

DIABETES MEDICATIONS

Registrar Education Series

Updated 10/2022

<u>ADA</u> <u>AACE</u> <u>USPSTF</u> <u>Choosing Wisely</u>



For each medication class determine:

- Effect on A1c
- How to explain how it works to a patient
- Risk of hypoglycemia
- Common adverse effects
- Good POEMs/DOEs
- Bad POEMs/DOEs
- Pearls







Mechanism: sensitizes

this means that 150 of insulin may have the same effect as 200 of insulin in someone who is not taking it

Hypoglycemia: none people who do not have DM take 750mg bid for other conditions

Good:

decreases all cause mortality decreases cardiovascular mortality cheap - NHIMA pill form has extended-release form

Other:

CKD does not increase lactic acidosis avoid GI side effects by titrating (i.e. 500mg x3 days then 500mg bid x3 days then 1g bid) if it is not tolerated switch to ER version, 500mg x4 (can all be taken at the same time)

A1C ↓: 1 - 2.5%

Weight: loss

Bad: GI side effects if not titrated BID dosing





Mechanism: secretagogue squeezes insulin out of the pancreas

Hypoglycemia: high risk decrease in sugar and response is unpredictable

Good: decreases sugar cheap - NHIMA pill form

Other:

at 50% the max dose you will get 90% the efficacy It is said that efficacy wanes after 3 years of use both ADA and AACE discourage use due to the predictably unpredictable hypoglycemic effects Glimepiride is the safest of its class

A1C ↓: **1** to 3%

Weight: gain

Bad:

hypoglycemia Increases cardiovascular mortality Not a smart medication





Mechanism: excretes sugar through kidney If the sugar raises to high these channels will remain in place excreting sugar until the threshold is met

Hypoglycemia: none Only works when sugars are high

Good:

CV and CHF mortality benefit Renal protective Pill form Can decrease blood pressure

Other: Has caused normoglycemic DKA Can be used in Type1 DM but is off label use A1C ↓: 0.5-1.0%

Weight: loss

Bad: Expensive Can increase risk of UTI and yeast infections Can decrease blood pressure





Mechanism: InCretIn effect

When there is food in the gut it causes **IN**testinal se**CRET**ion of **IN**sulin, also decreases glucose production by the liver and slows gastric emptying

Hypoglycemia: none Only works when there is food in the gut

Good:

Pill form Once daily Can be used with renal failure

A1C ↓: 0.5-1.0%

Weight: neutral

Bad: Expensive Caution with pancreatitis

Other:

Never use with a GLP1 since they do the same thing. DPP4 is the enzyme that breaks down GLP1 so this medication indirectly leads to higher GLP1 levels





Mechanism: InCretIn effect

when there is food in the gut it causes **IN**testinal se**CRET**ion of **IN**sulin, also decreases glucose production by the liver and slows gastric emptying

Hypoglycemia: none Is used in people without DM for weight loss

Good: CV mortality benefit Can be used in renal failure, might be protective Can be once weekly Oral form is available (CVA benefit)

Other:

Never use with a DPP4 since they do the same thing. Can be used in place of DPP4 if you do not have the desired effect

A1C ↓: 0.5-1.5%

Weight: loss

Bad:

Expensive Daily or weekly injection (there is an oral form) GI side effects (needs to be titrated)





Mechanism: sensitizes

Hypoglycemia: none

Good: Cheap NHIMA pill A1C ↓: 0.5 to 1.5%

Weight: gain

Bad: Contraindicated in CHF

Other: Not a substitute for metformin



- Many medications come combined which can increase compliance and decrease cost
 - Metformin + DPP4
 - Also in extended release form
 - Metformin + SGLT2
 - Also in extended release form
 - DPP4 + SGLT2
 - GLP1 + Basal insulin

SUMMARY



Medication	Mechanism	Aıc	Нуро	Weight	Good	Bad
Metformin	Sensitizes	1-2.5	No	Loss	All cause mortality NHIMA	Reputation
Sulfonylurea	Secretagogue	1-3.0	YES!!!!	Gain	Cost NHIMA	hypoglycemia
GLP1	<u>InC</u> ret <u>I</u> n	0.5-1.0	No	Loss	CV/renal mortality	Injectable
DPP4	<u>InC</u> ret <u>I</u> n	0.5-1.0	No	Neutral	Safe, renal failure NHIMA	Cost
SGLT2	Renal excretion	0.5-1.0	No	Loss	CV/CHF Renal benefit NHIMA?	UTI/yeast
TZD	Sensitizes	0.5-1.5	No	Gain	Cost NHIMA	Contraindicated in CCF

AACE Summary

PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP1-RA	SGLT2I	DPP4i	AGI	TZD Imodecene ideory	SUGLN	COLSVL	BCR-QR	INSULIN	PRAML
нуро	Neutral	Neutral	Nestral	Neutral	Neutral	Neutral	Net Service Service	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Sight Loss	1.055	Loss	Neutral	Aleutral	Gen	Gein	Neutral	Neural	Gain	LOSS
RENAL / GU	Contra Indicated f eGPR -30 mL/min/ 1.73 m ²	Evenatorie Not Indicated CrCI = 30	Not Indicated for eGFR H45 mL/ may1.75 m ²	Dose Adjustment Necessary Except Unagliptin) Effective in Reducing Abuminuria	Neutral	Neutra	More Hypo Risk	Neucral	Neutral	Mariz Hype Rok	Neutral
			599.41								
			Genital Mycritic Inflictions								
		Potential Benefit of UK GLP14A	Potential CKD Bonefit: Soc #1								
GI SH	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral			Neutral	Moderate
CHIF	Neusral	Neutral	Prevent HF Hospitalization Voring's Histiff, See 62		Neutral	Moderant	Neutral	Neucral	Neutral	OHFILER	Neutral
ASCVD		Potential Denetic of LA GLPT-RA	ntial fit at See #3 PT-RA	5de #4		Muy Roduce Scroke Rhik	ASCVD Rest	LOWERS LDL/C	Safe	No.tral	
BONE	Neutral	Neutral	Neutral	Noutral	Neutral	Moderate Racture Risk	Neutral	Neutral	Neutral	Nostal	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur In Weitbis Screek Sottings	Neutral	Neutral	Neutral	Neutral	Neucod	Neutral	Neutral	Neutral
Few etverse events or preating levents Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/3 m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/m1 in patients with CXD 3 1 albummuna. Canagettam indicated for eC/R c20 m2/mm1/m1 in patients with CXD 3 m1/m1 in patients with CXD 3 m2/mm1/m1 in patients with CXD 3 m2/m1/m1 in patients with CXD 3 m2/m1/m1 in patients with CXD 3 m2/m1/m1 in patients with CXD 3 m3/m1 in patients with c20 m3/m1 in patients with CXD 3 m3/m1 in patients with c20 m3/m											



ADA Summary

		Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Rena	effects	Additional considerations	
					ASCVD	HF	0000		Progression of DKD	Dosing/use considerations*		
Metformir	1	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	 Contraindicated with eGFR <30 mL/min/1.73 m² 	Gastrointestinal side effects common (diarrhea, nausea) Potential for B12 deficiency	
SGLT2 inl	hibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin [‡] , canagliflozin [‡] , dapagliflozin [‡] , ertugliflozin	High	Oral	Benefit: canagliflozin ⁶ , empagliflozin, dapagliflozin [§]	 See labels for renal dose considerations of individual agents Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR 	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 1LDL cholesterol Risk of Fournier's gangrene	
GLP-1 RA	5	High	No	Loss	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	See labels for renal dose considerations of individual agents No dose adjustment for dulagluidie, irragluitide, semagluitide 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 thyoid C-cell tumors in rodents; human relevance not determined (liraglutide, 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 int	libitors	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 	
Thiazolldinediones		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 (ploglitazone, rosiglitazone) Fluid retention (edema; heart failure) Benefit in NASH Risk of bone fractures Bladder cancer (ploglitazone) ^LDL cholesterol (rosiglitazone)	
Sulfonylu (2nd gene	reas eration)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	 Glyburide: generally not recommended in chronic kidney disease 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) 	
nsulin	Human insulin	High	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	 Lower insulin doses required with a decrease in eGFR; titrate 	 Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premixed 	
	Analogs						High	SQ	per clinical response		formulations) vs. analogs	



ADA Algorithm

FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and TO AVOID management needs and generally includes metformin and comprehensive lifestyle modification^ THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT ASCVD/INDICATORS OF HIGH RISK, HF, CKD† NONE REGULARLY (3-6 MONTHS) **RECOMMEND INDEPENDENTLY OF BASELINE A1C,** INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡ Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals +ASCVD/INDICATORS +CKD** +HF* Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2) **OF HIGH RISK*** CKD and CKD without Consider additional comorbidities, patient-centered treatment factors, and management needs in choice albuminuria albuminuria EITHER/ of therapy, as below: SGLT2i (e.g., eGFR <60 (e.g., ≥200 mg/g OR with proven GLP-1 SGLT2i mL/min/1.73 m²) creatinine) benefit in this RA with with population¹ proven proven CVD CVD PREFERABLY **MINIMIZE WEIGHT GAIN/** benefit¹ benefit1 **MINIMIZE HYPOGLYCEMIA CONSIDER COST AND ACCESS** SGLT2i with primary evidence **PROMOTE WEIGHT LOSS** of reducing CKD progression Available in generic form at lower cost: PREFERABLY **IF A1C ABOVE TARGET** ----- OR -----No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD · Certain insulins: consider insulin SGLT2i with evidence of GLP-1 RA with good efficacy for weight loss reducing CKD progression in available at the lowest acquisition cost For SU or basal insulin, consider agents with ----- OR -----**CVOTs** lower risk of hypoglycemia^{3,4} For patients on a SU SGLT2i GLP-1 RA, consider ----- OR ------ TZD incorporating SGLT2i GLP-1 RA with proven CVD with proven CVD IF A1C ABOVE TARGET benefit¹ if SGLT2i not tolerated benefit and vice versa¹ **IF A1C ABOVE TARGET** IF A1C ABOVE TARGET or contraindicated TZD² Incorporate additional agents based on For patients with CKD (e.g., eGFR For patients on a GLP-1 RA, consider Incorporate additional agents based on comorbidities, patient-centered treatment <60 mL/min/1.73 m²) without incorporating SGLT2i and vice versa comorbidities, patient-centered treatment factors, and management needs albuminuria, recommend the factors, and management needs If GLP-1 RA not tolerated or indicated. following to decrease cardiovascular consider DPP-4i (weight neutral) risk GLP-1 SGLT2i Incorporate additional agents based on EITHER/ RA with comorbidities, patient-centered treatment OR with factors, and management needs proven proven CVD CVD benefit¹ benefit¹ If A1C above target, for patients on ^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss 1. Proven benefit refers to label indication (see Table 9.2) SGLT2i, consider incorporating a and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended GLP-1 RA and vice versa 2. Low dose may be better tolerated though (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes). less well studied for CVD effects †Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications. 3. Choose later generation SU to lower risk of hypoglycemia \$Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy. 4. Risk of hypoglycemia: degludec / glargine U-300 If A1C remains above target, consider treatment intensification based on comorbidities, *Refer to Section 10: Cardiovascular Disease and Risk Management. < glargine U-100 / detemir < NPH insulin **Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication patient-centered treatment factors, and management needs 5. Consider country- and region-specific cost of drugs label for eGFR criteria

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

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AACE Algorithm

GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

A1C ≤6.5% For patients without concurrent sorious itness and at low hypoglycemic risk A1C >6.5% For patients with concurrent serious It ness and at risk for hypoglycemia

LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred)

INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2I AND/OR LA GLP1-RA

Entry A1C >9.0% Entry A1C 27.5% - 9.0% TRIPLE THERAPY SYMPTOMS **DUAL THERAPY** NO YES CUIT-RA CUP1-RA Entry A1C <7.5% independent of SOLTAL SOLT2 NSULIN alycomic **MONOTHERAPY** Therapy MONTHS control, (170 DP74i Other Melfurmin estatvished OR Agents ASCVD or high SUG(N) 01-84 TZD) z risk, CKD 3, or TRIPLE SGLTH 0 Basad Irmidire HFrEF, start LA Marking the Therapy ž **DPP4I** GLP1-RA or DPP-II Basal Insulin m SGL12 with TZD Colesevelam proven AG Colesevelam efficacy* SU/CLN Bromocriptina QI Bromioriptine QR ADD OR INTENSIFY INSULIN AGI Refer to Insulin Aporithm MET LEGEND or other appent Feo adverse events at the postschie hesteller. Order of medications represents a suggested hierarchy of usage; length of levereflects among th of recommendation: If nut at goal in 3 months, proceed to next level therapy Ite with cautori PERENAL ANALYSIS AND ANALYSISTERS 2018 suggest to have a lattice discuss a "off a local for an university of species discuss, (a) a way not us to all how significant

PROGRESSION OF DISEASE

The AACE makes specialty based recommendations. An A1c of 6.5% is not a typical goal for the average person with DM and waiting 3 months prior to addressing high sugars is not recommended

CASES

- 1. 56yo F with DM, HTN, HLD has been on metformin 2500mg and daonil 20mg for 3 years and A1c is 8.0.
- 2. 43yo M with DM on metformin 1g bid, NPH 20AM, 30PM and fastings are controlled but postprandials are still 0.5-2.0 points high.
- 3. 32yo M recently diagnosed with DM with an A1c of 9.0.
- 4. 68yo F recently hospitalized with a stroke and new diagnosis of DM with an A1c of 9.7.
- 5. 26yo F with a 4 year history of DM controlled on metformin and daonil with an A1c of 6.8 who cannot lose weight despite being at goal with diet and exercise.



POSSIBLE TREATMENT OPTIONS

- 1. Decrease metformin to 1g bid, stop daonil and start an SGLT2-DPP4 combo
- 2. Add GLP1 to basal insulin in combo injection or add an SGLT2 or DPP4
- 3. Start metformin + DPP4 or SGLT2
- 4. Start metformin-DPP4 combo and GLP1
- 5. Stop daonil and add a GLP1 or SGLT2

