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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/rxfiles/uploads/documents/Diabetes-Oral-Agents-Comparison-Summary-Table.pdf See also: RxFiles Diabetes Landmark Trials Summary at: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-TrialsLinks.pdf Diabetes Oral Agents Comparison Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/numbers/17-Diabetes.pdf

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**A1C**

**Weight vs neutral vs gain**

**Risk of Hypoglycemia**

**Risk of HF/Edema**

**Effect on A1C**

**Effect on GI tolerability**

**Cost**

**Other**

**Overall**

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Death/MACE (MACE: Major adverse cardiovascular event)

1. Drug manufacturers must establish safety CV (one-sided upper boundary of 95% CI ≤ 1.3) vs comparator (typically placebo) in a RCT for all new agents in CV risk patients. 17

2. Metformin vs conventional diet; obese >120 kg BMI & small sample n=753; ↓ all-cause mortality NNT=14/10.7 yr. 18

3. Intensive Hba1c target (included gliclazide) vs standard Hba1c target; MACE 10% vs 16.6% p=N.S, all-cause mortality 8.9% vs 9.6% p=N.S. 19

4. Intensive therapy (chlorpropamide, glipizide) vs insulin vs conventional diet; all-cause mortality 17.9% vs 18.9% p=N.S, and stroke 5.6% vs 5% p=N.S. 20

5. Liraglutide vs placebo; Linagliptin

6. Death/MACE

7. Basal insulin vs basal/bolus insulin; small sample n=152; CV mortality 3.8% vs 6.7% p=N.S, MACE 20% vs 32% p=N.S. 31

8. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up ↓ MACE NNT=23/17 yr. 32

9. Basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9% p=N.S, MI 15.8% vs 17.9%

10. Death/MACE (MACE: Major adverse cardiovascular event) - cont’d p=N.S, and stroke 5.4% vs 5.0% p=N.S. 33

11. Basal insulin vs bolus (with intensive therapy vs standard therapy; ↑ MACE NNT=33/3.5 yr and CV death NNT=125/3.5 yr. 34

12. Insulin degludec vs insulin glargine (T2DM; ~50/50 split bolus vs basal/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). 35

13. 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/4 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/4 yr; rosiglitazone statistically significant ↑ weight vs. both metformin & glyburide 1 ADOPT

A5. Acarbose: ↓ 1.15 kg/3 yr 1 STOP-NIDDM

A6. Repaglinide: ↑ ~1.7 kg/12-24 wks; 4,5 nateglinide: ↑ 0.7-1.6 kg/16-24 wks 4,6

A7. DDP4-inhibitors (generally considered neutral)

• saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) 5 SAVOR TIMI 53

• alogliptin ↑ 1 kg/18 months (similar to placebo) 6 EXAMINE

• sitagliptin ↑ ≤ 0.5 kg/12 weeks 10

A8. GLP-1 agonists

• exenatide ↓ 2.8 kg/24-52 weeks 11

• liraglutide ↓ 2.3 kg/3.8 yr 12 LEADER

• dulaglutide ↓ 1.3-3 kg/5-52 weeks 13

A9. SGLT2 inhibitors 14

• canagliflozin ↓ 2.8-4.4 kg/4-52 weeks 15,16 CANTATA-M

• dapagliflozin ↓ 2 kg/12-52 weeks 17

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

A10. Insulin

• intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 4.3 kg/3.5 y; weight ↑ >10 kg 28% vs 14% p=0.019 ACCORD

• Note: detemir -1.27 to -0.8 kg with NPH (glargine no difference vs NPH) 36

HF/Edema

22. MF should be considered 1st line in HF patients with eGFR > 30 mL/min [Grade D, Consensus]. 1

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% 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). 2

24. Intensive A1c target (included gliclazide) vs standard A1c target; HF (death, HF hospitalization, worsening NYHA class) 3.9% vs 4% p=N.S. 3 ADVANCE

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

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 or SU vs control; ↑ hospitalization for HF or death NNH=69/5.5 yr. 6 RECORD

28. Acardbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A 8 STOP-NIDDM
39. Pioglitazone & Rosiglitazone

38. Other

37. Liraglutide vs placebo; hospitalization for HF: 3.9% vs 3.3% p=0.12; subgroup without a history of HF at baseline ↑ hospitalization for HF NNH=111/1.5 yr.23

36. Liraglutide: 8.7/1000 ptyrs (0.77%/yr) NNH=134/2.1 yr.23

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

34. Other- continued

33. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.20 EMPA-REG EMPagliflozin in HF patients (regardless of diabetes status) ongoing trial estimated to be complete 2020 EMPORER-Reduced & Preserved Canagliflozin vs placebo; hospitalization for HF: 5.5/1000 ptyrs (0.55%/yr) vs 8.7/1000 ptyrs (0.87%/yr) (HR 0.67, 95% CI 0.52-0.87) follow up 3.6 yr but exploratory.27a CANVAS Dapagliflozin vs placebo; hospitalization for HF: 2.5%/1000 patient year vs 3.3%/1000 patient year HR0.73 (95% CI 0.61-0.88) but exploratory.28 DECLARE

32. Basal insulin (glargine) vs standard care; hospitalization for HF 4.9% vs 5.5% p=NS;21 ORIGIN

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

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Other
References: Weight


Increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet). Available:


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