

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

Drug Class	Sulfonylureas		TZDs			Meglitinides	DDP-4 Inhibitors	GLP-1 Agonists (Subcut)	SGLT-2 Inhibitors	Insulin in T2DM		
Generic → BRAND	Metformin (MF) GLUCOPHAGE, GLYCON	Glipizide DIAMICRON [Glipizide GLUCOTROL USA SPREAD-DIMCAD]	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 Dulaglutide TRULICITY Lixisenatide ADLYXINE, LYXUMIA Semaglutide USA, Albiglutide EPERZAN	Canagliflozin INVOKANA Dapagliflozin FORXIGA / FARXIGA Empagliflozin JARDIANCE Ertugliflozin	Intensity: <b>Less</b> (NPH HS + MF)	Intensity: <b>More</b> (Multiple daily doses)
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	(Prevention trial: Stop-NIDDM)	-	SAVOR-TIMI 53 TECOS, EXAMINE CARMELINA (2018) PROLOGUE (2016)	ELIXA LEADER SUSTAIN6 EXSCCEL (2017), REWIND (2018), HARMONY (2019)	EMPA-REG CANVAS (2017), DECLARE (2019), VERTIS CV (2019)	T2DM UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN. Placebo group had ↑ insulin use in LEADER. T1DM: DCCT/EDIC (Also Boussageon et al Meta-analysis. BMJ 2011;343:d4169)	
↓ Risk of Death / Major CV <sup>1</sup>	✓✓✓ <sup>2</sup> in obese, ↓ mortality NNT=14/10y ↓ MI NNT=14/10y (UKPDS-34)	✓3,4,5 X <sup>25,6</sup> glipizide ↑ MACE vs MF NNH=10/5yr (SPREAD-DIMCAD)	✓4,5	✓✓✓ <sup>7</sup> ↓ MACE NNT=50/ 2.9yr, but 1 <sup>o</sup> composite NS (ProACTIVE) ↓ MACE (IRIS) (pts with insulin resistance & recent CVA/TIA)	X <sup>8</sup>	✓✓ <sup>9</sup> in IFG, ↓ MACE NNT=40/ 3.3yr	?	✓ <sup>10</sup> saxagliptin, alogliptin, sitagliptin ↔ non-inferior to placebo for MACE, But see ?HF below  ? <sup>11</sup> (linagliptin ongoing). Sitagliptin no effect on intima-media thickness PROLOGUE	✓✓✓ <sup>12</sup> liraglutide ↓ MACE NNT=53/3.8yr (North American subgroup neutral), ↓ mortality NNT=72/3.8yr (LEADER), semaglutide ↓ MACE NNT=44/2yr (SUSTAIN-6)  ✓ <sup>13</sup> lixisenatide ↔ non-inferior to placebo for MACE (ELIXA)  ? <sup>14</sup> (dulaglutide, albiglutide ongoing) Exenatide: no effect on CV (EXSCCEL)	✓✓✓ <sup>15</sup> empagliflozin ↓ MACE NNT=63/3.1yr, ↓ mortality NNT=39/3.1yr (EMPA-REG) canagliflozin ↓ MACE NNT=220/yr (CANVAS) but mortality NS & ↑ MACE 1 <sup>st</sup> 30d (n=13 vs n=1, p=NS) <sup>interim analysis</sup>  <sup>16</sup> (dapagliflozin, ertugliflozin ongoing)	✓✓✓ <sup>17,18</sup>	✓ <sup>18,19,20</sup> /X <sup>21</sup> > 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)	✓✓✓ A1	X A2	X A2	XX A3	XX A4	✓✓ A5	X A6	✓ A7	✓✓✓ A8	✓✓✓ A9	✓ A10	XX A10
↓ Risk of Hypoglycemia	✓✓✓	✓ ? If less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓✓ Low risk with monotherapy	✓	✓✓✓	✓✓✓	✓✓?	✓✓?	✓✓ Risk when given with sulfonylurea or insulin	✓	XX Rate of 1.8%/yr
↓ Risk of HF / Edema	✓✓✓ <sup>22,23</sup> 1st line in HF with eGFR >30 mL/min (CDA <sup>13</sup> )	✓ <sup>23,24</sup> (↑ CHF risk)	✓ <sup>23,25</sup> (↑ CHF risk)	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), ↑ HF NNH=250/3yr (DREAM)	✓ <sup>28</sup>	✓ <sup>29</sup>	X <sup>30</sup> ↑ HF saxagliptin NNH=143/2.1yr (SAVOR), alogliptin (post hoc) (EXAMINE) sitagliptin HF neutral	✓ <sup>31</sup> liraglutide (LEADER) and lixisenatide (ELIXA) neutral	✓ <sup>32</sup> empagliflozin ↓ HF hospitalizations (EMPA-REG) & canagliflozin but exploratory (CANVAS)	✓ <sup>33,34</sup> (?↑ CHF risk)	✓ <sup>34</sup> (↑ CHF risk)
Effect on GI tolerability	X Start low & titrate	✓✓	✓✓ rate of 1.8%/yr	✓✓	✓✓	XX	✓✓	✓✓	✓ Nausea, vomiting, diarrhea	✓ Nausea/diarrhea with dapagliflozin	✓✓✓	✓✓✓
Cost	✓✓✓	✓✓✓	✓✓✓	X	X	✓✓	✓✓	X	XX	X	✓	XX
Other	May have to hold or ↓ dose in acute illness/HF/renal dysfx (? lactic acidosis); may ↓ B12. <b>1<sup>st</sup> line for obese T2DM (UKPDS-34)</b>	Used in combination with metformin (ADVANCE)	Caution: ↓ renal function (& older adults)	X FDA +/- HC warnings. <sup>35</sup> ?↑ HF (see above), ?↑ fractures (NNH~30/~3.5 y) ?↑ macular edema (conflicting data) Pio: ?↑ bladder ca >12 mos (27.5 excess /100,000 person yrs), avoid co-admin with dapagliflozin <sup>36</sup> Rosi: Restricted access in CDN (SK-EDS) (↑ CV risk concerns) <sup>37</sup>	✓✓ PPG, Possible benefit of laxative effect in some	✓✓ PPG, flexibility with meals	✓ PPG FDA +/- HC warning: <sup>38</sup> HF (saxa & alogliptin); arthralgia, hypersensitivity rx, ?↑ pancreatitis (ARI 0.13%), <sup>39</sup> pancreatic cancer <sup>40</sup> Linagliptin: no renal dose adjustment	✓ PPG injection site irritation ?↑ pancreatitis, <sup>39</sup> pancreatic cancer, <sup>40</sup> ?↑ thyroid cancer (liraglutide) <sup>41</sup> (new once weekly agents may have ↓ GI adverse events) <sup>42</sup> ?gallbladder disease <sup>46</sup>	X new agents – outcome & safety data still limited FDA +/- HC warning: ↑ ketoacidosis (DKA); ↑ AKI (caution: ↓ intravascular volume & renal fx <sup>Canva + Dapa</sup> ), ↓ BP; ↑ (HR ~2) limb amputations <sup>Canva, 43</sup> ↑ urosepsis/pyelonephritis, (UTI OR 1.34 & genital tract infection OR 3.5 vs placebo), <sup>44</sup> ↑ fracture (HR 1.3)/↓ BMD <sup>Canva</sup> , dapagliflozin ?↑ bladder/ breast cancer (avoid with pioglitazone) <sup>45</sup>	✓ Fear/perception of insulin injections	✓✓ PPG  Fear/perception of insulin injections	
Overall	✓✓✓?	✓✓	✓	✓?	X?	✓	✓	✓?	?✓✓ Liraglutide (CV+mortality benefit)	?✓✓ Empagliflozin (CV+mortality benefit)	✓✓	✓✓ 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 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>

An Advantage ✓✓✓	✓✓	Neutral ✓	X	A Disadvantage XX	Unknown/Ongoing ?
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**Individualize approach considering balance of potential benefits & harms. Over-aggressive pursuit of targets can ↑ mortality.** ACCORD

## 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</sup> FDA
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</sup> UKPDS-34 10 yr observational follow-up  $\downarrow$  **all-cause mortality NNT=14/~20 yr**, and  $\downarrow$  **MI NNT=16/~20 yr**.<sup>3</sup> 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%  $p=NS$ .<sup>4</sup> ADVANCE
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</sup> UKPDS-33 10 yr observational follow-up  $\downarrow$  **all-cause mortality NNT=29/~20 yr**, and  $\downarrow$  **MI NNT=36/~20 yr**.<sup>3</sup> UKPDS-80
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 (0.87-1.42,  $I^2=12\%$ ), MI OR 0.92 (0.76-1.12,  $I^2=NR$ ), stroke OR 1.16 (0.81-1.66,  $I^2=NR$ ).<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</sup> SPREAD-DIMCAD
7. Pioglitazone vs placebo; T2DM & high CV risk;  $\downarrow$  **MACE NNT=50/2.9 yr**,<sup>8</sup> PROACTIVE insulin resistance & recent TIA/stroke;  $\downarrow$  **MACE NNT=36/4.8 yr**.<sup>9</sup> IRIS
8. Rosiglitazone vs placebo;  $\uparrow$  **MACE 2.9% vs 2.1%  $p=0.08$  (NS)**, trial stopped 5 mons early,<sup>10</sup> DREAM  $\uparrow$  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</sup> ADOPT
9. Acarbose vs placebo; impaired glucose tolerance;  $\downarrow$  **MACE NNT 40/3.3 yr**.<sup>13</sup> STOP-NIDDM
10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.99$ ).<sup>14</sup> SAVOR-TIMI 53 Alogliptin vs placebo; MACE 11.3% vs 11.8%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.32$ ).<sup>15</sup> EXAMINE Sitagliptin vs placebo; MACE 9.6% vs 9.6%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.65$ ).<sup>16</sup> TECOS 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 CV trial ongoing, estimated completed 2018.<sup>18</sup> CARMELINA
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</sup> LEADER Semaglutide vs placebo; MACE **superior**; (nephropathy was better; however, retinopathy complications were worse).<sup>20</sup> SUSTAIN6
13. Lixisenatide vs placebo; MACE 13.4% vs 13.2%, **non-inferior** ( $p<0.001$ ), but not superior ( $p=0.81$ ).<sup>21</sup> ELIXA
14. Exenatide CV trial 2017; non-inferior for safety but non-superior for efficacy (MACE 11.4% vs 12.2% over 3.2 yr;  $p=0.06$ ).<sup>22</sup> EXSCEL Dulaglutide<sup>USA</sup> CV trial ongoing, estimated completed 2018.<sup>23</sup> REWIND Albiglutide CV trial ongoing, estimated completed 2019.<sup>24</sup> HARMONY
15. Empagliflozin vs placebo; **MACE 10.5% vs 12.1%**, **superior** ( $p=0.04$ , **NNT=63/3.1 yr**);  $\downarrow$  **CV death NNT=46/3.1 yr** and  $\downarrow$  **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;  $\uparrow$  MACE in 1<sup>st</sup> 30 days ( $n=13$  vs  $n=1$ ,  $p=NS$ , non-dose related);  $\downarrow$  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
16. Dapagliflozin CV trial ongoing, estimated completed 2019.<sup>28</sup> DECLARE Ertugliflozin CV trial ongoing, estimated completed 2019.<sup>29</sup> VERTIS CV
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>
19. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up  $\downarrow$  **MACE NNT=23/~17 yr**.<sup>32</sup> DCCT, <sup>33</sup> 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%  $p=NS$ .<sup>5</sup> UKPDS-33 10 yr observational follow-up  $\downarrow$  **all-cause mortality NNT=29/~20 yr**, and  $\downarrow$  **MI NNT=36/~20 yr**.<sup>3</sup> UKPDS-80

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

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</sup> ACCORD
22. 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</sup> DEVOTE

**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</sup> ADOPT
- A2. Sulfonylureas:  $\uparrow$  1.6 kg/4 yr <sup>1</sup> ADOPT
- A3. Pioglitazone:  $\uparrow$  3.6 kg/3 yr <sup>2</sup> PROACTIVE
- A4. Rosiglitazone:  $\uparrow$  4.8 kg/4 yr; rosiglitazone statistically significant  $\uparrow$  weight vs. both metformin & glyburide <sup>1</sup> ADOPT
- A5. Acarbose:  $\downarrow$  1.15 kg/3 yr <sup>3</sup> STOP-NIDDM
- A6. Repaglinide:  $\downarrow$  ~1.7 kg/12-24 wks;<sup>4,5</sup> nateglinide:  $\uparrow$  0.7-1 kg/16-24 wks<sup>4,6</sup>
- A7. DDP4-inhibitors (generally considered neutral)<sup>7</sup>
  - saxagliptin  $\downarrow$  0.4 kg/2.1 year (similar to placebo) <sup>8</sup> SAVOR-TIMI 53
  - alogliptin  $\uparrow$  1 kg/18 months (similar to placebo) <sup>9</sup> EXAMINE
  - sitagliptin  $\uparrow$   $\leq$  0.5 kg/12 weeks<sup>10</sup>
- A8. GLP-1 agonists
  - exenatide  $\downarrow$  2.8 kg/24-52 weeks<sup>11</sup>
  - liraglutide  $\downarrow$  2.3 kg/3.8 yr <sup>12</sup> LEADER
  - 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</sup> CANTATA-M
  - dapagliflozin  $\downarrow$  2 kg/12-52 weeks<sup>17</sup>
  - empagliflozin  $\downarrow$  ~1.5-2 kg/3.1 yr<sup>18</sup> EMPA-REG
- A10. Insulin
  - intensive therapy vs standard therapy; avg weight  $\uparrow$  3.5 kg vs 0.4 kg/3.5 yr; weight  $\uparrow$   $>10$  kg 28% vs 14%  $p<0.001$ <sup>19</sup> ACCORD
  - 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  $\downarrow$  **all-cause mortality aHR 0.85 (95% CI 0.75-0.98)**, MF + SU vs MF  $\downarrow$  **all-cause mortality aHR 0.89 (95% 0.82-0.96)**, 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).<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;  $\downarrow$  **HF (serious events) NNT 167/3.5 yr**,  $\downarrow$  **HF (total events) NNT=67/3.5 yr**.<sup>4</sup> ADOPT
26. Pioglitazone vs placebo;  $\uparrow$  **hospitalization for HF NNH=50/2.9 yr** (not adjudicated),  $\uparrow$  **edema (without HF) NNH=8/2.9 yr**.<sup>5</sup> PROACTIVE
27. Rosiglitazone +metformin or SU vs control;  $\uparrow$  **hospitalization for HF or HF death NNH=69/5.5 yr**.<sup>6</sup> RECORD Rosiglitazone vs placebo;  $\uparrow$  **HF NNT=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
29. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%,  $p=N/A$ .<sup>9</sup>
30. Saxagliptin vs placebo;  $\uparrow$  **hospitalization for HF NNH=143/2.1 yr**; however, subgroup without a history of HF at baseline  $\uparrow$  **hospitalization for HF NNH=147/2.1 yr**, subgroup eGFR  $<60$  mL/min  $\uparrow$  **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  $\uparrow$  **hospitalization for HF NNH=111/1.5 yr**.<sup>12,13</sup> EXAMINE Sitagliptin vs

## HF/Edema- cont'd

- 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>=42%).<sup>16</sup> FDA warnings for both saxagliptin & alogliptin.<sup>17</sup>
31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14.<sup>18</sup> **LEADER** Lixisenatide vs placebo; hospitalization for HF: 4.0% vs 4.2% p=0.75.<sup>19</sup> **ELIXA**
32. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.<sup>20</sup> **EMPA-REG** 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**
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

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 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-yr**s 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**, **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).<sup>23</sup>
39. Incretin agents (DPP-4 inhibitors and GLP-1 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 **aOR 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 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 GLP-1 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>
42. ?↑/↓ 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

## Other- continued

Neutral GI: dulaglutide once weekly 39.4% vs liraglutide daily 38.3%.<sup>36</sup> **AWARD-6**

43. SGLT-2 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>42,43</sup> May2017 **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](https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery)
44. ?↑UTI; SGLT2 inhibitor vs placebo: **OR 1.34 (1.03-1.74, I<sup>2</sup>=0%)**, vs active agent: OR 1.42 (1.06-1.9, I<sup>2</sup>=25%). ↑ genital tract 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).

daily 52%, exenatide once weekly 19.1% vs liraglutide daily 44.5%.<sup>33</sup> DURATION-5,<sup>34</sup> HARMONY-7,<sup>35</sup> DURATION-6

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