Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors Are They Equal?

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Learning Objectives

1. Explain the kidney's role in glucose homeostasis and regulation.
2. Discuss the mechanism of action of SGLT2 inhibitors in type 2 diabetes mellitus (T2DM).
3. Assess the safety of SGLT2 inhibitors.
4. Compare the efficacy of the SGLT2 inhibitors available in the US.

Diabetes Background

A. Prevalence
   a. In 2012, 29.1 million Americans or 9.3% of the U.S. population had diabetes. Of the 29.1 million, 21.0 million were diagnosed and 8.1 million were undiagnosed.[1] It is estimated that the prevalence of diabetes will increase to 36.0 million Americans in 2030.[2]

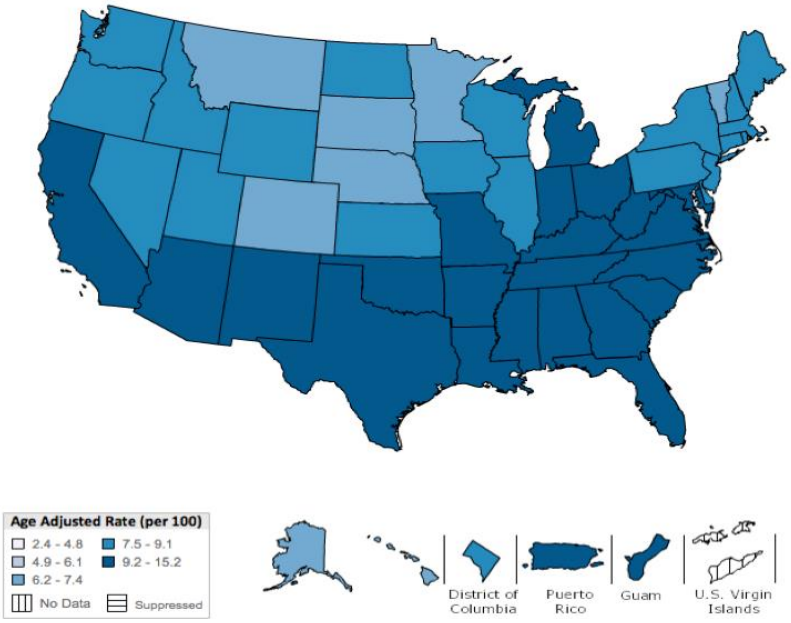


Figure 1: Diagnosed Diabetes, Age Adjusted Rate (per 100), Adults[1]

B. Morbidity and Mortality[1]
   a. Diabetes is associated with microvascular complications including retinopathy, nephropathy, and neuropathy.
      i. Glucose-lowering is associated with a reduction in microvascular complications.[3-5]
   b. Macrovascular complications include cardiovascular disease (CVD) and stroke.
      i. During 2003-2006, CVD death rates were about 1.7 times higher among adults aged 18 years or older with diagnosed diabetes than among adults without diagnosed diabetes.
      ii. In 2010, hospitalization rates for heart attack were 1.8 times higher among adults aged 20 years or older with diagnosed diabetes than among adults without diagnosed diabetes
      iii. In 2010, hospitalization rates for stroke were 1.5 times higher among adults with diagnosed diabetes aged 20 years or older compared to those without diagnosed diabetes.
   c. Diabetes was the 7th leading cause of death in the U.S. in 2010, with 69,071 death certificates listing it as the underlying cause of death, and a total of 234,051 death certificates listing diabetes as an underlying or contributing cause of death.

C. Economic Burden[1]
    a. In 2012, the total medical cost for diabetes was $245 billion (direct medical costs of $176 billion and indirect medical costs of $69 billion).

Pathophysiology & Treatment

A. T2DM is a condition characterized by insulin resistance which leads to a progressive insulin secretory defect.[6]
B. There are multiple treatment guidelines available for the management of T2DM. Examples include the American Diabetes Association (ADA), the American Association of Clinical Endocrinologist (AACE), and the European Association for Diabetes (EASD). The ADA is commonly referred to in the U.S.
C. ADA HbA_{1c} goals[6]
    a. The HbA_{1c} goal for most patients is <7%.
    b. A more strict HbA_{1c} goal of <6.5% is recommended for patients without significant hypoglycemia who are only treated with lifestyle changes or metformin, have a long life expectancy with a short duration of diabetes, and have no significant CVD.
    c. A less stringent HbA_{1c} goal of <8% is recommended for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complication(s), extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain.
D. Non-pharmacologic therapy[6]
    a. A variety of diet plans such as the Mediterranean-style, Dietary Approaches to Stop Hypertension (DASH)-style, plant-based, low-fat, and low-carb have been effective in diabetes. Patients should receive individualized medical nutrition therapy, preferably by a dietician. Macronutrients should be individualized per patient, but carbohydrate intake should be monitored, and the main sources should come from vegetables, fruit, legumes, dairy, and whole grain products. Patients should consume 14 g fiber/1,000 kcal and avoid high glycemic foods. Group diabetes education programs that offer nutrition therapy or individualized education sessions have reported HbA_{1c} reductions of 0.5-2% in T2DM.[7-10]
    b. Modest weight loss of 2-8 kg may provide clinical benefit, especially in those patients in the early phases of diabetes. Redmon et al. showed that a 5-kg weight loss at 1 year was associated with a HbA_{1c} reduction of 0.4% in T2DM patients.[11]
    c. Diabetic patients should perform at least 150 minutes per week of moderate-intensity aerobic physical activity, divided over at least 3 days per week. It is also recommended to perform resistance training at least twice per week. Structured exercise interventions for at least 8 weeks have been shown to reduce HbA_{1c} on average by 0.66% in T2DM.[12]

E. Pharmacologic therapy

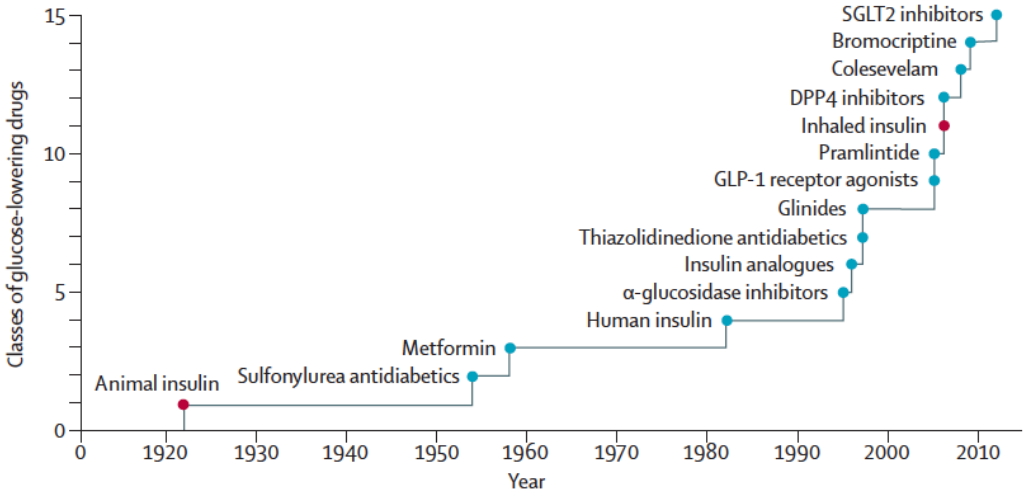


Figure 2: Antihyperglycemic Therapy over the Years[13]

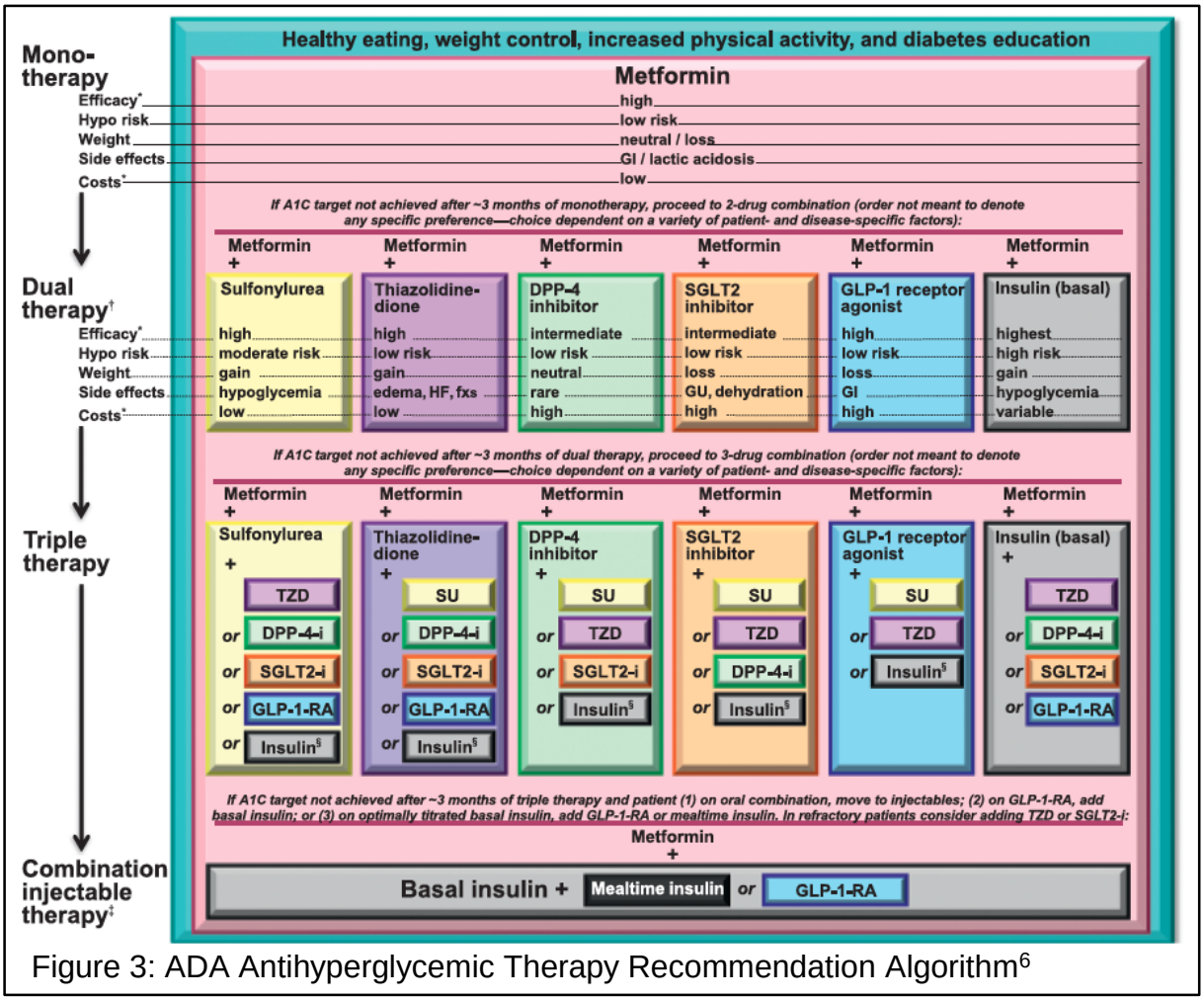


Figure 3: ADA Antihyperglycemic Therapy Recommendation Algorithm[6]

Kidneys' Role in Glucose Regulation

A. The kidneys are responsible for regulating glucose homeostasis through glucose utilization, gluconeogenesis, glucose reabsorption by SGLTs, and glucose transporters (GLUTs).[14]
    a. Under normal physiological conditions in healthy individuals, the kidneys reabsorb all filtered glucose (~ 160-180 g of glucose daily). This occurs by both SGLTs and GLUTs. The SGLT2 co-transporter is responsible for the majority of renal glucose reabsorption. It is located at the luminal brush border of the early proximal tubule, where it couples the active transport of sodium and glucose. Glucose is then reabsorbed back into systemic circulation by GLUT at the basolateral membrane. Any remaining glucose is reabsorbed by SGLT1 at the distal proximal tubule.

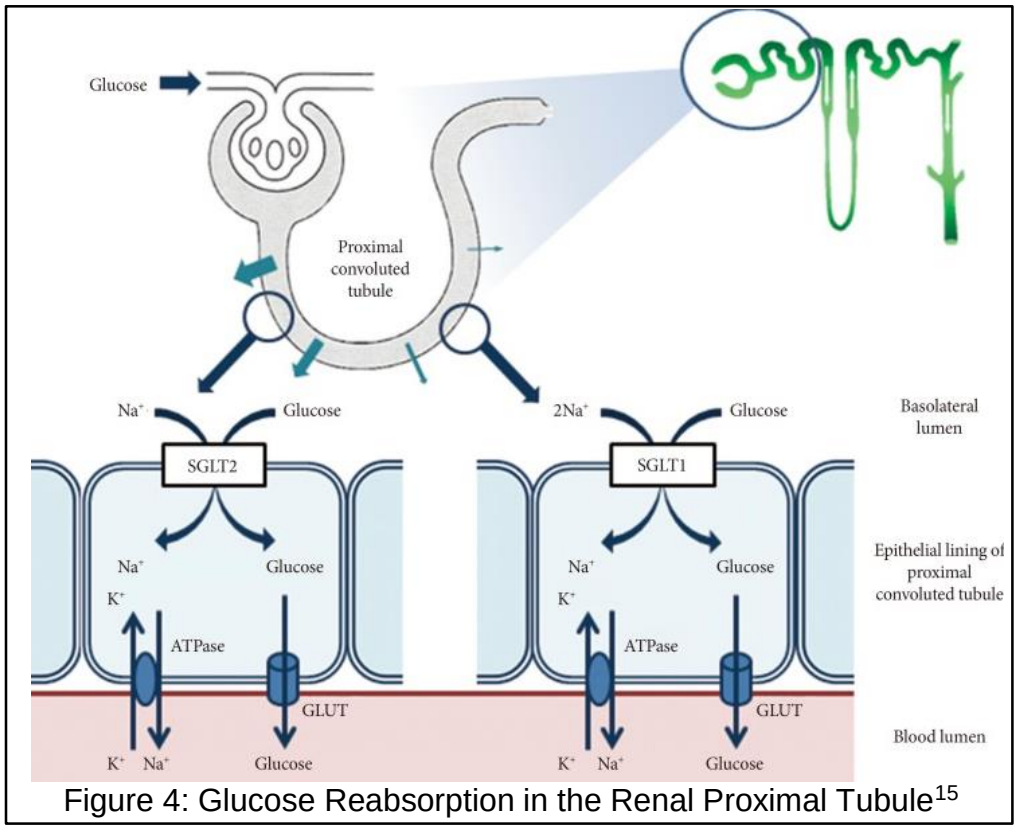


Figure 4: Glucose Reabsorption in the Renal Proximal Tubule[15]

    b. The renal threshold for glucose excretion (RT_G) is the plasma glucose concentration at which glucose reabsorption capacity is exceeded and glucosuria occurs. RT_G may be elevated in T2DM due to up regulation of SGLT and GLUT expression, thereby increasing renal tubular reabsorption of glucose and contributing to worsening hyperglycemia. Although there is some interindividual variability, RT_G is normally ~ 180 mg/dL in healthy individuals and is elevated up to 240 mg/dL in T2DM patients. It is also important to note that RT_G may be substantially lower in patients with impaired renal function.

SGLT2 Inhibitors

A. SGLT2 inhibitors' mechanism involves lowering the RT_G and inducing urinary glucose excretion (UGE) by inhibiting SGLT2, thereby decreasing plasma glucose.

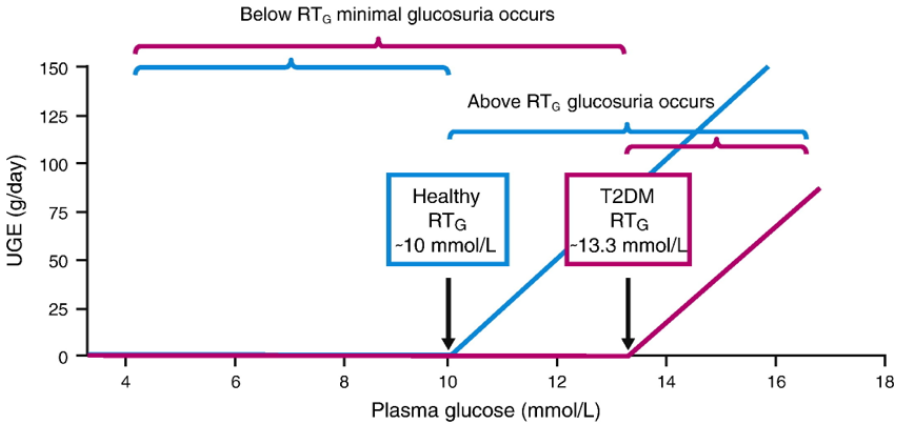


Figure 5: Linear Relationship between UGE and Plasma Glucose Concentration in Healthy Individuals and in T2DM Patients[14]

Table 1: FDA-Approved SGLT2 Inhibitors

	Canagliflozin (Invokana ®)[16]	**Dapagliflozin (Farxiga ®)[17]**	**Empagliflozin (Jardiance ®)[18]**
FDA Approval Date	3/29/13	1/8/14	8/1/14
Dosing (mg daily)	100-300	5-10	10-25
CrCl <60 mL/min (mg daily)	100	Use not recommended	No adjustment
CrCl <45 mL/min	Use not recommended		
Metabolism	UGT1A9 and UGT2B4	UGT1A9	UGT2B7, UGT1A3, UGT1A8,UGT1A9
Cost (30-day supply)	$374	$374	$361
UGE (g/day)	80-100	70	64-78

B. Advantages[14]
   a. Sustained improvements in glycemic control
   b. Sustained reductions in body weight
   c. Sustained reductions in systolic blood pressure (SBP)
   d. Insulin-independent mechanism of action
   e. Low risk of hypoglycemia
   f. Improvements in insulin sensitivity and β cell function

C. Disadvantages[14]
   a. Increased incidence of mild to moderate genital mycotic infections and UTIs
   b. Higher incidence of osmotic diuresis-related adverse effects (AE)
   c. Increased incidence of volume depletion-related AEs in elderly patients and in patients with eGFR <60 mL/min/1.73 m^2
   d. Slightly increased LDL

SGLT2 Inhibitors vs. Placebo

Table 2: Comparison of HbA_{1c} Reduction with SGLT2 Inhibitors vs. Placebo

Intervention	Study	Design	Population	HbA_{1c} ↓
Canagliflozin 300 mg	Yang XP, et al.[19]	Systematic review & meta-analysis (2 RCTs 12 & 26 weeks)	T2DM ≥4 years, 85.4-93.8 kg, 52.9-68.6 years old, average baseline HbA_{1c} ~8% (n=533)	-1.08%
Dapagliflozin 2.5 mg daily 5 mg daily 10 mg daily	Ferrannini E, et al.[20]	24-Week, phase III, placebo-controlled, double-blind, RCT	T2DM, average baseline HbA_{1c} ~8% (n=485)	 -0.58%, -0.77%, -0.89%
Empagliflozin 5 mg daily 10 mg daily 25 mg daily 50 mg daily	Kadowaki T, et al.[21]	12-Week, phase II, placebo-controlled, double-blind, RCT	T2DM, average baseline HbA_{1c} ~8% (n=547)	 -0.72%, -0.7%, -0.95%, -0.91%

RCT=randomized controlled trial

SGLT2 Inhibitors + Metformin vs. Metformin Monotherapy

Table 3: CANTATA-SU[22]	
Design	52-Week, double-blind, active-controlled, phase III, non-inferiority, multicenter, RCT
Setting	157 centers in 19 countries (54 North America, 39 Europe, 9 central or South American, remaining 55 spread out throughout the world)
Objective	Compare the efficacy and safety of canagliflozin with glimepiride in T2DM patients uncontrolled with metformin
Inclusion	18-80 years of age, T2DM, HbA_{1c} of 7-9.5%, receiving metformin therapy (≥2,000 mg or ≥1,500 mg daily if higher dose not tolerated) ≥10 weeks
Exclusion	≥1 Severe hypoglycemic episode within 6 months, repeated fasting plasma glucose (FPG) or fasting self-monitoring of blood glucose (SMBG) ≥15 mmol/L (≥270 mg/dL) during pretreatment phase, glomerular filtration rate (GFR) <55 mL/min/1.73m^2 (or <60 mL/min/1.73m^2 if based on restriction of metformin use in local label) or SCr ≥124 µmol/L (1.4 mg/dL) for ♂and ≥115 µmol/L (1.3 mg/dL) for ♀, given thiazolidinedione within 16 weeks before screening
Treatment	• Glimepiride up-titrated to 6 mg or 8 mg daily [mean max dose achieved=5.6 mg] (n=482) • Canagliflozin 100 mg daily (n=483) • Canagliflozin 300 mg daily (n=485) • + Metformin in all 3 arms Glycemic rescue therapy with pioglitazone if at max level of study drug titration and met specific criteria
Outcomes	Primary: HbA_{1c} Δ from baseline to week 52 Secondary: body weight Δ from baseline, proportion of patients with documented hypoglycemic episodes (glucose ≤3.9 mmol/L [≤70 mg/dL] with or without symptoms), severe hypoglycemic episodes (requiring assistance of another individual or resulting in seizure or loss of consciousness) Additional: achieving HbA1c <7% or 6.5%, FPG Δ, BP Δ, fasting plasma lipids Δ, body fat composition Δ in study subset
Statistics	Last observation carried forward (LCOF) analysis for intention-to-treat, secondary per-protocol analysis, analysis of covariance (ANCOVA) model, estimated least squares (LS) mean differences between groups and two-sided 95% CIs, non-inferiority margin of 0.3%

<table>
<tr><td>Results</td><td>
<u>Baseline characteristics</u>: similar, ♂ and ♀, mean age: 56, ethnicity: ~70% White and ~20% Asian, mean HbA_{1c}: 7.8%, mean BMI: 31 kg/m^2, median duration of T2DM: 5 years
<u>Primary</u>: HbA_{1c} Δ from baseline to week 52

Glimepiride -0.81%, canagliflozin 100 mg -0.82%, canagliflozin 300 mg -0.93%
Canagliflozin 100 mg non-inferior to glimepiride – LS mean difference -0.01% (95% CI -0.11 to 0.09)
Canagliflozin 300 mg was superior to glimepiride – LS mean difference -0.12% (95% CI -0.22 to -0.02)

<table>
<tr><th>Secondary & additional endpoints</th><th>Glimepiride</th><th>Canagliflozin 100 mg</th><th>Canagliflozin 300 mg</th></tr>
<tr><td>Body weight Δ (kg)</td><td>0.7</td><td>-3.7</td><td>-4</td></tr>
<tr><td>Documented hypoglycemia (%)</td><td>34</td><td>6</td><td>5</td></tr>
<tr><td>Severe hypoglycemia (%)</td><td>3</td><td><1</td><td><1</td></tr>
<tr><td>Achieving HbA_{1c} goal of <7%</td><td>56%</td><td>54%</td><td>60%</td></tr>
<tr><td>Achieving HbA_{1c} goal of <6.5%</td><td>31%</td><td>26%</td><td>31%</td></tr>
<tr><td>FPG Δ (mmol/L) [mg/dL]</td><td>-1.02 [-18.36]</td><td>-1.35 [-24.3]</td><td>-1.52 [-27.36]</td></tr>
<tr><td>SBP Δ (mmHg)</td><td>0.2</td><td>-3.3</td><td>-4.6</td></tr>
<tr><td>DBP Δ (mmHg)</td><td>-0.1</td><td>-1.8</td><td>-2.5</td></tr>
<tr><td>TG Δ (mmol/L) [mg/dL]</td><td>-0.01 [-0.39]</td><td>-0.22 [-8.49]</td><td>-0.1 [-3.86]</td></tr>
<tr><td>LDL Δ (mmol/L) [mg/dL]</td><td>0.05 [1.9]</td><td>0.12 [4.6]</td><td>0.25 [9.65]</td></tr>
<tr><td>HDL Δ (mmol/L) [mg/dL]</td><td>-0.01 [-0.39]</td><td>0.08 [3.09]</td><td>0.10 [3.86]</td></tr>
</table>

Patients receiving rescue therapy: glipizide 11%, canagliflozin 100 mg 7%, canagliflozin 300 mg 5%

</td></tr>
<tr><td>Author's Conclusion</td><td>Canagliflozin is well tolerated with a greater HbA_{1c} reduction, significant weight loss, and lower risk of hypoglycemia compared to glimepiride over 52 weeks in T2DM patients on metformin therapy.</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><th>Side effects</th><th>Glimepiride</th><th>Canagliflozin 100 mg</th><th>Canagliflozin 300 mg</th></tr>
<tr><td>Genital infection ♀ (%)</td><td>2</td><td>11</td><td>14</td></tr>
<tr><td>Genital infection ♂ (%)</td><td>1</td><td>7</td><td>8</td></tr>
<tr><td>UTI (%)</td><td>5</td><td>6</td><td>6</td></tr>
<tr><td>Pollakiuria (%)</td><td><1</td><td>3</td><td>3</td></tr>
<tr><td>Polyuria (%)</td><td><1</td><td><1</td><td><1</td></tr>
<tr><td>GFR Δ (mL/min/1.73 m^2)</td><td>-1.7</td><td>-3</td><td>-5.1</td></tr>
</table>
<u>Strengths</u>: appropriate up-titration of glimepiride based on similar efficacy and hypoglycemia to previous trials, assessed % fat from weight loss, 52 weeks, 1,450 study participants
<u>Weaknesses</u>: funding by Janssen, primary author served as manufacturer consultant, unknown HbA_{1c} ↓ in population with baseline HbA_{1c} >9.5%, too short of duration to assess long-term risks and benefits
</td></tr>
<tr><td>Take Away</td><td>Canagliflozin 100 mg and 300 mg daily reduced HbA_{1c} by ~0.8% and 0.9%, respectively in patients with a baseline HbA_{1c} of 7.8% who are uncontrolled with metformin monotherapy at 52 weeks. Canagliflozin 100 mg was shown to be non-inferior to glimepiride, and canagliflozin 300 mg was superior to glimepiride. Canagliflozin additionally had a greater reduction in FPG, body weight (fat loss > lean mass loss), BP, and decreased risk of hypoglycemia. Canagliflozin had a slight increase in LDL, osmotic diuresis-related adverse events, and UTI. Genital mycotic infections were increased with canagliflozin, but were mild to moderate in intensity.</td></tr>
</table>

<table>
<tr><th colspan="2">Table 4: 2013 Bailey et al [23]</th></tr>
<tr><td>Design</td><td>102-Week, multicenter, placebo-controlled, double-blind, parallel-group, extension of a 24-week phase III trial, RCT</td></tr>
<tr><td>Setting</td><td>80 sites (30 in US, 21 in Canada, 11 in Argentina, 10 in Mexico, 8 in Brazil)</td></tr>
<tr><td>Objective</td><td>Examine the long-term efficacy and safety of dapagliflozin as add-on therapy to metformin in uncontrolled T2DM</td></tr>
<tr><td>Inclusion</td><td>18-77 Years of age, T2DM, HbA_{1c} 7-10%, BMI ≤45 kg/m^2, taking metformin ≥1,500 mg daily ≥8 weeks</td></tr>
<tr><td>Exclusion</td><td>Scr ≥133 µmol/L (1.5 mg/dL) ♂ or ≥124 µmol/L (1.4 mg/dL) ♀, AST/ALT > 3 times upper limit of normal, CK >3 times upper limit of normal, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during 3 months before enrolment), clinically significant renal, hepatic, hematological, oncological, endocrine, psychiatric, or rheumatic disease; recent CV event within 6 months or New York Heart Association class III or IV congestive heart failure, SBP ≥180 mmHg, DBP ≥110 mmHg</td></tr>
<tr><td>Treatment</td><td>• Dapagliflozin 2.5 mg daily (n=137), 5 mg daily (n=137), or 10 mg daily (n=135)
• Placebo (n=137)
• + Metformin ≥1,500 mg daily
Rescue therapy (primarily pioglitazone or acarbose) if: received during the 1st 24 weeks, HbA_{1c} >8% during weeks 24-50, >7.5% during weeks 50-76, >7% after week 76</td></tr>
<tr><td>Outcomes</td><td><u>Primary</u>
• HbA_{1c} Δ from baseline at 102 weeks
<u>Secondary</u>
• Fasting plasma glucose (FPG) Δ
• Weight Δ
• Proportion achieving HbA_{1c} <7%</td></tr>
<tr><td>Statistics</td><td>ANCOVA model, LOCF, no p values for exploratory endpoints, only summary statistics reported for safety, patients receiving rescue therapy not included in final efficacy analysis</td></tr>
<tr><td>Results</td><td><u>Baseline Characteristics</u>
• Similar, ♂ and ♀, mean HbA_{1c} 8.06%, ~54 years of age, BMI 31.5 kg/m^2, duration of T2DM ~6 years, SBP/DBP ~127/80 mmHg
<u>Primary endpoint:</u> HbA_{1c} Δ from baseline at 102 weeks
• Dapagliflozin 2.5 mg -0.48% (95% CI -0.68 to -0.29), 5 mg -0.58% (95% CI -0.77 to -0.39), and 10 mg -0.78% (95% CI -0.97 to -0.6)
  ◦ Difference vs. placebo: dapagliflozin 2.5 mg -0.5% (95% CI -0.79 to -0.21, p=0.0008), dapagliflozin 5 mg -0.6% (95% CI -0.89 to -0.31, p<0.0001), dapagliflozin 10 mg -0.8% (95% CI -1.08 to -0.52, p<0.0001)
• Placebo: 0.02% (95% CI -0.2 to 0.23)
• HbA_{1c} Δ from baseline at 24 weeks: placebo -0.3% (95% CI -0.44 to -0.16), dapagliflozin 2.5 mg -0.67% (95% CI -0.81 to -0.53, p=0.0002), dapagliflozin 5 mg -0.7% (95% CI -0.85 to -0.56, p<0.0001), dapagliflozin 10 mg -0.84% (95% CI -0.98 to -0.7, p<0.0001)
<table>
<tr><th>Secondary endpoints</th><th>Placebo</th><th>Dapagliflozin 2.5 mg</th><th>Dapagliflozin 5 mg</th><th>Dapagliflozin 10 mg</th></tr>
<tr><td>FPG Δ (mmol/L) [mg/dL]</td><td>-0.58 [-10.44], 95% CI -0.97 to -0.19</td><td>-1.07 [-19.26], 95% CI -1.42 to -0.72</td><td>-1.47 [-26.46], 95% CI -1.78 to -1.16</td><td>-1.36 [-24.48], 95% CI -1.65 to -1.07</td></tr>
<tr><td>Weight Δ (kg) at week 24</td><td>-0.4</td><td>-1.96</td><td>-2.92</td><td>-2.65</td></tr>
<tr><td>Weight Δ (kg) at week 102</td><td>1.36</td><td>-1.1</td><td>-1.7</td><td>-1.74</td></tr>
<tr><td>Proportion achieving HbA_{1c} <7% (%)</td><td>15.4, 95% CI 9.5 to 21.3</td><td>20.7, 95% CI 14 to 27.3</td><td>26.4%, 95% CI 19.4 to 33.4</td><td>31.5%, 95% CI 23.7 to 39.3</td></tr>
</table>
• Rescued or discontinued for failing to achieve glycemic targets: placebo 60.6%, dapagliflozin 2.5 mg 51.8%, dapagliflozin 5 mg 46%, dapagliflozin 10 mg 42.2%</td></tr>
<tr><td>Authors' Conclusion</td><td>Dapagliflozin + metformin provides a sustained reduction in HbA_{1c}, FPG, and weight without hypoglycemia risks in T2DM patients uncontrolled on metformin monotherapy.</td></tr>
</table>

Comments

Side effects & laboratory parameters	Placebo	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg
Hypoglycemia (%)	5.8	3.6	5.1	5.2
Hypotension, dehydrations, hypovolemia (%)	1.5	0	2.2	1.5
UTI (%)*	5.8	4.4	5.8	11.9
Suggestive of genital infection (%)	5.1	11.7	14.6	12.6
Renal impairment or failure (%)	1.5	4.4	2.9	1.5
SCr Δ (µmol/L) [mg/dL]	-0.9 [-0.01]	-1.8 [-0.02]	-3.5 [-0.04]	-2.7 [-0.03]
SBP Δ (mmHg) at week 24	-0.2	-2.1	-4.3	-5.1
SBP Δ (mmHg) at week 102	1.5	0.7	-1.1	-0.3
DBP Δ (mmHg) at week 24	-0.1	-1.8	-2.5	-1.8
DBP Δ (mmHg) at week 102	-1	-0.1	-1.5	-1.2

* Women > men, >65% within first 24 weeks, responded to standard treatment typically without interruption of dapagliflozin therapy and rarely led to recurrence, no pyelonephritis reported

- Dapagliflozin had 1 patient with history of hematuria that predated randomization experienced a bladder transitional cell cancer; dapagliflozin also had 1 patient with breast cancer

Strengths: Double-blinded design throughout 102-week period, efficacy analyses generally excluded rescue, low rate of discontinuation (indicated favorable tolerability profile), strict glycemic control criteria to ensure all pts received quality of care consistent with current guidelines (so HbA_{1c} exceeding 7.5% at 50 weeks or 7% at 76 weeks received rescue therapy and not included in final efficacy analysis), safety analyses included all data regardless of rescue in order to get a comparison to placebo that was as unbiased as possible

Weaknesses: patients requiring rescue medication in placebo group may limit statistical interpretation of durability of the glucose lowering effect of dapagliflozin but also emphasizes the clinical utility; study sponsors involved in design, data collection, data review, data analysis, and contributed to report preparation; unknown HbA_{1c} ↓ in population with baseline HbA_{1c} >10%, too short of duration to assess long-term risks and benefits, 546 study participants, investigators ability to adjust antihypertensive therapy according to need may have masked BP benefits with dapagliflozin

Take Away	Dapagliflozin 2.5, 5, and 10 mg daily significantly reduces HbA_{1c} by up to 0.78% in patients uncontrolled with metformin monotherapy with a baseline HbA_{1c} of 8.06% at 102 weeks. The HbA_{1c} reduction was slightly greater with dapagliflozin at 24 weeks, up to 0.84%. This trial demonstrates sustained glycemic and weight-loss benefits. UTI risk was similar with dapagliflozin 2.5 and 5 mg compared to placebo and slightly increased with dapagliflozin 10 mg. Genital infection risk was up to 10% higher with dapagliflozin compared to placebo. However, these events were rare and mild to moderate in severity.

Table 5: EMPA-REG MET[24]	
Design	24-Week, placebo-controlled, double-blind, phase III, multicenter, RCT
Setting	148 Centers in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the U.S.)
Objective	Evaluate efficacy, safety, and tolerability of empagliflozin vs. placebo as add-on to metformin in uncontrolled T2DM
Inclusion	≥18 Years of age, BMI ≤45 kg/m^2, HbA_{1c} ≥7% to ≤10%, stable immediate-release metformin regimen (unchanged for ≥12 weeks prior to randomization), patients with a HbA_{1c} >10% were eligible to participate in an open-label treatment arm
Exclusion	Uncontrolled hyperglycemia with glucose >13.3 mmol/L (>240 mg/dL) after an overnight fast confirmed by a second measurement; acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to informed consent; indication of liver disease; impaired renal function (eGFR <30 mL/min/1.73 m^2), CI to metformin, bariatric surgery; cancer or cancer treatment history within past 5 years; blood dyscrasias; antiobesity drug use 3 months prior to consent; use of any treatment leading to unstable body weight; treatment with systemic steroids at time of consent; thyroid hormone dose change within 6 weeks prior to consent; alcohol or drug abuse within 3 months of consent; investigational drug intake in another trial within 30 days prior to current trial
Treatment	• Empagliflozin 10 mg daily (n=217), empagliflozin 25 mg daily (n=214), empagliflozin 25 mg daily in open-label arm with HbA_{1c} >10% (n=69) • Placebo daily (n=207) • + Metformin ≥1,500 mg daily in all arms Rescue medication initiation, choice, and dose at the discretion of the investigator if fasting glucose >13.3 mmol/L (240 mg/dL) during weeks 1-12, fasting glucose >11.1 mmol/L (200 mg/dL) weeks 12-24, or HbA_{1c} >8.5%
Outcomes	• Primary: HbA_{1c} Δ from baseline at 24 weeks • Secondary: Δ from baseline in body weight and weighted mean daily glucose (MDG) level using an 8-point blood glucose profile • Exploratory endpoints: % of patients with baseline HbA_{1c} ≥7% who had an HbA_{1c} <7%; Δ from baseline in FPG, waist circumference, SBP, and DBP; % of patients with >5% reduction in body weight; % of patients with uncontrolled BP at baseline who had controlled BP (SBP <130 and DBP <80 mmHg), use of rescue medication, Δ from baseline in 2-h postprandial glucose (PPG) in subset of patients (n=167) based on meal tolerance test (MTT)
Statistics	Efficacy analysis, ANCOVA model for primary endpoint, values observed after patient received rescue medication were set to missing, LOCF used to impute missing continuous efficacy data

Results	Baseline characteristics
	• Mean (SD): age 55.7 years (9.9), BMI 29.2 kg/m^2 (5.5), HbA_{1c} 7.9% (0.85)
	• Similar, ♂ and ♀, predominately white and Asian, baseline body weight ~80 kg, SBP/DBP ~ 130/90 mmHg
	• Time since T2DM diagnosis: ≤1 year = 9%, >1-5 years = 32-40%, >5-10 years = 31-35%, >10 years = 19-24%
	Primary endpoint: HbA_{1c} Δ from baseline at 24 weeks
	• Empagliflozin 10 mg: -0.7%
	  • Difference of empagliflozin 10 mg vs. placebo: -0.57% (95% CI -0.7 to -0.43), p<0.001
	• Empagliflozin 25 mg: -0.77%
	  • Difference of empagliflozin 25 mg vs. placebo: -0.64% (95% CI -0.77 to -0.50), p<0.001
	• Placebo: -0.13%
	• Open-label empagliflozin 25 mg: 3.23%

Secondary & exploratory endpoints	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Open-label empagliflozin 25 mg
MGD Δ (mmol/L) [mg/dL]	-0.11 [-1.98]	-0.54 [-9.72]	-0.8 [-14.4]	-4.23 [-76.14]
MGD Δ (mmol/L) [mg/dL] vs. placebo		-0.42 [-7.56], 95% CI -0.72 to -0.13, p=0.006	-0.69 [-12.42], 95% CI -0.99 to -0.39, p<0.001	
Body weight Δ (kg)	-0.45	-2.08	-2.46	-1.91
Body weight Δ (kg) vs. placebo		-1.63, 95% CI -2.11 to -1.15, p<0.001	-2.01, 95% CI -2.49 to -1.53, p<0.001	
HbA_{1c} level <7% at week 24 (%)	12.5	37.7	38.7	8.7
FPG Δ (mmol/L) [mg/dL]	0.35 [6.3]	-1.11 [-19.8]	-1.24 [-22.3]	-3.02 [-54.36]
2-h PPG Δ (mmol/L) (mg/dL)	0.33 [6]	-2.55 [-46]	-2.47 [-45]	
>5% Weight ↓ (%)	4.8	21.2	23	15.9
Waist circumference Δ (cm)	-0.54	-1.55	-1.57	-2.52
SBP Δ (mmHg)	-0.4	-4.5	-5.2	-2.4
DBP Δ	0	-2	-1.6	-3.6
% Patients with uncontrolled BP who achieved <130/80 mmHg	13.2	35.9	30.4	36.2

- Rescue therapy: 48 patients (7.5%) received rescue therapy; more required this in the placebo group (29 patients for placebo, 12 patients in empagliflozin 10 mg, and 7 patients with empagliflozin 25 mg); 14.5% in open-label empagliflozin 25 mg

Author's Conclusion

Empagliflozin as add-on therapy to metformin is well-tolerated and improves glycemic control while leading to reduced weight and BP with a low risk of hypoglycemia.

Comments

Side effects	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Open-label empagliflozin 25 mg
Hypoglycemia (%)	0.5	1.8	1.4	2.9
UTI (%)*	4.9	5.1	5.6	
Genital infection (%)ɬ	0	3.7	4.7	
eGFR Δ (mL/min/1.73m^2)	1	0.1	-1.7	-0.03
LDL Δ (mmol/L) [mg/dL]	0.03 [1.16]	0.15 [5.79]	0.15 [5.79]	0.09 [3.47]
LDL Δ vs. placebo (mmol/L) [mg/dL]		0.12 [4.63], p=0.043	0.12 [4.63], p=0.032	

* 79% were mild intensity, no severe, none led to discontinuation, no urosepsis or pyelonephritis, majority only having 1 event, mainly in ♀

ɬ Mild – moderate intensity, only 1 discontinuation in each empagliflozin group

Strengths: minimal discontinuations, also showed subset of patients with HbA_{1c} >10%

Weaknesses: funded by Eli Lilly, too short of duration to assess long-term risks and benefits, only 24-week duration, more placebo group received rescue therapy, 707 study participants

Take Away

Empagliflozin 10 mg and 25 mg daily reduces HbA_{1c} by 0.7-0.77% and has a HbA_{1c} difference from placebo of up to 0.64% in patients uncontrolled with metformin monotherapy with a baseline HbA_{1c} of 7.9%. Empagliflozin has an even greater HbA_{1c} reduction of ~3% in those patients with a baseline HbA_{1c} >10%. Empagliflozin also reduces FPG, MDG, 2-h PP, BP and body weight and has a low risk similar to placebo for UTIs and hypoglycemia. Although genital infection risk is increased, events were rare and mild to moderate in severity.

Long-Term Benefits and Safety

A. The CV benefits and risks of SGLT2 inhibitors are unknown. Reduction in glucose, weight, and BP could all influence the incidence of CV events. Multiple trials are currently investigating the CV effects of SGLT2 inhibitors.
    a. CANVAS[25,26]
        i. Aim: assess canagliflozin in T2DM with CV risk for major adverse cardiac events (MACE)
        ii. Design: parallel, double blind, RCT
        iii. Primary: MACE including CV death, nonfatal MI, and non-fatal stroke
        iv. Secondary: fasting insulin secretion measurement, progression of albumin in the urine, effectiveness of lowering blood glucose
        v. Enrollment: 4,365; estimated primary completion date: April 2017, estimated study completion date: June 2018
    b. DECLARE-TIMI58[27]
        i. Aim: determine if dapagliflozin added on to current anti-diabetic agents will reduce cardiovascular events
        ii. Design: parallel, double-blind, placebo-controlled, multicenter, RCT
        iii. Primary: time to first event included in the composite endpoint of CV death, MI or ischemic stroke up to 6 years
        iv. Secondary: time to first event of hospitalization for congestive heart failure; time to first event included in the composite endpoint of CV death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for any revascularization; time to all-cause mortality; body weight change from baseline
        v. Enrollment: 17,150; estimated primary completion date: April 2019
    c. EMPA-REG OUTCOME[28,29]
        i. Aim: investigate safety of empagliflozin in patients with T2DM and high CV risk
        ii. Design: parallel, double-blind, phase III, international, multicenter, RCT
        iii. Primary: time to first occurrence of the primary composite endpoint CV death (fatal stroke and fatal myocardial infarction (MI)), non-fatal MI, and non-fatal stroke
        iv. Secondary: composite of primary endpoints, incidence of new onset albuminuria, incidence of silent MI, incidence of heart failure requiring hospitalization, incidence of new onset macroalbuminuria, and composite microvascular outcome
        v. Estimated enrollment: 7,000; estimated primary completion date: April 2015, estimated study completion date: April 2015

B. Renal protection may be a benefit of SGLT2 inhibitor therapy. Glomerular hyperfiltration is observed in early T2DM.[30] Evidence shows that the extent of fractional proximal reabsorption is positively correlated with GFR, which reinforces the concept of a strong tubular control of glomerular filtration in T2DM.[31,32] If an increase in SGLT-mediated sodium-glucose reabsorption is implicated in this complex scenario in T2DM, then SGLT2 inhibitors might have the potential to reduce the hyperfiltration of the diabetic kidney. This hypothesis infers that chronic SGLT2 inhibition might have a protective effect against deterioration of renal function in diabetic patients. The CREDENCE trial will investigate canagliflozin's effects on incidence of end stage kidney disease, serum creatinine doubling, and renal and CV death in 3,627 patients with T2DM and stage 2 and 3 CKD.[33]
C. A pooled analysis of 4 placebo-controlled trials (n=2312) and 8 active-controlled trials (n=9439) confirmed the finding that genital mycotic infection incidences were higher among canagliflozin vs. placebo or control in T2DM subjects. Incidence with canagliflozin ranged from ~10%-15%. Events were more common in females, were generally mild-moderate, and responded to standard therapy.[34]
D. Bladder cancer and breast cancer cases have been observed in dapagliflozin trials. In a study of over 5,000 subjects, there were 10 cases of bladder cancer in the dapagliflozin group. In a study of 2,100 women, 9 cases of breast cancer developed in the dapagliflozin arm. [35] However, molecular evidences and animal studies do not suggest a positive link between exposure to SGLT2 inhibitors and cancer risk. Long term effects should be carefully evaluated with a larger numbers of patients exposed to different SGLT2 inhibitors for a longer duration to address any associated increased risk of bladder or breast cancer.[36,37]

Recommendations

A. Overview: The ADA currently recommends metformin as first line therapy and does not give preference to a second antidiabetic medication. SGLT2 inhibitors are the newest class of antidiabetic agents, which reduce HbA_{1c} by ~ 1% as monotherapy and up to 0.77%-0.9% when added on to metformin therapy.
B. Consideration for selecting patients: Providers should conduct a risk vs. benefit discussion with patients. Renal function, HbA_{1c} goal, age, concurrent medications, and comorbidities must be assessed in each patient prior to recommending SGLT2 inhibitor therapy.
C. Follow-up: Response to therapy, side effects, and renal function should be monitored.
D. Final treatment recommendation: Canagliflozin has a greater UGE in comparison to dapagliflozin and empagliflozin. Canagliflozin, dapagliflozin, and empagliflozin have demonstrated similar HbA_{1c} reduction when compared to placebo. Although empagliflozin's HbA_{1c} reduction was slightly lower when added on to metformin in comparison to the HbA_{1c} with canagliflozin and dapagliflozin with metformin, this may be due to differences in study design and is unlikely to be clinically significant. Therefore, the greater UGE with canagliflozin does NOT correlate to greater efficacy with HbA_{1c} reduction. Preference of one SGLT2 inhibitor over another should NOT be based on UGE. No head-to-head trials are currently available to directly assess the HbA_{1c} reduction among these three SGLT2 inhibitors.

Appendix

Panel 1: Oral drugs approved for treatment of hyperglycaemia in type 2 diabetes*

Second-generation sulfonylurea antidiabetics
- Glibenclamide (also known as glyburide)
- Gliclazide
- Glimepiride
- Glipizide

Biguanide antidiabetics
- Metformin

Peroxisome proliferator-activated receptor γ agonists (thiazolidinedione antidiabetics)
- Pioglitazone
- Rosiglitazone

α-glucosidase inhibitors
- Acarbose
- Miglitol
- Voglibose

DPP4 inhibitors
- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin
- Vildagliptin

SGLT2 inhibitors
- Canagliflozin
- Dapagliflozin

Glinides
- Nateglinide
- Repaglinide

Bile-acid-binding resins
- Colesevelam

Dopamine-receptor agonists
- Bromocriptine

DPP4=dipeptidyl peptidase 4. SGLT2=sodium-glucose co-transporter 2. *Not all drugs available in all countries.

Panel 2: Injectable drugs approved for treatment of hyperglycaemia in type 2 diabetes*

Islet amyloid polypeptide (amylin) analogues
- Pramlintide

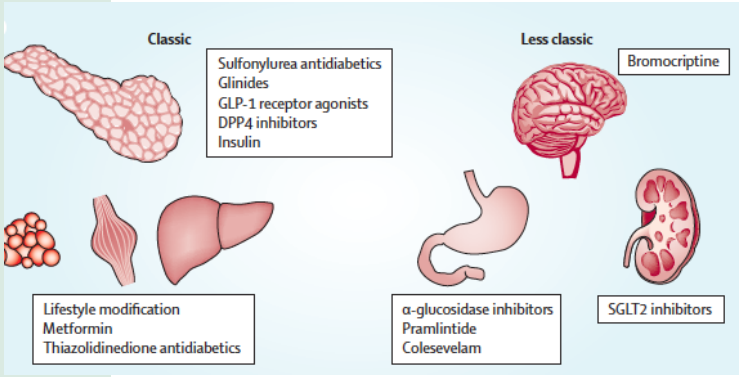
GLP-1 receptor agonists
- Exenatide
- Liraglutide
- Lixisenatide

Rapid-acting and short-acting insulin
- Soluble insulin (also known as regular insulin)
- Insulin aspart
- Insulin glulisine
- Insulin lispro
- Insulin zinc–amorphous (also known as insulin semilente)

Intermediate-acting insulin
- Isophane insulin (also known as NPH insulin)
- Insulin zinc (also known as insulin lente)

Long-acting insulin
- Insulin zinc–crystalline (also known as insulin ultralente)
- Insulin detemir
- Insulin glargine

GLP-1=glucagon-like peptide 1. NPH=neutral protamine Hagedorn. *Not all drugs available in all countries.



Figures 6, 7, 8: Antihyperglycemic Agents and Their Site of Action[13]

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