### ANTIHYPERGLYCEMIC DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

**Drug Class**

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<th>Metformin (MF)</th>
<th>Glyburide</th>
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<th>Rosiglitazone</th>
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**Sulfonylureas**

- UKPDS-33,34,38 (ADOPT; some use in ADVANCE)
- ADVANCE
- UKPDS-33,38 (ADOPT)
- ProACTIVE

**TZDs**

- ACE (prevention trial: Stop-NIDDM)
- SAVOR-TIMI 53
- Tecos, Exame prologue, Carmelina (2018)
- CAROLINA (2019)

**DPP-4 Inhibitors**

- X78 saxagliptin, alogliptin, sitagliptin non-inferior to placebo for MACE. But see 79th below

**GLP-1 Agonists (Subcut)**

- X15 empagliflozin + MACE NNT=31.9yr, mortality NNT=39.3yr (Empa-Kidney 2022)

- SUSTAIN

**SGLT-2 Inhibitors**

- LEADER, SUSTAIN-6 ELIXA, EXCEL, REWIND (2018), PIONEER, HARMONY (2019)

**Intensity: Less**

- (NH) HS + MF

**Intensity: More**

- (Multiple daily doses)

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**Major trials to support findings/Outcomes**

- UKPDS-33,34,38 (ADOPT; some use in ADVANCE)
- ADVANCE
- UKPDS-33,38 (ADOPT)
- ProACTIVE

**Risk of Death / Major CV**

- X28 in obese, mortality NNH=61/yr SPREAD-DIMCAD

- X28 in IFG, MACE NNT=40/3.3yr; in established CVD (Chinese NS)

- X28 in established CV risk (2019)

**Effect on A1C**

- A1

- A1

**Risk of Hypoglycemia**

- X

- X

**Risk of HF / Edema**

- NNH=14/yr (2018) SPREAD

- NNH=3.8/yr (2018) SPREAD

**Effect on GI tolerability**

- X

**Cost**

- X

**Other**

- Used in combination with metformin (ADVANCE)

- Caution: renal function (older adults)

- TID dosing

- TID dosing

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**An Advantage**

- X

**Neutral**

- X

**A Disadvantage**

- X

**Unknown/Ongoing**

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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.**
Drug manufacturers must establish CV safety (one-sided upper boundary of 95% CI ≤ 1.3) vs liraglutide ↓ 2.3 kg/3.8 yr. **TECOS**

Sitagliptin ↓ 2 kg/12-52 weeks **SAVOR-TIMI 53**

Intensive HbA1c target (included gliclazide) vs standard HbA1c target; MACE 10% vs 10.6% p=NS, all-cause mortality (NS) after 30 days (HR 0.89, 95% CI 0.64, 1.25); ACE

NNT=10/5 yr **ACCORD**

Acarbose vs placebo; impaired glucose tolerance; **Lixisenatide vs placebo (post-ACS); MACE 13.4% vs 13.2%, p<0.001**, but not superior (p=0.65). **CARMELINA**

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. **ADOPT**

Acarbose vs placebo; impaired glucose tolerance; ↓ MACE NNT 40/3.3 yr. **STOP-NIDDM**

Saxagliptin vs placebo; MACE 7.3% vs 7.2%, non-inferior (p<0.01), but not superior (p=0.99). **SAVOR-TIMI 53**

Alogliptin vs placebo; MACE 11.3% vs 11.8%, non-inferior (p<0.01), but not superior (p=0.32). **EXAMINE**

Sitagliptin MACE vs placebo; MACE 9.6% vs 9.6%, non-inferior (p<0.01), but not superior (p=0.65). **TECOS**

NNT=63/4.8 yr. **ACCORD**

Rosiglitazone vs placebo 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). **ADVANCE**

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

Pioglitazone vs placebo; T2DM & high CV risk; ↓ MACE NNT=50/2.9 yr. **PROACTIVE**

Insulin degludec vs insulin glargine (T2DM; ~50/50 split bolus vs bolus/basal baseline & no difference in 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). **DEVOTE**

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

A1. Metformin: ↓ 2.9 kg/4 yr **ADOPT**

A2. Sulfonylureas: ↑ 1.6 kg/4 yr **ADOPT**

A3. Pioglitazone: ↑ 3.6 kg/3 yr **PROACTIVE**

A4. Rosiglitazone: ↑ 4.8 kg/4 yr; rosiglitazone statistically significant ↑ weight vs both metformin & glipizide **ADOPT**

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

A6. Repaglinide: ↑ -1.7 kg/12-24 wks; nateglinide: ↑ 0.7-1.6 kg/12-24 wks

A7. DPP4-inhibitors (generally considered neutral) **SAVOR-TIMI 53**

• saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) **EXAMINE**

• alogliptin ↑ 1 kg/18 months (similar to placebo) **EXAMINE**

• sitagliptin ↑ ≤ 0.5 kg/12 weeks

A8. GLP-1 agonists

• exenatide ↓ 2.8 kg/24-52 weeks

• lixisenatide ↓ 2.3 kg/3.8 yr **LEADER**

• dulaglutide ↓ 1.3-3 kg/5-25 weeks **CARMELINA**

A9. SGLT2 inhibitors **CANTATA-M**

• canagliflozin ↓ 2.8-4 kg/4-52 weeks **CANTATA-M**

• dapagliflozin ↓ 2 kg/12-52 weeks **CANTATA-M**

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

A10. Insulin

• intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 4.3/5 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)

**HF/Edema**

22. MF should be considered 1st line in HF patients with eGFR > 30 mL/min [Grade D, Consensus]. **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% CI 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). **CDA’13**

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. **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 NNH=50/2.9 yr (not adjudicated), ↑ edema (without HF) NNH=8/2.9 yr. **PROACTIVE**

27. Rosiglitazone +metformin or SU vs control; ↑ hospitalization for HF or death NNH=69/5.5 yr. **RECORD**

28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A. **STOP-NIDDM**

29. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%, p=N/A. **CDA’13**

30. Saxagliptin vs placebo; ↑ hospitalization for HF NNH=143/2.1 yr; however, subgroup without a history of HF at baseline ↑ hospitalization for HF NNH=147/2.1 yr, subgroup eGFR <60 mL/min ↑ hospitalization for HF NNH=68/2.1 yr & no difference from 12 months on HR 1.05, 95% CI 0.81-1.35.
Insulin basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9%; MI 15.8% vs 17.9%

HF/Edema- continued

1.35, 10, 11 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 ↑ hospitalization for HF NNH=111/1.5 yr. 12, 13 EXAMINE 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]). 14, 15 TEOS Meta-analysis [SAVOR-TIMI 53, EXAMINE, TECOS] HF admission RR 1.12 (95% CI, 1.00-1.25, I²=42%). 16 FDA warnings for both saxagliptin & alogliptin. 17

31. Liraglutide vs placebo; hospitalization for HF: 4.7% vs 5.3% p=0.14. 18 LEADER Lixisenatide vs placebo; hospitalization for HF: 4.0% vs 4.2% p=0.75. 19 ELIXA

32. Emmagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002. 20 EMPA-REG Emmagliflozin in HF patients (regardless of diabetes status) ongoing trial estimated to be complete 2020 EMPORER-Reduced & Preserved

Canagliflozin vs placebo; hospitalization for HF: 5.5/1000pvyrs (0.55%/yr) vs 8.7/1000pvyrs (0.87%/yr) (HR 0.67, 95% CI 0.52-0.87) follow up 3 yr but exploratory. 27a CANVAS

Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS. 22 ArchInternMed1997

Other

35. Pioglitazone & Rosiglitazone FDA +/- Health Canada warnings/label changes:

- ↑↑↑↑↑ diabetes 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. 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 hemodialysis, and n=4 cases resulted in death. 38 ~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; 15.4/1000pvyrs (1.54%/yr) vs 11.9/1000pvyrs (1.19%/yr) NNT= 285/yr (HR 1.26, 95% CI 1.04-1.52). 25 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 6.3/1000pvyrs (0.63%/yr) vs 3.4/1000pvyrs (0.34%/yr) NNH=345/yr (HR 1.97, 95% CI 1.41-2.75) & ↑↑↑↑↑ major amputation (ankle, below/above knee) 1.8/1000pvyrs (0.18%) vs 0.9/1000pvyrs (0.09%/yr) NNH=1000/yr (HR 2, 95% CI 1.08-3.82). CANVAS Other trials neutral. 42, 43


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 person-yrs 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:

- ↑↑↑↑↑↑ 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 developing joint pain; n=8 cases reported a positive rechallenge (2006-2013). 23

39. Incretin agents (DPP-4 inhibitors and GLP-1 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. 26a US case control study; incretin agent (exenatide or sitagliptin) within 30 days aOR 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. 26FDA: 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. 27 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). 24, 28

41. Liraglutide: ↑↑↑↑↑↑↑↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent). 29
42. GI (nausea, diarrhea, vomiting) AE with long acting agents30,31. GI AE: taspoglutide once.


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