ANTI-HYPERGLYCEMIC AGENTS in T2DM: Outcomes Comparison Summary Table

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Sulfonylureas</th>
<th>GLP1 Agonists</th>
<th>SGLT2 Inhibitors</th>
<th>Insulin in T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic BRAND</td>
<td>Metformin (MF) GLUCOPHAGE</td>
<td>Glipizide GLUCOLIN</td>
<td>LeADER, EXCEL, FREEDOM CV, REVIND, SUSTAIN-6, PIONEER-6, ELIXA, Harmony, ГАЛЕРИА</td>
<td>More (e.g., NPH, multiple daily doses)</td>
</tr>
<tr>
<td>Brand Strength</td>
<td>UKPDS-33,34,30 (ADOPT; see in ADVANCE)</td>
<td>UKPDS-33,30 (ADOPT)</td>
<td>LEADER, EMPEROR-REDUCE, FORSYDA, FORSYDA2021</td>
<td>T2DM: UKPDS-33,30; ADVANCE, VADT, ORIGIN, DEVOTE, GRACE T1DM: DCC/DCT (Also Bousoujan et al. Meta-analysis. BVI 2011:33, 641-659)</td>
</tr>
<tr>
<td>Risk of Death/Major CV</td>
<td>TF21 if &gt;meds/insulin use with very intensive target, may ↑ all-cause death NNH=93.5yr, CV death NNH=125.7yr (RR 0.82 high-risk pool)</td>
<td>NNT=14</td>
<td>NNT=38</td>
<td></td>
</tr>
<tr>
<td>Effect on A1c</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight loss vs neutral gain</td>
<td>A1</td>
<td>X2^2</td>
<td>X2^2</td>
<td>XA</td>
</tr>
<tr>
<td>Risk of Hypoglycemia</td>
<td>X</td>
<td>X less risk with MR formulation</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Risk of HF/EDEMA</td>
<td>22,23</td>
<td>23.24</td>
<td>23.25</td>
<td>X</td>
</tr>
<tr>
<td>Effect on Glucose tolerability</td>
<td>X</td>
<td>Start low &amp; titrate</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cost</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>May have to hold or ↓ dose in acute illness (HF), renal dysh</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Used in combination with metformin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Overall</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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**Notes:**
- **Effect on A1c:** 3** = significant (95% CI for 1% A1c decrease 0.7% to 0.9%)
- **Weight loss vs neutral gain:** 2** = significant, 1.5** = moderate, 0.5** = small
- **Risk of Hypoglycemia:** X = very low risk of hypoglycemia, □ = low risk of hypoglycemia
- **Risk of HF/EDEMA:** 22,23 = first line in HF with eGRF >30 mL/min (DCM^18)
- **Effect on Glucose tolerability:** X = start low & titrate
- **Cost:** X = may have to hold or ↓ dose in acute illness (HF), renal dysh
- **Other:** X = may have to hold or ↓ dose in acute illness (HF), renal dysh

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**Risk of Death/Major CV:**
1. **Risk of Death/Major CV:**
   - **Risk of Death/Major CV:**
   - **Effect on A1c:**
   - **Weight loss vs neutral gain:**
   - **Risk of Hypoglycemia:**
   - **Risk of HF/EDEMA:** 22,23 = first line in HF with eGRF >30 mL/min (DCM^18)
   - **Effect on Glucose tolerability:** X = start low & titrate
   - **Cost:** X = may have to hold or ↓ dose in acute illness (HF), renal dysh
   - **Other:** X = may have to hold or ↓ dose in acute illness (HF), renal dysh

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**Overall:**
- **Overall:**
- **Effect on A1c:**
- **Weight loss vs neutral gain:**
- **Risk of Hypoglycemia:**
- **Risk of HF/EDEMA:** 22,23 = first line in HF with eGRF >30 mL/min (DCM^18)
- **Effect on Glucose tolerability:** X = start low & titrate
- **Cost:** X = may have to hold or ↓ dose in acute illness (HF), renal dysh
- **Other:** X = may have to hold or ↓ dose in acute illness (HF), renal dysh

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**Notes:**
- **Drug that lower glucose outcome 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 meta-analysis that have evaluated patient-oriented outcomes. Direct comparisons between agents are not done to evaluate each drug for its relative advantages & disadvantages. **A1c** will vary depending on dose, combinations & initial A1c.
- **Newer medications:** 1) Liraglutide (VERITIS) - Benefits: ↓ all-cause death, major CV, risk of HF & end-stage kidney disease; Harms: ↑ hyperkalemia; 2) Tirzepatide MOURNOAR - Benefits: ↓ weight, Harms: severe GI AEs, SHI SR & NMA**
- **See full version of this ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table online for additional details:** http://www.refs.ca/refs/uploads/documents/ANTI-HYPERGLYCEMIC DIABETES AGENTS-OutcomesComparisonSummaryTable.pdf

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**Additional Information:**
- **AKI:** acute kidney injury; **DKA:** diabetic ketoacidosis; **GI:** gastrointestinal; **IFG:** impaired fasting glucose; **MACE:** major adverse cardiovascular events; **PPBG:** postprandial blood glucose
GLP1 Agonists & SGLT2 Inhibitors - SUBSET of DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

**Drug Class**

<table>
<thead>
<tr>
<th>GLP1 Agonists</th>
<th>SGLT2 Inhibitors</th>
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<tbody>
<tr>
<td><strong>Generic ▶ BRAND</strong></td>
<td><strong>GLP1 Agonists</strong></td>
</tr>
<tr>
<td><strong>Major trial(s) to support findings/Outcomes</strong></td>
<td><strong>REWIND</strong></td>
</tr>
<tr>
<td></td>
<td>▶ MACE</td>
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<td>▶ MACE</td>
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<td>▶ MACE</td>
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<td>▶ MACE</td>
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<tr>
<td></td>
<td>▶ MACE</td>
</tr>
<tr>
<td><strong>Risk of Major CV - MACE</strong></td>
<td><strong>LEADER</strong></td>
</tr>
<tr>
<td></td>
<td>HR 0.87 (0.73-1.05)</td>
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<tr>
<td></td>
<td>HR 1.11 (0.77-1.61)</td>
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<tr>
<td></td>
<td>HR 0.86 (0.48-1.55)</td>
</tr>
<tr>
<td><strong>Less Renal Disease</strong> (composite/surrogates)</td>
<td><strong>CANVAS</strong></td>
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<tr>
<td></td>
<td><strong>NNT=40/5.4yr</strong> (17.1% vs 19.6%)</td>
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<tr>
<td></td>
<td><strong>NNT=67/3.8yr</strong> (5.7% vs 7.2%)</td>
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<tr>
<td></td>
<td><strong>NNT=44/2.1yr</strong> (3.8% vs 6% NS)</td>
</tr>
<tr>
<td></td>
<td><strong>NNT=44/2.1yr</strong></td>
</tr>
<tr>
<td><strong>Effect on A1c</strong></td>
<td><strong>TRULICITY</strong></td>
</tr>
<tr>
<td></td>
<td><strong>HR 1.05 (0.74-1.50) 3.8% vs 3.6%/2.1yrs (NS)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NNT=19/4.2yr</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NNT=19/2.4yr</strong></td>
</tr>
<tr>
<td><strong>Weight Loss</strong></td>
<td><strong>Semaglutide</strong></td>
</tr>
<tr>
<td></td>
<td><strong>↓ 1.3kg-5/52 wks</strong></td>
</tr>
<tr>
<td></td>
<td><strong>↓ 2.3 kg-3.8yrs</strong></td>
</tr>
<tr>
<td></td>
<td><strong>↓ 3.4kg-2/1yrs</strong></td>
</tr>
<tr>
<td><strong>Less Risk of Hypoglycemia</strong></td>
<td><strong>2° endpoint</strong></td>
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</table>

**Risk when given with sulfonylurea or insulin**

- **Less Risk of HF**
  - **See also PIONEER-6**
  - **HR 0.98 (0.74-1.3)**
  - **NNT=40/1.3yr**

**Cost – 1 month**

| XX | $110 | $110 |
| X | $225 | $110 |
| | $90-$235 | $40 |
| | $120-$220 | $90 |
| | $260 | $110 |
| | $35 | $110 |

**Other**

- Well tolerated, except GI.
- Environmental impact - single use disposable pen.
- GI adverse events.
- **GI adverse events.**
- **GI adverse events.**

**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, potent possibly more after that. Discontinue DPP4 inhibitors, if on.

**Time Tested**

- 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**
  - **oral once daily**

**Overall**

- ?

**Note:** the "Neutral" designation indicates 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**
  - **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 glimepiride, vs lixisenatide vs sitagliptin; lixisenatide associated with favorable CV/death outcomes vs others overall.**

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

**SGLT2 Inhibitors**

- **CANVAS**
  - **Non-inferior to Placebo**
  - **HR 0.93 (0.84-1.03)**
  - **Superiority (NS) over 4.2yr**

**EMPA-KIDNEY**

- **HR 0.66 (0.53-0.81)**
  - **HR 0.72 (0.60-0.87)**
  - **NNT=27/2yr**

- **FDA +/- HC warning: ↑ DKA; ↑ AKI (caution on initiation, especially if ↓ intravascular volume & ↑ renal fxs); genetical mycotic infections. Rare: ?Fournier’s gangrene; ↑ UTI/urosepsis/Pyelonephritis. Electrolyte imbalance. See AE Infographic.**

- **2° endpoint**
  - **HR FE/Hf CV death:**
  - **NNT=19/1.3yr**
  - **HR FE/Hf CV death:**
  - **NNT=19/1.3yr**

- **NIHB open benefit.**

- **Group** 2.6% vs 3% insulin use.
- **Higher risk group:** CVD or CKD 84.7% 3.8% vs 6% NS 74% had established CVD, CKD or both 0.79 (0.57-1.11) Many trial limitations, e.g. short
ANTI-HYPERGLYCEMIC DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

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


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; ↑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. ↑UKPDS-34 10 yr observational follow-up ↓ all-cause mortality NNT=14/20 yr, and ↓ MI NNT=16/20 yr. ↑UKPDS-84 Evidence overall somewhat weak. SHI et al. SR/NMA 31-34
3. Intensive Hba1c target (including gliclazide) vs standard Hba1c target; MACE 10% vs 10.6% p=NS, all-cause mortality 8.9% vs 9.6% p=NS. ↑ADVANCE
4. Intensive therapy (chlorpropamide, glipizideG, 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. ↑UKPDS-33 10 yr observational follow-up ↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=36/20 yr. ↑UKPDS-84
5. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up ↓ MACE NNT=23/17 yr. ↑ACCORD
6. Insulin basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9% p=NS, MI 15.8% vs 17.9% p=NS. ↑ACCORD
7. 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. ↑ACCORD
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). 

**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 3. Stop-NIDDM
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 & glipizide 1. Adopt
A5. Acarbose: ↓ 1.15 kg/3 yr 3. Stop-NIDDM
A6. Repaglinide: ↑ ~1.7 kg/12-24 wks1,6 nateglinide: ↑ 0.7-1 kg/16-24 wks1,6
A7. DPP-4 inhibitors (generally considered neutral, or small increase):6 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 weeks10,11
A8. GLP1 agonists
  - exenatide ↓ 2.8 kg/24-52 wks11
  - liraglutide ↓ 2.3 kg/3.8 yr 12. LEADER
  - dulaglutide ↓ 1.3-3 kg/5-52 weeks12
A9. SGLT2 inhibitors14
  - canagliflozin ↓ 2.8-4 kg/4-52 wks15,16 CANTATA-M
  - dapagliflozin ↓ 2 kg/12-52 weeks17
  - emagliflozin ↓ ~1.5-2 kg/3.1 yr18 EMPA-REG
A10. Insulin
  - intensive therapy vs standard therapy; avg weight ↑ 3.5 kg or 4.3 kg/3.5 yr; weight ↑ >10 kg 28% vs 14% p<0.00120 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/Edeema**

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 glinidazide) standard A1C target; 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 1. 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 +metformin or SU vs control; ↑ hospitalization for HF or death NNH=69/5.6 yrs. RECORD Rosiglitazone vs placebo; ↑ HF NNH=250/3 yr7. DREAM
28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A. 5. 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).23,28
41. Liraglutide: ↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent).29
42. 7↓ GI; Gl (nausea, diarrhea, vomiting) AE with long acting agents30,31; ↑ GI AE: taspoglutide once
31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14, LEADER (Lixisenatide vs placebo; hosp for HF: 4.0% vs 4.2% p=0.75, ELIXA) As a class, GLP1a’s - hosp for HF (OR 0.91 0.83-0.99) SHY SR & NMA 32. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002, 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. DECLARE (Dapagliflozin 10mg po once daily vs placebo; composite primary outcome: worsening HF 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, ORIGIN 34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS, ArchInternMed2017

**Other/Additional Trials Recently Published**

35. Pioglitazone & Rosiglitazone FDA +/- - Health Canada warnings/label changes:
- ↑ HF (see above) 1 PROACTIVE, 2 RECORD, 3 AstraZeneca 4, 5
- ↑ fractures; pioglitazone vs placebo 5.1 vs 2.5%, calculated p=0.005 6 Rosiglitazone vs MF 7↑ fractures 8 NNH=38/2.9 yr (unpublished data). 6Rosiglitazone vs MF 8↑ 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, T2D 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. Pioglitazone: ↑ bladder cancer; France, retrospective observational cohort pioglitazone exposure vs other diabetic agent HR 1.22 (1.03-1.43), pioglitazone exposure cumulative dose > 28000 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), & pioglitazone 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-ys vs never exposed; 15,16

37. Rosiglitazone 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. 24 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). 23 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%. 27 DURATION-9, 34 HARMONY-3, 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 TZDM 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 hospital admission, 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; 15.4/1000ptys (1.54%/yr) vs 11.9/1000ptys (1.19%/yr) NNT= 285/yr (HR 1.25, 95% CI 1.04-1.52), CANSAS ↑ 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 6.3/1000ptys (0.63%/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). CANSAS Other trials neutral. 42,43 May 2017 FDA: canagliflozin -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, I²=0%), as active agent: OR 1.45 (1.06-1.9, I²=25%); however recent real world surveillance data suggests this may not be an issue. 44,45 https://annals.org/aim/article-abstract/2739786/sodium-glucose-cotransporter-2-inhibitors-associated-severe-urinary-tract-infections?searchresult=1 - genital tract skin infection; SGLT2 inhibitor vs placebo OR 3.50 (2.46-4.99, I²=0%), as active agent: OR 5.06 (3.44-7.45, I²=0%). 44,45

45. Dagaplipozin: ↑ bladder/breast cancer; approved by FDA 2016 (rejected in 2012 due to breast & bladder cancer concerns). Dagaplipozin vs control; bladder cancer: n=10 cases vs n=1 case & breast cancer: n=12 cases vs n=3 cases (up to 2013). 46

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. 47,48


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37. Summary Safety Review- SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin)- Assessing the risk of the body producing high levels of acid in the blood (diabetic ketoacidosis).