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	Rosiglitazone AVANDIA	Acarbose GLUCOBAY	Repaglinide GLUCONORM D/C Nateglinide STARLIX	Saxagliptin ONGLYZA Sitagliptin JANUVIA Alogliptin NESINA Linagliptin TRAJENTA	Liraglutide VICTOZA Dulaglutide TRULICITY Semaglutide OZEMPIC, RYBELSUS (PO) Lixisenatide ADLYXINE; ALBIGLUTIDE D/C D/C Exenatide BYETTA, BYDUREON	Empagliflozin JARDIANCE Canagliflozin INVOKANA Dapagliflozin FORXIGA, FARXIGA USA D/C Ertugliflozin STEGLATRO	Intensity: Less (e.g. NPH, or glargine @HS + MF)	Intensity: More (Multiple daily doses)
		Glipizide GLUCOTROL SPREAD-DIMCAD Glimepiride AMARYL GRADE 2023										
Major RCTs to support findings/ Outcomes* Also SHI SR & NMA*	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, GRADE 2023	LEADER, EXSCEL, FREEDOM CVO, REWIND, SUSTAIN-6, PIONEER-6, ELIXA, HARMONY, GRADE 2023	EMPA-REG, CANVAS, CREDENCE, VERTIS-CV, DECLARE, DAPA-HF, DAPA-CKD 2020, EMPEROR-Reduced 2020 & Preserved 2021, DELIVER 2022 EMPA-KIDNEY 2023	T2DM: UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN, DEVOTE, GRADE 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=72/1.3yr PIONEER-6	✓✓15 empagliflozin ↓ MACE NNT=63/3.1yr, ↓ mortality empagliflozin NNT=38/3.1yr EMPA-REG dapagliflozin NNT=44/1.5y DAPA-HF NNT=48/2.4yr DAPA-CKD canagliflozin ↓ MACE NNT≈220/yr CANVAS dapagliflozin (DECLARE), ertugliflozin (VERTIS) ↔ MACE	17,18	18,19,20 X?[21] if >meds/insulin use with very intensive target, may ↑ all-cause death NNH=95/3.5yr, & CV death NNH=125/3.5yr (ACCORD high-risk pop)
Effect on A1c**	✓✓	✓✓	✓✓	✓	✓		✓		✓✓	✓ (eGFR ≥30, minimal <30)	✓	✓✓
Weight (loss vs neutral vs gain)	✓ A1	X A2	X A2	XX A3	XX A4	✓ A5	X A6	X? A7	✓✓A8	✓ A9	X A10	XX A10
Risk of Hypoglycemia	✓✓	X less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓ Low risk with monotherapy		✓✓	✓✓	✓?	✓? ↑ risk when given with sulfonylurea or insulin	✓	X	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	XX26 ↑ HF NNH=50/2.9yr, edema NNH=8/2.9yr	XX25,27 ↑ 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 may be beneficial for reducing HF hospitalizations, but potential variation between agents.	✓✓32 ↓ CV Death or worsening HF/hospitalization dapagliflozin NNT=21/1.5yr (DAPA-HF), empagliflozin 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 Strategies help: e.g. start low, titrate, adjust diet; often improves with time!		✓✓	✓✓
Cost	✓✓	✓✓	✓-✓✓	X	X	✓	✓	X -only sita & saxa g	XX	X –(but g dapagliflozin $35)		XX
Other	May have to hold or ↓ dose in acute illness/HF/ renal dysfx (? lactic acidosis, see SADMANS); may ↓ B12. 1st line for T2DM (UKPDS-34)	Used in combination with metformin (ADVANCE) Caution: accumulates Hold if acute illness see SADMANS tool	Caution if ↓ renal function (& in older adults)	X FDA +/- HC warnings:[35] ?↑ HF *(see above)*, ?↑ fractures ♀ (NNH≈30/~3.5yr) ?↑ macular edema (conflicting data) Pio:?↑ bladder ca >12 mos (27.5 excess /100,000 person yrs), avoid co-admin with dapagliflozin[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	✓PPBG injection site irritation ?↑ pancreatitis,[39] ?↑ pancreatic cancer,[40] (*once weekly* agents may have ↓ GI adverse events)[42] gallbladder disease/bile duct[46] Fear/perception of injections X ?worsening retinopathy FDA +/- HC warning: multiple endocrine neoplasia syndrome type 2, hx of medullary thyroid cancer (?↑ thyroid cancer, liraglutide data from mice/rats)[41], ?pancreatitis, ?pancreatic ca.	✓✓46 cana, empa, dapa: ↓composite renal/CV death CREDENCE; DAPA-CKD; EMPA-CKD X FDA +/- HC warning: ↑DKA; ?↑AKI (caution: ↓ intravascular volume & ↓renal function), ↓BP; ?↑UTI/urosepsis/pyelonephritis; genital mycotic 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]. ?↑(HR ~2) limb amputations Cana;[43] Acute Illness: Hold; SADMANS Tool	Fear/ perception of insulin injections	✓PPBG Fear/ perception of insulin injections Need for increased glucose monitoring
Overall	✓✓?	✓		?	X?				? ✓liraglutide (CV + mortality benefit), ? ✓semaglutide subcut, (PO ✆ NIHB) (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, as well as a systematic review and network metaanalysis 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.

Newer medications: 1) Finerenone KERENDIA – Benefits: ↓ all-cause death, major CV, risk of HF & end-stage kidney disease; Harms: hyperkalemia; 2) Tirzepatide MOUNJARO – Benefits: ↓↓ body weight; Harms: severe GI AEs. SHI SR & NMA

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 **GI**=gastrointestinal **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 Subcut TRULICITY (Subcut weekly)	Liraglutide Subcut VICTOZA (Subcut Daily)	Semaglutide Subcut OZEMPIC (Subcut weekly)	Semaglutide PO 14mg RYBELSUS (po daily)	Canagliflozin INVOKANA	Dapagliflozin FORXIGA / FARXIGA USA	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) GRADE n=5047 / 5 yr	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-Reduced & DELIVER-Preserved DAPA-CKD n=4304 / 2.4 yr	EMPA-REG n=7020 / 3.1 yr Emperor-Reduced & Preserved EMPA-KIDNEY n=6609 / 2 yr stopped early
↓ 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 62/3.6yr)	✓? Non-inferior to Placebo HR 0.93 (0.84-1.03) Superiority (NS) over 4.2yr	✓✓ ↓ MACE NNT=63/3.1yr 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	✓✓ 2° endpoint NNT=44/1.5yr DAPA-HF NNT=48/2.4yr DAPA-CKD	✓✓ 2° endpoint NNT=38/3.1yr EMPA-REG
Less Renal Disease (composite/surrogates)	✓ NNT=40/5.4yr (17.1 vs 19.6%)	✓ NNT=67/3.8yr (5.7% vs 7.2%)	✓ NNT=44/2.1yr (3.8% vs 6.1%) ongoing semaglutide FLOW	?	✓✓ HR 0.66 (0.53-0.81) NNT=23/2.6yr CREDENCE	✓✓ HR 0.76 (0.67-0.87) NNT=19/2.4yr DAPA-CKD	✓✓ HR 0.72 (0.64-0.82) NNT=27/2yr EMPA-KIDNEY
Effect on A1c**	✓✓	✓✓	✓✓	✓✓	✓	✓	✓
Weight Loss	✓✓ ↓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		
	Risk when given with sulfonylurea or insulin						
Less Risk of HF See Perspectives	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 CANVAS, CREDENCE	✓✓ HFrEF ↓ worsening HF / CV death NNT=21/1.5yr DAPA-HF HFpEF ↓HHF DELIVER	✓✓ HFrEF ↓ HHF/ CV death NNT=19/1.3yr Emperor-Reduced HFpEF ↓HHF Emperor-Preserved
	? As a class, ↓ hospitalization for HF. Shi et al. SR & NMA						
Effect on GI & D/C due to Tolerability	X GI D/C due to AE 9% vs 6% NNH=36/5.4yr	X GI D/C due to AE 9.5% vs 7.3% NNH=46/3.8yr	X GI D/C due to AE 11.5-14.5% vs 5.7-7.6% NNH≈14/2yr	X D/C due to GI: 6.8% vs 1.6% D/C due to AE 11.6% vs 6.5%; NNH=20/1.3yr	D/C due to AE 12% vs 13%; ?NNH=100/2.6yr	D/C due to AE 8.1% vs 6.9%; NNH=84/4.2yr DECLARE	D/C due to AE 17.3 vs 19.4%; NNH= 48/3.1yr
? AE Concerns Associated with Class	AEs: injection site irritations if subcut. **Rare/?**: ?↑ pancreatitis, ?pancreatic cancer; ?↑ thyroid cancer (liraglutide);[41] gallbladder disease;[46] ?diabetic retinopathy complications.[SUSTAIN-6] **Caution**: GI dx e.g. Crohn's, IBS. See AE Infographic. *Once weekly* agents may have ↓ GI adverse events.[42]				FDA +/- HC warning: ↑DKA; ?↑AKI (caution on initiation, especially if ↓ intravascular volume & ↓ renal fx); **genital mycotic infections.** Rare: ?Fournier's gangrene; ?↑UTI/urosepsis/pyelonephritis. Electrolyte imbalance. See AE Infographic.		
Cost – 1 month Some cost programs may be available	XX $225 ✗⊗	XX $90-$235 ✗⊗	XX $120-$220 ☎▼ NIHB	XX $260 ✗✆ NIHB	X $110 ☎✆	X but g dapa $35- on SPDP & NIHB	X $110 ☎▼ NIHB
Other	Well tolerated, except GI. Environmental impact - single use disposable pen	Gallbladder AE: NNH=84	NIHB open benefit	Smaller, shorter trial. SAE lower in tx group.	?↑(HR ~2, rare) limb amputations	↑bladder/ breast cancer (avoid with pioglitazone). 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; pts may struggle with AEs in first few wks, but many will adjust diet, gain tolerability & do OK. Insulin dose can be reduced 20-30% initially;[Expert] possibly more after that. **Discontinue DPP4 inhibitors**, if on.				Minimal A1c lowering eGFR<30. Uncertain multi-mechanism of action e.g. lower BP. Monitor BP and assess for postural hypotension, especially in older adults. May require dose reduction of insulin or SU to minimize hypoglycemia.		
Time Tested	Newer agents – but well studied; some safety data & real world use still limited				Newer agents – but well studied; some safety data & real world use 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 Metformin: 77%, insulin 60%; smaller, shorter trial; SAE leading to ↓ discontinuation rate in tx group, 2.6% vs 3%. Higher risk group: CVD or CKD 84.7%

GRADE patients on metformin and A1c between 6.8-8.5, comparative effectiveness of glargine vs glimiperide, vs liraglutide vs sitagliptin; liraglutide associated with favourable CV/death outcomes vs others overall.

See also **Shi et al Systematic Review & Network Meta-analysis (SR/NMA) 2023**

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 [1° outcome if no CV disease history, HR= 0.98 (0.74-1.3)] patients with and without diabetes studied; similar benefit in both groups.

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

DAPA-HF: HFrEF, EF≤40%; **DELIVER** HFpEF, EF>40%; similar benefit in pts with and without diabetes.

DAPA-CKD: eGFR 25-75 (mean 43) + ACR 22.6-565 + ACE/ARB 98%; similar benefit in pts with & without DM.

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

EMPEROR-REDUCED: HFrEF, EF≤40%; **EMPEROR-PRESERVED**: HFpEF, EF>40%; similar benefit in pts with and without diabetes.

EMPA-KIDNEY: eGFR 20-75 (mean 37) + ACR ≥ 200; ACE/ARB ~85%; similar benefit in pts with & without DM.

See also **Shi et al Systematic Review & Network Meta-analysis (SR/NMA) 2023**

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A1c=glycosylated hemoglobin **ACEI=**angiotensin converting enzyme inhibitor **ACR=**albumin: creatinine ratio **AE=**adverse events **AKI=**acute kidney injury **ARB=**angiotensin II receptor blocker **BMD=**bone mineral density **BP=**blood pressure **CA=**cancer **CAD=**coronary artery disease **CDN=**Canadian **CKD=**chronic kidney disease **CV=**cardiovascular **CVA=**cerebrovascular accident **CVD=**cardiovascular disease **D/C=**discontinued **DKA=**diabetic ketoacidosis **DM=**diabetes mellitus **DPP4=**dipeptidyl peptidase-4 **dx=**disease/diagnosis **dysfx=**dysfunction **EDS=**exception drug status **EF=**ejection fraction **eGFR=**estimated glomerular filtration rate **ESRD=**end-stage renal disease **FDA=**approved Food & Drug Admin **fx=**function **GI=**gastrointestinal **GLP1=**glucagon-like peptide-1 receptor agonist **HC=**Health Canada **HF=**heart failure **HF-pef/HF-ref**=heart failure preserved/reduced injection **HR=**heart rate or hazard ratio **HS=**bedtime **hx=**history **IBS=**irritable bowel syndrome **IFG=**impaired fasting glucose **MACE=**major adverse cardiovascular events **MF=**metformin **MI=**myocardial infarction **NIHB=**non-insured health benefits for First Nations **NNH=**number needed to harm **NNT=**number needed to treat **NPH=**neutral protamine Hagedorn **NS=**non-significant **PAD=**peripheral artery disease **po=**oral **PPBG=**postprandial (2hr) blood glucose **Pt=**patient **SCr=**serum creatinine **SGLT2=**sodium-glucose cotransporter-2 **SK=**Saskatchewan **SKH=**Saskatchewan Health **SU=**sulfonylurea **subcut=**subcutaneous **T1DM=**type 1 diabetes mellitus **T2DM=**type 2 diabetes mellitus **TIA=**transient ischemic attack **TID=**three times daily **UTI=**urinary tract infection **vs=**versus **wk=**week **yr(s)=**year(s)

A1c	45
Acarbose	45
ACTOS	45
ADLYXINE	45
Alogliptin	45
AVANDIA	45
BYDRUEON	45
BYETTA	45
Canagliflozin	45
Dapagliflozin	45
DIABETA	45
Diabetes	**45**
DIAMICRON	45
Dulaglutide	45
Empagliflozin	45
Exenatide	45
FARXIGA	45
FORXIGA	45
Gliclazide	45
GLUCOBAY	45
GLUCONORM	45
GLUCOPHAGE	45
Glucose	45
Glyburide	45
Insulin	45
INVOKANA	45
JANUVIA	45
JARDIANCE	45
Linagliptin	45
Liraglutide	45
Lixisenatide	45
Metformin	45
NESINA	45
ONGLYZA	45
OZEMPIC	45
Pioglitazone	45
Repaglinide	45
Rosiglitazone	45
RYBELSUS	45
Saxagliptin	45
Semaglutide	45
SGLT2 Inhibitors	45
Sitagliptin	45
TRAJENTA	45
TRULICITY	45

Type 2 Diabetes Mellitus	**45**
VICTOZA	45
A1c	46
Canagliflozin	46
Dapagliflozin	46
Diabetes	**46**
Dulaglutide	46
Empagliflozin	46
FARXIGA	46
FORXIGA	46
GLP1 Agonist	46
JARDIANCE	46
Liraglutide	46
Lixisenatide	46
OZEMPIC	46
RYBELSUS	46
Semaglutide	46
SGLT2 Inhibitors	46
TRULICITY	46
Type 2 Diabetes Mellitus	**46**
VICTOZA	46

References for GLP1 and SGLT2 Subset Colour Chart (www.RxFiles.ca)

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Notes / References for Diabetes Agents Colour Outcomes Comparison Chart (www.RxFiles.ca)

Death/MACE (MACE: Major adverse cardiovascular event)

1. Drug manufacturers must establish CV safety (one-sided upper boundary of 95% CI ≤ 1.3) vs comparator (typically placebo) in a RCT for all new agents in ↑ CV risk patients.[1] FDA
2. Metformin vs conventional diet; obese >120% IBW & small sample n=753; **↓ all-cause mortality NNT 14/10.7 yr**, and **↓ MI NNT=14/10.7 yr**.[2] UKPDS-34 10 yr observational follow-up **↓ all-cause mortality NNT=14/~20 yr**, and **↓ MI NNT=16/~20 yr**.[3] UKPDS-80 Evidence overall somewhat weak. SHI et al. SR/NMA
3. Intensive HbA1c target (included gliclazide) vs standard HbA1c target; MACE 10% vs 10.6% p=NS, all-cause mortality 8.9% vs 9.6% p=NS.[4] ADVANCE
4. Intensive therapy (chlorpropamide, glipizide[USA], glibenclamide or insulin) vs conventional diet; all-cause mortality 17.9% vs 18.9% p=NS, MI 14.7% vs 17.4% p=NS, and stroke 5.6% vs 5% p=NS.[5] UKPDS-33 10 yr observational follow-up **↓ all-cause mortality NNT=29/~20 yr**, and **↓ MI NNT=36/~20 yr**.[3] UKPDS-80
19. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up **↓ MACE NNT=23/ ~17 yr**.[32] DCCT, [33] EDIC
20. Insulin basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9% p=NS, MI 15.8% vs 17.9%

Death/MACE (MACE: Major adverse cardiovascular event)- cont'd

p=NS, and stroke 5.4% vs 5.0% p=NS.[5] UKPDS-33 10 yr observational follow-up **↓ all-cause mortality NNT=29/~20 yr**, and **↓ MI NNT=36/~20 yr**.[3] UKPDS-80

21. Greater insulin use (any & bolus) with intensive therapy vs standard therapy; **↑ MACE NNT=33/3.5 yr** and **↑CV death NNT=125/3.5 yr**.[34] ACCORD

5. SU (2nd or 3rd generation) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, I^2=0%), CV mortality OR 1.12 (0.87-1.45, I^2=12%), MI OR 0.92 (0.76-1.12, I^2=NR), stroke OR 1.16 (0.81-1.66, I^2=NR).[6]
6. Metformin vs glipizide; Chinese, small sample n=304, & medically undertreated 100% CAD, but ≤10% taking ACEi; Metformin ↓ **MACE NNT=10/5 yr**.[7] SPREAD-DIMCAD
7. Pioglitazone vs placebo; T2DM & high CV risk; ↓ **MACE NNT=50/2.9 yr**,[8] PROACTIVE insulin resistance & recent TIA/stroke; ↓**MACE NNT=36/4.8 yr**.[9] IRIS
8. Rosiglitazone vs placebo; ↑ **MACE** 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mons early,[10] DREAM ↑ MI NNH=167 & CV death 0.87% vs 0.39% p=0.06.[10] Rosiglitazone vs glyburide ↑ **MACE NNH 63/4 yr**.[12] ADOPT
9. Acarbose vs placebo; impaired glucose tolerance; ↓ **MACE NNT 40/3.3 yr**.[13] STOP-NIDDM Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95% CI, 0.86-1.11, p=0.73.[13] ACE
10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, **non-inferior** (p<0.001), but not superior (p=0.99).[14] SAVOR-TIMI 53 Alogliptin vs placebo; MACE 11.3% vs 11.8%, **non-inferior** (p<0.001), but not superior (p=0.32).[15] EXAMINE Sitaglipin MACE vs placebo; MACE 9.6% vs 9.6%, **non-inferior** (p<0.001), but not superior (p=0.65).[16] TECOS Meta-analysis(SAVOR-TIMI 53, EXAMINE, TECOS) MACE RR 0.99 (95% CI, 0.93-1.06, I^2=0%).[17]
11. Linagliptin vs placebo; MACE 12.4% vs 12.1% **non-inferior** (p<0.001), but not superior (p=0.74).[18] CARMELINA Linagliptin vs glimepiride: MACE 11.8% vs 12% non-inferior (p<0.001) but not superior.CAROLINA2019
12. Liraglutide vs placebo; **MACE** 13% vs 14.9%, **superior** (p=0.01, **NNT=53/3.8 yr**), but results neutral in North America subgroup; ↓ **CV death NNT=77/3.8 yr** and ↓ **all-cause mortality NNT 72/3.8 yr**.[19] LEADER Semaglutide SC weekly vs placebo; MACE **superior**; (nephropathy was better; however, retinopathy complications were worse).[20] SUSTAIN6
13. Lixisenatide vs placebo (post-ACS); MACE 13.4% vs 13.2%, **non-inferior** (p<0.001), not superior (p=0.81).[21] ELIXA
14. Exenatide extended release vs placebo (~70% CVD, ~30% primary prevention); MACE 11.4% vs 12.2% over median 3.2 yr, **non-inferior** (p<0.001), but not superior (p=0.06).[22] EXSCEL DulaglutideUSA CV trial ongoing, estimated completed 2018.[23] REWIND Albiglutide CV trial ongoing, estimated completed 2018.[24] HARMONY Semaglutide PO CV trial semaglutide po vs placebo: MACE, non-inferior; ↓ all-cause death 1.4% vs 2.8% 2ndy endpoint 2019. PIONEER-6
15. Empagliflozin vs placebo; **MACE** 10.5% vs 12.1%, **superior** (p=0.04, **NNT=63/3.1 yr**); ↓ **CV death NNT=46/3.1 yr** and ↓ **all-cause mortality NNT 39/3.1 yr**.[25] EMPA-REG Canagliflozin vs placebo; **MACE** 26.9/1000ptyrs (2.7%/yr) vs 31.5/1000ptyrs (3.15%/yr), **superior** (p=0.02, **NNT~220/yr**), f/u duration 3.6yr, no signfigant difference in components of primary composite or death; ↑ MACE in 1st 30 days (n=13 vs n=1, p=NS, non-dose related); ↓ MACE (NS) after 30 days (HR 0.89, 95% CI 0.64, 1.25); numeric imbalance not present in non-CANVAS trials. [26,27,27a] CANVAS Dapagliflozin vs placebo; MACE 8.8% vs 9.4% p<0.001 **non-inferior**, but not superior p=0.17; ↓ CV death & HF hospitalization combo outcome.[28] DECLARE
16. Sotagliflozin CV trial ongoing, estimated completed 2022. SCORE
17. Basal insulin (glargine) vs standard care; all-cause mortality 15.2% vs 15.4% p=NS, MI 5.4% vs 5.2% p=NS, and stroke 5.3 vs 5.1% p=NS.[30] ORIGIN
18. Basal insulin vs basal/bolus insulin; small sample n=152; CV mortality 3.8% vs 6.7% p=NS, MACE 20% vs 32% p=NS.[31]

HF/Edema- cont'd

29. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%, p=N/A.[9]
30. Saxagliptin vs placebo; ↑ **hospitalization for HF NNH=143/2.1 yr**; however, subgroup without a history of HF at baseline ↑ **hospitalization for HF NNH=147/2.1 yr**, subgroup eGFR <60 mL/min ↑ **hospitalization for HF NNH=68/2.1 yr** & no difference from 12 months on (HR 1.05, 95% CI 0.81-1.35).[10, 11] SAVOR-TIMI 53 Alogliptin vs placebo; hospitalization for HF 3.9% vs 3.3% p=0.22; subgroup without a history of HF at baseline ↑ **hospitalization for HF NNH=111/1.5 yr**.[12,13] EXAMINE Sitaglipin vs placebo; hospitalization for HF 3.1% vs 3.1% p=0.98; and neutral results when adjusted for baseline HF (aHR 1.00, 95% CI 0.83-1.20 [unpublished data]).[14,15] TECOS Meta-analysis(SAVOR-TIMI 53, EXAMINE, TECOS) HF admission RR 1.12 (95% CI, 1.00-1.25, I^2=45%).[16] FDA warnings for both saxagliptin & alogliptin.[17] Linagliptin vs placebo; hospitalization for heart failure 6.0% vs 6.5% for an absolute incidence rate difference of −0.27 (95% CI, −0.82 to 0.28), with no significant difference between the 2 treatment groups (HR, 0.90; 95% CI, 0.74-1.08; P = .26).CARMELINA

Insulin degludec vs insulin glargine (T2DM; ~50/50 split bolus vs bolus/basal baseline & no difference between basal/bolus insulin use between groups at the end of study): MACE 8.5% vs 9.3% (95% CI 0.78- 1.06; p<0.001 non-inferiority).[34a] DEVOTE

Weight (weight gain/loss variable, diabetic agents used in conjunction with diet and lifestyle interventions as well as other concomitant medications)

A1. Metformin: ↓ 2.9 kg/4 yr [1] ADOPT
A2. Sulfonylureas: ↑ 1.6 kg/4 yr [1] ADOPT
A3. Pioglitazone: ↑ 3.6 kg/3 yr [2] PROACTIVE
A4. Rosiglitazone: ↑ 4.8 kg/5 yr; rosiglitazone statistically significant ↑ weight vs. both metformin & glyburide [1] ADOPT
A5. Acarbose: ↓1.15 kg/3 yr [3] STOP-NIDDM
A6. Repaglinide: ↑ ~1.7 kg/12-24 wks;[4,5] nateglinide: ↑ 0.7-1 kg/16-24 wks[4.6]
A7. DPP4-inhibitors (generally considered neutral, or small increase)[7,] SHI SR & NMA
- saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) [8] SAVOR-TIMI 53
- alogliptin ↑ 1 kg/18 months (similar to placebo) [9] EXAMINE
- sitagliptin ↑ ≤ 0.5 kg/12 weeks[10]

A8. GLP1 agonists
- exenatide ↓ 2.8 kg/24-52 weeks[11]
- liraglutide ↓ 2.3 kg/3.8 yr [12] LEADER
- dulaglutide ↓1.3-3 kg/5-52 weeks[13]

A9. SGLT2 inhibitors[14]
- canagliflozin ↓ 2.8-4 kg/4-52 weeks[15,16] CANTATA-M
- dapagliflozin ↓ 2 kg/12-52 weeks[17]
- empagliflozin ↓ ~1.5-2 kg/3.1 y[18] EMPA-REG

A10. Insulin
- intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 0.4 kg/3.5 y; weight ↑ >10 kg 28% vs 14% p<0.00[19] ACCORD; ↑ 3.26 kg (2.10-4.41) , SHI SR & NMA
- Note: detemir -1.27 to -0.8 kg vs NPH (glargine no difference vs NPH)[20]

HF/Edema

22. MF should be considered 1st line in HF patients with eGFR > 30 mL/min [Grade D, Consensus].[1] CDA'13
23. Retrospective cohort (n=10,920 patients hospitalized with HF); MF vs SU ↓ **all-cause mortality aHR 0.85 (95% CI 0.75-0.98)**, MF + SU vs MF ↓ **all-cause mortality aHR 0.89 (95% 0.82-0.96),** MF + insulin vs SU neutral aHR0.96 (95% CI 0.82-1.13), MF+SU+insulin neutral aHR 0.94 (0.77-1.15).[2]
24. Intensive A1C target (included gliclazide) vs standard A1C target; HF (HF death, HF hospitalization, worsening NYHA class) 3.9% vs 4.1% p=NS.[3] ADVANCE
25. Glyburide vs rosiglitazone; ↓**HF** (serious events) **NNT 167/3.5 yr, ↓HF** (total events) **NNT=67/3.5 yr.**[4] ADOPT
26. Pioglitazone vs placebo; ↑ **hospitalization for HF NNH=50/2.9 yr** (not adjudicated), ↑ **edema (without HF) NNH=8/2.9 yr**.[5] PROACTIVE
27. Rosiglitazone +meformin or SU vs control; ↑ **hospitalization for HF or HF death NNH=69/5.5 yr**.[6] RECORD Rosiglitazone vs placebo; ↑ **HF NNH=250/3 yr**.[7] DREAM
28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A.[8] STOP-NIDDM

Other- continued

or sitagliptin/metformin of which n=58 cases were hospitalized (n=4 cases admitted to the ICU), n=2 cases of hemorrhagic or necrotizing pancreatitis.[27] Listed adverse event for other agents (e.g., liraglutide) in product monograph.

40. Incretin agents (DPP-4 inhibitors and GLP1 agonists) ?↑ pancreatic cancer: n=13 pancreatic cancer cases suspected of being associated with all incretin-based therapies (July 31, 2014).[24,28]
41. Liraglutide: ?↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent).[29]

45.?↑/↓ GI (nausea, diarrhea, vomiting) AE with long acting agents[30,31]: ↑ **GI AE**: taspoglutide once

31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14.[18] LEADER Lixisenatide vs placebo; hosp for HF: 4.0% vs 4.2% p=0.75.[19] ELIXA As a class, GLP1a's ↓ hosp for HF (OR 0.91 0.83-0.99) SHI SR & NMA
32. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.[20] EMPA-REG Empagliflozin in HF patients (regardless of diabetes status) ongoing trial estimated to be complete 2020 EMPEROR-Reduced & Preserved. Canagliflozin vs placebo; hospitalization for HF: 5.5/1000ptyrs (0.55%/yr) vs 8.7/1000ptyrs (0.87%/yr) (HR 0.67, 95% CI 0.52-0.87) follow up 3.6yr but exploratory.[27a] CANVAS Dapagliflozin vs placebo; hospitalization for HF: 2.5%/1000 patient year vs 3.3%/1000 patient year HR0.73 (95% CI 0.61-0.88) but exploratory.[28] DECLARE Dapagliflozin 10mg po once daily vs placebo; composite primary outcome: worsening HF (hospitalization or urgent visit resulting in IV therapy for heart failure) or CV death:
16.3% vs 21.2% p=<0.001. DAPA-HF
33. Basal insulin (glargine) vs standard care; hospitalization for HF 4.9% vs 5.5% p=NS.[21] ORIGIN
34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS.[22] ArchInternMed1997

Other/Additional Trials Recently Published

35. Pioglitazone & Rosiglitazone FDA +/- Health Canada warnings/label changes:
    - ?↑ HF (see above) [1] PROACTIVE, [2] RECORD, [3] DREAM,[4, 5]
    - ?↑ fractures ♀; pioglitazone vs placebo 5.1 vs 2.5%, calculated p=0.005 ?↑ fractures ♀ **NNH=38/2.9 yr** (unpublished PROACTIVE data).[6] Rosiglitazone vs MF ↑ fractures ♀ **NNH=24/4 yr**, rosiglitazone vs glyburide ↑ fractures ♀ **NNH=17/4 yr**.[8] ADOPT Post marketing data: pioglitazone exposure in women associated **0.8 excess fractures (distal upper and lower limbs)/100 patient-years** vs comparator treated group.[8] No ↑ risk in males.[8,9]
    - ?↑ diabetic macular edema: retrospective cohort, TZD users vs nonusers ↑ macular edema 1 yr follow up aOR 2.3 (1.5-3.6) & 10 yr follow up HR 2.3 (1.7-3.0).[10] Cross-section of **ACCORD** ↑macular edema aOR, 0.97 (0.67-1.40).[11] Note- only rosiglitazone has a warning.[12]
36. Piog: ?↑ bladder cancer; France, retrospective observational cohort pioglitazone exposure vs other diabetic agent HR 1.22 (1.03-1.43), pioglitazone exposure **cumulative dose > 28 000** mg vs other diabetic agent HR 1.75 (1.22-2.5), pioglitazone **exposure >12 months** vs other diabetic agent HR 1.28 (1.09-1.51).[13] US, prospective observational cohort (5 yr interim analysis) pioglitazone exposure vs never exposed HR 1.2 (0.9-1.5), pioglitazone exposure >12 months vs never exposed HR 1.4 (0.9-2.1), & piogltazone exposure >24 months vs never exposed HR 1.4 (1.03-2.0).[14] FDA calculated pioglitazone >12 months associated **27.5 excess cases of bladder cancer /100,000 person-yrs** vs never exposed.[15,16]
37. Rosigltazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ?↑ CV events- see MACE/mortality.[17-21]
38. DPP-4 inhibitors FDA +/- Health Canada warnings/label changes:
    - ?↑ HF risk with saxagliptin and alogliptin (see above).[10, 11] SAVOR-TIMI 53, [12,13] EXAMINE,[16, 22]
    - ?↑ arthralgia risk; n=33 cases of severe arthralgia, of which n=10 cases were hospitalized due to disabling joint pain; n=8 cases reported a positive rechallenge (2006-2013).[23]
39. Incretin agents (DPP-4 inhibitors and GLP1 agonists) ?↑ pancreatitis:[24] Meta-analysis of SAVOR-TIMI 53, EXAMINE, & TECOS (n=36,395) demonstrated ↑ acute pancreatitis **OR 1.79 (1.13-2.82) and ARI of 0.13%** vs placebo.[24a] US case control study; incretin agent (exenatide or sitagliptin) within 30 days **OR 2.24 (95% CI, 1.36-3.68)**.[25] FDA: n=30 cases of pancreatitis with exenatide of which n=21 cases hospitalized, n=3 cases reported positive rechallenge.[26] FDA: n=88 cases of pancreatitis with sitagliptin weekly 59% vs exenatide BID 35% (clinical development of taspoglutide has been stopped).[32] ↓ **GI AE:** Exenatide once weekly 28% vs exenatide BID 48%, albiglutide once weekly 29.8% vs liraglutide daily 52%, exenatide once weekly 19.1% vs liraglutide daily 44.5%.[33] DURATION-5,[34] HARMONY-7,[35] DURATION-6 Neutral GI: dulaglutide once weekly 39.4% vs liraglutide daily 38.3%.[36] AWARD-6
43. SGLT2 inhibitors FDA +/- Health Canada warnings/label changes:
    - ?↑ diabetic ketoacidosis; n=5 Canadian cases, some requiring hospitalization (May 2016); n= 73 US cases (n=44 T2DM cases, n=15T1DM cases, n=13 NR) (Mar 2013-2015) all requiring hospitalization or emergency department care.[37,38]
    - ?↑ urosepsis & pyelonephritis; n=19 cases requiring hospitalizations (canagliflozin [n=10 cases] and dapagliflozin [n=9 cases]), of which n=4 cases required ICU admission and n=2 cases required hemodialysis (Mar 2013-Oct 2014).[38]
    - ?↑ AKI; n=2 Canadian cases (Canagliflozin) (Oct 2015); n=101 US cases (Mar 2013-Oct 2015), of which n=96 cases required hospitalization (n=22 cases required ICU admission), n=15 cases required hemodialysis, and n=4 cases resulted in death. ~50% of cases occurred within 1 month of drug initiation; empagliflozin not included in review due to recent approval.[39,40]
    - ?↑ fracture; canagliflozin 100 mg-300 mg vs placebo follow up 3.6yr; 15.4/1000ptyrs (1.54%/yr) vs 11.9/1000ptyrs (1.19%/yr) NNT= 285/yr (HR 1.26, 95% CI 1.04-1.52),. CANVAS ?↓BMD (total hips, lumbar spine, femoral neck, & distal forearm).[41]
    - ?↑ lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6yr; ↑ all amputation 6.3/1000ptyrs (.63%/yr) vs 3.4/1000ptyrs (0.34%/yr) NNH=345/yr (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below/above knee) 1.8/1000ptyrs (0.18%/yr) vs 0.9/1000ptyrs (0.09%/yr) NNH>1000/yr (HR 2, 95% CI 1.08-3.82) .CANVAS Other trials neutral.[e.g., CANVAS-R 45,43] May2017 FDA: canaglifozin -increased risk of leg and foot amputations. https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
    Aug 2020 FDA: Removed lower limb amputation warning for canagliflozin.
44. ?↑UTI; SGLT2 inhibitor vs placebo: **OR 1.34 (1.03-1.74, I^2=0%)**, vs active agent: OR 1.45 (1.06-1.9, I^2=25%); however recent real world surveillance data suggests this may not be an issue [47, 48] https://annals.org/aim/article-abstract/2739786/sodium-glucose-cotransporter-2-inhibitors-risk-severe-urinary-tract-infections?searchresult=1 .
    ↑ **genital tract skin infection**; SGLT2 inhibitor vs placebo **OR 3.50 (2.46-4.99, I^2=0%)**, vs active agent: OR 5.06 (3.44-7.45, I^2=0%).[44]
45. Dapagliflozin: ? ↑ bladder/breast cancer; approved by FDA 2014 (rejected in 2012 due to breast & bladder cancer concerns). Dapagliflozin vs control; bladder cancer: n=10 cases vs n=1 case & breast cancer: n=12 cases vs n= 3 cases (up to 2013).
46. Canagliflozin 100mg once daily vs placebo: ↓primary composite outcome of ESKD, doubling of SCr & renal or CV death: 11.1% vs 15.5% p= 0.00001. CREDENCE
47. FDA Warning (May 2019): SGLT2 inhibitors associated with **Fournier Gangrene**. 55 cases reported to FDA between 2013-19 with SGLT2i. Likely class effect (cana = 21, dapa = 16, empa=18). 2019 review: https://annals.org/aim/article-abstract/2732837/fournier-gangrene-associated-sodium-glucose-cotransporter-2-inhibitors-review-spontaneous

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