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 / 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 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, DAPA-HF, VERTIS-CV (2019), 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]		✓3,4,5 X?5,6 glipizide ↑ MACE vs MF NNH=10/5yr (SPREAD-DIMCAD)	✓4,5	2.9yr , composite NS ↓ MACE (IRIS) (pts with insulin resistance & recent CVA/TIA)		✓ established CVD (Chinese)		✓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 SC wkly ↓MACE NNT=44/2.1yr SUSTAIN-6 dulaglutide ↓ MACE NNT=72/5.4yr REWIND ✓13,14 lixisenatide, exenatide extended release, semaglutide po ↔ non-inferior to placebo for MACE (ELIXA, EXSCEL, PIONEER-6); 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)		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)												
Risk of Hypoglycemia				✓✓ Low risk w monother								
↓ Risk of HF /Edema				XX26 ↑ HF NNH=50/2.9yr, edema NNH=8/2.9yr	XX25,27 ↑ HF NNH=69 /5.5yr (RECORD), ↑ HF NNH=250 /3yr (DREAM)			X?30 ↑ HF saxagliptin NNH=143/2.1yr (SAVOR), alogliptin (EXAMINE posthoc)	✓31 Entire class of GLP1 agonists neutral for HF hospitalizations.			
Effect on GI tolerability												
Cost												
	hold or ↓ dose T2DM (UKPDS-34)			X FDA +/- HC warnings:35 fractures ♀ (NNH~30/~3.5 y) (SK-EDS; not covered on NIHB) (↑ CV risk concerns) 37		TID dosing	TID dosing	FDA +/- HC warning: X new agents – outcome & safety data still limited	X new agents – outcome & safety data still limited	✓✓✓46 canagliflozin ↓ESRD, doubled SCr & renal/CV death NNT= 23/2.6 yrs (CREDENCE) dapagliflozin ?↑bladder/ breast cancer (avoid with pioglitazone);45 Fournier's gangrene47		Fear/ perception of insulin injections
Overall	✓✓✓?	✓✓	✓	✓?	X?	✓	✓	✓	? ✓✓ liraglutide (CV + mortality benefit), semaglutide SC (CV benefit, 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 next page for breakout GLP1 & SGLT2 data.

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

See also: ***RxFiles Diabetes Landmark Trials Summary*** *at:* http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf ***Diabetes Oral Agents Comparison Chart***: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-diabetes.pdf

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

An Advantage ✓✓✓	✓✓	Neutral ✓	X	A Disadvantage XX	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

L Regier BSP BA - www.RxFiles.ca May 2020

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
↓ 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)	✓ 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)	✓✓✓ 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% /3.8yr	?	✓✓✓ HR 0.66 (0.53-0.81) NNT= 23/2.6 yrs CREDENCE	✓✓ ✓?class effect HR 0.76 (0.67-0.87)	✓✓ ✓?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	✓✓ 2° endpoint ↓HF hospitalizations
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 (AE): injection site irritations if SC; ?/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); Rare: Fournier's gangrene; **genital skin infection** (OR 3.5 vs placebo) ? ↑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
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 hx; 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 SC once **weekly**	✓ SC once daily	✓✓ SC once **weekly**	✓✓✓ **Oral** once daily	✓✓✓ **Oral** once daily		
Overall	?	?	?	?	? Safety	?	?

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

**Note: the "Neutral" designation is given a checkmark indicating that there is little or no disadvantage; however, there is also little or no advantage.

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

Type 2 Diabetes: Strategies, Drug Therapy, & Tools

All references are available online at www.RxFiles.ca

Other RxFiles Books Available Include:

Editors & Writers: Alex Crawley, Marlys LeBras, Taisa Trischuk, Loren Regier, Debbie Bunka, Lynette Kosar, Brent Jensen Graphic Design: Debbie Bunka

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
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
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 (0.87-1.42, 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
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% 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
    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

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

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/4 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)[7]
- 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]

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 Dulaglutide[USA] 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. Ertugliflozin CV trial ongoing, estimated completed 2019.[29] VERTIS CV 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=42%).[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
31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14.[18] LEADER Lixisenatide vs placebo; hospitalization for HF: 4.0% vs 4.2% p=0.75.[19] ELIXA
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
    - 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
- 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]
42. ?↑/↓ GI (nausea, diarrhea, vomiting) AE with long acting agents[30,31]: **↑ GI AE**: taspoglutide once 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 [42,43] 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

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
44. ?↑UTI; SGLT2 inhibitor vs placebo: **OR 1.34 (1.03-1.74, I^2=0%)**, vs active agent: OR 1.42 (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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