

DIABETES MEDICATIONS: NOT JUST FOR DIABETES

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NDAFP Annual Meeting – Grand Forks
October 25, 2024

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OBJECTIVES

- Define the different classes of non-insulin diabetes medications.
- Summarize how non-insulin diabetes medications work including clinical uses, adverse effects, and precautions.
- Discuss the use of non-insulin diabetic medications, beyond glycemic control in T2DM, for cardiovascular and renovascular diseases, obesity and others.

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NEWER T2DM THERAPY

- Positive CV & renal outcome studies with GLP-1RA and SGLT2i
- Therapy not ONLY for glucose control anymore
 - Shift from glycemic control alone to simultaneous improvement of CV & renal outcomes
- Guidelines now recommend adding to metformin SGLT2i or GLP-1RA for benefit in CVD, kidney disease, and HF

Ann Intern Med 24;177:658-66

ADA 2024 Guideline

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PATHOPHYSIOLOGY T2DM

- Impaired pancreas **insulin secretion** and $< \beta$ cell mass
- **Increased glucagon secretion** (lack of suppression by α cells) – Gluconeogenesis/glycogenolysis
- **Insulin resistance** (muscle, adipose, liver)
 - Decreased glucose uptake
- Increased glucose reabsorption by renal tubule
 - **Increased SGLT2 expression**
 - Increased inflammation & fibrosis
- Brain
 - Neurotransmitter dysfunction with appetite regulation
 - Increased sympathetic tone
 - Decreased dopamine activity

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PATHOPHYSIOLOGY T2DM

- Increased endogenous **hepatic glucose production**
- GI tract
 - **Decreased incretin effect**
 - Abnormal emptying
 - Gut dysbiosis
 - Increased glucose absorption
- Increased chronic **inflammation**
- Immune dysregulation
- Increased lipolysis – increased lipid storage
- Islet amyloid polypeptide (IAPP) deposition in pancreas

ADA-EASD Position Statement Diabetes Care 12;35:1364-79 Diab Care 14;37(suppl 1):S14
Diab Care 15;38:140-9 Mayo Clin Proc 18;93:217-39 Diabetes Care 18;41:1543-56
Am J Med 13;126:S2-9 Lancet. Online Nov 1, 2022. doi.org/10.1016/S0140-6736(22)01655-5
Metabolism 137 (2023) 155332

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DIABETES THERAPY AGENTS

Prior to 2002

- Sulfonylureas 1955
 - 1st generation
 - 2nd generation
 - Glyburide – Glynase, Micronase, generics
 - Glipizide – Glucotrol, generics
 - Glimpiride – Amaryl, generics
- Biguanides (Metformin) 1995
- Alpha-glucosidase inhibitor 1995
 - Acarbose – Precose
 - Miglitol – Glyset
- Thiazolidinediones 1996
 - Pioglitazone – Actos, generics
- Meglitinides 1997
 - Nateglinide – Starlix
 - Repaglinide – Prandin
- Insulins
 - 1922 in a patient
 - Porcine & bovine insulins until 1980s
 - “human” rDNA insulin 1970s

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ANTI-DIABETES AGENTS After 2002

- **GLP-1 receptor agonists**
 - Dulaglutide – Trulicity
 - Exanatide – Byetta (IR), Bydureon (ER)
 - Liraglutide – Victoza
 - Lixisenatide – Adlyxin
 - Discontinued 1/1/23
 - Semaglutide – Ozempic
- **DPP-4 inhibitors 2006**
 - Alogliptin – Nesina
 - Linagliptin – Tradjenta
 - Saxagliptin – Onglyza
 - Sitagliptin – Januvia

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ANTI-DIABETES AGENTS After 2002

- **More Insulin products**
 - Rapid-acting
 - Regular
 - Intermediate-acting
 - Basal long-acting
 - Inhaled
- **Amylin analogue**
 - Pramlintide – Symlin
- **SGLT2 inhibitors 2013**
 - Bexagliflozin - Brenzabby
 - Canagliflozin – Invokana
 - Dapagliflozin – Farxiga
 - Empagliflozin – Jardiance
 - Ertugliflozin – Steglatro
 - Sotagliflozin – Inpefa
 - 1/2 inhibitor
- **Bile acid resin**
 - Colesevelam – Welchol
- **Dopamine-2 agonist**
 - Bromocriptine – Cycloset

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SULFONYLUREAS

- **Advantages**
 - **Lowering A1c 1-2%**
 - Many years of use
 - Low GI
 - 1xd dosing
 - **Low cost**
 - CKD – Glipizide (Glucotrol) no dosage change
 - Glimepiride (Amaryl) lower dose
- **Disadvantages**
 - **May induce β -cell failure** – “tolerance” develops
 - **Increases insulin release**

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SULFONYLUREAS

- **Disadvantages (cont.)**
 - **Hypoglycemia**
 - > with elderly & renal/hepatic dysfunction, missed meals
 - > with Glyburide
 - **Weight gain** of 1.5-2 kg in 1st year is common
 - Due to hyperinsulinemia
 - Contributes to insulin resistance & drug failure
 - > with Glyburide
 - Avoid Glyburide in renal dysfunction
 - Hypersensitivity – sulfa
- **NO CV or renal benefit**

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METFORMIN

- **Preferred initial agent for T2DM without obesity, CVD, CKD or HF in most guidelines**
- **Advantages**
 - Reducing A1c 1-2% (= sulfonylureas; > DPP4i, glynides)
 - **Weight neutral or weight loss** of 0.6-2.9 kg
 - **Little risk of hypoglycemia** with monotherapy
 - **May decrease CV events and mortality vs. SU**
 - May be useful for **pre-DM to decrease DM onset**
 - **Safe in stable HF and moderate renal dysfunction**
 - **Low cost**

NEJM 02;346:393-403 Diabetologia 17;60:1620-9
Diabetes Metab Syndr: Clin Res Rev 15 (2021) 102239
Prim Care Clin Office Pract 22;49:315-26 ADA Guidelines 2024

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METFORMIN

- **Disadvantages**
 - **GI side effects**, start low with low dose
 - **Lactic acidosis risk? Very rare.**
 - Multiple cautions & contraindications
 - Assess renal & liver function
- **Dose adjustments based on eGFR**
 - 45-59 – Continue use
 - 30-45 – Caution – New starts not recommended
 - < 30 – discontinue – contraindicated

NEJM 14;371:1547-8 Endocrinol Metab Clin N Am 13;42:947-70
ADA guidelines 2024 AACE 2023
Prim Care Clin Office Pract 22;49:315-26 Med Lett Drugs Ther. 22;64:177-84
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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METFORMIN USES

- FDA-approved indication
 - Adjunct to diet and exercise to improve glycemic control in > 10 y with T2DM
- **Prediabetes & at high risk for progression to T2DM, we suggest evaluating patient characteristics (eg, age, life expectancy, co-occurring conditions, BMI, other risk factors) and offering metformin or other select medications to reduce risk of progression from prediabetes to T2DM.** (strength weak for)

VA Dept Defense DM Guideline. Mayo Clin Proc 24;99:1323-36

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METFORMIN OTHER USES BESIDES DM

- May **improve fertility** by reducing insulin
 - Promotes ovulation esp in PCOS
- May **lessen weight gain** from antipsychotics
- Stimulates **gut good microbiome** with less inflammation and “leaky gut”
- May cause **lower total mortality**
- In T2DM may **reduce risk of colon polyps/colon cancer**
- **Prostate cancer as part of hormonal therapy may live longer**

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METFORMIN OTHER USES BESIDES DM

- In T2DM may **reduce incidence of breast cancer**
- **May prevent liver, pancreatic and colon cancer**
- In T2DM or obesity **may reduce risk of severe COVID-19**
- **May reduce risk of severe COVID, hospitalizations and long COVID and reduction in viral load**

Clin Infect Dis 24;79:354-63. 292-4 (editorial)
Diabetes Care online 9/17/24. <https://doi.org/10.2337/DC24-0032>

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METFORMIN OTHER USES BESIDES DM

- In T2DM may **lower rate of dementia and CVA**
- In T2DM **may slow aging and increase life expectancy**
- May reduce risk of **AMD including geographic atrophy or dry AMD with/without DM**

<https://www.goodrx.com/metformin/surprising-benefits-metformin-diabetes-fertility-cancer>. 8/11/22
<https://honesthealth.com/edge/benefits-of-metformin/#:~:text=Metformin%20could%20benefit%20your%20health,%20even%20if%20you.2/20/24>
<https://www.health.harvard.edu/blog/is-metformin-a-wonder-drug-202109222605#:~:text=Metformin,%20a%20medicine%20prescribed%20to%20treat%20type%20Medpage%207/22/24>. Meeting coverage Am Soc Retina Specialists

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METFORMIN OTHER USES BESIDES DM

- “While the research so far is promising, we need **more compelling evidence before endorsing its widespread use for people without diabetes**. But, for clinical researchers hoping to repurpose an old medicine as a new wonder drug, metformin would seem like a great place to start.”

Shmerling RH, Harvard Health Publicizing. 4/8/24.
<https://www.health.harvard.edu/blog/is-metformin-a-wonder-drug-202109222605#:~:text=Metformin,%20a%20medicine%20prescribed%20to%20treat%20type%20>

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THIAZOLIDINEDIONES (TZD)

- Pioglitazone (Actos) – oral ~\$10/mon
- FDA – Adjunct to diet and exercise
- May be of use in **prediabetes**
- **Potential CV benefit**, neutral renal benefits
- May be of benefit in **MASH** (metabolic dysfunction-assoc steatohepatitis)
- **Weight gain**, Fluid retention, **HF risk**
- **Low cost**

Endocrinol Metab Clin N Am 13;42:947-70 Med Lett Drugs Ther. 19;61:169-78
Med Clin N Am 21;105:955-66 Lancet. Online Nov 1, 2022.
[doi.org/10.1016/S0140-6736\(22\)01655-5](https://doi.org/10.1016/S0140-6736(22)01655-5) ADA Guidelines 2024 AACE 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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GLP-1 Receptor Agonists (GLP-1RA)

- SC dosing except oral semaglutide
- Dulaglutide (Trulicity)
- Exenatide (Byetta), Exenatide ER (Bydureon BCise)
- Liraglutide (Victoza), (Saxenda for weight loss)
- Semaglutide (Ozempic), Oral (Rybelsus), (Wegovy SC for weight loss)
- Tirzepatide (Mounjaro) GIP & GLP-1 receptor agonist, (Zepbound for weight loss)
- **Costly** > \$800-1,300/month, weight loss ~\$1,300/mon

Med Lett Drugs Ther 24;66:e1-3
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2024

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GLP-1RA

- Incretin mimetic binds to GLP-1 receptor on pancreatic β cells
 - Stimulates insulin synthesis & secretion as PG rise (**glucose-dependent**) & restores 1st-phase insulin release
 - Decreases glucagon
 - Promotes satiety with \downarrow wt ~2 kg
 - Slows gastric emptying
 - Decrease A1C about 1-1.5%
- Reduces PPG with mild decrease in FPG

Clin Therapeut. In press. 014http://dx.doi.org/10.1016/j.clinthera.2014.01.018
Hosp Med Clin 16;5:542-54 Mayo Clin Proc 18;93:217-39
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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ADVERSE EFFECTS

- GI adverse effects 20-50% - > at initiation
 - Nausea, vomiting and diarrhea, gastroparesis, ileus
- Reported risk acute pancreatitis, cholelithiasis
 - Do not use if history of pancreatitis or neoplasia

FDA Alert 8/18/08, 10/07, NEJM 08;358:1970
Clin Therapeut. In press. 014http://dx.doi.org/10.1016/j.clinthera.2014.01.018
Diabetes Care 19;42(suppl 1):S90-102 AACE Guideline Update 2023 ADA 2023
Crit Care Clin 19;35:315-28
Med Lett Drugs Ther 23;65:205-7 Med Lett Drugs Ther 23;65:191-2
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2024
Int J Mol Sci 24;25:4346

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ADVERSE EFFECTS

- Retinopathy – may occur with high doses and rapid glucose lowering
- Medullary thyroid cancer, pancreatic cancer
 - Based on animal studies
 - FDA – box warning about thyroid C-cell tumors; don't use if h/o or family h/o medullary thyroid cell cancer or multiple endocrine neoplasia syndrome type 2a or 2b (MEN2)
 - Thyroid cancer <1% lit review Int J Mol Sci 24;25:4346

Cleve Clin J Med 22;890:457-64 AACE 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2024

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• FDA-APPROVED INDICATIONS

- Dulaglutide
 - Adjunct to diet and exercise to improve glycemic control in ≥ 10 y with T2DM
 - Reduce risk of MACE (CV death, nonfatal MI, or nonfatal stroke) in adults with T2DM who have established CVD or multiple CV risk factors.
- Exenatide
 - Byetta
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
 - Bydureon BCise (exenatide ER)
 - Adjunct to diet and exercise to improve glycemic control in > 10 ywith T2DM

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• Liraglutide

- Victoza
 - Adjunct to diet and exercise to improve glycemic control in > 10 y with T2DM
 - Reduce the risks of MACE in adults with T2DM and established CVD
- Saxenda – adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
 - Adults with initial BMI of ≥ 30 kg/m² or ≥ 27 kg/m² in presence of ≥ 1 weight-related comorbid condition (eg, HTN, T2DM, or dyslipidemia)
 - ≥ 12 y with body weight above 60 kg (132 lbs) and initial BMI corresponding to ≥ 30 kg/m² for adults (obese)

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- **Semaglutide**
 - Ozempic
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
 - Reduce risk of MACE in adults with T2DM and established CVD
 - Wegovy – combination with a reduced calorie diet and increased physical activity:
 - Reduce risk of MACE in adults with established CVD and either obesity or overweight
 - Reduce excess body weight and maintain weight reduction long term:
 - ≥ 12y with obesity
 - Adults overweight in presence of ≥1 weight-related comorbidity
 - Rybelsus
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM

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- ### CV & Renal Benefits
- **CV benefit**
 - Dulaglutide, liraglutide, semaglutide injection
 - Reduce first occurrence CV death, nonfatal MI or CVA

NEJM 16;375:311-22 NEJM 16;375:1834-44 Lancet 18;392:1519-29
Cleve Clin J Med 22;890:457-64
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2024
 - **Modify risk factors for CKD progression and DM nephropathy**
 - Promote diuresis and natriuresis
 - SGLT2 inhibitors are more effective

NEJM 17;377:839-48 Cleve Clin J Med 22;890:457-64 AACE 2023 ADA 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
Expert Opin Drug Saf 24;23:797-810

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- ### GLP-1RA UNDERUSE
- “Despite the recommendations of international guidelines, the use of GLP-1RAs remains rather low in clinical practice and surprisingly even lower in patients with T2DM and ASCVD.”
 - “Bridging the gap between evidence-based CV protection and real-life GLP-1RA underuse in patients with T2DM at high CV risk is crucial from a public health viewpoint.”
- Expert Opin Drug Saf 24;23:797-810

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- ### GLP-1RA USES
- **GLP-1 receptors are expressed in CNS** associated with food intake and chemical-related reward
 - Hypothalamus and brain stem
 - Mesolimbic dopamine system
 - Ventral tegmental area and nucleus accumbens
 - **Current studies in process**
 - Alcohol use disorder, Cocaine use disorder
 - Smoking cessation without weight gain

Medical News & Perspectives. Could GLP-1RA Like Semaglutide Treat Addiction, Alzheimer Disease, and Other Conditions? JAMA 24;331:1519-21
Ann Intern Med. Online July 30, 2024 Ann Intern Med 24;177:1016-27

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- ### GLP-1RA USES
- | | |
|--|---|
| <ul style="list-style-type: none"> • Anti-inflammatory properties <ul style="list-style-type: none"> – Decrease cytokines e.g., IL-17, TNF-a, NFkB.3, VEGF • Depression • Alzheimer disease • Parkinson disease • Asthma, COPD <p style="font-size: x-small;">Explor Drug Sci 23;1:221-38
Medical News & Perspectives. Could GLP-1RA Like Semaglutide Treat Addiction, Alzheimer Disease, and Other Conditions? JAMA 24;331:1519-21
Ann Med 24;56:2357737</p> | <ul style="list-style-type: none"> • PCOS • Psoriasis • (MASH) Metabolic dysfunction-associated steatohepatitis • Neuro-ophthalmic <ul style="list-style-type: none"> – Diabetic retinopathy, glaucoma, & idiopathic intracranial HTN |
|--|---|

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- ### TIRZEPATIDE (MOUNJARO)
- GIP (glucose-dependent insulinotropic polypeptide) agonist/GLP-1 agonist
 - A twincretin
 - Increases insulin sensitivity, increases insulin secretion in response to elevated glucose, decreases glucagon secretion, slows gastric emptying
 - **A1C reduction ~2-2.5% (> GLP1 agonists)**
 - **> wt loss (~11 kg) than GLP1 agonists**
 - **No CV or renal outcomes data yet**
- Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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COMPOUNDED GLP-1 AGONISTS RECOMMENDATIONS

- Patients looking for lower cost &/or access when drug shortages
- FDA Drug Shortages
 - <https://dps.fda.gov/drugshortages/activeingredient/semaglutide-injection>
- Questionable sources include:
 - Online sellers that don't require an Rx, spas that tout "generic" GLP-1s, etc.
- Buy from licensed US pharmacies especially one licensed in compounding

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COMPOUNDED GLP-1 AGONISTS RECOMMENDATIONS

- Check details at websites for board of pharmacy and accrediting body such as the Pharm Compounding Accreditation Board
- Confirm getting semaglutide by looking at certificate of analysis
 - NOT semaglutide Na or other salts which are "research grade" chemicals that aren't for drug use

Pharmacist's Letter, July 2024

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COUNTERFEIT OZEMPIC

- FDA warns consumers not to use counterfeit Ozempic and needles found in US supply chain
- Retail pharmacies only purchase authentic Ozempic through authorized distributors of Novo Nordisk
- Patients should only obtain with a valid Rx through state-licensed pharmacies and check the product before using for any signs of counterfeiting.

12/21/23. FDA <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain>

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Dipeptidyl peptidase-4 inhibitors (DPP-4 Inhibitors)

- Alogliptin (Nesina)
- Linagliptin (Tradjenta)
 - Not renally excreted
- Saxagliptin (Onglyza)
- Sitagliptin (Januvia)
- Oral agents
- Generics ~\$50-80/mon
- MANY combinations with other agents

Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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DDP-4 Inhibitors

- Common adverse effects
 - Nasopharyngitis, URTIs, headache, arthralgia (may be severe), GI < GLP-1 agonists
- Rare pancreatitis cases reported
- **Low risk hypoglycemia**
- **Weight neutral**
- **Neutral effect on CV and renal**
 - Saxagliptin & alogliptin **may increase HF risk** in those with heart or renal disease

Pharmacist's Letter/Prescriber's Letter. September 2022. Modified Aug 2023

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Na-glucose cotransporter-2 inhibitors (SGLT2i)

- Bexagliflozin (Brenzavvy)
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
- Sotagliflozin (Inpefa) – dual SGLT1 & 2 inhibitor
- **COST ~\$55 (Bexagliflozin) - \$600/mon**

Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
Med Lett Drugs Ther 23;65:130-2

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SGLT2i

- **Inhibits SGLT2**
 - **Blocks glucose & Na reabsorption in proximal tubule**
 - Inhibit ~30-50% of filtered glucose
 - **Increases glucose excretion to ~ 80 g/d**
 - Osmotic diuresis
 - Decrease in FPG and PPG
 - **Insulin independent**
- **Reduces A1c 0.5-1%**

J Amer Medical Direct Assoc 14;15:786-801 Advan Chronic Kidney Dis 14;21:297-303
Diab Res Clin Pract 14;104:297-322 Med Clin N Am 15;99:131-43
Med Lett Drugs Ther 15;57:139-40 Mayo Clin Proc 18;93:1629-47
Diabetes Metab Syndr: Clin Res Rev 15 (2021) 102239
Heart Failure Clin 22;18:551-9
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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SGLT2i ADVERSE EFFECTS

- **Polyuria, frequency** – volume depletion, hypotension, dizziness
- **Genital yeast infections** ~3-8%, **3-5 X > risk**
- UTIs – 0% to ~0.3-2%
- Renal don't use if eGFR <30-60
 - GFR cutoff varies with agent
- **Hyperkalemia – DDI with ACEIs/ARBs, K-sparing diuretics and renal dysfunction**

Med Clin N Am 21;105:955-66 Heart Failure Clin 22;18:635-43
ADA Guideline 2024 AACE 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
J Am Coll Cardiol 23;81:1835-78 Med Lett Drugs Ther 23;65:114-6
2024 ACC HFREF J Am Coll Cardiol 24;83:1444-88

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SGLT2i ADVERSE EFFECTS

- **Ketoacidosis with low/nl PG** – rare
FDA Drug Safety. 5/15/15 <http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm>
- **Rare Fournier's gangrene (necrotizing fasciitis of the perineum)**
- **Canagliflozin may increase risk of amputations**
 - FDA removed boxed warning on 8/26/20
 - Still low risk – warning and precaution

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin>
ACC/AHA PAD Guide 2024. Circ 24;149:e1313-e410
Med Clin N Am 15;99:131-43 JACC 18;72:1845-55
Med Clin N Am 21;105:955-66 J Am Coll Cardiol 23;81:1835-78
Med Lett Drugs Ther 23;65:114-6 2024 ACC HFREF J Am Coll Cardiol 24;83:1444-88
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023

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SGLT2i EFFECTS

- Weight loss of ~2-4.7 kg – volume reduction
- Hypoglycemia risk low (OR 0.44 vs others)
- Reduces FPG and PPG
 - Decreases total glucose vs. time area under the curve
- Reduces pre-load and afterload – HF effects
- Osmotic diuresis – HF effects
- Reduces angiotensinogen – CV & HF
- Reduces total body Na – HF and BP lowering
- Decreases SBP ~2-10 mmHg & DBP ~1.3-1

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SGLT2i EFFECTS

- Reduces arterial stiffness – CV
- Improves endothelial dysfunction, inflammation
- Reduces serum uric acid
- Reduces epicardial adipose tissue
- Improves mitochondrial efficiency
- Reduces steatosis – fatty liver
- **CV and Renal benefits**

JACC 18;72:1845-55 Diabetologia 18;61:2134-9 Med Clin N Am 21;105:955-66
ADA Guidelines 2024 AACE 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
2024 ACC HFREF J Am Coll Cardiol 24;83:1444-88
Prim Care Clin Office Pract 24;51:171-8

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SGLT2i CARDIAC EFFECTS

- Benefits in HFrEF are attained regardless of DM, MRAs and/or ARNIs
- Reduce CV mortality and HF hospitalizations regardless of LVEF
- Lower risk vs. second-line therapy for CVD, CVA, AF, MI, HF
- Significant reduction in composite CV death or hospitalization for HF

Butler J, Zannad F, Filippatos G, Anker SD, Packer M. opinion. ESC on line 9/15/20

J Am Coll Cardiol 24;84:1089-90

Mayo Clin Proc 23;98:985-96

Am J Cardiol 24;218:24-31

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HF Guideline Directed Medical Therapy (GDMT)

- GDMT with the highest expected benefit should be prioritized
 - ↓ symptoms, hospitalizations, & mortality
- **1st-line meds**
 - ARNIs, ACEIs, ARBs, βBs, MRA, and **SGLT2i (Dapa, Empa, Sota)**
- **< 20% get GDMT “quad therapy”**
- **Improve HFrEF & CKD outcomes regardless of DM**

2024 ACC HFrEF J Am Coll Cardiol 24;83:1444-88

2024 ACC Consensus Hospitalized JACC 8/8/24 Pharmacist's Letter, September 2024

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COST OF DRUGS FOR HF

- ACEIs – Lisinopril 40 mg/d ~\$4/mon
- ARBs – Valsartan 160 mg 2xd ~\$40/mon
- βBs – Carvedilol 25 mg 2xd ~\$6/mon; Metoprolol succinate 200 mg/d ~\$25/mon
- ARNI – Sacubitril/valsartan 97/103 mg 2xd ~\$585/mon
- MRAs – Spironolactone 25 mg/d ~\$15/mon
- SGLT2i – Dapagliflozin 10 mg/d ~\$565/mon; Empagliflozin 10 mg/d ~\$593/mon, Sotagliflozin 200 mg/d ~\$598
- Digoxin 0.125 mg/d ~\$37/mon
- Isosorbide/hydralazine 40/75 mg 3xd ~\$690/mon
- Ivabradine 7.5 mg 2xd ~\$490/mon
- Vericiguat 10 mg/d ~\$585/mon

Med Lett Drugs Ther. 21;63:89-96 23;65:114-6

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SGLT2i RENAL EFFECTS

- Reversible decrease in eGFR during first 4 wks
- Nephroprotective
- Reduces progressive decline of eGFR with long-term use in CKD
- Delay in micro- and macroalbuminuria
- Reduces albuminuria
- Reduces CV risk in CKD

Lancet Diabetes Endocrinol 17;5:610-21 Circulation 18;137:119-29

Clin J Am Soc Nephrol 18;13:318-20

JACC 18;72:1845-55

Med Lett Drugs Ther 2020 Nov 16;62(1611):e184-8

Prim Care Clin Office Pract 22;49:315-26

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FDA-APPROVED INDICATIONS

- Bexagliflozin
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
- Canagliflozin
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
 - Reduce risk of MACE in adults with T2DM and established CVD
 - Reduce risk of ESKD, doubling of SCr, CV death, and hospitalization for HF in adults with T2DM and diabetic nephropathy with albuminuria > 300 mg/d

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- Dapagliflozin
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM
 - Reduce risk of hospitalization for HF in adults with T2DM and either established CVD or multiple CV risk factors
 - Reduce risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF
 - Reduce risk of sustained eGFR decline, ESKD, CV death, and hospitalization for HF in adults with CKD at risk of progression

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- Empagliflozin
 - Reduce risk of CV death and hospitalization for HF in adults with HF
 - Reduce risk of sustained decline in eGFR, ESKD, CV death, and hospitalization in adults with CKD at risk of progression
 - Reduce risk of CV death in adults with T2DM and established CVD
 - Adjunct to diet and exercise to improve glycemic control in ≥ 10 y with T2DM
- Ertugliflozin
 - Adjunct to diet and exercise to improve glycemic control in adults with T2DM

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- Sotagliflozin
 - **No T2DM glycemic control indication**
 - Reduce risk of CV death, hospitalization for HF, and urgent HF visit in adults with:
 - HF
 - OR
 - T2DM, CKD, and other CV risk factors
- FDA Prescribing Information

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- ### SGLT2i
- Effects on multiple organs and multiple diseases (e.g. DM, renal injury, HF, nonalcoholic fatty liver disease, inflammatory bowel disease, cognitive disorder)
 - Nonalcoholic fatty liver disease (NAFLD): AACE recommends as adjunctive therapy in patients with type 2 DM and NAFLD
JAMA Intern Med 24;184:375-83
 - PAD
Progress Cardiovascular Diseases 23;81:2-9
 - May slow aging, prevent disease and improve life expectancy

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- ### SGLT2i
- HTN with co-morbidities, eg, HFrEF and T2DM
Endocr Pract 24;30:481-9
 - Potential anti-arrhythmic activity
 - SGLT2i effect on Ca and Na and myocardial energy metabolism
Cardiovascular Diabetology 24;23:252
 - Reduce risk of gout in T2DM
 - May not be from a decrease in uric acid (uricosuric property) – may be from metabolic and anti-inflammatory effects
Diabetes Obes Metab. 2023;25:2697–2703

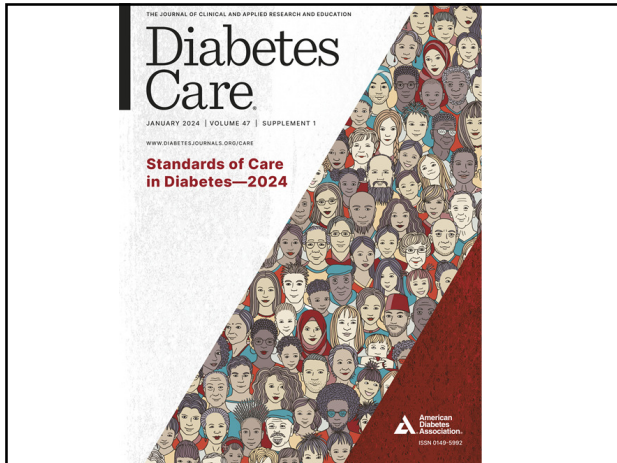
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- ### SGLT2i
- SGLT2i vs non-SGLT2i
 - Alzheimer’s disease 19% reduced risk
 - Vascular dementia 31%
 - All-cause dementia 21%
 - Parkinson’s disease 20%
Medscape Medical News. 9/13/24. Europ Assoc Study of Diabetes 2024 Annual Meeting
 - SGLT2i lower risk of sight-threatening retinopathy vs. DPP-4i, pioglitazone and sulfonylureas
JAMA Network Open 23;6:e2348431

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- ### Rx Patterns for SGLT2i in US Health Systems
- US Rx rates 2022-23 for Class 1 recommendations regardless of DM
 - DM 63.4% had class 1 recommendation – **11.9% taking SGLT2i**
 - Without DM 6.2% had class 1 recommendation – **3.1% taking SGLT2i**
 - **“SGLT2i Rx ... with a Class 1a recommendation is low. Interventions are needed to increase uptake of guideline-recommended SGLT2i use.”**
J Am Coll Cardiol 24;84:683-93

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ADA 2024 T2DM PHARMACOLOGIC THERAPY

- Shared decision-making
- Support weight management goals
- Without obesity, CV or renal risk
 - Metformin or other therapies to reach goal
- ASCVD or high CVD risk, CKD, or HF
 - SGLT2i &/or GLP-1 receptor agonist with demonstrated CVD benefit recommended
- HFrEF or HFpEF
 - SGLT2i recommended for glucose control & prevention of HF hospitalizations

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ADA 2024 T2DM PHARMACOLOGIC THERAPY

- CKD (eGFR 20-60 and/or albuminuria)
 - SGLT2i to reduce CKD progression and CV events and decrease HF hospitalization
- CKD (eGFR <30)
 - GLP-1RA preferred due to lower risk of hypoglycemia and decrease CV events
- GLP-1 receptor agonist preferred to insulin
- If insulin used, combination with GLP-1RA recommended for greater efficacy and effects on weight with less hypoglycemia

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ADA 2024 T2DM PHARMACOLOGIC THERAPY

- Overweight or obesity
 - Preferred GLP-1RA or GIP/GLP-1RA (i.e., semaglutide or tirzepatide)
- Overweight or obesity with NAFLD
 - Consider GLP-1RA with demonstrated benefits in nonalcoholic steatohepatitis (NASH)
- Biopsy-proven NASH or those at high risk with clinically significant liver fibrosis using noninvasive tests
 - Pioglitazone or GLP-1RA are preferred

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ACP NEWER TREATMENTS IN T2DM GUIDELINE

- Recommend adding SGLT-2i inhibitor or GLP-1RA to metformin and lifestyle with inadequate control (strong recommendation; high-certainty evidence).
 - SGLT-2 inhibitor to reduce risk for all-cause mortality, MACE, progression of CKD, and HF hospitalization
 - GLP-1RA to reduce risk for all-cause mortality, MACE, and stroke

Ann Intern Med 24;177:658-66

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COST

- Mark Cuban Cost Plus Drug Company
 - <https://costplusdrugs.com/>
- “Our pharmacy cuts out the middlemen to offer hundreds of common generic medications at wholesale prices.”
- Priced: our cost plus 15% plus the pharmacy fee
- Invokana (Canagliflozin) \$245.93/mon
- Dapagliflozin Propanediol (Generic for Farxiga) \$390.20/mon

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DM MEDS: CV & RENAL

- GLP-1RA
 - CV improves – Dulaglutide, Liraglutide, Semaglutide SQ
 - Neutral – Exanatide, Lixisenatide, Semaglutide oral
 - HF – neutral
 - Renal improves – Dulaglutide, Liraglutide, Lixisenatide, Semaglutide SQ – mostly by reduction in macroalbuminuria
 - Unknown - Exanatide

Pharmacist's Letter/Prescriber's Letter. September 2022. Modified Aug 2023
ADA Guideline 2024

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DM MEDS: CV & RENAL

- SGLT2i
 - CV improves – Canagliflozin, Empagliflozin
 - HF – Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin (may reduce HF hosp), Sotagliflozin
 - Neutral – Bexagliflozin,
 - Renal improves – Canagliflozin, Dapagliflozin, Empagliflozin
 - Neutral – Ertugliflozin

Pharmacist's Letter/Prescriber's Letter. September 2022. Modified Aug 2023
ADA Guideline 2024

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