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

**Generic BRAND**
- Metformin (MF)
- Sulfonylureas
- GLP-1R (DPP) Inhibitors
- Meglitinides
- SGLT2 Inhibitors

**TZDs**
- ProActive
- RECORD interim, ADOPT, DREAM
- TID2 in Japan, USA

**Sulfonylureas**
- Metformin, Diamicron®
- Glibizide, Diaplus®
- Glimepiride, Avandia®
- Acarbose, Glucool®

**GLP-1R (DPP) Inhibitors**
- Saxagliptin,
- Sitagliptin,
- Albiglutide,
- Nateglinide

**Meglitinides**
- Repaglinide,
- AVANDIA
- TRULICYT
- Daptapoglitazone

**Outcomes**
- A1C will vary depending on dose, combinations & initial A1C.

### Risk of Death / Major CV³

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>UKPDS-33,34,80 (ADOPT)</th>
<th>UKPDS-33,80 (ADOPT)</th>
<th>ProACTIVE</th>
<th>RECORD interim, ADOPT, DREAM</th>
<th>A1C (Prevention trial: Stop-NIDDM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>ADVANCE</td>
<td>ADVANCE with eGFR</td>
<td></td>
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<tr>
<td>GLP-1R</td>
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<tr>
<td>SGLT2</td>
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</tbody>
</table>

### Major trials to support findings/Outcomes* & Intensity

- **A1C**
  - XX A10
  - XX A11
  - XX A12
  - XX A13
  - XX A14

- **Weight**
  - XX A16
  - XX A17

- **Risk of Hypoglycemia**
  - XX A18
  - XX A19

- **Risk of HF**
  - XX A20
  - XX A21

- **Effect on Glucose**
  - XX A22
  - XX A23

### Cost

- XX A24

### Other

- XX A25

### Intensity:

- **Less**
  - XX A26
  - XX A27

### Summary

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Intensity:</th>
<th>Intensity:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C</strong></td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Risk of Hypoglycemia</strong></td>
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<td></td>
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<tr>
<td><strong>Risk of HF</strong></td>
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</tbody>
</table>

### Notes

- **A1C** will vary depending on dose, combinations & initial A1C.
- Intensity will depend on use of insulin.

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*Drugs that lower blood glucose come with varying levels of evidence regarding their balance of benefits & harms. This chart relies on 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

<table>
<thead>
<tr>
<th>An Advantage</th>
<th>Neutral</th>
<th>A Disadvantage</th>
<th>Unknown/Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>XX A28</td>
<td>XX A29</td>
<td>XX A30</td>
<td>XX A31</td>
</tr>
</tbody>
</table>

**Footnotes:**
- **A1C:** acute kidney injury
- **DKA:** diabetic ketoacidosis
- **IFG:** impaired fasting glucose
- **MAC:** major adverse cardiovascular events
- **PPG:** post-prandial glucose
## 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>Dulaglutide</strong> (TRULICYC (SC weekly))</td>
<td><strong>REWINd</strong></td>
<td><strong>DECLARE-TIMI</strong></td>
</tr>
<tr>
<td><strong>Liraglutide</strong> (VICTOZA (DC daily))</td>
<td><strong>LEADER</strong></td>
<td><strong>FARXIGA</strong></td>
</tr>
<tr>
<td><strong>Semaglutide SC (OZEMPIC (SC weekly))</strong></td>
<td><strong>SUSTAIN-6</strong></td>
<td><strong>INVOKANA</strong></td>
</tr>
<tr>
<td><strong>Semaglutide PO (10mg)</strong></td>
<td><strong>PIONEER-6</strong></td>
<td><strong>EMPA-REG</strong></td>
</tr>
</tbody>
</table>

### Risk of Major CV - MACE

- **↓ Risk of MACE**
  - NNT=72/5.4yrs

### Risk of Death

- **↓ Risk of Death**
  - NNT=53/3.8yrs

### Less Risk of Diabetes

- **Less Risk of Diabetes**
  - NNT=6/3.6yrs

### Effect on GI

- **↓ GI**
  - Composite/surrogates

### Cost – 1 month

- **Cost – 1 month**
  - X $225
  - XX $90-$235
  - XX $120-$220
  - XX $260

### Effect on GI & D/C due to Tolerability

- **D/C due to AE**
  - X Gl
  - X Gl

### Adverse Events

- **↑ pancreatitis, ↑ pancreatic cancer, ↑ thyroid cancer**
  - (liraglutide), gallbladder disease, diabetic retinopathy complications

### Cost – 1 month

- **Cost – 1 month**
  - X $110
  - XX $110
  - XX $110

### Other

- **Well tolerated, except Gl.
  - ↓ BP 1.7/0.5 mmHg.
  - Environmental impact - single use disposable pen.

### Practicial / Clinical Considerations

- **Upper Gl effects often worse than lower Gl effects; a low fat diet is better small, frequent meals, gradual dose titration; patients may struggle with AEs in first ~2 weeks, but many will gain tolerability and do OK.
  - Often insulin dose can be reduced by 20%, and possibly more after that.

### Time Tested

- **X new agent – outcome & safety data still limited
  - X >10yr history, but... limited real world use.
  - X new agent – outcome & safety data still limited
  - X new agent – outcome & safety data still limited

### Convenience

- **Single Use Pen
  - subcut once weekly
  - subcut once daily
  - oral once daily

### Overall

- **? Safety
  - Unknown/Ongoing

### **An Advantage**

- **Neutral**

### **A Disadvantage**

- **Unknown/Ongoing**

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**Note:** The “Neutral” designation is given a checkmark indicating that there is little or no disadvantage; however, there is also little or no advantage.
References for GLP1 and SGLT2 Subset Colour Chart (www.RxFiles.ca)


**Notes / Mortality for Diabetes Agents Carbon-Oxygen Outcomes Comparison Chart (www.RxFiles.ca)**

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

1. Drug manufacturers must establish CV safety (one-sided upper bound at 95% CI ≤ 1.3) vs comparator (typically placebo) in a RCT for all new agents in ↑ CV risk patients; 1² FDA

2. Metformin vs conventional diet; obese ≥120% IBW & small sample n=753; ↓ all-cause mortality NNT=14/10.7 yr, and ↓ MI NNT=14/10.7 yr. ² UPDS-34 10 yr observational follow-up ↓ all-cause mortality NNT=14/20 yr, and ↓ MI NNT=16/20 yr.³ UPDS-80

3. Intensive HbA1c target (included glulisine) vs standard HbA1c target; MACE 10% vs 10.6%; all-cause mortality 8.9% vs 9.6%; p=NS.² ADVANCE

4. Intensive therapy (chlorpropamide, glipizide, 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 5.0%; p=NS.³ UPDS-33 10 yr observational follow-up ↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=36/20 yr.¹ UPDS-80

5. SU (2rd or 3rd generation) vs control (diet, placebo, other antihyperglycemic); ↓ all-cause mortality OR 1.12 (0.96-1.13, p=0.09), CV mortality OR 1.12 (0.87-1.42, p=0.12), MI OR 0.92 (0.76-1.12, p=0.24), stroke OR 1.16 (0.81-1.66, I=NR).⁶

6. Metformin vs glipizide; Chinese, small sample n=304, & medically undertreated 100% CAD, but ≤10% taking ACES; Metformin ↓ MACE NNT=10/5 yr.⁷ SPREAD-DIMCAD

7. Pioglitazone vs placebo; TZDM & high CV risk; ↓ MACE NNT=50/2.9 yr,⁸ PROACTIVE insulin resistance & recent TIA/stroke; ↓ MACE NNT=36/4.8 yr.⁹ IRS

8. Rosiglitazone vs placebo; ↓ MACE 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mos early.¹⁰ DREAM ↑ MI NNH=167 & CV death 0.87% vs 0.39% p=0.06.¹⁰ Rosiglitazone vs glyburide ↓ MACE NNH 63/4 yr.¹² ADAPT

9. Acarbose vs placebo; impaired glucose tolerance; ↓ MACE NNT=40/3.3 yr.¹³ STOP-NIDDM Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95% CI, 0.86-1.11, p=0.73.¹³ ACE

10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, non-inferior (p<0.001), but not superior (p=0.99).¹⁴ SAVOR-TIMI 53 Saxagliptin vs placebo; 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 EXAMINE Meta-analysis (SAVOR-TIMI 53, EXAMINE, EXCEED) 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 CARDUNELA2019

12. Lisinagliptin vs placebo; MACE 13.4% vs 13.9%, superior (p=0.01, NNT=53/3.8 yr), but results neutral in North America subgroup; ↓ CV death NNT=77/3.8 yr and ↓ all-cause mortality NNT 72/3.8yr.¹⁹ LEADER Semaglutide SC weekly vs placebo; MACE superior; (nephropathy was better; however, retinopathy complications were worse).²⁰ SUSTAIN6

13. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up ↓ MACE NNT=23/~17 yr.³ DCCT, 33 EDIC

14. 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, ³ UPDS-33 10 yr observational follow-up ↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=36/20 yr.³ UPDS-80

15. 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.³ Accord

Insulin degludec vs insulin glargine (TZDM; ~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).⁶ DEVOTE

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

1. Metformin: ↓ 2.9 kg/4 yr ¹ ADOPT

2. Sulfonylureas: ↑ 1.6 kg/4 yr ¹ ADOPT

3. Pioglitazone: ↑ 3.6 kg/3 yr ² PROACTIVE

4. Rosiglitazone: ↓ 4.8 kg/4 yr; rosiglitazone statistically significant ↑ weight vs. both metformin & glyburide ¹↑

5. Acarbose: ↓ 1.15 kg/3 yr ³ STOP-NIDDM

6. Repaglinide: ↑ ~1.7 kg/12-24 wks;⁴,⁵ nateglinide: ↑ 0.7-1 kg/16-24 wks ⁴,⁵

7. DPP4-inhibitors (generally considered neutral)²

   · saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo)² SAVOR-TIMI 53
   · alogliptin ↑ 1 kg/18 months (similar to placebo)⁹ EXAMINE
   · sitagliptin ↑ ≤ 0.5 kg/12 weeks¹⁰

8. GLP1 agonists

   · exenatide ↓ 2.8 kg/24-52 weeks¹¹
   · liraglutide ↓ 2.3 kg/3.8 yr ¹² LEADER
   · dulaglutide ↓ 1.3-3 kg/5-52 weeks¹³

9. SGLT2 inhibitors²

   · canagliflozin ↓ 2.8-4 kg/4-52 weeks¹⁵,¹⁶ CANTATA-M
   · dapagliflozin ↓ 2 kg/12-52 weeks¹⁷
18. Exenatide extended release vs placebo (~70% CVD, ~30% primary prevention); MACE 14.4% vs 12.2% over median 3.2 yr, non-inferior (p=0.06).16 ESOL Dulaglutide14 CV trial ongoing, estimated completed 2018.20 REMIND Albilituglu CV trial ongoing, estimated completed 2018.21 HARMONY Semaglutide PO CV trial semaglutide vs placebo; MACE, non-inferior; all-cause death 1.4% vs 2.8% by 2nd endpoint 2019.22,23

19. Empagliflozin vs placebo; MACE 10.5% vs 12.1%, superior (p=0.04, NNT=63/3.1 yr); CV death NNT=46/3.1 yr and all-cause mortality NNT 39.3/1 yr.25 EMPA-REG Canagliflozin vs placebo; MACE 26.9/1000 ptyrs (2.7%/yr) vs 31.5/1000 ptyrs (3.15%/yr), superior (p=0.02, NNT=220/yr), l/tu duration 3.6yr, no significant differences in components of primary composite or death; MACE in 1st 30 days (n=13 vs n=1, p=NS, non-dose related); MACE (NS) after 30 days (HR 0.89, 95% CI 0.64, 1.25); numeric imbalance not present in non-CANVAS trials.20,27,27a CANVAS Dapagliflozin vs placebo; MACE 8.8% vs 9.4% p<0.001 non-inferior, but not superior p=0.17; CV death & HF hospitalization combo outcome.28 DECLARE

20. Ertugliflozin CV trial ongoing, estimated completed 2019.29 VERTIS CV Sotagliflozin CV trial ongoing, estimated completed 2022.30 SCORE

21. Basal insulin (glargine) vs standard care; all-cause mortality 15.2% vs 15.4% p=NS, MI 5.4% vs 5.2% p=NS, and stroke 5.3 vs 5.1% p=NS.30 ORIGIN

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 vs 5.1% p=NS.30 ORIGIN

**HF/Edema**

23. MF should be considered 1st line in HF patients with eGFR > 30 mL/min (Grade D, Consensus).1 CDA/13

24. 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 0.82-0.96), MF + insulin vs neutral aHR 0.94 (0.77-1.15).2

25. Intensive A1C target (including glitazone) vs standard A1C target; HF (HF, HF hospitalization, worsening NYHA class) 3.9% vs 4.1% p=NS 3 ADVANCE

26. Glyburide vs rosiglitazone; HF/Edema (serious events) NNT 167/3.5 yr, HF (total events) NNT=67/3.5 yr.4 ADOPT

27. Pioglitazone vs placebo; ↑ hospitalization for HF NNH=50/2.9 yr (not adjudicated), ↑ edema (without HF) NNH=8/2.9 yr 5 PROACTIVE

28. Rosiglitazone +metformin or SU vs control; ↑ hospitalization for HF or death NNH=65/5.5 yr.6 RECORD Rosiglitazone vs placebo; ↑ HF NNH=250/3 yr 7 DREAM

29. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=NS.A 8 STOP-NIDDM

**Other-continued**

Other trials

- | 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.
- | Incretin agents (DPP-4 inhibitors and GLP1 agonists) ↑ pancreatic cancer: n=13 pancreatic cancer cases suspected of being associated with all incretin-based therapies (July 31, 2014).24,28
- | Liraglutide: ↑ T-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent).29
- | ↑ GI: Nausea, diarrhea, vomiting AE with long acting agents;30,31 ↑ GI AE: Taspoglutide once weekly 59% vs exenatide BID 35% (clinical development of taspoglutide has been stopped).32 ↓ GI AE: Exenatide once weekly 28% vs exenatide BID 48%, albiglutide once weekly 29.8% vs liraglutide 32%.11,12,27a,34,35 DURATION-5,36 DURATION-6 Neutral GI: dulaglutide once weekly 39.4% vs liraglutide daily 38.3%.36 AWARD-6

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

- | ↑ diabetic ketoacidosis; n=5 Canadian warnings, some requiring hospitalization (May 2016); n=7 US cases (n=44 TZDM cases, n=151DM cases, n=13 NR) (Mar 2013–2015) all requiring hospitalization or emergency department care.37,38
- | ↑ Prosepsis & 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
- | ↑ Lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6yr; 15.4/1000 ptyrs (1.54%/yr) vs 11.9/1000 ptyrs (1.19%/yr) NNT=285/yr (HR 1.26, 95% CI 1.04-1.52).3a CANVAS ↑ Lower limb amputation (ankle, below/above knee) 1.8/1000 ptyrs (0.18%/yr) vs 0.9/1000 ptyrs (0.09%/yr) NNT=1000/yr (HR 2, 95% CI 1.08-3.82).3a CANVAS Other trials neutral.3a CANVAS 4-42,43 May 2017 FDA: canagliflozin – increased risk of leg and foot amputations. https://www.fda.gov/Drugs/DrugSafety/ucm735707.htm?source=gothelpindex.usa-medicinesandout_source=gothelpindex
References: Death/MACE
8. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study of the use of a sulfonylurea or a metformin-like agent HR 1.75 (1.22 - 2.5), pioglitazone calculated pioglitazone >12 months associated 27.5 excess cases of bladder cancer /100,000 person-yrs vs never exposed. 15,16
9. Rosiglitazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ? CV events- see MACE/mortality. 17,21
10. DPP-4 inhibitors FDA +/- Health Canada warnings/label changes:
  • ?HR risk with saxagliptin and alogliptin (see above). 10, 11 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: as 30 cases of pancreatitis with exenatide of which n=21 cases hospitalized, n=3 cases reported positive rechallenge.26 For n=88 cases of pancreatitis with sitagliptin
References: HF/Edema