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PHARMACOLOGIC APPROACHES FOR GLYCEMIC TREATMENT IN TYPE 2 DIABETES

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Respond at **PollEv.com/hpwhitley**

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AUDIENCE RESPONSE QUESTIONS

Poll Everywhere

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FACULTY DISCLOSURE/CONFLICT OF INTEREST

I, Heather Whitley, have no actual or potential conflict of interest in relation to this program.

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OBJECTIVES

- **Compare** the pathophysiology of type 1 to type 2 diabetes mellitus
- **Explain** the mechanism through which glycemic benefit is achieved with antihyperglycemic medications commonly used in the treatment of type 2 diabetes mellitus
- **Apply** drug and patient specific factors when selecting an antihyperglycemic medication for a patient with type 2 diabetes mellitus

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DIFFERENCE IN DIABETES

Hyperglycemia

Type 1

- Fast onset
- Usually occurs in childhood
- Autoimmune mediated
- Complete lack of insulin production
  - Exogenous insulin required

Type 2

- Slow onset
- More often in adulthood
  - Increasing prevalence in children
- High insulin resistance
  - Multiple therapeutic options
  - Insulin eventually necessary

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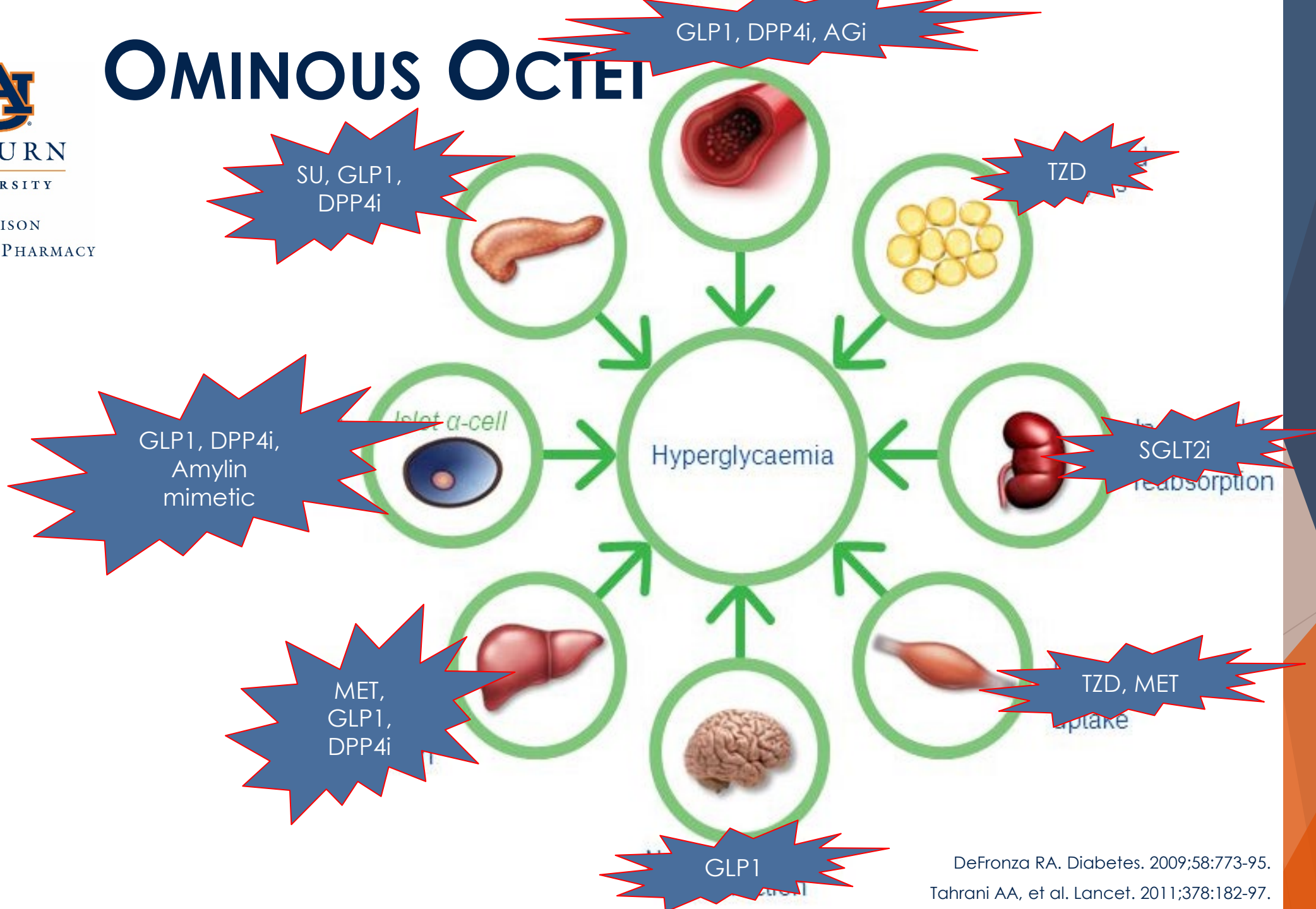
OMINOUS OCTET



DeFronza RA. Diabetes. 2009;58:773-95.

Tahrani AA, et al. Lancet. 2011;378:182-97.

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		Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
					ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors		Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs		High	No	Loss	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m^2 ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

Diabetes Care. 2021;41(Suppl. 1):S111-S124.

Common Non-Insulin Antihyperglycemic Medications

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Sensitizers

Biguanides
Metformin

TZDs
Pioglitazone
Rosiglitazone

Incretin Replacement

GLP-1 RA
Liraglutide
Semaglutide (SC & PO)
Exenatide (BID & LAR)
Lixisenatide
Dulaglutde
~~Albigutide~~

Incretin Enhancers

DPP-4 inhibitors
Alogliptin
Linagliptin
Saxagliptin
Sitagliptin

Secretagogues

Sulfonylureas
Glimepiride
Glipizide
Glyburide

Meglitinides
Nateglinide
Repaglinide

Inhibitors

SGLT-2 inhibitors
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

a-glucosidase inhibitors
Acarbose
Miglitol

ADA, Standards of Medical Care in Diabetes, 2019.
Inzucchi SE et al. *Diabetes Care* 2015;38:140-9.

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OVERVIEW GLUCOSE-LOWERING AGENTS

Class	Expected A1C Reduction, %	Advantages	Disadvantages	Cost
Biguanides	1.0-2.0	Extensive clinical experience; rare hypoglycemia; ↓ CVD events (UKPDS)	GI side effects; lactic acidosis risk (rare); vitamin B_{12} deficiency	Low (generic)
TZDs	0.5-1.4	Rare hypoglycemia; durability; ↓ CVD events (pioglitazone)	Edema; heart failure; weight gain; bone fractures; ↑ LDL-C and CVD events (rosiglitazone)	Low (generic)
Sulfonylureas	1.0-1.5	Extensive clinical experience; ↓ microvascular risk (UKPDS)	Hypoglycemia; weight gain, less durability	Low (generic)
Meglitinides	0.5-1.0	Short duration of action; hepatic clearance; postprandial benefit	Hypoglycemia; weight gain; low efficacy; TID doing	Moderate (generic)
DPP-4 inhibitors	0.5-0.8	Rare hypoglycemia; minimal side effects; postprandial benefit	Risk of pancreatitis; joint pain	High
GLP-1 RA	0.6 – 1.2	Rare hypoglycemia; ↓ weight & BP; ↓ CV events; ↓ proteinuria	GI side effects; most SC, injection site reactions	High
SGLT-2 inhibitors	0.5-1.0	Rare hypoglycemia; ↓ weight and blood pressure; effective at all stages of T2D; ↓ CV, renal, hHF events	GU infections; volume depletion/hypotension	High

ADA, Standards of Medical Care in Diabetes, 2021. Ismail-Beigi F. *N Engl J Med.* 012;366:1319-27. Inzucchi SE et al. *Diabetes Care* 2015;38:140-9.

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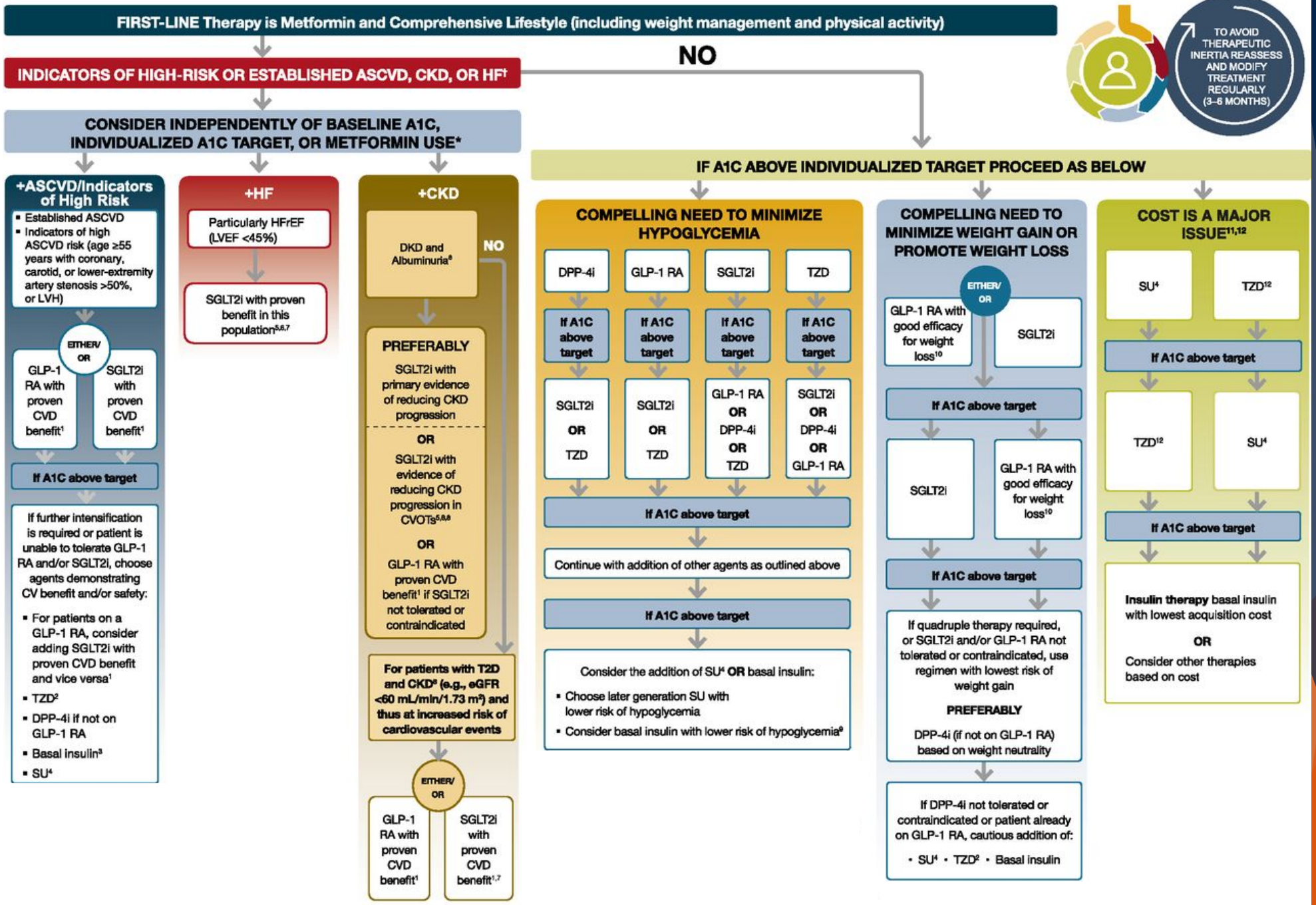

Diabetes Care. 2021;41(Suppl. 1):S111-S124.

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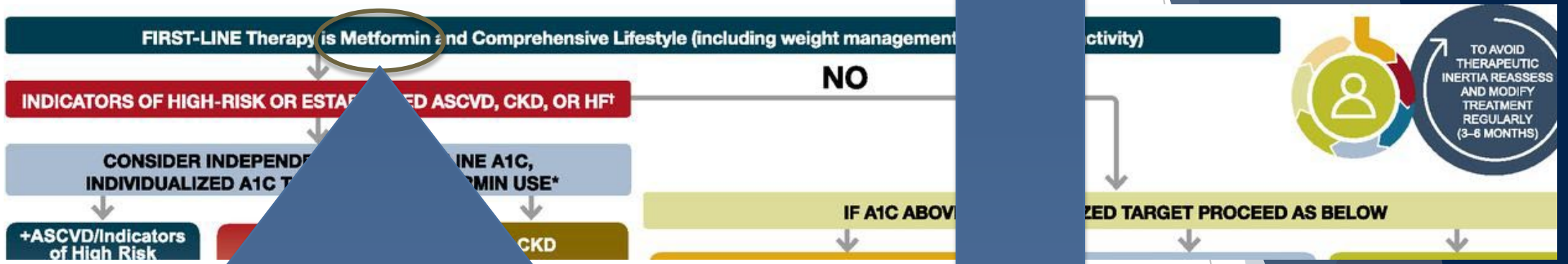

Diabetes Care. 2021;41(Suppl. 1):S111-S124.

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AUDIENCE QUESTION

Why is metformin recommended as the first-line pharmacotherapy option consistently among guidelines?

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Why is metformin recommended as the first-line pharmacotherapy consistently among guidelines?

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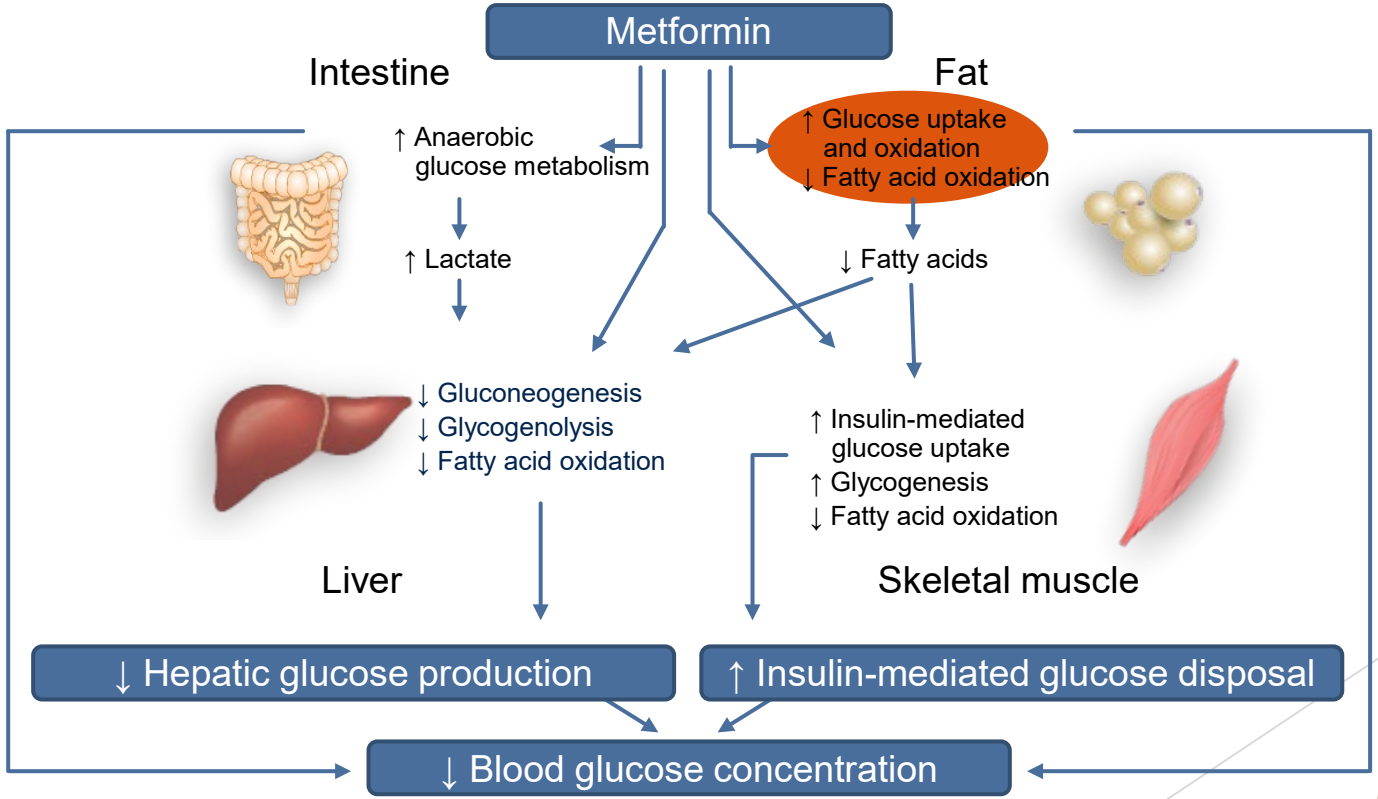
METFORMIN MECHANISM OF ACTION

1. Decrease of hepatic glucose production
2. Decrease of gastrointestinal glucose absorption
3. Increase insulin sensitivity



Campbell IW. *Br J Diabetes Vasc Dis* 2006;6:207-15.
Kirpichnikov D et al. *Ann Intern Med* 2002;137:25-33.

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METFORMIN

- 1-2% A1C Decrease
  - Weeks to reach optimal glycemic effect
- Dosing: 1-3 x/day (IR); 1-2 x/day (XR)
  - Reduce dose in renal insufficiency
- Benefits:
  - Rare hypoglycemia
  - Possible weight loss
  - Possible CVD benefit
  - Inexpensive
- Common ADE: GI-related
  - Diarrhea, nausea, abdominal pain
- Rare ADE: lactic acidosis
  - Likely in cases of metformin overdose
  - 'Overdose' of metformin can be caused by renal failure

1. ADA, Standards of Medical Care in Diabetes, 2021
2. Ismail-Beigi F. *N Engl J Med* 2012;366:1319-27
3. Glucophage® [Prescribing Information]. Princeton, NJ: Bristol-Myers Squibb, 2017
4. Garber AJ et al. *Endocr Pract* 2017;23:207-38

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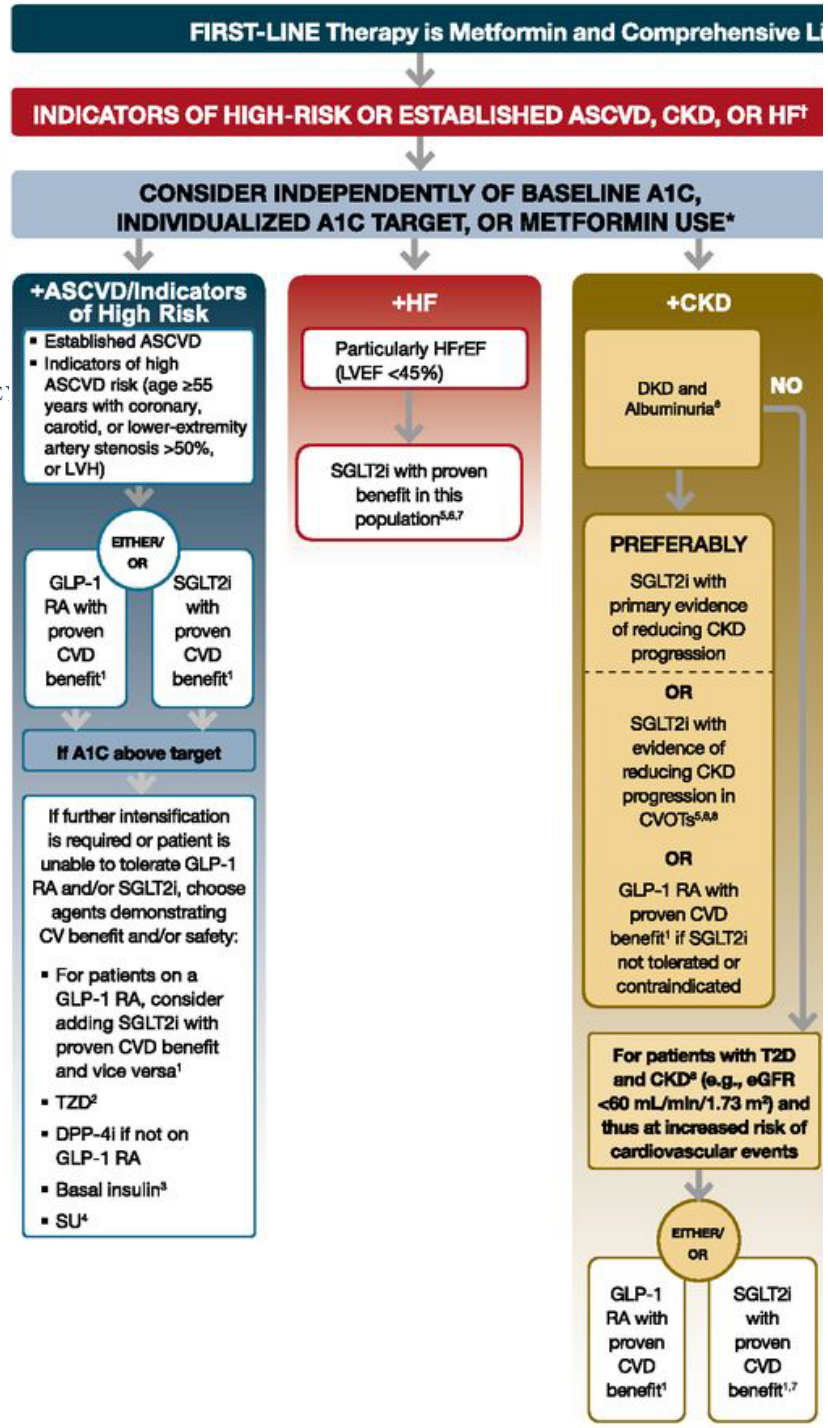


ASCVD, HF, CKD: SGLT2I AND GLP-1 RA

- Use agents with established benefit
  - Preferably agent with primary outcome data
- Independent of A1C
  - Consider adjustment of background therapy:
  - Blood glucose & HTN Rx
- If further intensification is required, add the opposing therapy

Diabetes Care. 2021;41(Suppl. 1):S111-S124.

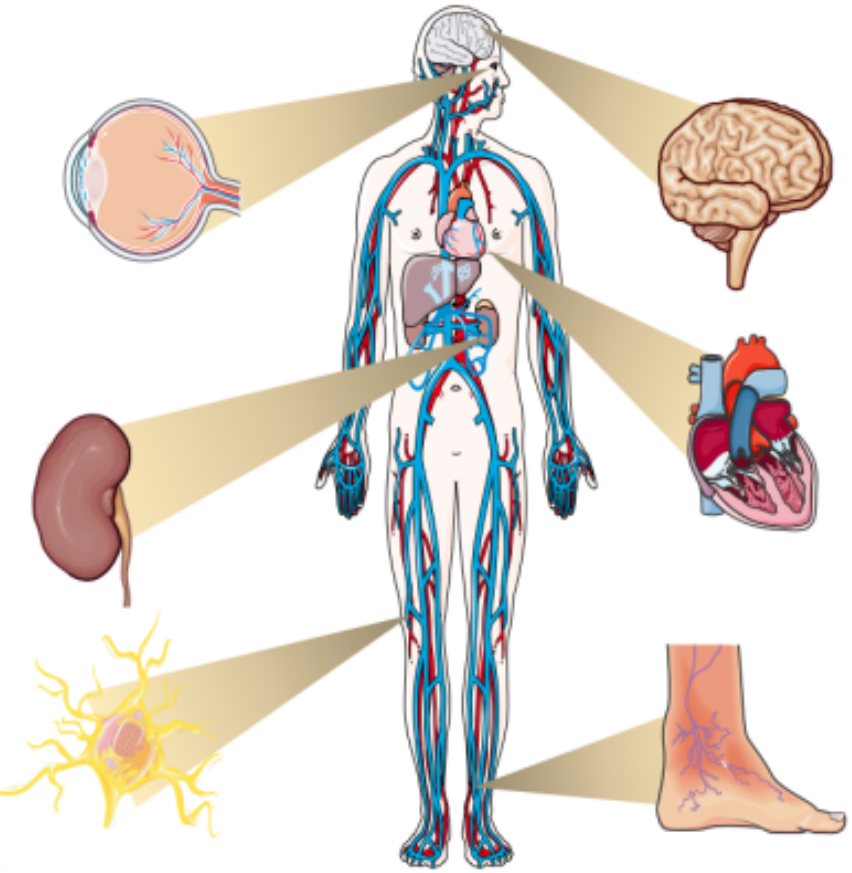
Complications of Diabetes

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

https://pdb101.rcsb.org/global-health/diabetes-mellitus/monitoring/complications

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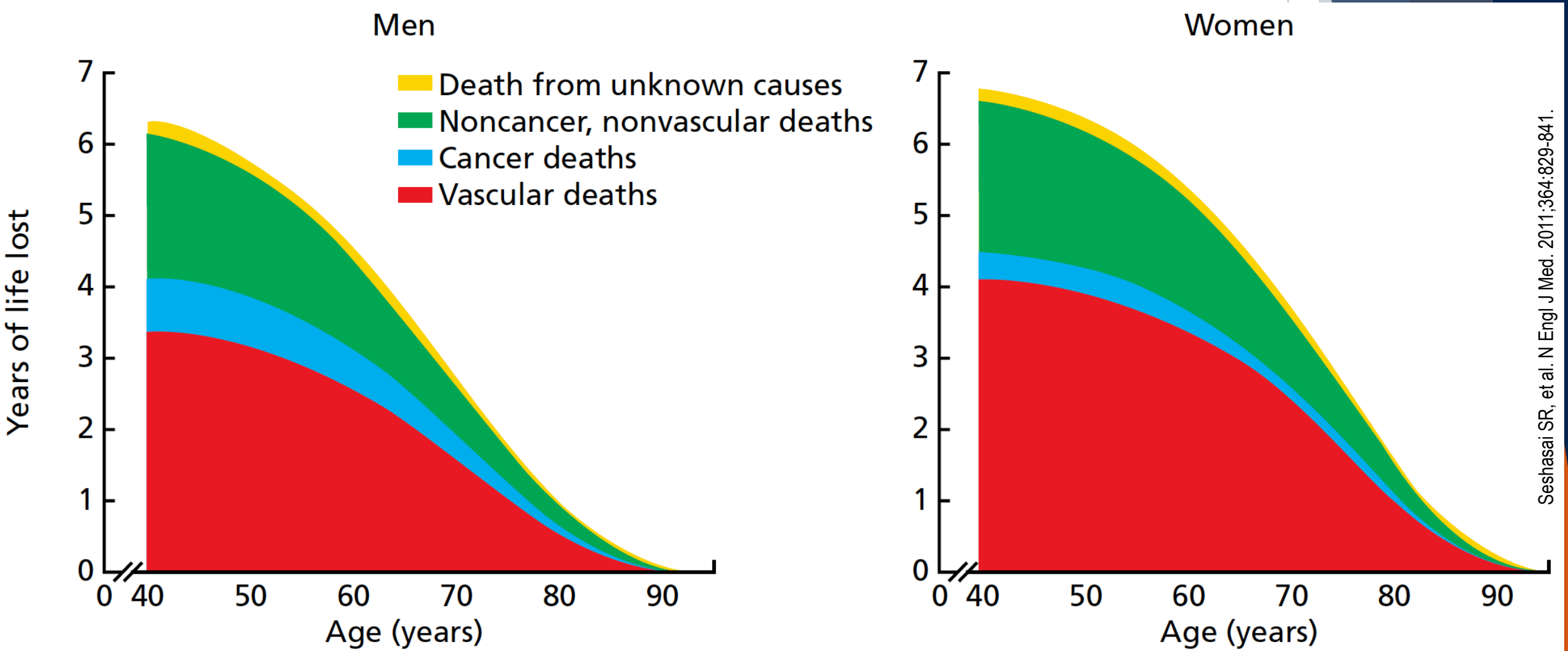
ESTIMATED YEARS OF LIFE LOST DUE TO DIABETES



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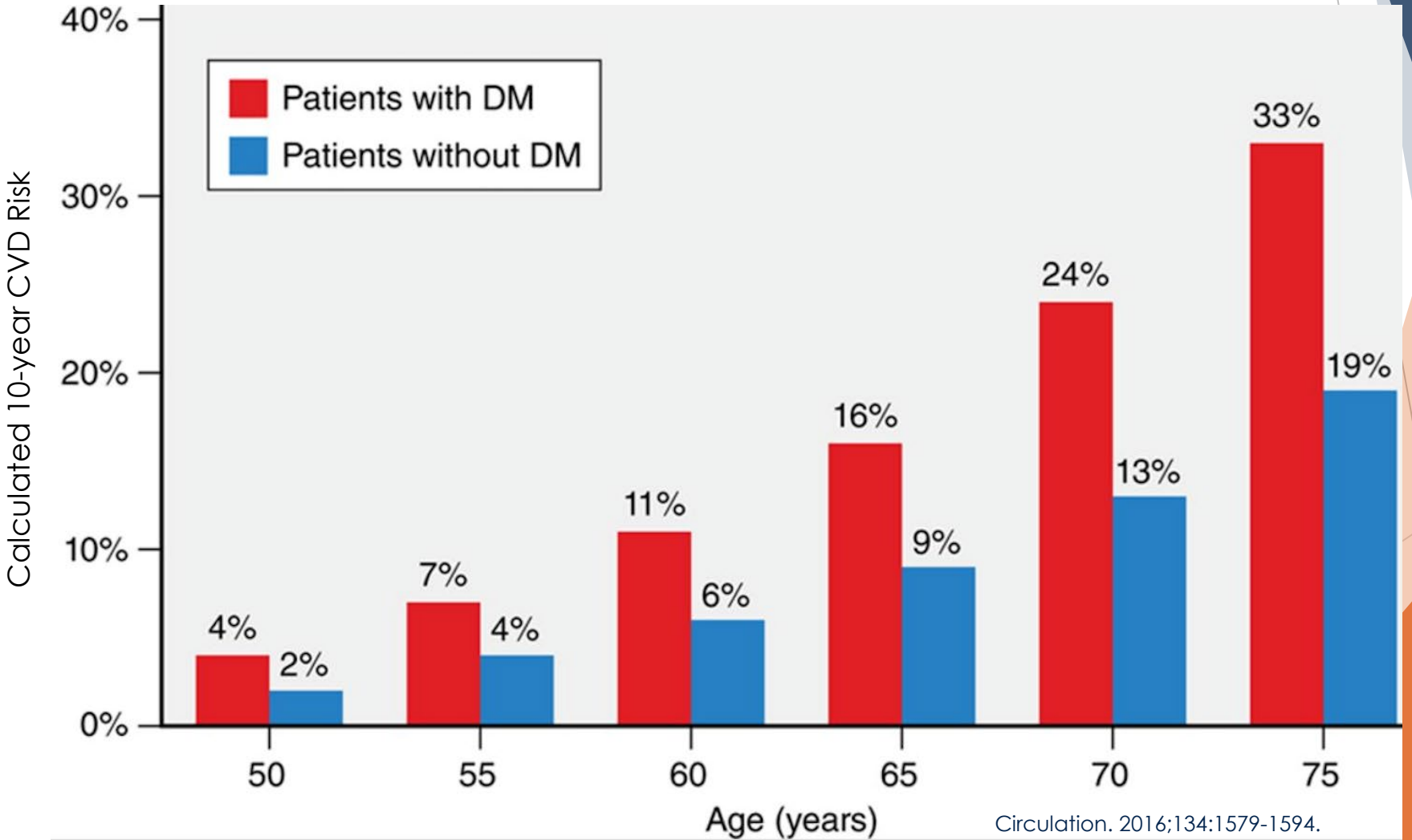
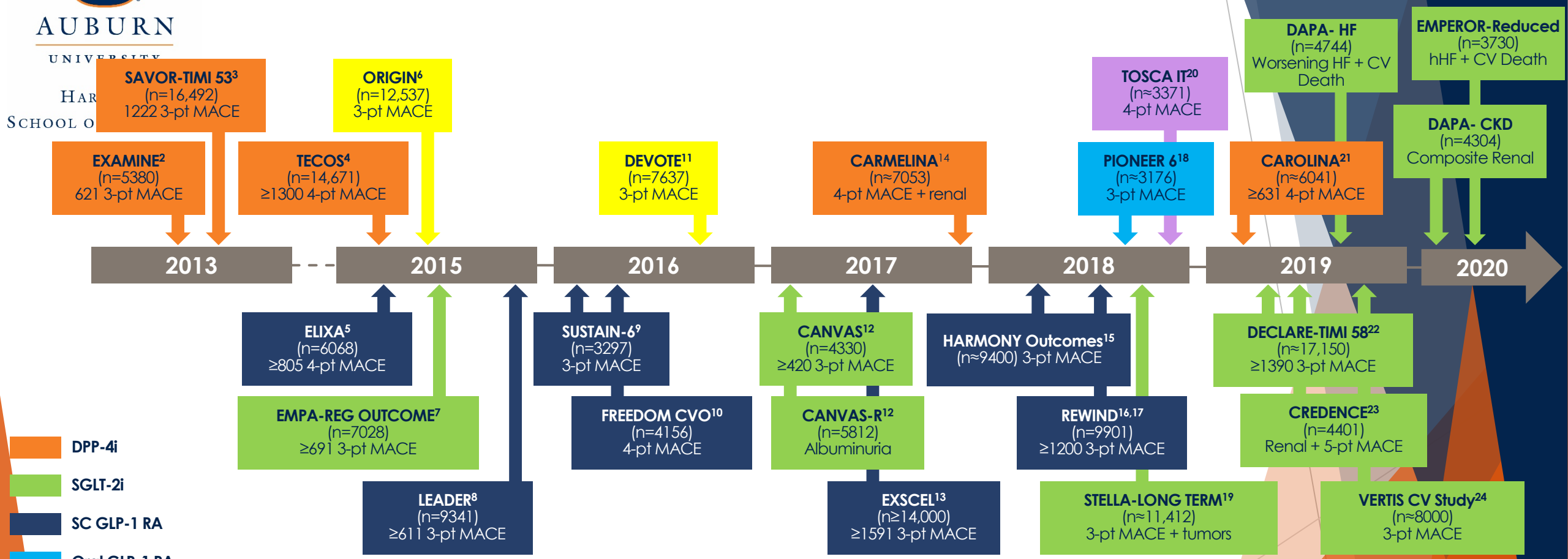
10-YEAR CVD RISK WITH AND WITHOUT DIABETES



Circulation. 2016;134:1579-1594.

TIMELINE OF RECENT TYPE 2 DIABETES CVOTs[1]



DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium glucose transport protein 2 inhibitor.; TZD, thiazolidinedione.

Note: Dates represent estimated completion dates according to ClinicalTrials.gov.

1. Johansen OE. *World J Diabetes.* 2015;6(9):1092-6.; 2. White WB, et al. *N Engl J Med.* 2013;369(14):1327-35.; 3. Scirica BM, et al. *N Engl J Med.* 2013;369(14):1317-26.; 4. Green JB, et al. *N Engl J Me* 2015;373(3):232-42.; 5. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.; 6. The ORIGIN Trial Investigators. *N Engl J Med.* 2012;367(4):319-28.; 7. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-28.; 8. Mars SP, et al. *N Engl J Med.* 2016;375(4):311-22.; 9. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.; 10. ClinicalTrials.gov. NCT01455896.; 11. Marso SP, et al. *N Engl J Med.* 2017;377(8):723-32.; 12. Neal B, et al. *Engl J Med.* 2017;377(7):644-57.; 13. Holman RR, et al. *N Engl J Med.* 2017;377(13):1228-39.; 14. Rosenstock J, et al. *JAMA.* 2019;321(1):69-79.; 15. Hernandez AF, et al. *Lancet.* 2018;392(10157):1519-29.; 16. Gerstei HC, et al. *Lancet.* 2019;394(10193):121-30.; 17. Gerstein HC, et al. *Lancet.* 2019;394(10193):131-8.; 18. Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.; 19. Nakamura I, et al. *Adv Ther.* 2019;36(4):923-49.; 20 ClinicalTrials.gov. NCT00700856.; 21. Rosenstock J, et al. *JAMA.* 2019.; 22. Wiviott SD, et al. *N Engl J Med.* 2019;380(4):347-57.; 23. Perkovic V, et al. *N Engl J Med.* 2019;380(24):2295-306.; 24. Cannon, et al. N Engl J Med. 2020. 25. McMurray, et al. N Engl J Med. 2019;381:1995-2008.; 26. Heerspink, et al. N Engl J Med. 2020;383:1436-1446.; 27. Packer, et al. N Engl J Med. 2020;383(15):1413-1424.

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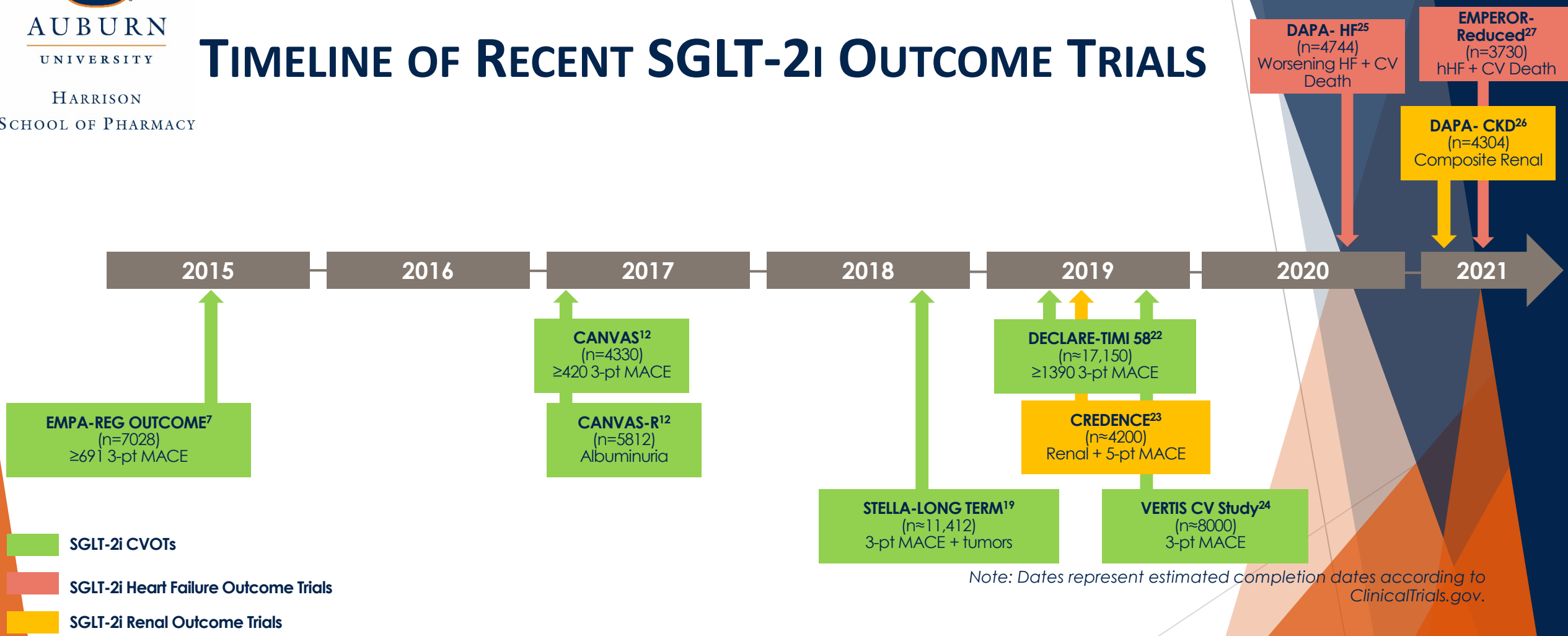
TIMELINE OF RECENT SGLT-2I OUTCOME TRIALS



Note: Dates represent estimated completion dates according to ClinicalTrials.gov.

SGLT-2i, sodium glucose transport protein 2 inhibitor. MACE, major adverse cardiovascular events; HF, heart failure; CV, cardiovascular; hHF, hospitalization for heart failure

7. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-28.; 12. Neal B, et al. *N Engl J Med.* 2017;377(7):644-57.; Nakamura I, et al. *Adv Ther.* 2019;36(4):923-49.; 22. Wiviott SD, et al. *N Engl J Med.* 2019;380(4):347-57.; 23. Perkovic V, et al. *N Engl J Med.* 2019;380(24):2295-306.; 24. Cannon, et al. N Engl J Med. 2020. 25. McMurray, et al. N Engl J Med. 2019;381:1995-2008.; 26. Heerspink, et al. N Engl J Med. 2020;383:1436-1446.; 27. Packer, et al. N Engl J Med. 2020;383(15):1413-1424.

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AUDIENCE QUESTION

Are the non-glycemic benefits from SGLT2i a class effect?

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Are the non-glycemic benefits from SGLT2 inhibitors a class effect?

Yes

No

Not sure

SGLT2 Inhibitor CVOTs

Study Identifier	No. of Patients	Follow-up Time	Study Design	Primary Endpoint	Results HR (95% CI)
EMPA-REG OUTCOME[1] CVD; HbA1c ≥7.0-10.0%	7,028	3.1 y	Empagliflozin Placebo	3P-MACE	**0.86 (0.74-0.99)** p=0.04[a] (superiority)
CANVAS[2] High risk/history of CV event HbA1c 7.0-10.5%	4,330	3.6 y	Canagliflozin 100 mg Canagliflozin 300 mg Placebo	3P-MACE	**0.86 (0.75-0.97)** p=0.02 (superiority)
CANVAS-R[2] High risk/history of CV event HbA1c ≥7.0-≤10.5%	5,812			Progression of albuminuria	
DECLARE-TIMI 58[3] CVD	17,160	4.2 y	Dapagliflozin Placebo	3P-MACE CV death + HF hospitalization	**0.93 (0.84-1.03)** p=0.17 (noninferiority) **0.83 (0.73-0.95)** p=0.005 (superiority)
VERTIS CV Study[6] CVD HbA1c 7.0-10.5%	8,246	3.5 y	Ertugliflozin 5 mg Ertugliflozin 15 mg Placebo	3P-MACE	**0.97 (0.85-1.11)** P=0.001 (noninferiority)

1. Zinman B et al. *N Engl J Med* 2015;373:2117-28
2. Neal B et al. *N Engl J Med* 2017;Ahead of print
3. Wiviott SD, et al. *N Engl J Med.* 2018;380:347-357
4. Perkovic, et al. N Engl J Med. 2019;380:2295-2306.
5. McMurray, et al. N Engl J Med. 2019;381:1995-2008.
6. https://clinicaltrials.gov/ct2/show/NCT01986881

SGLT2 Inhibitor Large Outcome Trial

Heart Failure SGLT2i Trials

Study Identifier	No. of Patients	Follow-up	Study Design	Primary Endpoint	Results HR (95% CI)
DAPA-HF[5] HFrEF ± T2DM	4,744	18.2 mo	Dapagliflozin 10 mg Placebo	Worsening HF/CV death	**0.74 (0.65-0.85)** P<0.001 (superiority)
EMPEROR-Reduced HFrEF ± T2DM	3,730	16 mo	Empagliflozin 10 mg Placebo	hHF / CV death	**0.75 (0.65-0.86)** P<0.001 (superiority)
EMPEROR-Preserved HFpEF ± T2DM	5,988	38 mo	Empagliflozin 10 mg Placebo	CV death, hHF	**April 2021** anticipated completion

Renal SGLT2i Trials

Study Identifier	No. of Patients	Follow-up	Study Design	Primary Endpoint	Results HR (95% CI)
CREDENCE[4] eGFR 30-90, UACR >300, HbA1c 6.5-12.0%	4,401	2.62 y; stopped early	Canagliflozin 100 mg Placebo	ESRD, doubling of sCR, or renal/CV death	**0.7 (0.59-0.82)** P=0.00001; NNT=23 (superiority)
DAPA-CKD eGFR 25-75, UACR > 200, ± T2DM	4,304	2.4 y; stopped early	Dapalgliflozin 10 mg Placebo	ESRD, ≥ 50% sustained eGFR decline, renal/CV death	**0.61 (0.51-0.72)** P<0.001; NNT=19
EMPA-Kidney eGFR 20-45 or 45-90 + UACR >200	~6,000	Started: January 2019	Empagliflozin 10 mg Placebo	ESRD, ≥ 40% sustained eGFR decline, sustained decline to <10 eGFR, renal/CV death	**October 2022** anticipated completion

1. Zinman B et al. *N Engl J Med* 2015;373:2117-28
2. Neal B et al. *N Engl J Med* 2017;Ahead of print
3. Wiviott SD, et al. *N Engl J Med*. 2018;380:347-357
4. Perkovic, et al. N Engl J Med. 2019;380:2295-2306.
5. McMurray, et al. N Engl J Med. 2019;381:1995-2008
6. https://clinicaltrials.gov/ct2/show/NCT01986881

SGLT2 Inhibitors Expanded FDA-Approved Indications

Medication	Expanded FDA Indication
Empagliflozin (Jardiance)	**CV:** Risk reduction of cardiovascular mortality in adults with T2D and established CVD **HF:** Under consideration
Canagliflozin (Invokana)	**CV:** Risk reduction of MACE in adults T2D and established CVD **Renal:** Risk reduction of ESRD, doubling of serum creatinine, CV death, and hHF in adults with T2D and diabetic nephropathy with UACR > 300 mg/day
Dapagliflozin (Farxiga)	**CV:** None **HF:** Risk reduction of hHF in patient with T2D and established CVD or multiple CV risk factors; Risk reduction of CV death and hHF in adults with HFrEF (NYHA class II – IV) **Renal:** Risk reduction of sustained eGFR decline, ESKD, CV death, and hHF in adults with CKD at risk of progression
Ertuglifozin (Steglatro)	**CV:** None

MACE; major adverse cardiovascular disease. hHF; hospitalization for heart failure. T2D; type 2 diabetes mellitus

Jardiance [package insert]. Lilly; 2020; Invokana [package insert]. Janssen; 2020.; Farxiga [package insert]. AstraZeneca; Year; Steglatro [package insert]. Merck; 2021

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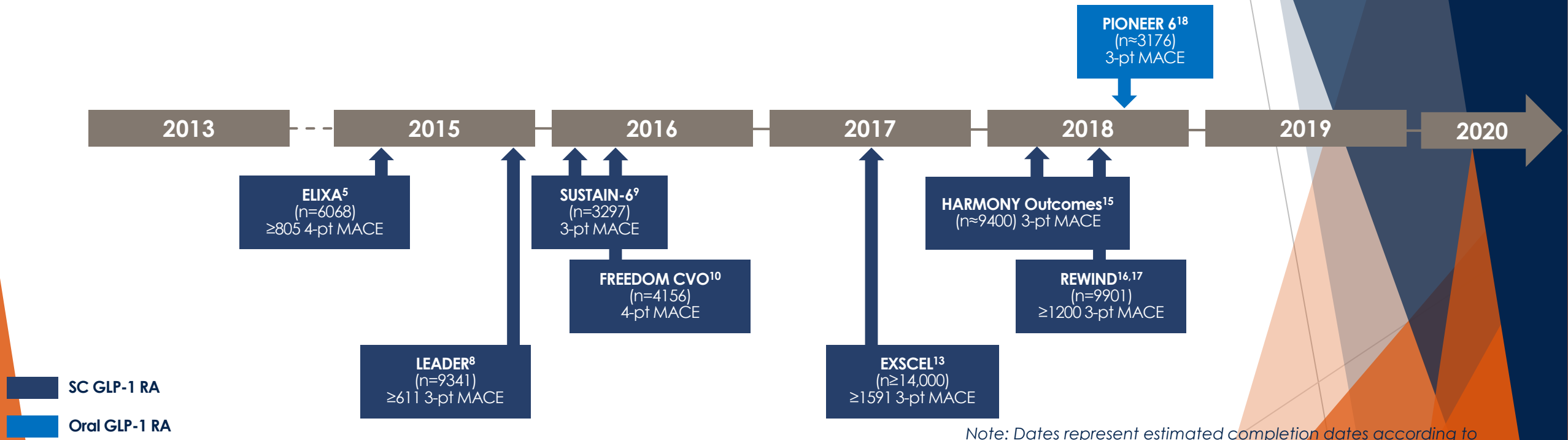
TIMELINE OF RECENT GLP1-RA CVOTS



Note: Dates represent estimated completion dates according to ClinicalTrials.gov.

5. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57 8. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.; 9. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44. 10. ClinicalTrials.gov. NCT01455896.; 13. Holman RR, et al. *N Engl J Med.* 2017;377(13):1228-39.; 15. Hernandez AF, et al. *Lancet.* 2018;392(10157):1519-29.; 16. Gerstein HC, et al. *Lancet.* 2019;394(10193):121-30.; 17. Gerstein HC, et al. *Lancet.* 2019;394(10193):131-8.; 18. Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.

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AUDIENCE QUESTION

Are the CV benefits gained from GLP-1 RAs a class effect?

Respond at **PollEv.com/hpwhitley**

Are the CV benefits gained from GLP-1 RAs a class effect?

Yes

No

Not sure

Overview of GLP-1 RA CVOTs

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Study identifier	No. of patients	Follow-up Time	Study design	Primary endpoint	Results HR (95% CI)
ELIXA[1] ACS <180 days; A1C 5.5%–11%	6,068	2.1 y	Lixisenatide Placebo	4-pt MACE	**1.02 (0.89–1.17)** P<0.001 (non-inferiority) p=0.81 (superiority)
LEADER[2] CV risk/CVD; A1C ≥7.0%	9,340	3.8 y	Liraglutide Placebo	3-pt MACE	**0.87 (0.78–0.97)** p=0.01 (superiority)
SUSTAIN 6[3] CVD; A1C ≥7.0%	3,297	2.1 y	Semaglutide (SC) Placebo	3-pt MACE	**0.74 (0.58–0.95)** p=0.02 (superiority)
PIONEER 6[4] CVD or CKD	3,183	1.3 y	Semaglutide (PO) Placebo	3-pt MACE	**0.79 (0.57–1.11)** P<0.001 (non-inferiority) P=0.17 (superiority)
EXSCEL[5] High CV risk/CVD; A1C 6.5%–10.0%	14,752	3.2 y	Exenatide XR Placebo	3-pt MACE	**0.91 (0.83–1.00)** P<0.001 (non-inferiority) p=0.06 (superiority)
REWIND[6] High CV risk; A1C ≤9.5%	9,901	5.4 y	Dulaglutide Placebo	3-pt MACE	**0.88 (0.79–0.99)** p=0.026 (superiority)

1. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-57.; 2. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-22.;3. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-44.; 4. Husain M, et al. *N Engl J Med.* 2019;381(9):841-51.; 5. Holman RR et al. *N Engl J Med* 2017;377(13):1228-39.; 6. Gerstein HC, et al. Lancet. 2019;394(10193):121-30.

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GLP-1 RA EXPANDED FDA-APPROVED CARDIOVASCULAR INDICATIONS

Medication	Expanded CV FDA Indication
Liraglutide (Victoza)	"…reduce the risk of major adverse CV events in adults with T2D and established CVD"
Semaglutide (Ozempic)	"…to reduce the risk of major adverse CV events in adults with T2D and established CVD"
Semaglutide (Rybelsus)	None
Exenatide XR (Bydureon, Bydureon BCise)	None
Dulaglutide (Trulicity)	"…to reduce the risk of major adverse CV events in adults with T2D who have established CVD or multiple CV risk factors."
Lixisenatide (Adlyxin)	None

Bydureon BCise [package insert]. AstraZenica; 2020; Ozempic [package insert]. Novo Norsdisk; 2020; Rybelsus [package insert]. Novo Nordisk; 2020; Trulicity [package insert]. Lilly; 2020; Victoza [package insert]. Novo Nordisk; 2020.

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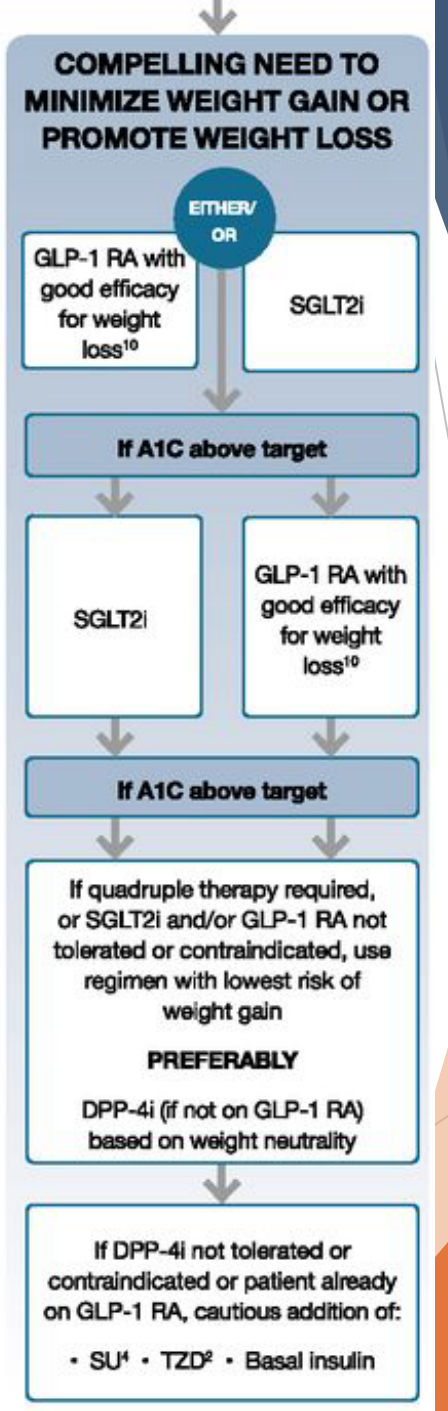
WEIGHT LOSS: SGLT2I AND GLP-1 RA

- GLP-1 RA
  - Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- SGLT2 Inhibitors
- If A1C above target, add opposing therapy
- Quadruple therapy:
  - Choose weight neutral options (DPP4i)



Diabetes Care. 2021;41(Suppl. 1):S111-S124.

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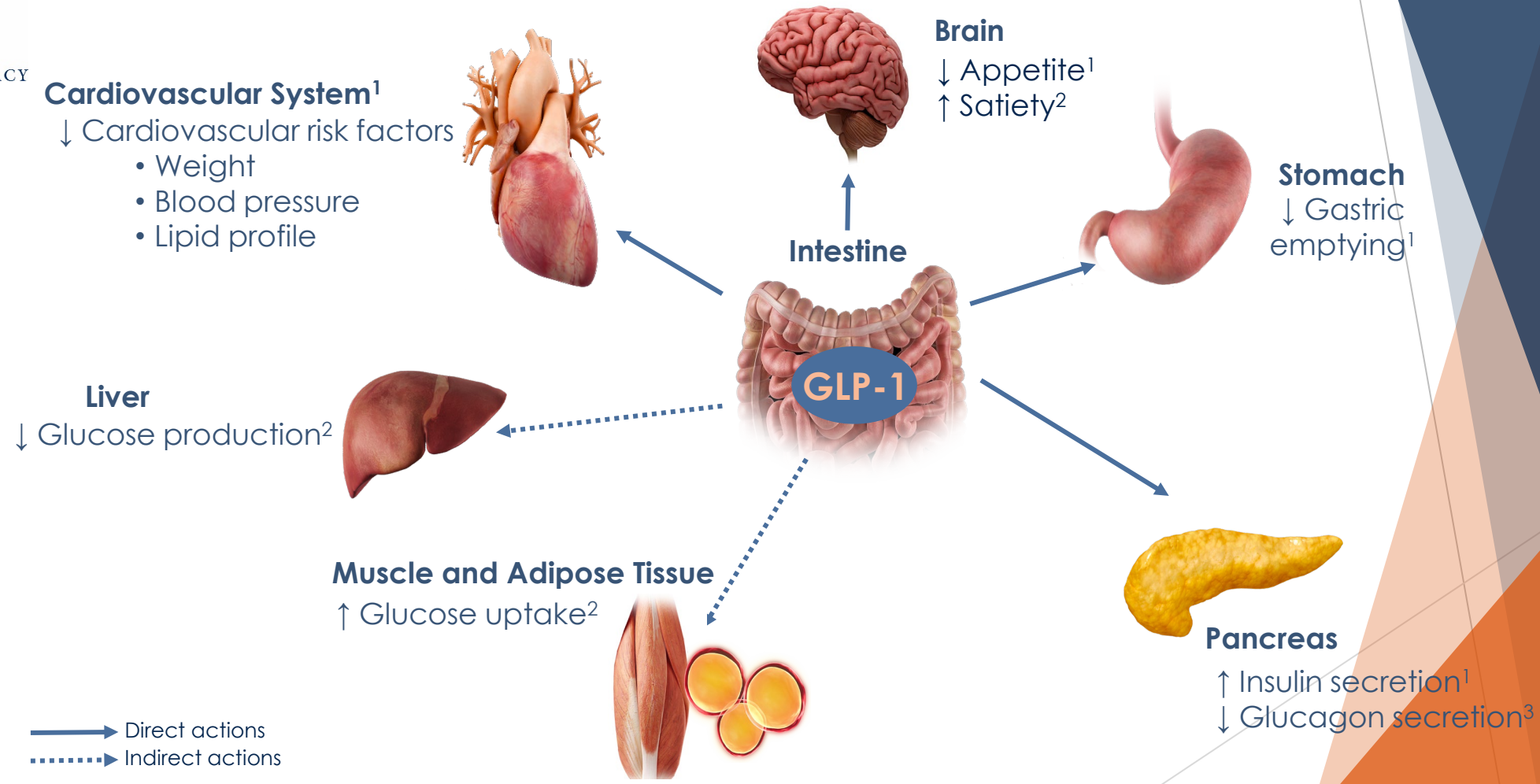
ENDOGENOUS GLP-1 BIOLOGIC ACTIVITY



1. Smilowitz et al. *Circulation*. 2014;129(22):2305-2312.
2. Gupta. *Indian J Endocrinol Metab.* 2013;17(3):413-421.
3. Kalra S, et al. *Indian J Endocrinol Metab.* 2016;20(2):254-267.

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GLP-1 Receptor Agonists

Liraglutide, Exenatide, Lixisenatide, Semaglutide, Albiglutide, Dulaglutide

- Dosing: SC (BID, QD, QW), PO qday
  - Verify dose adjustment in renal dysfunction
- Benefits:
  - 1-1.5% A1C decline
    - Sema > Lira = Dula >Exena > Lixi
  - CV benefit
  - Reduced proteinuria
  - Weight loss
    - Sema > Lira > Dula > Exena > Lixi
  - Rare hypoglycemia
    - Increased when combined with secretagogue or insulin
- Drawbacks:
  - Relatively expensive
- Side effects:
  - GI discomfort (N/V)
  - Possible acute pancreatitis risk
  - Retinopathy (semaglutide)

1. ADA, Standards of Medical Care in Diabetes, 2019
2. Inzucchi SE et al. *Diabetes Care* 2015;38:140-9
3. Kim SH et al. *Diabetes Metab J* 2016;40:339-353
4. Sharma SK et al. *Diabetes Metab Syndr Obes* 2016;9:251-60
5. https://www.nlm.nih.gov/medlineplus/medlineplus.html
6. http://www.ema.europa.eu/ema/
7. Garber AJ et al. *Endocr Pract* 2017;23:207-38
8. Ismail-Beigi F. *N Engl J Med* 2012;366:1319-27
9. Scheen AJ. *Expert Opin Pharmacother* 2015;16:43-62

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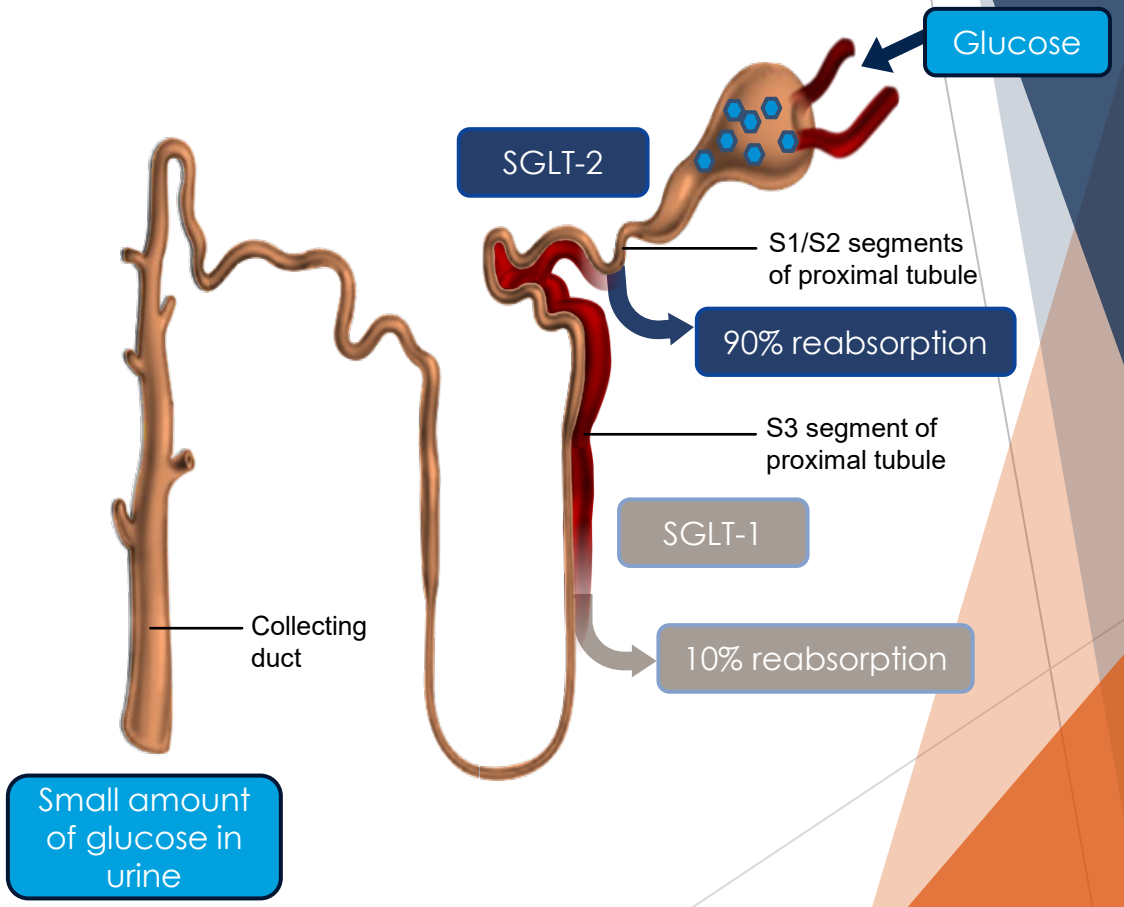
SGLT-2 INHIBITORS: MECHANISM OF ACTION

- Glucose filtered by glomeruli
- Nearly completely reabsorbed back to the blood stream via the SGLT-2 and SGLT-1
- SGLT-2 is expressed almost exclusively in the kidney



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SGLT-2 INHIBITORS

DAPAGLIFLOZIN, CANAGLIFLOZIN, EMPAGLIFLOZIN, ERTUGLIFLOZIN

- Dosing: po once daily
- Primary benefits:
  - 0.5-1.0% A1C decline
  - Reduction in CV events
  - Preserves renal function
  - Decreases hospitalization for heart failure (hHF)
- Secondary benefits:
  - Moderate weight loss
  - May reduce blood pressure
  - Rare hypoglycemia
    - Increased when combined with secretagogue or insulin

- Drawbacks:
  - Relatively expensive
  - Dose per eGFR
- Side effects:
  - Genital mycotic infections
  - Dehydration/hypotension
  - Diabetic ketoacidosis
  - Risk of urinary tract infections
  - Bone fractures (canagliflozin, dapagliflozin)
  - Amputation, toes (canagliflozin, ertugliflozin)

1. ADA, Standards of Medical Care in Diabetes, 2017
2. https://www.nlm.nih.gov/medlineplus/medlineplus.html
3. Inzucchi SE et al. *Diabetes Care* 2015;38:140-9
4. Garber AJ et al. *Endocr Pract* 2017;23:207-38
5. Zinman B et al. *N Engl J Med* 2015;373:2117-28
6. Neal B et al. *N Engl J Med* 2017
7. Mosley JF 2nd et al. P T 2015;40:451-62

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AUDIENCE QUESTION

Besides insulin, which antihyperglycemic class is MOST likely to cause hypoglycemia?

Respond at **PollEv.com/hpwhitley**

Besides insulin, which antihyperglycemic class is MOST likely to cause hypoglycemia?

DPP-4 inhibitors

Sulfonylureas (SU)

Thiazolidinediones (TZD)

SGLT2 inhibitors

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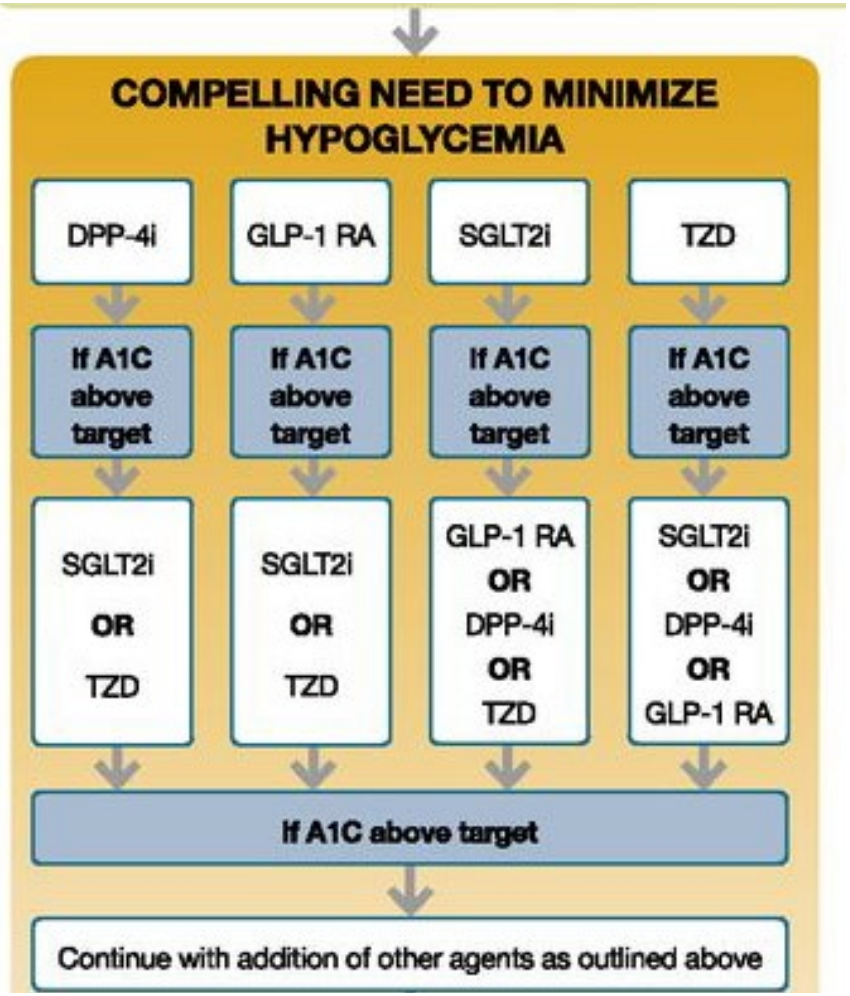
HYPOGLYCEMIA: SGLT2I, GLP1 RA, DPP4I, TZD



Diabetes Care. 2021;41(Suppl. 1):S111-S124.

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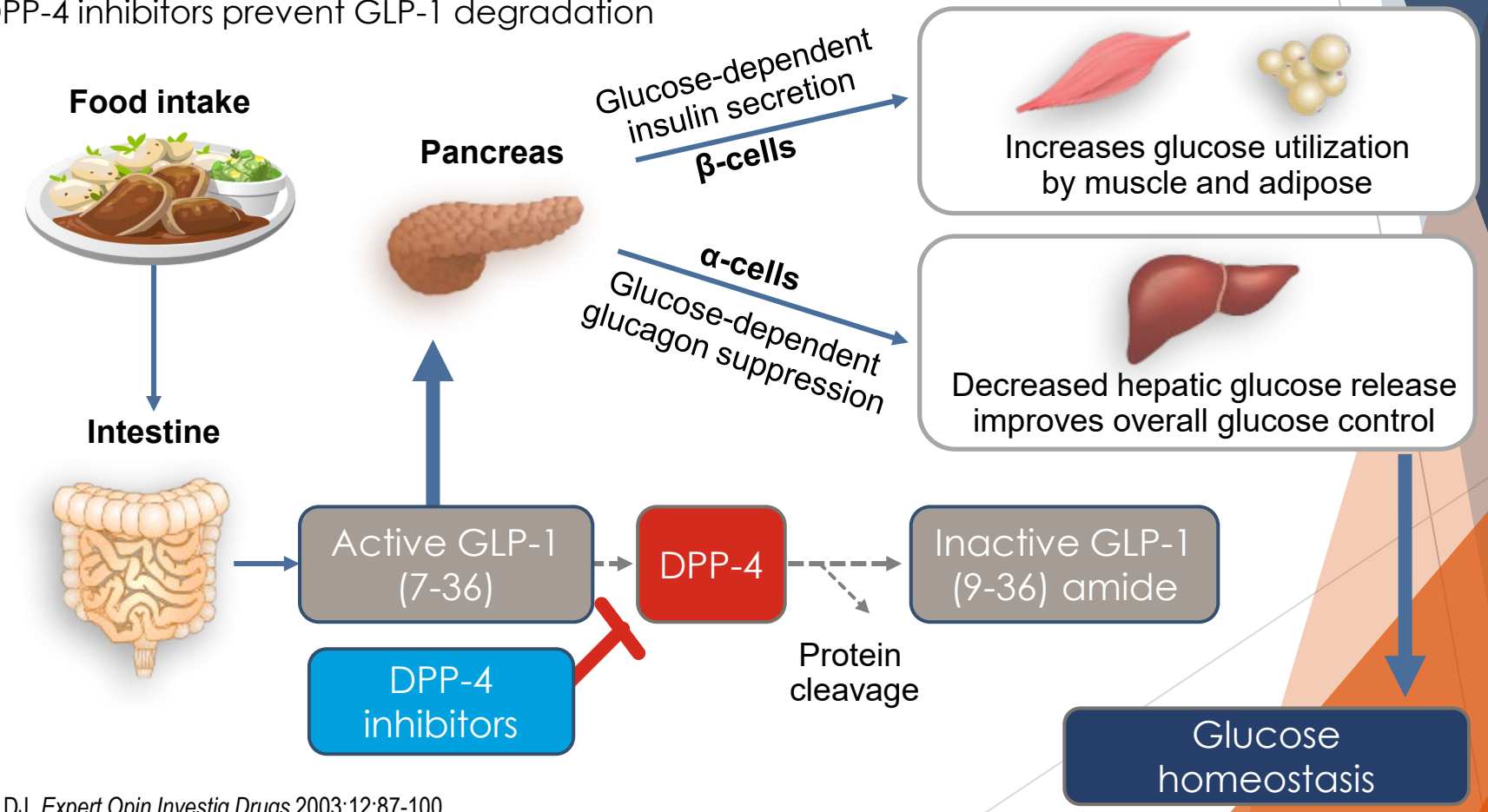
DPP-4 INHIBITORS: MECHANISM OF ACTION

- Incretins (GLP-1, GIP) mediate glucose-stimulated insulin release
- GLP-1 has reduced activity in diabetes
- GLP-1 is quickly degraded by DPP-4 enzyme
- DPP-4 inhibitors prevent GLP-1 degradation



1. Drucker DJ. *Expert Opin Investig Drugs* 2003;12:87-100
2. Ahrén B. *Curr Diab Rep* 2003;3:365-72

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DPP-4 INHIBITORS

SITAGLIPTIN, SAXAGLIPTIN, LINAGLIPTIN, ALOGLIPTIN

- Dosing: po once daily
  - Dose adjustment in renal dysfunction
    - Except linagliptin
- Benefits:
  - 0.5-0.8% A1C decline
  - Weight neutral
  - Rare hypoglycemia
- Drawbacks:
  - Relatively expensive
- Side effects:
  - Well-tolerated
  - Possible congestive heart failure risk
    - Saxagliptin, alogliptin
  - Possible acute pancreatitis risk

1. ADA, Standards of Medical Care in Diabetes, 2019
2. Inzucchi SE et al. *Diabetes Care* 2015;38:140-9
3. Kim SH et al. *Diabetes Metab J* 2016;40:339-353
4. Sharma SK et al. *Diabetes Metab Syndr Obes* 2016;9:251-60
5. https://www.nlm.nih.gov/medlineplus/medlineplus.html
6. http://www.ema.europa.eu/ema/
7. Garber AJ et al. *Endocr Pract* 2017;23:207-38
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9. Scheen AJ. *Expert Opin Pharmacother* 2015;16:43-62

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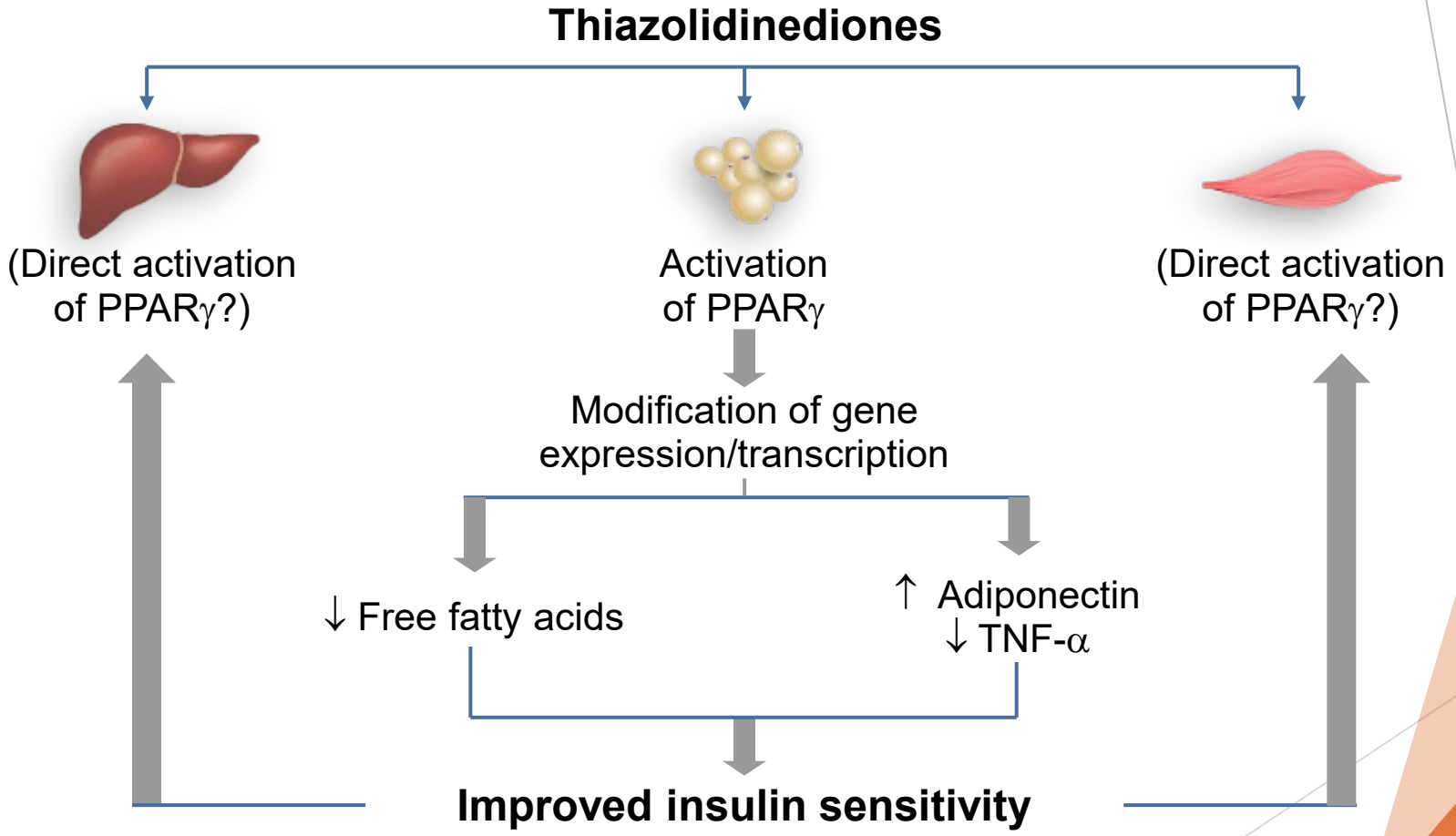
THIAZOLIDINEDIONES MECHANISM OF ACTION



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THIAZOLIDINEDIONES

- Pioglitazone
  - Dosing: Once-daily
- Benefits:
  - 0.5-1.4% A1C decline
  - Durable effect on glycemic control
  - Possible decrease in CVD events (pioglitazone)
  - Rare hypoglycemia
  - Inexpensive
- Drawbacks:
  - Weeks or months to reach optimal glycemic effect
- Side effects:
  - Weight gain
    - Edema/heart failure
  - Possible bone fractures

1. ADA, Standards of Medical Care in Diabetes, 2017
2. https://www.nlm.nih.gov/medlineplus/medlineplus.html
3. Ismail-Beigi F. *N Engl J Med* 2012;366:1319-27

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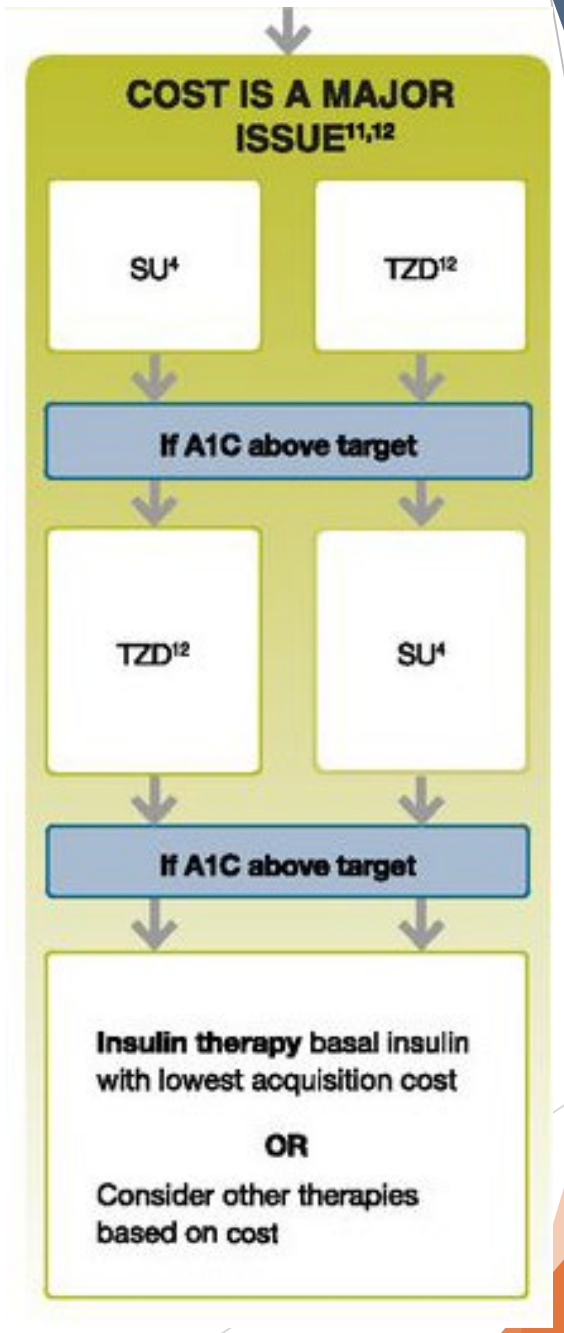
COST CONSCIOUS:
THIAZOLIDINEDIONE (TZD); SULFONYLUREA (SU)



Diabetes Care. 2021;41(Suppl. 1):S111-S124.

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SECRETAGOGUES:
SULFONYLUREAS & MEGLITINIDES

Glimepiride, Glipizide, Glyburide

- MOA: increase insulin secretion
- Dosing 1-2 times daily
- Benefits:
  - 1-1.5% A1C decline
  - Rapid effect on blood glucose
  - Inexpensive
- Risk:
  - Hypoglycemia
  - Weight gain
  - Low durability

Repaglinide, Nateglinide

- MOA: increase insulin secretion
- Shorter duration of action vs SUs
- Dosed before each meal daily
- Benefits:
  - 0.5-1% A1C decline
  - Marked effect on postprandial glycemia
- Risk:
  - Hypoglycemia < SU

ADA, Standards of Medical Care in Diabetes, 2019
Inzucchi SE et al. *Diabetes Care* 2015;38:140-9
https://www.nlm.nih.gov/medlineplus/medlineplus.html

Quianzon CC and Cheikh IE. *J Community Hosp Intern Med Perspect* 2012;2:1-4
Ismail-Beigi F. *N Engl J Med* 2012;366:1319-27
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AUDIENCE QUESTION

At what point should basal insulin typically be initiated in patients with T2DM?

Respond at **PollEv.com/hpwhitley**

At what point should basal insulin typically be initiated in patients with T2DM?

At the time of diagnosis

Second-line to metformin

Third-line option

Fourth-line option

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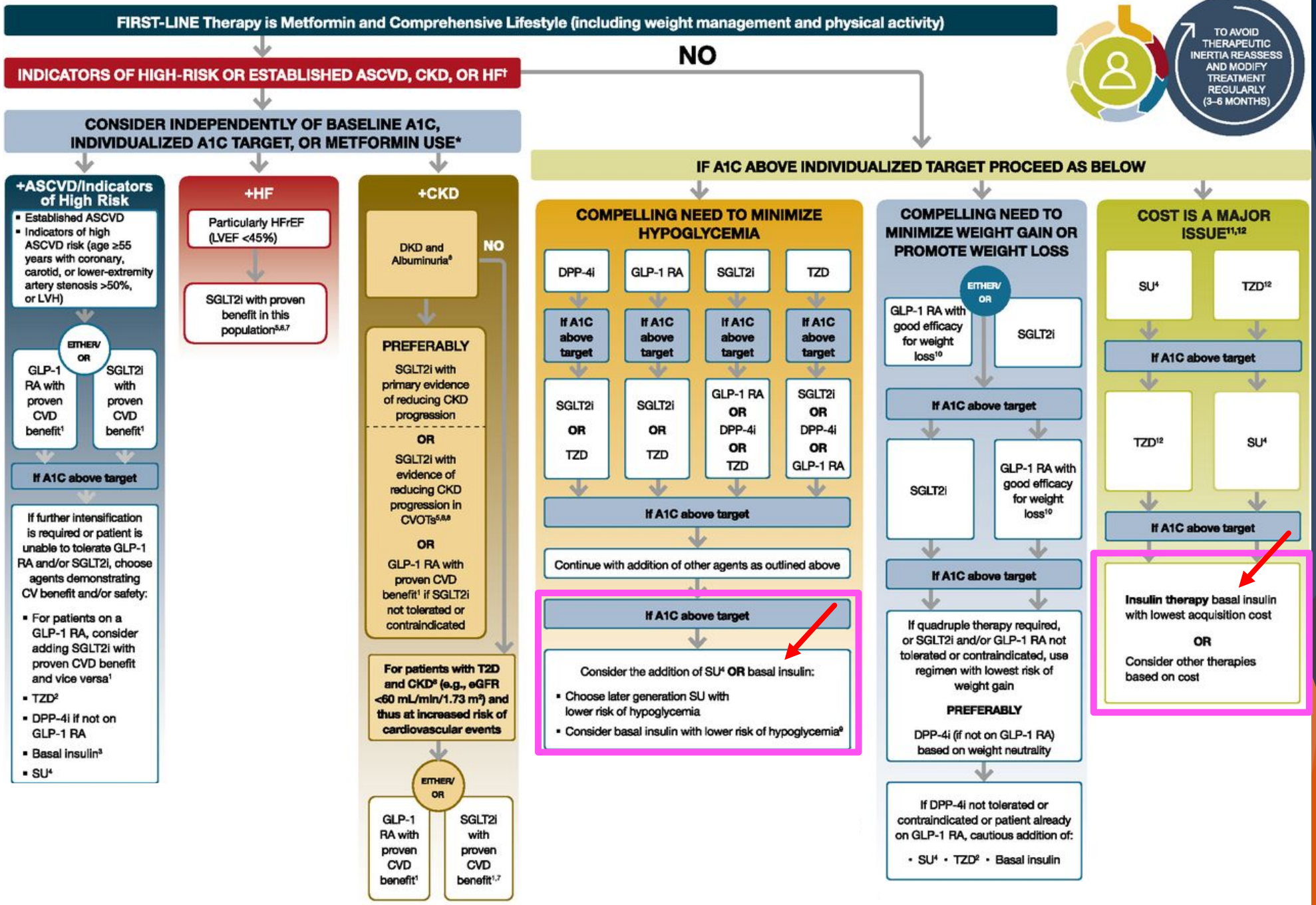

Diabetes Care. 2021;41(Suppl. 1):S111-S124.

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BASAL INSULIN: WHEN TO ADD

- Type 2 diabetes: as 3rd or 4th line therapy
- A1C >11%
  - BG > 300 mg/dL
  - or with symptoms of hyperglycemia
- Evidence of ongoing catabolism (weight loss)
  - * As glucose toxicity resolves, the regimen may, potentially, be simplified

- Type 1 diabetes

Diabetes Care. 2019;42(Suppl. 1):S90-S102.

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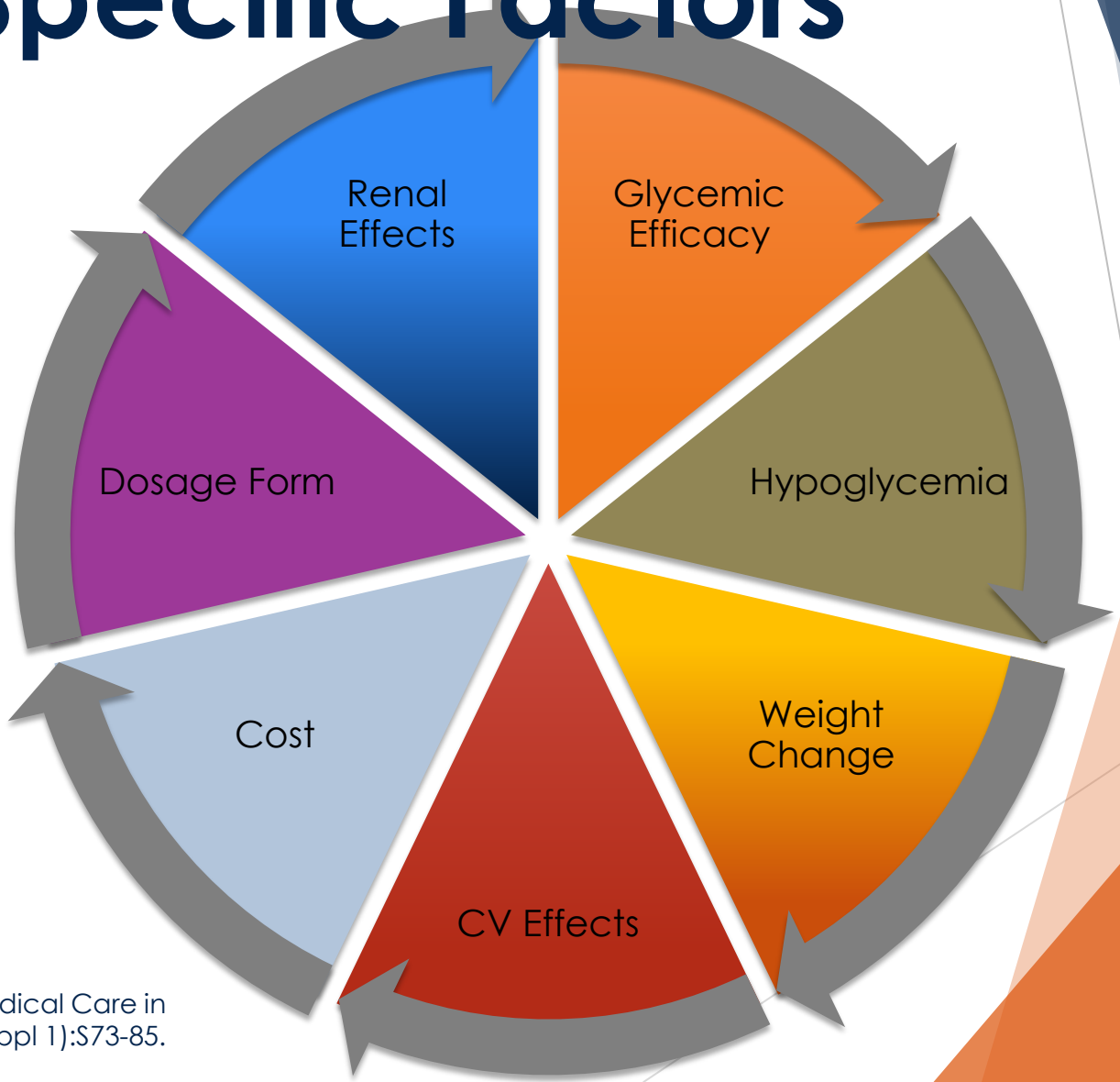
Considering Drug- and Patient-Specific Factors



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PHARMACOLOGIC TREATMENTS FOR TYPE 2 DIABETES

Heather P. Whitley, PharmD, BCPS, CDCES
Clinical Professor
Auburn University, Harrison School of Pharmacy

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QUESTIONS????

Thank you for attending this AUHSOP continuing education program. The Attendance Code for this program is _____. Participants must enter the attendance code to advance to the program evaluation page within the course.

Please direct any questions to: hsopce@auburn.edu