<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Sulfonylureas</th>
<th>Meglitinides</th>
<th>DPP4 Inhibitors</th>
<th>SGLT2 Inhibitors</th>
<th>Insulin in T2DM</th>
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<tr>
<td></td>
<td>Glipizide GLUCOTROL USP, IUSP</td>
<td>Rosiglitazone AVANDIA</td>
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<td>Nateglinide STARLUX D/C</td>
<td>Acarbose GLUCOBAY</td>
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<tr>
<td>Major trials to support findings/Outcomes*</td>
<td>UKPDS-33,34,80 (ADOPT; some use in ADVANCE)</td>
<td>PROACTIVE</td>
<td>SAVOR-TIMI 53, TECOS, EXAMINE PROLOUGE, CARMELINA, CAROLINA</td>
<td>LEADER, EXCSEL, FREDOM CVO, REWIND, SUSTAIN-6, PIONEER-6, ELIKA, HARMONY</td>
<td>T2DM: UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN, DEVOTE T2DM: DCCT/EDIC (Also Bousresous et al. Meta-analysis. BMJ 2011;343:d1619)</td>
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<td>↓ Risk of Death/ Major CV†</td>
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<td>UKPDS-33,30 (ADOPT)</td>
<td>ACE (Prevention trial: Stop-NIDDM)</td>
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<td>Effect on A1C**</td>
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<td>Weight (GAL vs neutral vs gain)</td>
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<td>Risk of Hypoglycemia</td>
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<td>↓ Risk of HF/Edema</td>
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<td>Effect on GI tolerability</td>
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<td>Other</td>
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*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/files/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

AKI=acute kidney injury DKA=diabetic ketoacidosis IFG=impaired fasting glucose MACEmajor adverse cardiovascular events PPBG=postprandial blood glucose

**See next page for GLP1 & SGLT2 color comparison chart
## 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>Generic BRAND</td>
<td>Dulaglutide SC</td>
<td>Canagliflozin INVKOANA</td>
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<td>TRUELYC (SC WEEKLY)</td>
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<tr>
<td></td>
<td>Liraglutide SC</td>
<td>Dapagliflozin FORXIGA / FORXIGA LTHA</td>
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<tr>
<td></td>
<td>VICTOZA (SC DAILY)</td>
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<tr>
<td></td>
<td>Semaglutide SC</td>
<td>Empagliflozin JARDIANCE</td>
</tr>
<tr>
<td></td>
<td>OZEMPIC (SC WEEKLY)</td>
<td></td>
</tr>
<tr>
<td>Major trial(s) to support findings/Outcomes*</td>
<td>REWIND n=9061 / 1.5y</td>
<td>DECLARE-TIMI n=17200 / 1.3y in heart failure pts</td>
</tr>
</tbody>
</table>

### ↓ Risk of Major CV - MACE
- **REWIND**
  - **MACE**
  - **NNT=72/5.4yrs**
  - **LEADER**
  - **MACE**
  - **NNT=53/3.8yrs**
  - **SUSTAIN-6**
  - **MACE**
  - **NNT=44/2.1yrs**
  - **PIONEER-6**
  - **MACE**
  - **NNT=35/1.7yrs**

### ↓ Risk of All-Death
- **REWIND**
  - **HR 0.9 (0.80-1.01)**
  - **10.8% vs neutral vs gain**
  - **MF: 77%, insulin 60%; Smaller, shorter trial; SAE leading to lower discontinuation rate in tx group, 2.6% vs 3%.
  - **High risk group: 83% had established CVD, CKD or both**
  - **Lower risk group; e.g. 21% had past CVD; others higher risk.
  - **Renal: macroalbuminuria, eGFR decline 30% or more, chronic renal replacement tx**

### Less Renal Disease
- **SUSTAIN-6**
  - **NNT=72/3.8yrs**
  - **Lower risk group; e.g. 21% had past CVD; others higher risk.

### Effect on GI & D/C due to Tolerability
- **REWIND**
  - **Down GI effects**
  - **Upper GI effects: GI adverse events.**
  - **Environmental impact - single cancer (liraglutide); NNT=72/5.4yrs**
  - **Subcut once daily**
  - **Use disposable pen**
  - **$225-$90-$235**

### Less Risk of Hypoglycemia
- **PIONEER-6**
  - **Down 2.3 kg/3.8 yrs**
  - **↓ 2kg/12-52 wks CANTATA-M**
  - **↓ 1.5-2 kg/3.1 yrs**

### Less Risk of HF /Edema
- **ORIGIN-HF**
  - **HR: 0.9 (0.77-1.22)**
  - **HR: 0.87 (0.73-1.05)**
  - **HR: 1.11 (0.77-1.61)**
  - **HR: 0.86 (0.48-1.55)**
  - **↓ MACE**
  - **Non-inferior to Placebo (HR 0.74-1.00) (≈ NNT=19/2.4 yrs)**
  - **< 2 endpoint**

### Cost – 1 month
- **XX $225 x X**
  - **XX $90-$235 x X**
  - **XX $120-$220 x NIH**
  - **XX $260 x NIH**
  - **XX $110 = x NIH**
  - **XX $110 = x NIH**

### Other
- **Well tolerated, except Gl. ↓ BP 1/5 mmHg.**
  - **Environmental impact - single use disposable pen**
  - **GI adverse events**
  - **↑ pancreafifis, ↑ pancreatic cancer; ↑ thyroid cancer (liraglutide);↑ gallbladder disease; ↑ diabetic retinopathy complications.**
  - **FDA +/- HC warning: ↑ DKA; ↑ AKI (caution: ↓ intravascular volume & renal fx); genital mycotic infections.**
  - **Genital mycotic infections.**
  - **Genital mycotic infections.**
  - **Genital mycotic infections.**
  - **Genital mycotic infections.**
  - **Genital mycotic infections.**

### Practical / Clinical Considerations
- **Upper GI effects often worse than lower GI 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.**
  - **GI adverse events.**
  - **GI adverse events.**
  - **GI adverse events.**
  - **GI adverse events.**

### Time Tested
- **XX new agent – outcome & safety data still limited**
  - **Single Use Pen: subcut once weekly**
  - **XX ≥10yr history, but... limited real-world use**
  - **XX new agent – outcome & safety data still limited**
  - **XX new agent – outcome & safety data still limited**
  - **XX new agent – outcome & safety data still limited**
  - **XX new agent – outcome & safety data still limited**
  - **XX new agent – outcome & safety data still limited**

### Convenience
- **XX Oral once daily**
  - **XX Oral once daily**
  - **XX Oral once daily**

### Overall
- **XX Neutral**
  - **XX Neutral**
  - **XX Neutral**

### An Advantage
- **XX Neutral**
  - **XX Neutral**
  - **XX Neutral**

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% or more, 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 Inhibitors
- **CANVAS**
  - **High risk group: 66% had established/hx of CVD [10 outcome if no CV disease history, HR= 0.98 (0.74-1.3)]**
- **DECLARE-TIMI**
  - **High risk group: >40% had atherosclerotic CVD; 33% CAD, 6% PAD, 7.6% cerebrovascular dx, 10% HF**
- **EMPA-REG**
  - **High risk group: 100% had established CVD. Patients had not received glucose-lowering agents for >12 weeks**

###无人驾驶
- **L Regier BSP BA - www.RxFiles.ca Oct 2020**
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</table>
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=773), ↓ all-cause mortality NNT=14/10.7 yr, and ↓ MACE NNT=14/10.7 yr. UKPDS-34 10 yr observational follow-up ↓ all-cause mortality NNT=14/20 yr, and ↓ MACE NNT=16/20 yr. UKPDS-80

3. Intensive HbA1c target (included glimepiride) vs standard HbA1c target; MACE 10% vs 10.6% p=NS, all-cause mortality 8.9% vs 9.6% p<0.05. ADVANCE

4. Intensive therapy (chlorpropamide, glipizide15A, 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 ↓ MACE NNT=36/~20 yr. 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=97%), stroke OR 1.16 (0.81-1.66, I²=97%).

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

7. Pioglitazone vs placebo; T2DM & high CV risk; ↓ MACE NNT=50/2.9 yr. PROACTIVE Insulin resistance & recent TIA/stroke; ↓ MACE NNT=36/4.8 yr. IRIS

8. Rosiglitazone vs placebo; ↑ MACE 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mons early. DREAM ↑ MI NNH=167 & CV death 0.87% vs 0.39% p=0.06. Rosiglitazone vs glyburide ↓ MACE NNH 63/4 yr. ADOPT

9. Acarbose vs placebo; impaired glucose tolerance; ↓ MACE NNT 40/3.3 yr. STOP-NIDDM Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95% CI, 0.86-1.11, p=0.73. ACE

10. Saxagliptin vs placebo; T2DM 7.3% vs 7.2%, non-inferior (p<0.001), but not superior (p=0.99). SAVOR-TIMI 53 Saxagliptin vs placebo; MACE 11.3% vs 11.8%, non-inferior (p<0.001), but not superior (p=0.32). EXAMINE Saxagliptin vs placebo; MACE 8.0% vs 8.7%, non-inferior (p<0.001). CARDIOLOGY

11. Linagliptin vs placebo; MACE 12.4% vs 12.1% non-inferior (p<0.001), but not superior (p=0.74). CARmELINA Linagliptin vs glimepiride: MACE 11.8% vs 12 non-inferior (p<0.001) but not superior. CARmELINA2019

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

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. UKPDS-33 10 yr observational follow-up ↓ all-cause mortality NNT=29/~20 yr, and ↓ MACE NNT=36/~20 yr. UKPDS-80

21. 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 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).

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/yr 1 ADOPT

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 & glyburide 1

A5. Acarbose: ↓ 1.15 kg/3 yr 3 STOP-NIDDM

A6. Repaglinide: ↑ ~1.7 kg/12-24 wks; nateglinide: ↑ 0.7-1 kg/16-24 wks

A7. 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

A8. GLP1 agonists

- exenatide ↓ 2.8 kg/24-52 weeks 11

- liraglutide ↓ 2.3 kg/3.8 yr 12 LEADER
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; ↓ CV death NNT=77/3.8 yr and ↓ all-cause mortality NNT 72/3.8 yr. LEADER Semaglutide SC weekly vs placebo; MACE superior; (nephropathy was better; however, retinopathy complications were worse). SUSTAIN

13. Lixisenatide vs placebo (post-AClS) MACE 13.4% vs 13.2%, non-inferior (p=0.001), not superior (p=0.83) ELIKA

14. Exenatide extended release vs placebo (~70% CVD, ~30% prevention mortality); MACE 11.4% vs 12.2% over median 3.2 yr, non-inferior (p=0.001), but not superior (p=0.06). EXICAL Dulaglutide254 CV trial ongoing, estimated completed 2018. REMIND Albilglutide CV trial ongoing, estimated completed 2018. HARMONY Semaglutide PO CV trial semaglutide vs placebo: MACE, non-inferior; ↓ all-cause death 1.4% vs 2.8% 2nd endpoint 2019. PIONIER-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. EMPA-REG Canagliflozin vs placebo; MACE 26.9/1000ptys (2.7%/yr) vs 31.5/1000ptys (3.15%/yr), superior (p=0.02) 22/20/yr, f/u duration 3.6yr, no significant difference in components of primary composite or death; ↑ MACE in 1st 30 days (n=13 vs n=11, 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. 26,27,27a 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. DECLARE

16. Ertugliflozin CV trial ongoing, estimated completed 2019. VERTIS CV Sotaglipiflozin 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. 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. ORIGIN

HF/Edema

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 SU ↓ all-cause mortality aHR 0.89 (95% 0.82-0.96), MF + insulin vs SU neutral aHR 0.94 (0.77-1.15). 3

24. Intensive A1C target (included glitazide) vs standard A1C target; HF (death, HF hospitalization, worsening NYHA class) 3.9% vs 4.1% p=NS. ADVANCE

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

26. Pioglitazone vs placebo; ↑ hospitalization for HF NNT=50/2.9 yr (not adjudicated), ↑ edema (without HF) NNN=8/2.9 yr. PROACTIVE

27. Rosiglitazone +metformin or SU vs control; ↑ hospitalization for HF or HF death NNN=69/5.6 yr. RECORD Rosiglitazone vs placebo; ↑ HF NNN=250/3 yr. DREAM

28. Acarbose vs placebo; improved glucose tolerance; HF 0% vs 0.3% p=N.A. 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., liraglutide) in product monograph.


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

42. ↑ Gl (nausea, diarrhea, vomiting) AE with long acting agents 0.31; ↑ Gl AE: tosogliflozin once weekly 59% vs exenatide BID 35% (clinical development of tosogliflozin has been stopped). 17 Gl 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%, 32,33 DURATION-5,34 HARMONY-3,35 DURATION-6 Neutral Gl: 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 T2DM cases, n=15T1DM cases, n=13 NR) (Mar 2013-2015) all requiring hospitalization or emergency department care.

- ↑ 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 2018).

- ↑ AKI; n=2 Canadian cases (Canagliflozin) (Oct 2015); n=101 US cases (Mar 2013-Oct 2015), of which n=6 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.

- ↑ fracture; canagliflozin 100 mg-300 mg vs placebo follow up 3.6 yr; 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 ↓BMI (total hips, lumbar spine, femoral neck, & distal forearm).

- ↑ lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6 yr; ↓ all amputation 6.3/1000ptys (0.63%/yr) vs 3.4/1000ptys (0.34%/yr) NNN=345/yr (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below above knee) 1.8/1000ptys (0.18%/yr) vs dulaglutide ↓1.3-3 kg/5-12 weeks 15

9. SGLT2 inhibitors 14

- canagliflozin ↓ 2.8-4 kg/4-52 weeks 15,16 CANTATA-M

- dapagliflozin ↓ 2.7-2.7 kg/12-52 weeks 17

- empagliflozin ↓ ~1.5-2 kg/3.1 y 18 EMPA-REG

A10. Insulin

- intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 0.4 kg/3.5 yr; weight ↑ >10 kg 28% vs 14% p<0.001 ACCORD

Note: detemir -1.27 to -0.8 kg vs NPH (glargine no difference vs NPH) 20

Other/Additional Trials Recently Published

35. Pioglitazone & Rosiglitazone FDA +/- Health Canada warnings/label changes:
- ↑ HF (see above) 1 PROACTIVE, 2 RECORD, 3 DREAM, 4, 5
References: Death/MACE


