<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Sulfonylures</th>
<th>TzDs</th>
<th>Meglitinides</th>
<th>DPP4 Inhibitors</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) GLUCOSUR, GLICYTON</td>
<td>Glipizide GLICIDIUS USE</td>
<td>Pioglitazone ACTOS</td>
<td>Nateglinide STARIUS D/C</td>
<td>Saxagliptin SITAGLIPTIN</td>
<td>Empagliflozin JARDIAN</td>
<td><strong>Less</strong> (NPH HS + MD)</td>
</tr>
<tr>
<td>Metformin (MF) GLUCOSUR, GLICYTON</td>
<td>Glipizide GLICIDIUS USE</td>
<td>Pioglitazone ACTOS</td>
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</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td><strong>ANTI</strong> Effect on <strong>Major CV</strong> Effect on <strong>neutral vs Generic</strong> <strong>Death / Overall Risk of HF</strong></td>
<td></td>
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</tbody>
</table>

**Major trials to support finding/Outcomes**

| **Risk of Death / Major CV** | **UKPDS- 33-34 (ADOPT)** some use in ADVANCE | **UKPDS- 33-34 (ADOPT)** | ProACTIVE | ACE | **SAVOR-TIMI 53, TECOS, EXAMINE PROLOUGE, CARMELINA, CAROLINA** |
| **Risk of Death / Major CV** | **UKPDS- 33-34 (ADOPT)** | | | | | |

**Effect on A1C**

| **Weight (loss vs neutral vs gain)** | **UKPDS- 33-34 (ADOPT)** | **UKPDS- 33-34 (ADOPT)** | **ProACTIVE** | **ACE** | **SAVOR-TIMI 53, TECOS, EXAMINE PROLOUGE, CARMELINA, CAROLINA** |
| **Risk of Hypoglycemia** | **1** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** |
| **Risk of HF / Edema** | **1** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** |
| **Effect on GI tolerability** | **1** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** |
| **Cost** | **1** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** |
| **Other** | **1** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** |
| **Overall** | **1** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** | **2,23, 24** |

*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 break out 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: Refluxes Diabetes Landscape Trials Summary at http://www.rxfiles.ca/rxfiles/uploads/documents/GMT-Score-Landscape-Trials Links.pdf Diabetes Oral Agents Comparison Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/compareoras19歌舞伎.pdf Copyright 2019 – RxFiles, University of Saskatchewan www.RxFiles.ca Disclaimer: http://www.rxfiles.ca/rxfiles/modules/miscellaneous/copyright.aspx
## GLP1 Agonists & SGLT2 Inhibitors - SUBSET of DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>GLP1 Agonists</th>
<th>SGLT2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
<td><strong>Dulaglutide SC</strong></td>
<td><strong>Canagliflozin</strong></td>
</tr>
<tr>
<td><strong>Brand</strong></td>
<td><strong>TRIGLYC (SC weekly)</strong></td>
<td><strong>CREDENCE (intravenous)</strong></td>
</tr>
<tr>
<td><strong>Major trial(s) to support findings/Outcomes</strong></td>
<td><strong>REWIND n=9042 / 1.4yr</strong></td>
<td><strong>CANVAS 45/46 / 66y</strong></td>
</tr>
<tr>
<td></td>
<td><strong>LEADER n=7.8yr</strong></td>
<td><strong>DECLARE-TIMI 56 / 6.2yr</strong></td>
</tr>
<tr>
<td></td>
<td><strong>SUSTAIN-6 n=1667 / 1.3yr</strong></td>
<td><strong>DAPA-HF 33516 / 1.5yr</strong></td>
</tr>
<tr>
<td></td>
<td><strong>PIONEER-6 n=1318 / 1.3yr</strong></td>
<td><strong>EMPA-REG n=7020 / 3.1yr</strong></td>
</tr>
<tr>
<td><strong>↓ Risk of Major CV - MACE</strong></td>
<td><strong>HR 0.9 (0.80-1.01)</strong></td>
<td><strong>HR 0.87 (0.74-1.03)</strong></td>
</tr>
<tr>
<td></td>
<td>10.8% vs 12.5% (p=0.04)**</td>
<td>9.6% vs 11.1% (p=0.04)**</td>
</tr>
<tr>
<td></td>
<td><strong>NNT=72/5.8yr</strong></td>
<td><strong>NNT=66/3.2yr</strong></td>
</tr>
<tr>
<td><strong>↓ Risk of All-Death</strong></td>
<td><strong>HR 1.05 (0.74-1.50)</strong></td>
<td><strong>HR 0.97 (0.75-1.24)</strong></td>
</tr>
<tr>
<td></td>
<td>3.8% vs 3.6% (p=0.89)**</td>
<td>5.1% vs 5.9% (p=0.89)**</td>
</tr>
<tr>
<td></td>
<td><strong>NNT=72/2.3yr</strong></td>
<td><strong>NNT=72/2.4yr</strong></td>
</tr>
<tr>
<td><strong>Less Renal Disease (composite/surrogates)</strong></td>
<td><strong>NNT=40/5.4yr</strong></td>
<td><strong>NNT=40/5.4yr</strong></td>
</tr>
<tr>
<td></td>
<td>17.1% vs 19.6% (p=0.03)**</td>
<td>19.6% vs 22.4% (p=0.03)**</td>
</tr>
<tr>
<td><strong>Effect on A1C</strong></td>
<td><strong>HR 0.93 (0.77-1.16)</strong></td>
<td><strong>HR 0.83 (0.68-1.00)</strong></td>
</tr>
<tr>
<td></td>
<td>1.11% vs 1.3% (p=0.03)**</td>
<td>1.47% vs 1.61% (p=0.03)**</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td><strong>↓ 2.3 kg/52 wks</strong></td>
<td><strong>↓ 2.1 kg/52 wks</strong></td>
</tr>
<tr>
<td></td>
<td>↓ 3.4 kg/2 yr</td>
<td>↓ 3.4 kg/2 yr</td>
</tr>
<tr>
<td></td>
<td>↓ 3.4 kg/1 yr</td>
<td>↓ 3.4 kg/1 yr</td>
</tr>
<tr>
<td><strong>Less Risk of Hypoglycoglycemia</strong></td>
<td><strong>Severe: 2.4% vs 3.3% P=0.02</strong></td>
<td><strong>Severe: 2.4% vs 3.3% P=0.02</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NNT=30/2.8yr</strong></td>
<td><strong>NNT=30/2.8yr</strong></td>
</tr>
<tr>
<td><strong>Less Risk of HF /Edema</strong></td>
<td><strong>HR 0.86 (0.66-1.15)</strong></td>
<td><strong>HR 0.74 (0.54-1.04)</strong></td>
</tr>
<tr>
<td></td>
<td>1.2% vs 1.6% (p=0.25)**</td>
<td>1.9% vs 2.2% (p=0.25)**</td>
</tr>
<tr>
<td></td>
<td><strong>NNT=72/5.3yr</strong></td>
<td><strong>NNT=72/5.3yr</strong></td>
</tr>
<tr>
<td><strong>Effect on GI &amp; D/C due to Tolerability</strong></td>
<td><strong>D/C due to AE 9% vs 6%</strong></td>
<td><strong>NNT=76/3.5yr</strong></td>
</tr>
<tr>
<td></td>
<td>5.3% vs 5.1% (p=0.15)**</td>
<td>4.0% vs 3.6% (p=0.15)**</td>
</tr>
<tr>
<td></td>
<td><strong>NNT=48/3.1yr</strong></td>
<td><strong>NNT=48/3.1yr</strong></td>
</tr>
<tr>
<td><strong>? AE Concerns Associated with Class</strong></td>
<td><strong>GI adverse events</strong></td>
<td><strong>GI adverse events</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NNT=23/6.8yr</strong></td>
<td><strong>NNT=23/6.8yr</strong></td>
</tr>
<tr>
<td><strong>Cost – 1 month</strong></td>
<td><strong>X</strong></td>
<td><strong>2nd endpoint</strong></td>
</tr>
<tr>
<td></td>
<td><strong>$225 / =</strong></td>
<td><strong>↓ worsening HF or CV death</strong></td>
</tr>
<tr>
<td></td>
<td><strong>$90-$235 / $</strong></td>
<td><strong>NNT=38/3.1yr</strong></td>
</tr>
<tr>
<td></td>
<td><strong>$225-$440 / $</strong></td>
<td><strong>NNT=38/3.1yr</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>Well tolerated, except GI</strong></td>
<td><strong>Well tolerated, except GI</strong></td>
</tr>
<tr>
<td></td>
<td>** ↓ BP 1.7/0.5mm Hg**</td>
<td>** ↓ BP 1.7/0.5mm Hg**</td>
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<tr>
<td></td>
<td><strong>Single Use Pen</strong></td>
<td><strong>Single Use Pen</strong></td>
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<tr>
<td></td>
<td><strong>Disposable Pen</strong></td>
<td><strong>Disposable Pen</strong></td>
</tr>
<tr>
<td><strong>Practical / Clinical Considerations</strong></td>
<td><strong>Upper Gl effects often worse than lower Gl effects; a low fat diet is better; patients may not enjoy the first ~2 weeks due to AE, but many will gain tolerability and do OK; often insulin dose can be reduced 20% initially, and possibly more after that.</strong></td>
<td><strong>Upper Gl effects often worse than lower Gl effects; a low fat diet is better; patients may not enjoy the first ~2 weeks due to AE, but many will gain tolerability and do OK; often insulin dose can be reduced 20% initially, and possibly more after that.</strong></td>
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<tr>
<td><strong>Time Tested</strong></td>
<td><strong>X new agent – outcome &amp; safety data still limited</strong></td>
<td><strong>X new agent – outcome &amp; safety data still limited</strong></td>
</tr>
<tr>
<td></td>
<td><strong>No T2O yet, but...</strong></td>
<td><strong>No T2O yet, but...</strong></td>
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<tr>
<td></td>
<td><strong>limited real world use</strong></td>
<td><strong>limited real world use</strong></td>
</tr>
<tr>
<td></td>
<td><strong>X new agent – outcome &amp; safety data still limited</strong></td>
<td><strong>X new agent – outcome &amp; safety data still limited</strong></td>
</tr>
<tr>
<td><strong>Convenience</strong></td>
<td><strong>Single Use Pen</strong></td>
<td><strong>Single Use Pen</strong></td>
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<tr>
<td></td>
<td><strong>SC once weekly</strong></td>
<td><strong>SC once daily</strong></td>
</tr>
<tr>
<td></td>
<td><strong>SC once weekly</strong></td>
<td><strong>SC once daily</strong></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>Unknown/Ongoing</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Safety</strong></td>
</tr>
</tbody>
</table>

**Advantage** | **Neutral** | **Disadvantage** | **XX** |

**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

- **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

- **Credence**
  - Patients with albuminuric CKD, eGFR 30–90, & 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 [13 outcome if no CV disease history, HR= 0.98 (0.74-1.3)]
- **DECLARE-TIMI 56**
  - 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
References for GLP1 and SGLT2 Subset Colour Outcomes Comparison 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; 1 FDA
2. Metformin vs conventional diet; obese ≥120 lb & 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=14/10.7 yr, and ↓ MI NNT=16/20 yr 3 UKPDS-80
3. Intensive HbA1c target (including gliclazide) vs standard HbA1c target; MACE 10% vs 16% p=NS, all-cause mortality 8.9% vs 9.6% p=NS. 4 ADVANCE
4. Intensive therapy (chlorpropamide, glibizide 5SA, 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, I²=0%), CV mortality OR 1.12 (0.87-1.42, I²=12%), MI OR 0.92 (0.76-1.12, I²=NR), stroke OR 1.16 (0.81-1.66, I²=NR). 6
6. Metformin & glipizide; Chinese, small sample n=304, & medically untreated ↓ 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 mos early. 10 DREAM ↑ MI NNT=167/2 CV death 0.87% vs 0.39% p=0.06. 10 Rosiglitazone vs glyburide ↑ MACE NHN 63/4 yr 12 ADOP
9. Acarbose vs placebo; impaired glucose tolerance; ↓ MACE NNT 40/3.3 yr 11 STOP-NIDDM Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95CI 0.86-1.01, p=0.73. 12 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 Saxagliptin 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, I²=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. 19 CAROLINA 2019
12. Liagliptide 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=77.8/3 yr and ↓ all-cause mortality NNT 72/3.8 yr. 20 LEADER Semaglutide SC weekly vs placebo; MACE superior; (nephropathy was better; however, retinopathy complications were worse). 20 SUSTAIN6
13. Lixisenatide vs placebo (post-ASCVD) MACE 13.4% vs 13.2%, non-inferior (p<0.001), not superior (p=0.83) 21 ELIKA
14. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up ↓ MACE NNT=23/7 yr 22 DCT, 23 EDIC
15. Sulfonylureas → ↓ 2.3 kg/3.8 yr 24 SECOMED
16. DPP4 inhibitors (generally considered neutral)?
   • 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
17. GLP1 agonists
   • exenatide ↓ 2.8 kg/24-52 weeks 11
   • lixisenatide ↓ 2.3 kg/3.8 yr 12 LEADER
   • dulaglutide ↓ 1.3-3 kg/52 weeks 13
18. SGLT2 inhibitors 14
   • canagliflozin ↓ 2.8-4 kg/4-52 weeks 15, 16 CANTATA-M
   • dapagliflozin ↓ 2 kg/12-52 weeks 17
18. Pioglitazone & Rosiglitazone

19. Basal insulin vs basal/bolus insulin; small sample

20. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14.

21. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%, p=N/A.

22. 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 5.3/1000 patient year vs 6.7/1000 patient year HR0.73 (95% CI 0.64, 1.25).

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% CI 0.82-1.06), MF + insulin vs SU neutral aHR 0.96 (95% CI 0.82-1.13). MF+SU insulin neutral aHR 0.94 (0.77-1.15). 2

24. Intensive A1C target (included glitazones) vs standard A1C target; HF (HF, 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 ADOPD

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 vs SU control; ↑ hospitalization for HF or death NNH=69/5.5 yr. 6 RECORD Rosiglitazone vs placebo; ↓ HF NN=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. Listed adverse event for other agents (e.g., irinotecan) in product monograph.

29. 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).4,28

30. Liraglutide: ↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent). 29

31. ↑GI: Nausea, diarrhea, vomiting (AE with long acting agents)20,21. ↑ GI AE: gastroparesis only weekly 59% vs exenatide BID 35% (clinical development of gastroparesis has been stopped). 32 ↓ GI AE: Exenatide once weekly 28% vs exenatide BID 48%, albiglutide once weekly 29.8% vs lixisenatide daily 52%, exenatide once weekly 19.1% vs lixisenatide daily 44.5%, liraglutide once daily 35%, lixisenatide once weekly 39.4% vs lixisenatide daily 38.3%. 36 AWARD

32. SGLT2 inhibitors FDA +/- Health Canada warnings/label changes:

- ↑ diabeteketoacidosis; n=5 Canadian cases, some requiring hospitalization (May 2016); n=73 US cases (n=44 T2DM cases, n=151DM cases, n=13 NR) (Mar 2013-2016) all requiring hospitalization or emergency department care. 7,38

- ↑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). 39 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 (0.63%yr) vs 3.4/1000ptyrs (0.34%yr) NNT=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) NNT=1000/yr (HR 2, 95% CI 1.08-3.82). 39 CANVAS Other trials neutral. 8 CANVAS 2014-2015. May 2017 FDA: canagliflozin -increased risk of leg and foot amputations. 42

• ↑ 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), & 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 personyrs 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:
• ↑ HR risk with saxagliptin and alogliptin (see above).10,11 SAVOR-TIMI 53, 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 revalidation (2006-2013).21

39. Incretin agents (DPP-4 inhibitors and GLP1 agonists) ↑ pancreaticitis: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 revalidation.26 FDA: n=88 cases of pancreatitis with sitagliptin


3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10 year 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


6. Australian Medical Association. The Australian Classification of Prescription Drugs (ACPD), 2008; edition 1 (a) and addenda.


