

Drug Class	Sulfonylureas	Thiazolidinediones	Meglitinides	DPP4 Inhibitors	GLP1 Agonists ***	SGLT2 Inhibitors ***	Insulin in T2DM					
<b>Generic → BRAND</b> <b>Metformin (MF) GLUCOPHAGE</b>	<b>Gliclazide DIAMICRON</b> <b>Glyburide DIABETA</b> <b>Glimepiride AMARYL GRADE 2023</b> <b>Glipizide GLUCOTROL SPREAD-DIMCAD</b>	<b>Pioglitazone ACTOS</b> <b>Rosiglitazone AVANDIA</b>	<b>Acarbose GLUCOBAY</b>	<b>Repaglinide GLUCONORM</b> D/C: Nateglinide STARLIX	<b>Saxagliptin ONGLYZA</b> <b>Sitagliptin JANUVIA</b> <b>Alogliptin NESINA</b> <b>Linagliptin TRAJENTA</b>	<b>Liraglutide VICTOZA</b> <b>Dulaglutide TRULICITY</b> <b>Semaglutide OZEMPIC, RYBELSUS (PO)</b> D/C: Lixisenatide ADLYXINE; Exenatide BYETTA, BYDUREON; Albiglutide	<b>Empagliflozin JARDINCE</b> <b>Canagliflozin INVOKANA</b> <b>Dapagliflozin FORXIGA, FARXIGA USA</b> D/C: Ertugliflozin STEGLATRO	Intensity: <b>Less</b> (e.g. HS NPH or gargline + metformin) Intensity: <b>More</b> (Multiple daily doses, basal + prandial)				
<b>Major RCTs to support findings/outcomes*</b> 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	ACE (Prevention trial: Stop-NIDDM)	SAVOR-TIMI 53, TECOS, EXAMINE PROLEGUE, CARMELINA, CAROLINA, GRADE 2023	LEADER, GRADE, EXSCEL, FREEDOM CVO, REWIND, SUSTAIN-6, FLOW STEP-HFpEF DM, PIONEER-6, SOUL, ELIXA, HARMONY	EMPA-REG, CANVAS, CREDENCE, VERTIS-CV, DECLARE, DAPA-HF, DAPA-CKD 2020, EMPEROR-Reduced & Preserved DELIVER 2022 EMPA-KIDNEY 2023	T2DM: UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN, DEVOTE, GRADE T2DM: DCCT/EDIC (Also Boussageon et al. Meta-analysis. BMJ 2011;343:d4169)				
<b>↓ Risk of Death / Major CV<sup>1</sup></b>	✓✓✓ <sup>2</sup> in obese, ↓ mortality NNT=14/10yr ↓ MI NNT=14/10yr (UKPDS-34, UKPDS-80)	3,4,5 X <sup>7,6</sup> glipizide ↑ MACE vs MF NNH=10/5yr (SPREAD-DIMCAD)	✓ <sup>7</sup> ↓ MACE NNT=50/2.9yr, but broader CV/MACE 1° composite NS (PROACTIVE) ↓ MACE (IRIS) (pt with insulin resistance & recent CVA/TIA)	X <sup>8</sup>	✓ <sup>9</sup> in IFG, ↓ MACE NNT=40/3.3yr; 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	✓✓ <sup>12</sup> liraglutide ↓ MACE NNT=53/3.8yr & ↓ mortality NNT=72/3.8yr LEADER, semaglutide subcut w/ly ↓ MACE NNT=44/2.1yr SUSTAIN-6 & ↓ mortality NNT=34/3.4yr FLOW dulaglutide ↓ MACE NNT=72/5.4yr REWIND semaglutide po ↓ MACE NNT=56/49.5mo SOUL 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	✓✓ <sup>15</sup> empagliflozin ↓ MACE NNT=63/3.1yr, ↓ mortality empagliflozin NNT=38/3.1yr EMPA-REG dapagliflozin NNT=44/1.5yr DAPA-HF NNT=48/2.4yr DAPA-CKD canagliflozin ↓ MACE NNT=220/yr CANVAS dapagliflozin (DECLARE), ertugliflozin (VERTIS) ↔ MACE	17,18 X <sup>21</sup> 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)		
<b>Effect on A1c**</b>	✓✓	✓✓	✓✓	✓	✓	✓	✓✓	✓✓	✓	✓✓		
<b>Weight (loss vs neutral vs gain)</b>	✓ A1	X A2	X A2	XX A3	XX A4	✓ A5	X A6	X? A7	✓✓ A8	✓ A9	X A10	XX A10
<b>Risk of Hypoglycemia</b>	✓✓	X less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓ Low risk with monotherapy	✓✓	✓✓	✓✓	✓?	✓?	✓	X	XX severe, 1.8%/yr; prescribe glucagon
<b>↓ Risk of HF /Edema</b>	✓ <sup>22,23</sup> use in HF with eGFR >30 mL/min (DC)	23,24	23,25	XX <sup>26</sup> ↑ HF NNH=50/2.9yr, edema NNH=8/2.9yr	XX <sup>25,27</sup> ↑ HF NNH=69/5.5yr (RECORD), edema NNH=250/3yr (DREAM)	28	29	X <sup>30</sup> ↑ HF saxagliptin NNH=143/2.1yr (SAVOR), alogliptin (EXAMINE posthoc) sitagliptin & linagliptin = HF neutral	31 semaglutide subcut ↓ HF sx in HFpEF & BMI ≥30 (STEP-HFpEF DM & STEP-HFpEF [no diabetes])	✓✓ <sup>32</sup> ↓ CV Death or worsening HF/hospitalization dapagliflozin NNT=21/1.5yr (DAPA-HF), empagliflozin NNT=19/1.3yr (Emperor-Reduced) HFpEF ↓ HHF (Emperor-Preserved)	33,34 (?↑ HF risk)	34 (↑ HF risk)
<b>Effect on GI tolerability</b>	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	✓✓	✓✓	✓✓
<b>Cost</b>	✓✓	✓✓	✓✓✓	X	X	✓	✓	X -only sita & saxa g	XX	X (but g dapagliflozin \$35/mo)	XX	XX
<b>Other</b>	may hold or ↓ dose in acute dehydration/illness/HF/renal dysfx (? lactic acidosis, see <b>SADMANS</b> ); may ↓B12 1 <sup>st</sup> line for T2DM (UKPDS-34)	combo with metformin (ADVANCE); preferred in older adults BEERS Caution: accumulates	Caution if ↓renal function (& in older adults)	X FDA +/- HC warnings: <sup>35</sup> ?↑ HF (see above), ?↑ fractures (NNH=30/~3.5yr) ?↑ macular edema (conflicting data) Pio: ?↑ bladder ca >12 mo (27.5 excess /100,000 person yr), avoid co-admin with dapagliflozin <sup>36</sup> Rosi: Restricted access in CDN (SK-EDS; not covered on NIHB) (↑CV risk concerns) <sup>37</sup>	PPBG, Possible benefit of laxative effect in some	PPBG, flexibility with meals	✓ PPBG FDA +/- HC warning: <sup>38</sup> HF (saxa- & alogliptin); arthralgia, hypersensitivity reaction, ?↑ pancreatitis (ARI 0.13%), <sup>39</sup> pancreatic cancer <sup>40</sup> Linagliptin: no renal dose adjustment	✓ PPBG Once weekly agents may have ↓ GI adverse events <sup>42</sup> Perception/fear of injections Recent data suggest no increase: pancreatitis, <sup>39</sup> Ayoub/25 pancreatic cancer, <sup>40</sup> Danker/24 X ?retinopathy progression FDA +/- HC warning: multiple endocrine neoplasia syndrome type 2, hx of medullary thyroid cancer (?↑ thyroid cancer, liraglutide rodent data) <sup>41</sup> Gallbladder disease/bile duct <sup>46</sup>	✓✓ <sup>46</sup> cana, empa, dapa: ↓ composite renal/CV death (CREDENCE, DAPA-CKD, EMPA-KIDNEY) X FDA +/- HC warning: ↑ euglycemic DKA; genital mycotic infection (OR 3.5 vs placebo). <sup>44</sup> Rare: ?Fournier's gangrene; <sup>47</sup> ?↑ UTI/uropoiesis/pyelonephritis; ?↑ limb amputations <sup>Cana,43</sup> ?↑ fracture/↓BMD. <sup>Cana</sup> Caution: hypovolemia, ↓BP (consider ↓BP meds / diuretics); Acute illness: hold; consider <b>SADMANS</b> tool.	Perception / fear of insulin injections	Perception / fear of insulin injections Need for increased blood glucose monitoring	
<b>Overall</b>	✓✓?	✓	✓	?	X?	✓	✓	?	?	?	✓	X?

\*These drugs come with various levels of evidence regarding their balance of benefits & harms. This chart relies on evidence, especially from RCTs, as well as a systematic review & network meta-analyses that 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. See online extras for additional notes. \*\*A1c will vary depending on dose, combinations, & initial A1c. SDM Tool: PEER. Other meds: 1) Finerenone KERENDIA – Benefits: major CV composite, mostly hosp for HF, & kidney composite, mostly sustained ↓eGFR ≥40-≥57%; Harms: hyperkalemia; ?≥30% ↓eGFR at day 30 esp when initiated with SGLT2. FIDELITY Analysis, FIGARO-DKD, FIDELIO-DKD, CONFIDENCE 2) Tirzepatide MOUNJARO: see bottom pg 46. AKI=acute kidney injury DKA=diabetic ketoacidosis HHF=hospitalizations for heart failure IFG=impaired fasting glucose MACE=major adverse cardiovascular events PPBG=postprandial blood glucose

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 <sup>USA</sup>	Empagliflozin JARDIANCE
Major trials to support findings/outcomes* Also SHI SR & NMA*	REWIND n=9901 / 5.4 yr	LEADER n=9340 / 3.8 yr GRADE n=5047 / 5 yr	SUSTAIN-6 n=3297 / 2 yr FLOW n=3533 / 3.4 yr stopped early renal dx HFpEF DM n=616 / 1 yr	PIONEER-6 n=3183 / 1.3 yr SOUL n=9650 / 49.5 mo CV&renal	CANVAS n=10142 / 3.6 yr CREDENCE n=4401 / 2.6 yr renal disease	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=72/5.4yr REWIND ? North America subgroup-neutral HR: 1.14 (0.89-1.47)	✓✓ ↓ MACE NNT=53/3.8yr LEADER ? North America subgroup-neutral HR: 1.01 (0.84-1.22)	✓✓ ↓ MACE NNT=44/2.1yr SUSTAIN-6 ? North America subgroup-marginal HR: 0.87 (0.57-1.34)	✓ ↓ MACE NNT=56/49.5mo SOUL Neutral MACE PIONEER-6 non-inferior to placebo 3.8% vs 4.8%; 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 EMPA-REG
↓ Risk of All-Death	HR 0.9 (0.80-1.01) 10.8% vs 12%/5.4yr (NS) REWIND	✓✓ NNT=72/3.8yr LEADER	HR 1.05 (0.74-1.50) SUSTAIN-6 ✓ 2° endpoint NNT=34/3.4yr (12.8% vs 15.8%) FLOW	✓? 2° endpoint NNT=72/1.3yr PIONEER-6	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%) REWIND	✓ NNT=67/3.8yr (5.7% vs 7.2%) LEADER	✓✓ semaglutide NNT=23/3.4yr (18.7% vs 23.2%) FLOW	HR: 0.91 (0.8-1.05) 8.4% vs 9%/49.5mo (NS) SOUL	✓✓ 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 wk	✓✓ ↓ 2.3 kg/3.8 yr	✓✓ ↓ 3-4kg/2.1 yr	✓✓ ↓ 3.4kg/1.3 yr	✓ ↓ 2.8-4 kg/4-52 wk CANTATA-M	✓ ↓ 2 kg/12-52 wk	✓ ↓ ~1.5-2 kg/3.1 yr
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 see RxFiles Chart: HF pg 23	HR: 0.93 (0.77-1.22)	HR: 0.87 (0.73-1.05)	✓ ↓ HF sx in HFpEF & BMI ≥30 <sup>HFPEF DM</sup>	HR: 0.86 (0.48-1.55)	2° endpoint ↓ HF hospitalizations CANVAS, CREDENCE	✓✓ HFrEF ↓ worsening HF / CV death NNT=21/1.5yr <sup>DAPA-HF</sup> HFpEF ↓ HFrEF DELIVER	✓✓ HFrEF ↓ HFrEF / CV death NNT=19/1.3yr <sup>Emperor-Reduced</sup> HFpEF ↓ HFrEF Emperor-Preserved
Effect on GI & D/C due to Tolerability	X GI (?better tolerated <sup>42</sup> ) 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 (?better tolerated <sup>42</sup> ) 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: GI, dizziness, ↑HR (clinical relevance uncertain for most). Rare/? : bile duct / gallbladder dx; <sup>46</sup> ? ↑ thyroid cancer (liraglutide <sup>rodent data</sup> ); <sup>41</sup> ?retinopathy progression, delayed gastric emptying/aspiration with anesthesia, ?ileus; <sup>sema</sup> ?self-harm/suicidality, ?↓BMD. <b>Caution:</b> GI e.g. Crohn's, IBS, severe gastroparesis. See <a href="#">AE Infographic</a> .				AEs: FDA +/- HC warning: ↑DKA; genital mycotic infections. Rare: ?Fournier's gangrene; ?↑UTI/urosepsis/pyelonephritis. Caution on initiation if ↓ intravascular volume (↓eGFR ~5mL/min expected, concern if ↑Scr >30%). See <a href="#">AE Infographic</a> .		
Cost – 1 month Some cost programs may be available	XX \$288 x ⊗	XX \$134-\$368 x ⊗	XX \$120-\$220 ⊗/NIHB	XX \$260 x ⊗/NIHB	X \$120 ⊗/NIHB but g \$65	X but g dapagliflozin \$35 - on SPDP & NIHB	X \$101 ⊗/NIHB
Other	Environmental impact - single use disposable pen	Gallbladder AE: NNH=84	NIHB open benefit (T2DM, combo with metformin & exercise)	Short trials. SAE lower in treatment group.	?↑(HR=2, rare) limb amputations NIHB open benefit	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; pt may struggle with AE in first few weeks, but many will adjust diet, gain tolerability, & do OK. Insulin dose can be reduced 20-30% initially; <sup>Expert</sup> possibly more after that. <b>Discontinue DPP4i or tirzepatide.</b>				Minimal A1c lowering eGFR<30. Uncertain multi-mechanism of action e.g. lower BP. Monitor BP and <b>assess for postural hypotension, especially in older adults.</b> May require dose reduction of insulin or SU to minimize hypoglycemia.		
Time Tested	FDA approval since 2010-2017; safety data & real world use still ongoing				FDA approval since 2013/2014; safety data & real world use still ongoing		
Convenience	✓ Single Use Pen subcut once weekly	subcut once daily	✓ subcut once weekly	✓ 30min pre-am meal; ≤120mL H <sub>2</sub> O oral once daily	✓✓ Oral once daily, combo tab with metformin see <a href="#">Table 1</a> pg 44.		
Overall	✓	✓	✓	✓?	✓? Safety	✓	✓

✓✓ An Advantage	✓	Neutral	X	XX A Disadvantage	? Unknown/Ongoing
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Note: the "Neutral" designation indicates little or no disadvantage; however, there is also little or no advantage; SDM Tool: PEER.

GLP1 Agonists	SGLT2 Inhibitors
<p><b>REWIND</b> Lower risk group; e.g. 21% CVD hx; others higher risk; Renal: macroalbuminuria, eGFR decline 30+%, chronic renal replacement treatment</p> <p><b>LEADER</b> High risk group; vs placebo but increased insulin use</p> <p><b>GRADE</b> patients on metformin, A1c between 6.8-8.5, comparative effectiveness of glargine vs glimeperide, vs liraglutide vs sitagliptin; liraglutide associated with favourable CV/death outcomes vs others overall.</p> <p><b>SUSTAIN-6</b> High risk: 83% had established CVD, CKD or both; sema 0.5-1mg/wk vs placebo but ↑ insulin use</p> <p><b>HFPEF DM</b> ~30% SGLT2i; semaglutide 2.4mg/wk (80%) subcut vs placebo; ↓HF hospitalization (exploratory)</p> <p><b>FLOW</b> T2DM + eGFR ≥25 &amp; elevated ACR, 95% on ACEi/ARB; semaglutide 1mg/wk</p> <p><b>PIONEER-6</b> Metformin: 77%, insulin 60%; Higher risk group: CVD or CKD 84.7%; smaller, shorter trial; SAE leading to ↓ discontinuation rate in tx group, 2.6% vs 3%.</p> <p><b>SOUL</b> High risk: all 50 years or older &amp; ~56% CVD, ~13% CKD (eGFR &lt;60), ~27% CVD/CKD. See also <a href="#">Shi et al Systematic Review &amp; Network Meta-analysis (SR/NMA)</a> <sup>2023</sup></p>	<p><b>CREDENCE</b>: Patients with albuminuric CKD, eGFR 30-90 mL/min, &amp; albuminuria; High risk group: 50% had CVD Renal: canagliflozin – composite primary endpoint: ↓ESRD, doubled Scr &amp; renal/CV death</p> <p><b>CANVAS</b>: 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.</p> <p><b>DECLARE-TIMI</b> High risk group: &gt;40% had atherosclerotic CVD; 33% CAD, 6% PAD, 7.6% cerebrovascular dx, 10% HF</p> <p><b>DAPA-HF</b>: HFrEF, EF≤40%; <b>DELIVER</b> HFrEF, EF&gt;40%; similar benefit in pt with and without diabetes.</p> <p><b>DAPA-CKD</b>: eGFR 25-75 (mean 43) + ACR 22.6-565 + ACEi/ARB 98%; similar benefit in pts with &amp; without DM.</p> <p><b>EMPA-REG</b>: High risk group: 100% had CVD. Patients had not received glucose-lowering agents for &gt;12 weeks</p> <p><b>EMPEROR-REDUCED</b>: HFrEF, EF≤40%; <b>EMPEROR-PRESERVED</b>: HFpEF, EF&gt;40%; similar benefit in pt with and without diabetes.</p> <p><b>EMPA-KIDNEY</b>: eGFR 20-90 (mean 37) + ACR ≥ 22.6 mg/mmol; ACEi/ARB ~85%; similar benefit in pt with &amp; without DM. See also <a href="#">Shi et al Systematic Review &amp; Network Meta-analysis (SR/NMA)</a>; <sup>2023</sup> <a href="#">Neufield/SMART-C Meta-Analysis</a> <sup>2022</sup></p>

Other: Glucagon-like peptide (GIP)/GLP1a; **Tirzepatide MOUNJARO** – Benefits: ↓↓ body wt <sup>SURMOUNT-1</sup>, ↓A1c <sup>SURMOUNT-2</sup>; NOTE Major Outcome RCTs (CV, mortality) in progress; Harms: severe GI AE. [SHI SR & NMA](#) Cost 30 days: **\$370-670**

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

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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
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## Notes / References for Diabetes Agents Colour Outcomes Comparison Chart ([www.RxFiles.ca](http://www.RxFiles.ca))

### Death/MACE (MACE: Major adverse cardiovascular event)

1. Drug manufacturers must establish CV safety (one-sided upper boundary of 95% CI  $\leq 1.3$ ) vs comparator (typically placebo) in a RCT for all new agents in  $\uparrow$  CV risk patients.<sup>1 FDA</sup>
2. Metformin vs conventional diet; obese  $>120\%$  IBW & small sample  $n=753$ ;  $\downarrow$  all-cause mortality **NNT 14/10.7 yr**, and  $\downarrow$  MI **NNT=14/10.7 yr**.<sup>2 UKPDS-34</sup> 10 yr observational follow-up  $\downarrow$  all-cause mortality **NNT=14/~20 yr**, and  $\downarrow$  MI **NNT=16/~20 yr**.<sup>3 UKPDS-80</sup> Evidence overall somewhat weak. <sup>5HI et al. 5R/NMA</sup>
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%  $p=NS$ .<sup>4 ADVANCE</sup>
4. Intensive therapy (chlorpropamide, glipizide<sup>USA</sup>, 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%  $p=NS$ .<sup>5 UKPDS-33</sup> 10 yr observational follow-up  $\downarrow$  all-cause mortality **NNT=29/~20 yr**, and  $\downarrow$  MI **NNT=36/~20 yr**.<sup>3 UKPDS-80</sup>
5. SU (2<sup>nd</sup> or 3<sup>rd</sup> 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,  $I^2=NR$ ).<sup>6</sup>
6. Metformin vs glipizide; Chinese, small sample  $n=304$ , & medically undertreated 100% CAD, but  $\leq 10\%$  taking ACEi; Metformin  $\downarrow$  **MACE NNT=10/5 yr**.<sup>7 SPREAD-DIMCAD</sup>
7. Pioglitazone vs placebo; T2DM & high CV risk;  $\downarrow$  **MACE NNT=50/2.9 yr**,<sup>8 PROACTIVE</sup> insulin resistance & recent TIA/stroke;  $\downarrow$  **MACE NNT=36/4.8 yr**.<sup>9 IRIS</sup>
8. Rosiglitazone vs placebo;  $\uparrow$  **MACE 2.9% vs 2.1%  $p=0.08$  (NS)**, trial stopped 5 mons early,<sup>10 DREAM</sup>  $\uparrow$  MI **NNH=167** & CV death 0.87% vs 0.39%  $p=0.06$ .<sup>10</sup> Rosiglitazone vs glyburide  $\uparrow$  **MACE NNH 63/4 yr**.<sup>12 ADOPT</sup>
9. Acarbose vs placebo; impaired glucose tolerance;  $\downarrow$  **MACE NNT 40/3.3 yr**.<sup>13 STOP-NIDDM</sup> Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95% CI, 0.86-1.11,  $p=0.73$ .<sup>13 ACE</sup>
10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.99$ ).<sup>14 SAVOR-TIMI 53</sup> Alogliptin vs placebo; MACE 11.3% vs 11.8%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.32$ ).<sup>15 EXAMINE</sup> Sitagliptin MACE vs placebo; MACE 9.6% vs 9.6%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.65$ ).<sup>16 TECOS</sup> Meta-analysis (SAVOR-TIMI 53, EXAMINE, TECOS) MACE RR 0.99 (95% CI, 0.93-1.06,  $I^2=0\%$ ).<sup>17</sup>
11. Linagliptin vs placebo; MACE 12.4% vs 12.1% **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.74$ ).<sup>18 CARMELINA</sup> Linagliptin vs glimepiride: MACE 11.8% vs 12% non-inferior ( $p<0.001$ ) but not superior.<sup>CAROLINA 2019</sup>
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;  $\downarrow$  **CV death NNT=77/3.8 yr** and  $\downarrow$  **all-cause mortality NNT 72/3.8 yr**.<sup>19 LEADER</sup> Semaglutide SC weekly vs placebo; MACE **superior**; (nephropathy was better; however, retinopathy complications were worse).<sup>20 SUSTAIN6</sup>

19. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up  $\downarrow$  **MACE NNT=23/ ~17 yr**.<sup>32 DCCT, 33 EDIC</sup>
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%  $p=NS$ .<sup>5 UKPDS-33</sup> 10 yr observational follow-up  $\downarrow$  **all-cause mortality NNT=29/~20 yr**, and  $\downarrow$  MI **NNT=36/~20 yr**.<sup>3 UKPDS-80</sup>
21. Greater insulin use (any & bolus) with intensive therapy vs standard therapy;  $\uparrow$  **MACE NNT=33/3.5 yr** and  $\uparrow$  **CV death NNT=125/3.5 yr**.<sup>34 ACCORD</sup>  
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).<sup>34a DEVOTE</sup>

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

- A1. Metformin:  $\downarrow$  2.9 kg/4 yr <sup>1 ADOPT</sup>
- A2. Sulfonylureas:  $\uparrow$  1.6 kg/4 yr <sup>1 ADOPT</sup>
- A3. Pioglitazone:  $\uparrow$  3.6 kg/3 yr <sup>2 PROACTIVE</sup>
- A4. Rosiglitazone:  $\uparrow$  4.8 kg/5 yr; rosiglitazone statistically significant  $\uparrow$  weight vs both metformin & glyburide <sup>1 ADOPT</sup>
- A5. Acarbose:  $\downarrow$  1.15 kg/3 yr <sup>3 STOP-NIDDM</sup>
- A6. Repaglinide:  $\uparrow$  ~1.7 kg/12-24 wks;<sup>4,5</sup> nateglinide:  $\uparrow$  0.7-1 kg/16-24 wks<sup>4,6</sup>
- A7. DPP4-inhibitors (generally considered neutral, or small increase)<sup>7, SHISR & NMA</sup>
  - saxagliptin  $\downarrow$  0.4 kg/2.1 year (similar to placebo) <sup>8 SAVOR-TIMI 53</sup>
  - alogliptin  $\uparrow$  1 kg/18 months (similar to placebo) <sup>9 EXAMINE</sup>
  - sitagliptin  $\uparrow$   $\leq 0.5$  kg/12 weeks<sup>10</sup>
- A8. GLP1 agonists
  - exenatide  $\downarrow$  2.8 kg/24-52 weeks<sup>11</sup>
  - liraglutide  $\downarrow$  2.3 kg/3.8 yr <sup>12 LEADER</sup>
  - dulaglutide  $\downarrow$  1.3-3 kg/5-52 weeks<sup>13</sup>
- A9. SGLT2 inhibitors<sup>14</sup>
  - canagliflozin  $\downarrow$  2.8-4 kg/4-52 weeks<sup>15,16 CANTATA-M</sup>
  - dapagliflozin  $\downarrow$  2 kg/12-52 weeks<sup>17</sup>

13. Lixisenatide vs placebo (post-ACS); MACE 13.4% vs 13.2%, **non-inferior** (p<0.001), not superior (p=0.81).<sup>21</sup> **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).<sup>22</sup> **EXSCEL** Dulaglutide<sup>USA</sup> CV trial ongoing, estimated completed 2018.<sup>23</sup> **REWIND** Albiglutide CV trial ongoing, estimated completed 2018.<sup>24</sup> **HARMONY** Semaglutide PO CV trial semaglutide po vs placebo: MACE, non-inferior; ↓ all-cause death 1.4% vs 2.8%<sup>2ndy endpoint</sup> 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**.<sup>25</sup> **EMPA-REG** Canagliflozin vs placebo; **MACE 26.9/1000ptys (2.7%/yr) vs 31.5/1000ptys (3.15%/yr), superior** (p=0.02, **NNT~220/yr**), f/u duration 3.6yr, no significant difference in components of primary composite or death; ↑ MACE in 1<sup>st</sup> 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.<sup>26,27,27a</sup> **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.<sup>28</sup> **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.<sup>30</sup> **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.<sup>31</sup>

### HF/Edema- cont'd

29. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%, p=N/A.<sup>9</sup>
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).<sup>10, 11</sup> **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**.<sup>12,13</sup> **EXAMINE** Sitagliptin 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]).<sup>14,15</sup> **TECOS** Meta-analysis (**SAVOR-TIMI 53, EXAMINE, TECOS**) HF admission RR 1.12 (95% CI, 1.00-1.25, I<sup>2</sup>=45%).<sup>16</sup> FDA warnings for both saxagliptin & alogliptin.<sup>17</sup> 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).<sup>18</sup> **CARMELINA**

31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14.<sup>18</sup> **LEADER** Lixisenatide vs placebo; hosp for HF: 4.0% vs 4.2% p=0.75.<sup>19</sup> **ELIXA** As a class, GLP1a's ↓ hosp for HF (OR 0.91<sup>0.83-0.99</sup>) **SHI SR & NMA**
32. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.<sup>20</sup> **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: 5.5/1000ptys (0.55%/yr) vs 8.7/1000ptys (0.87%/yr) (HR 0.67, 95% CI 0.52-0.87) follow up 3.6yr but exploratory.<sup>27a</sup> **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.<sup>28</sup> **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.<sup>21</sup> **ORIGIN**
34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS.<sup>22</sup> ArchInternMed1997

### Other/Additional Trials Recently Published

35. Pioglitazone & Rosiglitazone **FDA +/-** Health Canada warnings/label changes:
  - ?↑ HF (see above)<sup>1</sup> **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).<sup>6</sup> Rosiglitazone vs MF ↑ fractures ♀ **NNH=24/4 yr**, rosiglitazone vs glyburide ↑ fractures ♀ **NNH=17/4 yr**.<sup>8</sup> **ADOPT** Post marketing data: pioglitazone

- empagliflozin ↓ ~1.5-2 kg/3.1 y<sup>18</sup> **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<sup>19</sup> **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)<sup>20</sup>

### HF/Edema

22. MF should be considered 1<sup>st</sup> line in HF patients with eGFR > 30 mL/min [Grade D, Consensus].<sup>1</sup> **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).<sup>2</sup>
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.<sup>3</sup> **ADVANCE**
25. Glyburide vs rosiglitazone; ↓ **HF (serious events) NNT 167/3.5 yr**, ↓ **HF (total events) NNT=67/3.5 yr**.<sup>4</sup> **ADOPT**
26. Pioglitazone vs placebo; ↑ **hospitalization for HF NNH=50/2.9 yr** (not adjudicated), ↑ **edema (without HF) NNH=8/2.9 yr**.<sup>5</sup> **PROACTIVE**
27. Rosiglitazone +metformin or SU vs control; ↑ **hospitalization for HF or HF death NNH=69/5.5 yr**.<sup>6</sup> **RECORD** Rosiglitazone vs placebo; ↑ **HF NNH=250/3 yr**.<sup>7</sup> **DREAM**
28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A.<sup>8</sup> **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.<sup>27</sup> 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).<sup>24,28</sup>
- 41. Liraglutide: ?↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent).<sup>29</sup>
- 45. ?↑/↓ GI (nausea, diarrhea, vomiting) AE with long acting agents<sup>30,31</sup>: ↑ **GI AE**: taspoglutide once weekly 59% vs exenatide BID 35% (clinical development of taspoglutide has been stopped).<sup>32</sup> ↓ **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%.<sup>33</sup> **DURATION-5,34 HARMONY-7,35 DURATION-6** Neutral GI: dulaglutide once weekly 39.4% vs liraglutide daily 38.3%.<sup>36</sup> **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.<sup>37,38</sup>
  - ?↑ 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).<sup>38</sup>
  - ?↑ 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.<sup>39,40</sup>
  - ?↑ fracture; canagliflozin 100 mg-300 mg vs placebo follow up 3.6yr; 15.4/1000ptys (1.54%/yr) vs 11.9/1000ptys (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).<sup>41</sup>
  - ?↑ lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6yr; ↑ all amputation 6.3/1000ptys (.63%/yr) vs 3.4/1000ptys (0.34%/yr) NNH=345/yr (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below/above knee) 1.8/1000ptys (0.18%/yr) vs 0.9/1000ptys (0.09%/yr) NNH>1000/yr (HR 2, 95% CI 1.08-3.82) . **CANVAS** Other trials neutral. e.g., **CANVAS-R** <sup>45,43</sup> 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](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.

exposure in women associated **0.8 excess fractures (distal upper and lower limbs)/100 patient-years** vs comparator treated group.<sup>8</sup> No ↑ risk in males.<sup>8,9</sup>

- ?↑ 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).<sup>10</sup> Cross-section of **ACCORD** ↑ macular edema aOR, 0.97 (0.67-1.40).<sup>11</sup> Note- only rosiglitazone has a warning.<sup>12</sup>
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).<sup>13</sup> 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), & pioglitazone exposure >24 months vs never exposed HR 1.4 (1.03-2.0).<sup>14</sup> FDA calculated pioglitazone >12 months associated **27.5 excess cases of bladder cancer /100,000 person-yrs** vs never exposed.<sup>15,16</sup>
37. Rosiglitazone **FDA +/-** Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ?↑ CV events- see MACE/mortality.<sup>17-21</sup>
38. DPP-4 inhibitors FDA +/- Health Canada warnings/label changes:
- ?↑ HF risk with saxagliptin and alogliptin (see above).<sup>10, 11</sup> **SAVOR-TIMI 53**,<sup>12,13</sup> **EXAMINE**,<sup>16, 22</sup>
  - ?↑ 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).<sup>23</sup>
39. Incretin agents (DPP-4 inhibitors and GLP1 agonists) ?↑ pancreatitis:<sup>24</sup> 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.<sup>24a</sup> US case control study; incretin agent (exenatide or sitagliptin) within 30 days **OR 2.24 (95% CI, 1.36-3.68)**.<sup>25</sup> FDA: n=30 cases of pancreatitis with exenatide of which n=21 cases hospitalized, n=3 cases reported positive rechallenge.<sup>26</sup> FDA: n=88 cases of pancreatitis with sitagliptin

44. ?↑UTI; SGLT2 inhibitor vs placebo: **OR 1.34 (1.03-1.74, I<sup>2</sup>=0%)**, vs active agent: OR 1.45 (1.06-1.9, I<sup>2</sup>=25%); however recent real world surveillance data suggests this may not be an issue<sup>47, 48</sup>

<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<sup>2</sup>=0%)**, vs active agent: OR 5.06 (3.44-7.45, I<sup>2</sup>=0%).<sup>44</sup>
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).  
**A 2022 international multisite cohort study** found **no association** of bladder cancer with SGLT2is when compared to GLP1s (HR 0.90, 95% CI 0.81-1.00) or DPP4s (HR 0.99, 95% CI 0.91-1.09). Results were consistent across sensitivity analysis. Median follow up periods ranged from 1.5-2.6 years. <sup>Abrahami '22</sup>
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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