ANTI-HYPERGLYCEMIC DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

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Drug Class		Sulfonylureas		TZDs			Meglitinides	DPP4 Inhibitors	GLP1 Agonists ***	SGLT2 Inhibitors ***	Insulin in T2DM	
Generic ⇨ BRAND	Metformin (MF) GLUCOPHAGE	Gliclazide DIAMICRON	Glyburide DIABETA	Pioglitazone ACTOS, g	Rosiglitazone AVANDIA	Acarbose GLUCOBAY	Repaglinide GLUCONORM / Nateglinide STARLIX D/C	Saxagliptin ONGLYZA Sitagliptin JANUVIA Alogliptin NESINA Linagliptin TRAJENTA	Liraglutide VICTOZA Exenatide BYETTA, BYDUREON Dulaglutide TRULICITY Semaglutide OZEMPIC, RYBELSUS (PO) Lixisenatide ADLYXINE; ALBIGLUTIDE D/C	Empagliflozin JARDIANCE Canagliflozin INVOKANA Dapagliflozin FORXIGA, FARXIGA Ertugliflozin D/C STEGLATRO	Intensity: Less (NPH HS + MF)	Intensity: More (Multiple daily doses)
		[Glipizide GLUCOTROL USA SPREAD-DIMCAD]										
Major trials to support findings/ Outcomes*	UKPDS-33,34,80 (ADOPT; some use in ADVANCE)	ADVANCE	UKPDS-33,80 (ADOPT)	ProACTIVE Ferwana M. Meta-analysis 2013. SR-Liao [2017]; IRIS	Meta-analysis. RECORD interim, ADOPT, DREAM	ACE (Prevention trial: Stop-NIDDM)	-	SAVOR-TIMI 53, TECOS, EXAMINE PROLOGUE, CARMELINA, CAROLINA	LEADER, EXSCEL, FREEDOM CVO, REWIND, SUSTAIN-6, PIONEER-6, ELIXA, HARMONY	EMPA-REG, CANVAS, CREDENCE, DECLARE, VERTIS-CV (2020), DAPA-HF, DAPA-CKD (2020), EMPEROR-Reduced & -Preserved (2020), EMPA-Kidney (2022)	T2DM: UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN, DEVOTE T1DM: DCCT/EDIC (Also Boussageon et al. Meta-analysis. BMJ 2011;343:d4169)	
↓ Risk of Death / Major CV[1]	✓✓[2] in obese, ↓ mortality NNT=14/10yr ↓ MI NNT=14/10yr (UKPDS-34, UKPDS-80)	3,4,5 X?[5,6] glipizide ↑ MACE vs MF NNH=10/5yr (SPREAD-DIMCAD)	4,5	✓[7] ↓ MACE NNT=50/2.9yr, but 1° composite NS (ProACTIVE) ↓ MACE (IRIS) (pts with insulin resistance & recent CVA/TIA)	X?[8]	✓[9] in IFG, ↓ MACE NNT=40/3.3yr; ✓ in established CVD (Chinese) NS	?	[10,11] saxagliptin, alogliptin, sitagliptin, linagliptin ↔ non-inferior to placebo for MACE, *But see ?HF below.* [11] linagliptin vs glimepiride (CAROLINA) ↔ non-inferior for MACE	✓✓[12] liraglutide ↓ MACE NNT=53/3.8yr & ↓ mortality NNT=72/3.8yr [LEADER], semaglutide subcut wkly ↓MACE NNT=44/2.1yr [SUSTAIN-6] dulaglutide ↓ MACE NNT=72/5.4yr [REWIND] albiglutide ↓MACE NNT=50/1.6yr (HARMONY) [13,14] lixisenatide, exenatide extended release, semaglutide po ↔ non-inferior to placebo for MACE (ELIXA, EXSCEL, PIONEER-6); semaglutide po ?↓ mortality NNT=72/1.3yrs [PIONEER-6]	✓✓[15] empagliflozin ↓ MACE NNT=63/3.1yr, ↓ mortality NNT=39/3.1yr (EMPA-REG) canagliflozin ↓ MACE NNT~220/yr (CANVAS) but mortality NS dapagliflozin ↔ MACE (DECLARE) [16] (ertugliflozin ongoing)	17,18	18,19,20 X?[21] > insulin use with intensive target vs standard therapy, ↑ all-cause death NNH=95/3.5yr, & CV death NNH=125/3.5yr (ACCORD)
Effect on A1c**	✓✓	✓✓	✓✓	✓	✓		✓		✓✓	✓	✓	✓✓
Weight (loss vs neutral vs gain)	✓ A1	X A2	X A2	XX A3	XX A4	✓ A5	X A6	A7	✓✓ A8	✓ A9	A10	XX A10
Risk of Hypoglycemia	✓✓	? less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓ Low risk with monotherapy		✓✓	✓✓	✓?	✓? Increased risk when given with sulfonylurea or insulin	✓		XX Severe, occurs at 1.8%/yr
↓ Risk of HF /Edema	✓[22,23] 1st line in HF with eGFR >30 mL/min (DC'18)	23,24	23,25	XX[26] ↑ HF NNH=50/2.9yr, edema NNH=8/2.9yr	XX[25,27] ↑ HF NNH=69/5.5yr (RECORD), ↑ HF NNH=250/3yr (DREAM)	28	29	X?[30] ↑ HF saxagliptin NNH=143/2.1yr (SAVOR), alogliptin (EXAMINE [posthoc]) Sitagliptin & linagliptin = HF neutral	31 Entire class of GLP1 agonists neutral for HF hospitalizations.	✓[32] ↓HF hospitalizations empagliflozin (EMPA-REG) & canagliflozin [exploratory] (CANVAS) ✓✓[32] dapagliflozin ↓ worsening HF or CV Death [NNT=21/1.5yr DAPA-HF, NNT=19/1.3yr Emperor-Reduced]	33,34 (?↑ HF risk)	34 (↑ HF risk)
Effect on GI tolerability	X Start low & titrate	✓	✓ rate of 1.8%/yr	✓	✓	XX flatulence 74% diarrhea 31%	✓	✓	X Nausea, vomiting, diarrhea Titrate as tolerated (as per product monograph); often improves with time		✓✓	✓✓
Cost	✓✓	✓✓	✓✓	X	X	✓	✓	X	XX	X		XX
Other	May have to hold or ↓ dose in acute illness/HF/ renal dysfx (? lactic acidosis); may ↓ B12. 1st line for T2DM (UKPDS-34)	Used in combination with metformin (ADVANCE)	Caution: accumulation if ↓ renal function (& in older adults)	X FDA +/- HC warnings:[35] ?↑ HF *(see above)*, ?↑ fractures ♀ (NNH~30/~3.5 y) ?↑ macular edema (conflicting data) Pio:?↑ bladder ca >12 mos (27.5 excess /100,000 person yrs), avoid co-admin with dapaglifozin[36] Rosi: Restricted access in CDN (SK-EDS; not covered on NIHB) (↑ CV risk concerns) [37]		✓ PPBG, Possible benefit of laxative effect in some TID dosing	✓ PPBG, flexibility with meals TID dosing	✓PPBG FDA +/- HC warning:[38] HF (saxa- & alogliptin); arthralgia, hypersensitivity rx, ?↑ pancreatitis (ARI 0.13%),[39] pancreatic cancer[40] Linagliptin: no renal dose adjustment X new agents – outcome & safety data still limited	✓PPBG injection site irritation ?↑ pancreatitis,[39] pancreatic cancer,[40] ?↑ thyroid cancer (liraglutide) [41] (*once weekly* agents may have ↓ GI adverse events) [42] gallbladder disease (liraglutide)[46] X new agents – outcome & safety data still limited	✓✓[46] canagliflozin ↓ESRD, doubled SCr & renal/CV death [NNT= 23/2.6 yr CREDENCE; DAPA-CKD] X outcome & safety data limited FDA +/- HC warning: ↑DKA; ↑AKI (caution: ↓ intravascular volume & ↓renal function), ↓BP; ↑(HR ~2) limb amputations [Cana];[43] ?↑UTI/urosepsis/pyelonephritis; genital tract skin infection (OR 3.5 vs placebo);[44] ↑fracture (HR 1.3)/↓BMD [Cana]; dapagliflozin ?↑bladder/ breast cancer (avoid with pioglitazone);[45] Fournier's gangrene[47]	Fear/ perception of insulin injections	✓PPBG Fear/ perception of insulin injections
Overall	✓✓?	✓		?	X?				? ✓liraglutide (CV + mortality benefit), semaglutide SC (CV benefit, SKH ☎, NIHB coverage ▼)	? ✓ empagliflozin (CV + mortality benefit, SKH ☎ & NIHB coverage ▼)	✓	✓ X?

*Drugs that lower blood glucose come with various levels of evidence regarding their balance of benefits & harms. This chart relies on current evidence, especially from randomized controlled trials that have evaluated patient oriented outcomes. Direct comparisons between agents have not been done so one is left to evaluate each drug for its relative advantages & disadvantages. **A1c will vary depending on dose, combinations & initial A1c.
See full version of this ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table online for additional notes: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

AKI=acute kidney injury **DKA**=diabetic ketoacidosis **IFG**=impaired fasting glucose **MACE**=major adverse cardiovascular events **PPBG**=postprandial blood glucose

Individualize approach considering balance of potential benefits & harms. Over-aggressive pursuit of targets can ↑ mortality. [ACCORD]

✓✓ An Advantage	✓	Neutral	X	XX A Disadvantage	? Unknown/Ongoing

***See next page for GLP1 & SGLT2 color comparison chart

GLP1 Agonists & SGLT2 Inhibitors - SUBSET of DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

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Drug Class	GLP1 Agonists *				SGLT2 Inhibitors		
Generic ⇨ BRAND	Dulaglutide SC TRULICITY (SC WEEKLY)	Liraglutide SC VICTOZA (SC DAILY)	Semaglutide SC OZEMPIC (SC WEEKLY)	Semaglutide PO 14mg RYBELSUS (PO DAILY) FDA ; new Canada	Canagliflozin INVOKANA	Dapagliflozin FORXIGA / FARXIGA FDA	Empagliflozin JARDIANCE
Major trial(s) to support findings/Outcomes*	REWIND n=9901 / 5.4 yr	LEADER n=9340 / 3.8 yr vs placebo (but ↑ insulin use)	SUSTAIN-6 n=3297 / 2 yr vs placebo (but ↑ insulin use)	PIONEER-6 n=3183 / 1.3 yr	CANVAS n=10142 / 3.6 yr CREDENCE n=4401 / 2.6 yr renal dx pts	DECLARE-TIMI n=17160 / 4.2 yr DAPA-HF n=4744 / 1.5 yr heart failure pts	EMPA-REG n=7020 / 3.1 yr Emperor-Reduced n=3730 / 1.3 yr in heart failure pts
↓ Risk of Major CV - MACE	✓✓ ↓ MACE NNT=72/5.4yrs REWIND - ? N. America - neutral HR: 1.14 (0.89-=1.47)	✓✓ ↓ MACE NNT=53/3.8yr LEADER - ? N. America - neutral HR: 1.01 (0.84-1.22)	✓✓ ↓ MACE NNT=44/2.1yr SUSTAIN-6 - ? N. America – marginal HR: 0.87 (0.57-1.34)	Neutral for **MACE:** non-inferior to placebo 3.8% vs 4.8% PIONEER-6 HR: 0.79 (0.57-1.11) Many trial limitations, e.g. short	✓✓ ↓ MACE NNT~220/yr CANVAS (≈NNT of 62 / 3.6yrs)	✓? **Non-inferior** to Placebo HR 0.93 (0.84-1.03) Superiority (NS) over 4.2yr	✓✓ ↓ MACE NNT=63/3.1yrs EMPA-REG **10mg** as good as 25mg
↓ Risk of All-Death	HR 0.9 (0.80-1.01) 10.8% vs 12%/5.4 yrs (NS)	✓✓ NNT=72/3.8yrs LEADER	HR 1.05 (0.74-1.50) 3.8% vs 3.6%/2.1yrs (NS)	✓? 2° endpoint NNT=72/1.3yrs	HR 0.87 (0.74-1.01) CANVAS HR 0.83 (0.68-1.02) CREDENCE	HR 0.93 (0.82-1.04) DECLARE NNT=44/1.5yr DAPA-HF	✓✓ 2° endpoint NNT=39/3.1yr EMPA-REG
Less Renal Disease (composite/surrogates)	✓ NNT=40/5.4yrs 17.1 vs 19.6%/5.4 yrs	✓ NNT=67/3.8yr 5.7% vs 7.2% /3.8yrs	✓ NNT=44/2.1yr 3.8% vs 6.1% /3.8yrs	?	✓✓ HR 0.66 (0.53-0.81) NNT= 23/2.6 yrs CREDENCE	✓✓?class effect HR 0.76 (0.67-0.87) NNT= 19/2.4 yrs DAPA-CKD	✓✓?class effect ↓acute renal failure NNT=71
Effect on A1c**	✓✓	✓✓	✓✓	✓✓	✓	✓	✓
Weight (loss vs neutral vs gain)	✓✓ ↓1.3-3 kg/5-52 wks	✓✓ ↓ 2.3 kg/3.8 yrs	✓✓ ↓ 3-4kg/2.1yrs	✓✓ ↓ 3.4kg/1.3 yrs	↓ 2.8-4 kg/4-52 wks CANTATA-M	↓ 2 kg/12-52 wks	↓ ~1.5-2 kg/3.1 yrs
Less Risk of Hypoglycemia	✓?	✓ Severe: 2.4% vs 3.3% p=0.02 (placebo group had more insulin)	✓?	✓? Severe: 1.4% vs 0.8%	✓ Risk when given with sulfonylurea or insulin		
Less Risk of HF /Edema	HR: 0.93 (0.77-1.22)	HR: 0.87 (0.73-1.05)	HR: 1.11 (0.77-1.61)	HR: 0.86 (0.48-1.55)	✓ 2° endpoint ↓HF hospitalizations	✓✓ ↓ worsening HF or CV death NNT=21/1.5yr DAPA-HF	✓✓ ↓ worsening HF or CV death NNT=19/1.3yr Emperor-Reduced
Effect on GI & D/C due to Tolerability	X GI **D/C due to AE** 9% vs 6% NNH=36/5.4yrs	X GI **D/C due to AE** 9.5% vs 7.3% NNH=46/3.8yrs	X GI **D/C due to AE** 11.5-14.5% vs 5.7-7.6% NNH= ~14/2yrs	X D/C due to GI: 6.8% vs 1.6% **D/C due to AE** 11.6% vs 6.5%; NNH=20/1.3yrs	D/C due to AE 12% vs 13%; NNH= ? 100/2.6yrs	D/C due to AE 8.1% vs 6.9%; NNH=84/4.2yrs DECLARE	D/C due to AE 17.3 vs 19.4%; NNH= 48/3.1yrs
? AE Concerns Associated with Class	**Adverse Events**: injection site irritations if subcut. **Rare**/?: ?↑ pancreatitis, ?pancreatic cancer; ?↑ thyroid cancer (liraglutide);[41] gallbladder disease [46]; ?diabetic retinopathy complications.[SUSTAIN-6] See infographic pg 16. *Once weekly* agents may have ↓ GI adverse events.[42]				FDA +/- HC warning: ↑**DKA**; ↑AKI (caution: ↓ intravascular volume & ↓renal fx); **genital mycotic infections.** Rare: Fournier's gangrene;? ↑UTI/urosepsis/pyelonephritis. See infographic page 17.		
Cost – 1 month Some cost programs may be available	XX $225 ✗⊗	XX $90-$235 ✗⊗	XX $120-$220 ☎,▼ NIHB	XX $260 ✗⊗	X $110 ☎✆	X $110 ☎ ▼ NIHB	X $110 ☎ ▼ NIHB
Other	Well tolerated, except GI. ↓BP 1.7/0.5 mmHg. Environmental impact - single use disposable pen	Gallbladder AE: NNH=84	NIHB open benefit	Smaller, shorter trial. SAE lower in tx group.	?↑(HR ~2) **limb amputations** ?↑fracture (HR 1.3)/↓BMD HIP	↑bladder/ breast cancer (avoid with pioglitazone). HF benefit similar in DM & non-DM patients. NIHB open benefit.	NIHB open benefit
Practical / Clinical Considerations	Upper GI effects often worse than lower GI effects; a low fat diet is better (small, frequent meals, gradual dose titration; patients may struggle with AEs in first ~2 weeks, but many will gain tolerability and do OK. Often insulin dose can be reduced 20% initially, and possibly more after that.				Uncertain multi-mechanism of action e.g. lower BP. Monitor BP and assess for postural hypotension, especially in older adults.		
Time Tested	X new agent – outcome & safety data still limited	X >10yr history, but… limited real world use	X new agent – outcome & safety data still limited	X new agent – outcome & safety data still limited	X new agents – outcome & safety data still limited		
Convenience	✓ Single Use Pen subcut once **weekly**	subcut once daily	✓ subcut once **weekly**	✓ 30min pre-am meal; ≤120mL H_2O **oral** once daily	✓✓ **Oral** once daily		
Overall	?	?	?	?	? Safety	?	?

✓✓ An Advantage	✓	Neutral	X	XX A Disadvantage	? Unknown/Ongoing

Note: the "Neutral" designation indicates little or no disadvantage; however, there is also little or no advantage.

* Lixisenatide not included in this GLP1 agonist chart due to neutral cardiovascular outcome data from the **ELIXA** trial, but coverage is ☎ &▼. See https://www.rxfiles.ca/RxFiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf

GLP1 Agonists

REWIND
Lower risk group; e.g. 21% had past CVD; others higher risk.
Renal: macroalbuminuria, eGFR decline 30+%, chronic renal replacement tx

LEADER
High risk group

SUSTAIN-6
High risk group: 83% had established CVD, CKD or both

PIONEER-6
MF: 77%, insulin 60%; Smaller, shorter trial; SAE leading to lower discontinuation rate in tx group, 2.6% vs 3%.
Higher risk group: CVD or CKD 84.7%

SGLT2 Inhibitors

CREDENCE
Patients with albuminuric CKD, eGFR 30-<90 mL/min, & albuminuria; High risk group: 50% had CVD
Renal: canagliflozin – composite primary endpoint: ↓ESRD, doubled SCr & renal/CV death

CANVAS
High risk group: 66% had established/hx of CVD [1⁰ outcome if no CV disease history, HR= 0.98 (0.74-1.3)]

DECLARE-TIMI
High risk group: >40% had atherosclerotic CVD; 33% CAD, 6% PAD, 7.6% cerebrovascular dx, 10% HF

DAPA-HF
Both patients with and without diabetes studied; similar benefit in both groups.

EMPA-REG
High risk group: 100% had established CVD. Patients had not received glucose-lowering agents for >12 weeks