First-Line Therapy for Type 2 Diabetes: Time for a Change?

Devra Dang, PharmD, CDCES, FNAP
Associate Clinical Professor
UConn School of Pharmacy

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Learning Objectives

At the conclusion of this presentation, participants should be able to:

- List the American Diabetes Association (ADA)'s recommended approach to preventing diabetes-related long-term complications.
- Identify efficacy and safety data for the newest FDA-approved diabetes medication.
- Recall the most recent ADA's guideline recommendations on medication management of hyperglycemia in type 2 diabetes.

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Disclosures

- Speaker for Sanofi.
- All financial interests with ineligible companies have been mitigated.
- This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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AUDIENCE POLL

Which of the following is recommended as first-line medication therapy in an adult patient newly-diagnosed with type 2 diabetes?

- A. metformin
- B. a GLP-1 receptor agonist (eg, dulaglutide, semaglutide)
- C. a SGLT2 inhibitor (eg, dapagliflozin, empagliflozin)

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Example Case

- Mr. N is a 50 yo male with a new diagnosis of type 2 diabetes. His medical history include:
- PMH: type 2 diabetes (A1c 7.5%), HTN (bp 142/84), ED, and obesity (BMI 34 kg/m^2), lipids: TC 200, TG 150, HDL-C, cLDL-C 135 mg/dL
- Current medications: lisinopril 20 mg once daily, HTCZ 25 mg once daily
- SH: 1 glass of wine on weekends, cigarettes: ½ pack/day x 30 years
- **In addition to lifestyle modifications, how can we best treat his type 2 diabetes?**

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Therapeutic Goals in Management of Type 2 Diabetes

- Reduce A1c to goal
- Prevent development of complications of short- and long-term hyperglycemia
- Prevent adverse reactions from treatments
- Improve quality of life

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Long-term Complications of Diabetes

- Microvascular complications
  - Diabetes-related eye disease
  - Diabetes-related kidney disease
  - Neuropathy
    - Diffuse neuropathy
      - Distal symmetric polyneuropathy
      - Autonomic neuropathy
    - Mononeuropathy
    - Radiculopathy
- Macrovascular complications
  - Atherosclerotic cardiovascular disease (ASCVD) most common
- Co-existing conditions that increases CVD risk
  - Hypertension
  - Dyslipidemia
  - Higher weight, obesity
  - Smoking
  - Chronic kidney disease

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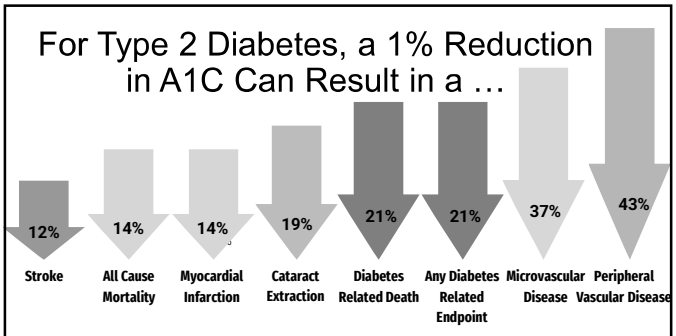
For Type 2 Diabetes, a 1% Reduction in A1C Can Result in a …



Stratton IM et al. BMJ. 2000;321:405-412.

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CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

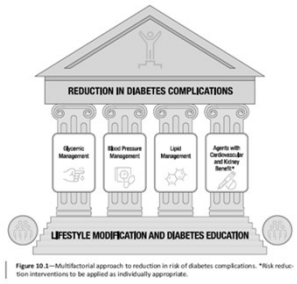

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

ADA Diabetes Guidelines January 2022

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S144-S174

I 9

American Diabetes Association. Connected for Life

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Example Case

- Mr. N asks about "this new medication that is all over social media" that can help with weight loss. He would like to know if he can be prescribed this medication. You realize that he is referring to tirzepatide, the medication approved by the FDA in May 2022 for type 2 diabetes in non-pregnant adults.
- Would you recommend this medication as initial therapy for Mr. N's type 2 diabetes?

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AUDIENCE POLL

Tirzepatide belongs to which of the following drug class?

- A. GLP-1 receptor agonists
- B. dual GIP/GLP-1 agonist
- C. SGLT2 inhibitors

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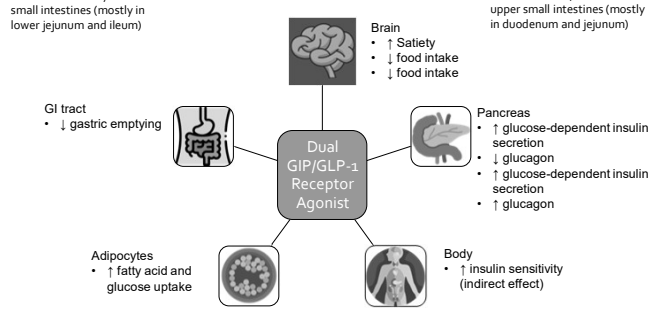
GLP-1: secreted by L-cells in small intestines (mostly in lower jejunum and ileum)

GIP: secreted by K-cells in upper small intestines (mostly in duodenum and jejunum)



Images: Flaticon.com

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Tirzepatide Pre-marketing RCTs

	SURPASS-1	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5
Comparator	Placebo	Semaglutide 1 mg	Insulin degludec (dose titrated to FBG < 90 mg/dL)	Insulin glargine (dose titrated to FBG < 100 mg/dL)	Placebo
Background therapy	None	Metformin	Metformin ± SGLT2-I (31.9% of population)	Metformin (94.9%), SGLT2-i (25.1%), sulfonylurea (54.5%) (any 2 of the 3)	Insulin glargine ± metformin (82.9%)
Mean age and DM duration	54 yo, 4.7 years	57 yo, 8.6 years	57 yo, 8.4 years	64 yo, 11.8 years	61 yo, 13.3 years
Duration of RCT	40 weeks	40 weeks	52 weeks	52-104 weeks	40 weeks

De Block et al. Diabetes Obes Metab. 2022 Aug 5.

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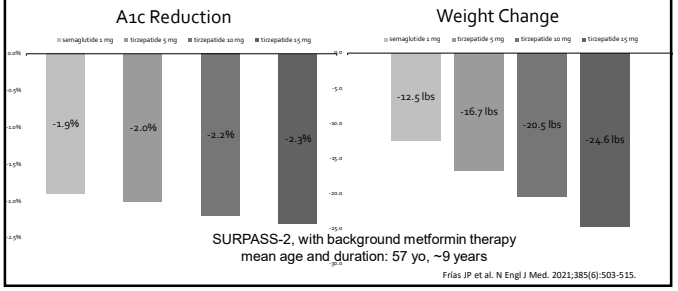
Tirzepatide Pre-Approval RCTs
Comparison with Semaglutide 1 mg



SURPASS-2, with background metformin therapy
mean age and duration: 57 yo, ~9 years

Frías JP et al. N Engl J Med. 2021;385(6):503-515.

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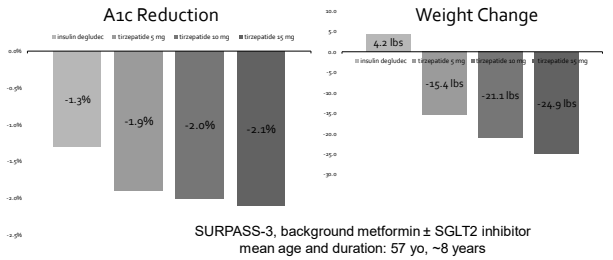
Tirzepatide Pre-Approval RCTs
Comparison with U-100 Insulin Degludec



SURPASS-3, background metformin ± SGLT2 inhibitor
mean age and duration: 57 yo, ~8 years

Ludvik B et al. Lancet. 2021;398(10300):583-598.

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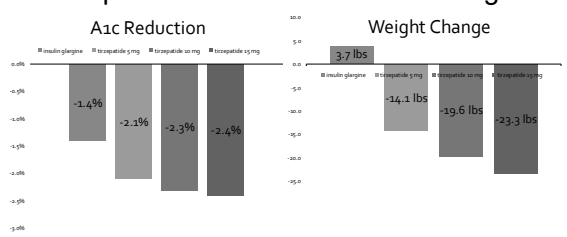
Tirzepatide Pre-Approval RCTs
Comparison with U-100 Insulin Glargine



SURPASS-4, background metformin ± sulfonylurea ± SGLT2 inhibitor
mean age and duration: 64 yo, ~12 years

Del Prato S et al. Lancet. 2021;398(10313):1811-1824.

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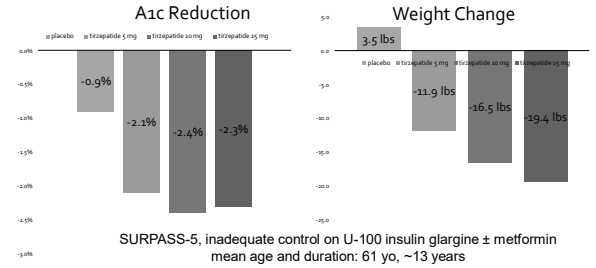
Tirzepatide Pre-Approval RCTs
Add-On to U-100 Insulin Glargine ± Metformin



SURPASS-5, inadequate control on U-100 insulin glargine ± metformin
mean age and duration: 61 yo, ~13 years

Dahl D et al. JAMA. 2022;327(6):534-545.

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Additional RCTs

- Obesity – SURMOUNT-1, mean BMI 38
  - Weight reduction with
    - Tirzepatide 5 mg: -15%
    - Tirzepatide 10 mg: -19.5%
    - Tirzepatide 15 mg: -20.9%
    - Placebo: -3.1%
    - 57% of patients achieved weight reduction of ≥20% with tirzepatide 15 mg
- Cardiovascular outcome trial ongoing
  - Compared to dulaglutide

Jastreboff AM et al; SURMOUNT-1 Investigators. N Engl J Med. 2022 Jul 21;387(3):205-216. Epub 2022 Jun 4.

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AUDIENCE POLL

Based on its mechanism of action, which of the following is an expected adverse drug reaction from tirzepatide?

- A. hypoglycemia
- B. nausea
- C. headache

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Tirzepatide

- Contraindications
  - Black Box Warning of risk of thyroid C-cell tumors
  - "…contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors."

Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.

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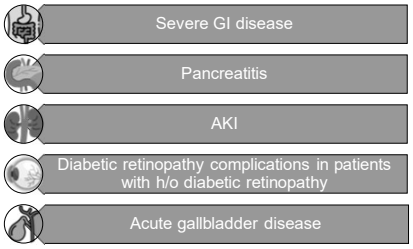
Tirzepatide – Precautions



Images: Flaticon.com

Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.

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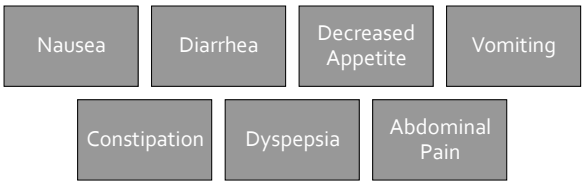
Tirzepatide – Common ADRs



Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.

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Tirzepatide

- Drug-drug interactions
  - Hypoglycemia with concomitant insulin or insulin secretagogues (eg, sulfonylurea)
  - Delays gastric emptying – may affect absorption of comcomitantly administered oral medications
  - Oral hormonal contraceptives
    - Switch to non-oral contraceptive method, or
    - Add a barrier method for 4 weeks after initiation and for 4 weeks after each dose escalation

Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.

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Tirzepatide

- Dosing
  - Start with 2.5 mg qweek, titrate q4weeks (as tolerated, as needed) to max of 15 mg once weekly
  - Subcutaneous administration – abdomen, thigh, or upper arm; rotate site with each dose

Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.

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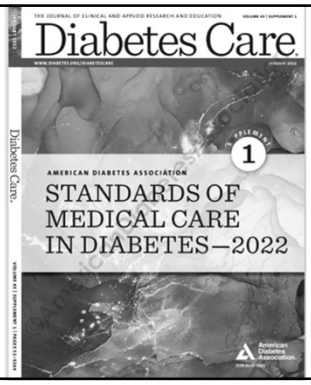
- Guidelines published annually by American Diabetes Association
- Published in *Diabetes Care* in January edition yearly (released online at end of December)



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Diabetes Care

American Diabetes Association

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies, Vanita R. Aroda, Billy S. Collins, Robert A. Gabbay, Jennifer Green, Nisa M. Maruthur, Sylvia E. Rosas, Stefano Del Prato, Chantal Mathieu, Geltrude Mingrone, Peter Rossing, Tsvetalina Tankova, Apostolos Tsapas, and John B. Buse

Diabetes Care 2022;45(11):2753–2786 | https://doi.org/10.2337/dci22-0034

Published September 2022

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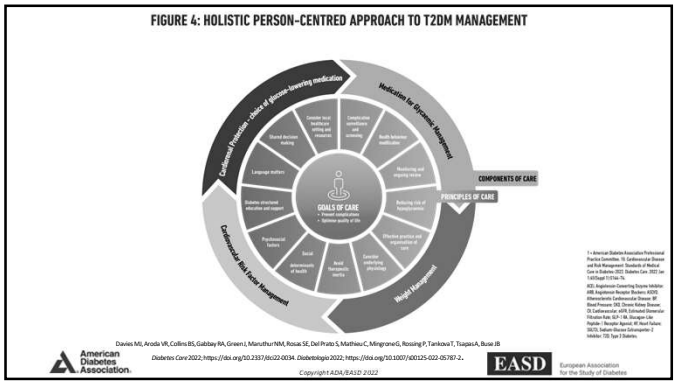

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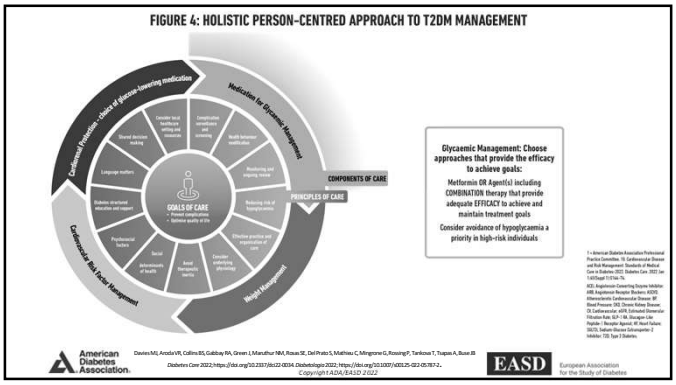

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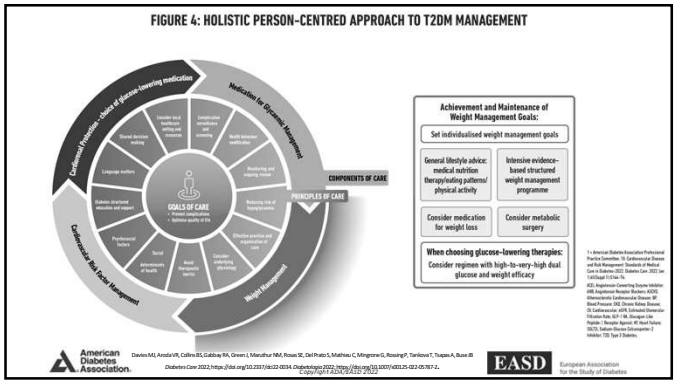

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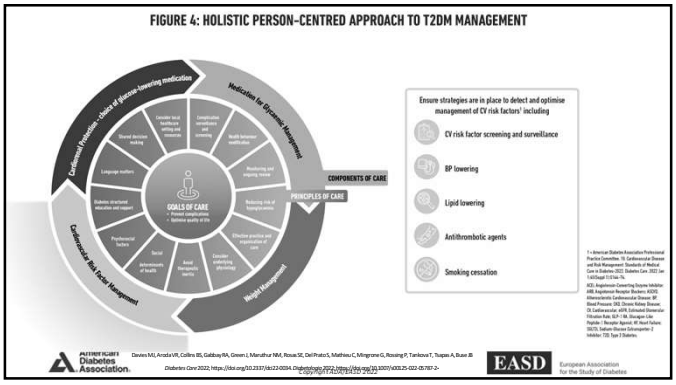

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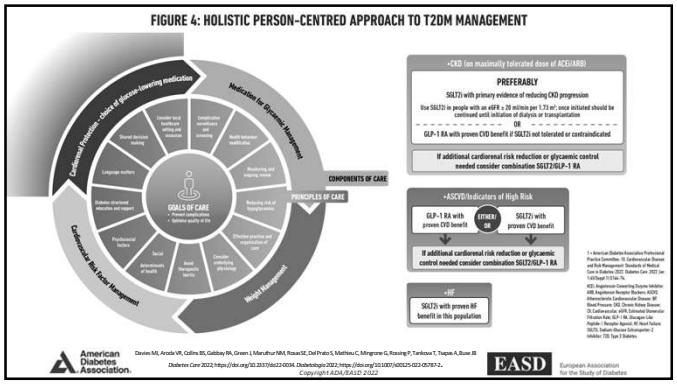

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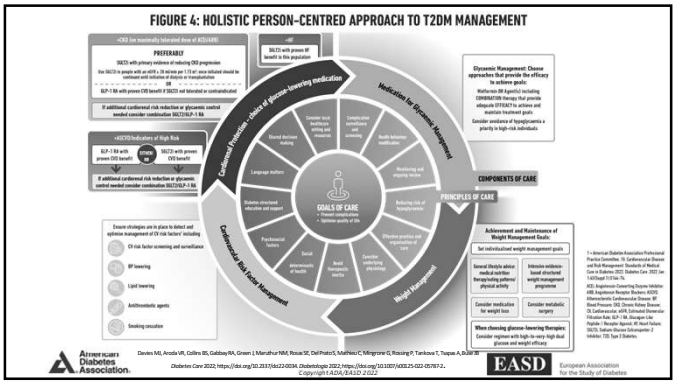

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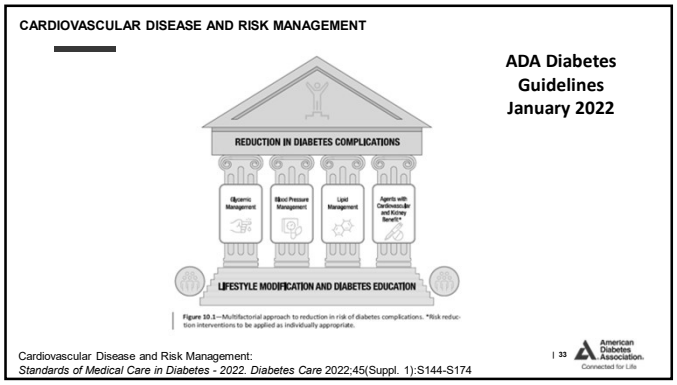

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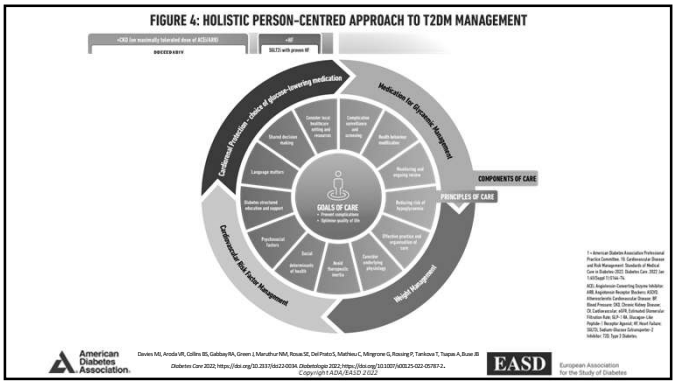

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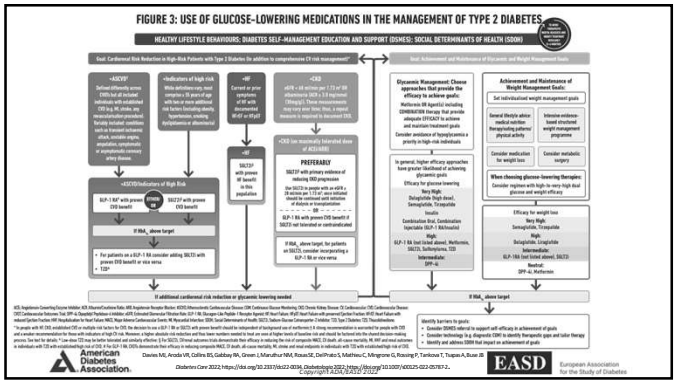

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	Efficacy (A1c)	Hypo-glycemia	Wt Reduction	↓ MACE	HF	Progression of DKD
Metformin	1-2%	None	Neutral (possible modest wt loss)	Potential	Neutral	Neutral
SGLT2 inhibitors	~0.8%	None	Intermediate	canagliflozin, empagliflozin	canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	canagliflozin, dapagliflozin, empagliflozin
GLP-1 receptor agonists	up to 2%	None	High	dulaglutide, liraglutide, semaglutide (SQ)	Neutral	dulaglutide, liraglutide, semaglutide (SQ) – benefit for renal outcomes in CVOTs driven by albuminuria outcomes
Dual GIP and GLP-1 receptor agonist	up to 2.4%	None	Very high	RCT underway	RCT underway	RCT underway

MACE = major adverse cardiovascular event

Adapted from ADA-EASD Management of Hyperglycemia in Type 2 Diabetes Consensus Report 2022

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	Route of Administration	Common ADRs	Rare but Serious ADRs	Cost
Metformin	Oral	GI Vitamin B12 depletion	Lactic acidosis	Low
SGLT2 inhibitors	Oral	Genital mycotic infxn, UTI, watch volume status and bp (may need to adjust bp meds)	Euglycemic DKA, Fournier's gangrene	High
GLP-1 receptor agonists	SQ, oral (semaglutide)	GI Avoid use in patients with GI neuropathy	Thyroid C-cell tumors in rodents, pancreatitis, cholelithiasis or cholecystitis	Very high
Dual GIP and GLP-1 receptor agonist	SQ	GI Avoid use in patients with GI neuropathy	Thyroid C-cell tumors in rodents, pancreatitis, cholelithiasis or cholecystitis	Very high

Adapted from ADA-EASD Management of Hyperglycemia in Type 2 Diabetes Consensus Report 2022.

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Example Case

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- Current medications: lisinopril 20 mg once daily, HTCZ 25 mg once daily
- SH: 1 glass of wine on weekends, cigarettes: ½ pack/day x 30 years
- In addition to lifestyle modifications, how can we best treat his type 2 diabetes?

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AUDIENCE POLL

- Which of the following would you recommend for Mr. N?
- A. metformin
- B. a GLP-1 receptor agonist
- C. tirzepatide

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First-Line Therapy for Type 2 Diabetes: Time for a Change?

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Session Code

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