg SC weekly x 4 wks. then titrate 0.5 mg SC weekly
    - (4) dulaglutide (Trulicity): 0.75 mg SC weekly
    - (5) \*exenatide (Bydureon/Byetta) & lixisenatide (Adlyxin): given their comparative lack of efficacy with CVD and weight loss, it is appropriate not to consider exenatide or lixisenatide unless formulary requires.
- d) **SGLT2i**
  - i) **Contraindications & Precautions**
    - (1) Ketoacidosis concerns: assess risk of ketoacidosis (alcoholism, calorie restriction and pancreatic disease) and discontinue the drug in situations known to predispose to ketoacidosis (e.g. prolonged fasting due to illness or surgery)
    - (2) Exercise caution when using SGLT2i class in high fall risk patients with known low bone mass; patients with history of frequent UTI's
    - (3) Caution with NSAIDs, ACEIs, ARBs, diuretics due to dehydration risk and hypotension or kidney injury.

- (4) SGLT2i class not recommended if GFR <45
- (5) FDA Canagliflozin (Invokana) warning of lower limb amputation exists in patients with established CVD or at risk of CVD. Before starting assess for risk (prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers). Discontinue if these occur.
- (6) Canagliflozin (Invokana) max dose = 100 mg when GFR 45-59.

ii) **CVD Usage & Initial Dosing**

- (1) Canagliflozin or Empagliflozin
- (2) Canagliflozin (Invokana): 100 mg PO once daily
- (3) Empagliflozin (Jardiance): 10 mg PO once daily
- (4) Addition of the non-utilized drug class (GLP-1 RA OR SGLT2i) can be added as 3rd pharmacologic agent if a1c remains above goal.

e) **Bariatric Surgery or Supervised Medical Weight Loss Consultation**

- i) If patient meets BMI criteria, bariatric surgical consultation should be considered for patients that have an a1c remaining above goal despite utilizing lifestyle modification, maximum tolerated dose of metformin, GLP-1 RA and SGLT2i OR the patient is intolerant or non-adherent to the prescribed therapy.
- ii) Supervised medical weight loss program can also be considered if patient not eligible or appropriate for bariatric surgery.

## PATIENT COST IS A MAJOR CONCERN

- a) **Optimize First Line Non-Pharmacologic Therapy & Metformin**
- b) **Either a TZD or SU can be considered as the next add on pharmacologic agent.**
  - i) TZD can be utilized as the second pharmacologic agent to metformin.
  - ii) **Contraindications & Precautions**
    - (1) Contraindicated in patients with NYHA Class I-IV Heart Failure, active bladder cancer or a history of bladder cancer.
  - iii) **Initial Dosing**
    - (1) Pioglitazone can be initiated in patients without history of heart failure at 15mg or 30 mg PO once daily.
    - (2) SU can be utilized as the second pharmacologic agent to metformin.
  - iv) **Usage Preference**
    - (1) Usually recommended as last option for treatment of T2DM
    - (2) If utilized, glimepiride or glipizide are suggested
  - v) **Contraindications & Precautions**
    - (1) Risk of hypoglycemia exists
    - (2) Contraindicated in patients with history of DKA
  - vi) **Initial Dosing**
    - (1) The usual starting dose of glimepiride is 1-2 mg PO once daily, administered with breakfast or the first main meal.
    - (2) The recommended starting dose of glipizide is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.
- c) **Basal Insulin**
  - i) Consider when patient intolerance for TZD or SU exists OR when patient requires additional pharmacological treatment to control a1c.

## **METFORMIN INTOLERANT PATIENTS**

### **a) Strategies to Consider for Patients Experiencing Metformin Intolerance**

- i) Utilize a low starting dose of 250 mg PO daily with largest meal
- ii) Titrate the dosage in the lowest possible amount (250 mg instead of 500 mg)
- iii) Slow down the rate of dose titration
- iv) Return to the last tolerated dose for at least 2 weeks and then gradually advance.
- v) Consider allowing the patient to titrate at their own pace with careful monitoring
- vi) Consider changing to ER formulation (often added cost) (avoid Glumetza or its generic form)
- vii) Consider checking for H. pylori infection (results in higher rates of GI intolerance)

### **b) Optimize First Line Non-Pharmacologic & implement pharmacologic therapies GLP-1 RA > SGLT2i > TZD or basal insulin > SU**

#### **c) GLP-1 RA**

##### **i) Contraindications & Precautions**

- (1) Not to be used if history of pancreatitis
- (2) Not to be used in patients with history of medullary thyroid cancer
- (3) Not to be used in patients with history of multiple endocrine neoplasia 2 (MEN-2)
- (4) Exercise caution when using GLP-1 RA class in patients with familial thyroid cancer

##### **ii) Usage Preference & Initial Dosing**

- (1) liraglutide > semaglutide > dulaglutide > exenatide\* or lixisenatide\*
- (2) liraglutide (Victoza): 0.6 mg SC daily x 7 days then titrate 1.2 mg SC daily (a lower starting dose of 0.3 mg with a slower titration schedule can be considered if GI intolerance is a concern)
- (3) semaglutide (Ozempic): 0.25 mg SC weekly x 4 wks. then titrate 0.5 mg SC weekly
- (4) dulaglutide (Trulicity): 0.75 mg SC weekly
- (5) \*exenatide (Bydureon/Byetta) & lixisenatide (Adlyxin): given their comparative lack of efficacy with CVD and

weight loss, it is appropriate not to consider exenatide or lixisenatide unless formulary requires.

**d) SGLT2i**

i) Recommended as add on to the GLP-1 RA class medication OR first line if GLP-1 RA class is not tolerated or contraindicated.

**ii) Contraindications & Precautions**

- (1) Ketoacidosis concerns: assess risk of ketoacidosis (alcoholism, calorie restriction and pancreatic disease) and discontinue the drug in situations known to predispose to ketoacidosis (e.g. prolonged fasting due to illness or surgery)
- (2) Exercise caution when using SGLT2i class in high fall risk patients with known low bone mass; patients with history of frequent UTI's
- (3) Caution with NSAIDs, ACEIs, ARBs, diuretics due to dehydration risk and hypotension or kidney injury.
- (4) SGLT2i class not recommended if GFR <45
- (5) FDA Canagliflozin (Invokana) warning for lower limb amputation exists in patients with established CVD or at risk of CVD. Before starting assess for risk (prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers). Discontinue if these occur.
- (6) Canagliflozin (Invokana) max dose = 100 mg when GFR 45-59.

**iii) CVD Usage & Initial Dosing**

- (1) Canagliflozin or Empagliflozin
- (2) Canagliflozin (Invokana): 100 mg PO once daily
- (3) Empagliflozin (Jardiance): 10 mg PO once daily

**e) Basal Insulin OR TZD**

i) Consider when patient intolerance for GLP-1 RA and/or SGLT2i exists OR when patient requires additional pharmacological treatment to control a1c.

**f) TZD**

**i) Contraindications & Precautions**

- (1) Contraindicated in patients with NYHA Class I-IV Heart Failure, active bladder cancer or a history of bladder cancer.

**ii) Initial Dosing**

- (1) Pioglitazone can be initiated in patients without history of heart failure at 15mg or 30 mg PO once daily.



**g) SU**

**i) Usage Preference**

- (1) Usually recommended as last option for treatment of T2DM
- (2) If utilized, glimepiride or glipizide are suggested

**ii) Contraindications & Precautions**

- (1) Risk of hypoglycemia exists
- (2) Contraindicated in patients with history of DKA

**iii) Initial Dosing**

- (1) The usual starting dose of glimepiride is 1-2 mg PO once daily, administered with breakfast or the first main meal.
- (2) The recommended starting dose of glipizide is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

## MEDICATION CLASS INFORMATION

- a) Metformin Class Information (First Line Pharmacologic Therapy)
  - i) Initial pharmacologic choice for T2DM
    - (1) Immediate Release OR Extended Release can be utilized (avoid Glumetza or its generic form)
    - (2) ER formulation especially useful when patients experience GI intolerance.
  - ii) Contraindications & Precautions
    - (1) GFR <30 metformin needs to be stopped
    - (2) Don't initiate metformin if GFR <45
    - (3) Assess risk/benefit of continuing metformin if GFR moves to <45 while on therapy and consider a 50% dose decrease.
  - iii) Dosing
    - (1) Immediate Release metformin (500 mg, 850 mg, 1,000 mg)
      - (a) If GFR >45 AND a1c <8.0%: initiate IR metformin 500 mg PO with dinner; in 2 weeks titrate to 500 mg PO BID with meals, then recheck a1c 8-12 weeks later
      - (b) If GFR >45 AND a1c >8.0% OR GFR >45 and a1c not controlled on 500 mg PO BID titrate to 500 mg PO am and 1,000 mg PO pm; in 2 weeks titrate to 1,000 mg PO BID with meals and recheck a1c 8-12 weeks later.
    - (2) Extended Release metformin (500 mg, 750 mg) (avoid Glumetza or its generic form)
      - (a) If GFR >45 AND a1c <8.0%: initiate 500 mg PO with dinner and slowly titrate to 2,000 mg if a1c >8.0%
  - iv) Monitoring
    - (1) Check a1c at least twice per year if <8.0% and Q 3 months if a1c >8.0%
    - (2) Serum creatinine annually
    - (3) Vitamin B12 annually (5-10% of patients receiving metformin develop B12 def. within 5 years).
  - v) Iodinated Contrast Material Protocol
    - (1) Hold metformin in patients with a GFR <60 and are about to receive iodinated IV contrast (not gadolinium) anytime within the next two days. Prescribers are

encouraged to recheck the GFR 48 hours post procedure and resume if GFR is stable and  $>30$ .

vi) Strategies to Consider for Patients Experiencing Metformin Intolerance

- (1) Utilize a low starting dose of 250 mg PO daily with largest meal
- (2) Titrate the dosage in the lowest possible amount (250 mg instead of 500 mg)
- (3) Slow down the rate of dose titration
- (4) Return to the last tolerated dose for at least 2 weeks and then gradually advance.
- (5) Consider allowing the patient to titrate at their own pace with careful monitoring
- (6) Consider changing to the ER formulation (often added cost) (avoid Glumetza or its generic form)
- (7) Consider checking for *H. pylori* infection (results in higher rates of GI intolerance)

b) GLP-1 RA Class Information

- i) Mechanism of action - (primary): enhance glucose dependent insulin secretion; (secondary): slow gastric emptying, decrease post prandial glucagon.
- ii) Benefits
  - (1) When ASCVD exists, GLP-1 RA OR SGLT2i class can be used as 1st choice to add to metformin if no contraindications exist due to reduced CVD risk.
  - (2) Preferred for CVD with CKD
  - (3) Weight loss
  - (4) No hypoglycemia
  - (5) Can be safely used in combination with SGLT2i class if a1c remains uncontrolled
- iii) Contraindications & Precautions
  - (1) Not to be used if history of pancreatitis
  - (2) Not to be used in patients with history of medullary thyroid cancer
  - (3) Not to be used in patients with history of multiple endocrine neoplasia 2 (MEN-2)
  - (4) Exercise caution when using GLP-1 RA class in patients with familial thyroid cancer
- iv) ASCVD Usage Preference & Initial Dosing
  - (1) liraglutide > semaglutide > dulaglutide > exenatide\* or lixisenatide\*
  - (2) liraglutide (Victoza): 0.6 mg SC daily x 7 days then titrate 1.2 mg SC daily (a lower starting dose of 0.3 mg with a slower titration schedule can be considered if GI intolerance is a concern)
  - (3) semaglutide (Ozempic): 0.25 mg SC weekly x 4 wks. then titrate 0.5 mg SC weekly
  - (4) dulaglutide (Trulicity): 0.75 mg SC weekly
  - (5) \*exenatide (Bydureon/Byetta) & lixisenatide (Adlyxin): given their comparative lack of efficacy with CVD and weight loss, it is appropriate not to consider exenatide or lixisenatide unless formulary requires.

c) SGLT2i Class Information

- i) Mechanism of action – reduce glucose by increasing urinary glucose excretion at the proximal tubule
- ii) Benefits
  - (1) When ASCVD exists, GLP-1 RA OR SGLT2i class can be used as 1st choice to add to metformin if no contraindications exist due to reduced CVD risk.
  - (2) Preferred 2nd line agent in HF patients and CKD patients if no contraindications exist
  - (3) No hypoglycemia
  - (4) Weight loss
  - (5) Can be safely used in combination with GLP-1 RA class if needed
- iii) Contraindications & Precautions
  - (1) Ketoacidosis concerns: assess risk of ketoacidosis (alcoholism, calorie restriction and pancreatic disease) and discontinue the drug in situations known to predispose to ketoacidosis (e.g. prolonged fasting due to illness or surgery)
  - (2) Exercise caution when using SGLT2i class in high fall risk patients with known low bone mass; patients with history of frequent UTI's
  - (3) Caution with NSAIDs, ACEIs, ARBs, diuretics due to dehydration risk and hypotension or kidney injury.
  - (4) SGLT2i class not recommended if GFR <45
  - (5) FDA Canagliflozin (Invokana) warning for lower limb amputation exists in patients with established CVD or at risk of CVD. Before starting assess for risk (prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers). Discontinue if these occur.
  - (6) Canagliflozin (Invokana) max dose = 100 mg when GFR 45-59.
- iv) ASCVD Usage & Initial Dosing
  - (1) Canagliflozin or Empagliflozin
  - (2) Canagliflozin (Invokana): 100 mg PO once daily
  - (3) Empagliflozin (Jardiance): 10 mg PO once daily
  - (4) CKD or HF Usage & Initial Dosing
  - (5) Canagliflozin or Dapagliflozin or Empagliflozin
  - (6) Canagliflozin (Invokana): 100 mg PO once daily

- (7) Dapagliflozin (Farxiga): 5 mg PO once daily in am
- (8) Empagliflozin (Jardiance): 10 mg PO once daily

d) DPP-4 Inhibitors Class Information

- i) Mechanism of action – inhibits DPP-4, an enzyme that deactivates chemicals that help to regulate glucose by stimulating insulin production.
- ii) Usage Preference
  - (1) Not highly effective and have a limited role in treatment of T2DM
- iii) Benefits
  - (1) Can be used as initial monotherapy in metformin intolerant patients or if metformin is contraindicated due to CKD.
- iv) Contraindications & Precautions
  - (1) No CVD or CKD benefits
  - (2) HF warning – increased risk of hospitalization
  - (3) Concern for pancreatitis
  - (4) Use of GLP1/DPP4 medications in combination is currently not supported
  - (5) Requires monitoring of GFR Q3mos if GFR <45 and Q6mos if GFR >45.
- v) Medications
  - (1) Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta)

e) TZD Class Information

i) Mechanism of Action

(1) Decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.

ii) Initial Dosing

(1) Pioglitazone can be initiated in patients without history of heart failure at 15mg or 30 mg PO once daily.

iii) Contraindications & Precautions

(1) Contraindicated in patients with NYHA Class I-IV Heart Failure, active bladder cancer or a history of bladder cancer.



f) SU Class Information

i) Mechanism of Action

(1) The primary mechanism of action of SU is stimulating release of insulin from functioning pancreatic beta cells.

ii) Usage Preference

(1) Usually recommended as last option for treatment of T2DM

(2) If utilized, glimepiride or glipizide are suggested

iii) Contraindications & Precautions

(1) Risk of hypoglycemia exists

(2) Contraindicated in patients with history of DKA

iv) Initial Dosing

(1) The usual starting dose of glimepiride is 1-2 mg PO once daily, administered with breakfast or the first main meal.

(2) The recommended starting dose of glipizide is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg