**Hypoglycemia**

**ANTI**

**Effect on Outcomes***

<table>
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<th>Death / Other Outcomes</th>
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**B1C**

**-**

**GI vs:**

RxFiles Diabetes Landmark Trials Summary

May have to consider balance of potential benefits & harms.

**Less** (NPH HS + MF)

**Intensity:**

More (Multiple daily doses)

**Major trials to findings/Outcomes***

<table>
<thead>
<tr>
<th>UKPDS-33,38,40 (ADOPT, some use in ADVANCE)</th>
<th>ADVANCE</th>
<th>UKPDS-33,38,40 (ADOPT)</th>
<th>ProACTIVE</th>
<th>Meta-analysis, RECORD interim, ADOPT, DREAM</th>
<th>ACE (Prevention trial: Stop-NIDDM)</th>
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**Risk of Death / Major CV***

<table>
<thead>
<tr>
<th>Risk of Hypoglycemia</th>
<th>Risk of HF / Edema</th>
<th>Risk of Hypoglycemia</th>
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<tbody>
<tr>
<td>X</td>
<td>X23.24</td>
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<td>X22.23</td>
<td>X26.25</td>
<td>X27.28</td>
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<td>X25.27</td>
<td>X28.29</td>
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<td>X31.32</td>
<td>X33.34</td>
<td>X35.36</td>
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**Effect on GI tolerability**

<table>
<thead>
<tr>
<th>Effect on GI tolerability</th>
<th>Cost</th>
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<tr>
<td>X</td>
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**Other**

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<tr>
<th>Other</th>
<th>Metformin (MF) Glucophage, Glicl孜on</th>
<th>Sulfonylureas</th>
<th>TZDs</th>
<th>Meglitinides</th>
<th>DDP-4 Inhibitors</th>
<th>GLP-1 Agonists (Subcut)</th>
<th>SGLT-2 Inhibitors</th>
<th>Insulin in T2DM</th>
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<tbody>
<tr>
<td>TID dosing</td>
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**Overall**

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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.*


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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.  
2. Metformin vs conventional diet; obese ≥120 IBW & small sample n=753; ↓ all-cause mortality NNT 14/10.7yr, and ↓ MI NNT=14/10.7yr.  
3. Intensive HbA1c target (vs standard HbA1c target); MACE 10% vs 10.6% p=NS, all-cause mortality 8.9% vs 9.6% p=NS. ADVANCE  
4. Intensive therapy (chloorpropamide, glipizide, glyburide 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. ADVANCE  
5. SU 2nd or 3rd generation vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, l²=0%), CV mortality OR 1.12 (0.87-1.42, l²=12%), MI OR 0.92 (0.76-1.12, l²=NR), stroke OR 1.16 (0.81-1.66, l²=NR).  
6. Metformin vs glipizide; Chinese, small sample n=304, & medically undertreated 100% CAD, but ≤10% taking ACEIs; Metformin ↓ MACE NNT=10/5yr.  
7. Pioglitazone vs placebo; T2DM & high CV risk; ↓ MACE NNT=50/2.9yr. PROACTIVE insulin resistance & recent TIA/stroke; ↓ MACE NNT=36/4.8yr. 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 63/4yr.  
9. Acarbose vs placebo; impaired glucose tolerance; ↓ MACE NNT 40/3.3yr. STOP-NIDDM Acarbose vs placebo; coronary heart disease; (Chinese) HR 0.98 95% CI, 0.86-1.11, p=0.73.  
10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, non-inferior (p=0.001), but not superior (p=0.99). SAVOR-TIM3  
11. Alogliptin vs placebo; MACE 11.3% vs 11.8%, non-inferior (p=0.001), but not superior (p=0.32). EXAMINE  
12. Sitagliptin vs placebo; MACE 9.6% vs 9.6%, non-inferior (p<0.001), but not superior (p=0.65). TECOS Meta-analysis (SAVOR-TIM3, EXAMINE, TECOS) MACE RR 0.99 (95% CI, 0.93-1.01, l²=0%).  
13. Linagliptin vs placebo; MACE 12.4% vs 12.1% non-inferior (p<0.001), but not superior (p=0.74). CARMAELINA  
14. Liraglutide vs placebo; MACE 13% vs 14.9%, superior (p=0.01, NNT=53/3.8yr), but results neutral in North America subgroup; ↓ CV death NNT=77/3.8yr and ↓ all-cause mortality NNT 72/3.8yr.  
15. Canagliflozin vs placebo; MACE 13% vs 14.9%, superior (p<0.05, NNT=53/3.8yr), but results neutral in North America subgroup; ↓ CV death NNT=77/3.8yr and ↓ all-cause mortality NNT 72/3.8yr.  
16. Empagliflozin vs placebo; MACE 13% vs 14.9%, non-inferior (p<0.05), but not superior (p>0.81). ELIXA  
17. Exenatide extended release vs placebo (~70% CVD, ~30% primary prevention); MACE 11.4% vs 12.2% over median 3.2yr, non-inferior (p>0.001), but not superior (p=0.06). EXICAL Dulaglutide vs placebo CV trial ongoing, estimated completed 2018. REVIND Albiglutide CV trial ongoing, estimated completed 2018. HARMONY  
18. Empagliflozin vs placebo; MACE 10.5% vs 12.1%, superior (p<0.04, NNT=63/3.1yr); ↓ CV death NNT=46/3.1yr and ↓ all-cause mortality NNT 39/3.1yr. EMPA-REG Canagliflozin vs placebo; MACE 26.9/1000ptys (2.7%/yr) vs 31.5/1000ptys (3.1%/yr), superior (p=0.02, NNT=220/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=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. DECLARE  
19. Intensive insulin vs standard insulin; TIDM population; ~11yr observational follow up ↓ MACE NNT=23/17yr. DCTT, 31 EDIC  
20. Insulin basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9% p=NS, MI 15.8% vs 17.9%  

Weight  
A1. Metformin: ↓ 2.9 kg/4yr 1 ADAPT  
A2. Sulfonlureas: ↑ 1.6 kg/4yr 1 ADAPT  
A3. Pioglitazone: ↑ 3.6 kg/3yr 2 PROACTIVE  
A4. Rosiglitazone: ↑ 4.8 kg/4yr; rosiglitazone statistically significant ↑ weight vs. both metformin & glyburide 1 ADAPT  
A5. Acarbose: ↓ 1.15 kg/3yr 3 STOP-NIDDM  
A6. Repaglinide: ↑ 1.7 kg/12-24wks;4,5 nateglinide: ↑ 0.71-16/24wks 4,6  
A7. DPP4-inhibitors (generally considered neutral)  
- saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) 5 SAVOR-TIM3  
- alogliptin ↑ 1 kg/18 months (similar to placebo) 9 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/5-21 weeks 13  
A9. SGLT2 inhibitors 14  
- canagliflozin ↓ 2.8-4 kg/4-52 weeks 15,16 CANTATA-M  
- dapagliflozin ↓ 2 kg/12-52 weeks 17  
- empagliflozin ↓ ~1.5-2 kg/3.1yr 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 19 ACCORD  
- Note: detemir -1.27 to -0.8 kg vs NPH (glargine no difference vs NPH) 20}
Other

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

- ↑ HF (see above) \( \text{PROACTIVE, 2 RECORD, 3 DREAM, 4, 5} \)
- ↑ fractures \( \text{PROACTIVE, 3 RECORD, 2 DREAM} \)
- ↑ NHH=38/2.9 yr \( \text{unpublished} \) \( \text{PROACTIVE, 3 RECORD} \)
- Rosiglitazone & MF \( \text{fractures} \) \( \text{NH}=24/4.9 \) yr, rosiglitazone & glyburide \( \text{fractures} \) \( \text{NH}=17/4.2 \) \( \text{ADOP} \)
- Post marketing data: pioglitazone exposure in women associated 0.8 excess fractures (distal upper and lower limbs)/100 patient-years vs comparator treated group. \( \text{No ↑ in males} \).
- ↑ 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). \( \text{Cross-section of ACCORD} \)
- ↑ macular edema aOR, 0.97 (0.67-1.40). \( \text{Note- only rosiglitazone has a warning} \).

36. Pioglitazone :
- ↑ 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 other diabetic agent HR 1.75 (1.22-2.5). \( \text{pioglitazone exposure >12 months vs other diabetic agent HR 1.28 (1.09-1.51)} \) \( \text{US, prospective observational cohort} \)
- 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). \( \text{FDA calculated pioglitazone >12 months associated 27.5 excess cases of bladder cancer /100,000 person-yrs vs never exposed.} \)

37. Rosiglitazone [FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ↑ CV events- see MACE/mortality. \( \text{17-21} \)

38. DPP-4 inhibitors FDA +/- Health Canada warnings/label changes:

- ↑ HF risk with saxagliptin and alogliptin (see above). \( \text{10} \)
- ↑ 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).

39. Incretin agents (DPP-4 inhibitors and GLP-1 agonists) ↑ pancreaticitis; \( \text{Meta-analysis of SAVOR-TIMI 53, EXAMINE, & TECOS (n=36,395) demonstrated ↑ acute pancreatitis OR 1.79 (1.13-2.82) and ARI of 0.13% vs placebo.} \)
- US case control study; incretin agent (exenatide or sitagliptin) within 30 days aOR 2.24 (95% CI, 1.36-3.68). \( \text{FDA: n=30 cases of pancreatitis with exenatide of which n=21 cases} \)

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. \( \text{27 Listed adverse event for other agents (e.g., liraglutide) in product monograph.} \)

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). \( \text{24, 28} \)

41. Liraglutide: ↑ thyroid C-cell tumor (including medullary thyroid carcinoma) in animal studies (both genders, dose-dependent, and treatment-duration-dependent). \( \text{29} \)

42. ↑ GI (nausea, diarrhea, vomiting) AE with long acting agents \( \text{30, 31} \)
- ↑ GI AE: taspoglutide once weekly (n=59 vs exenatide BID 35% (clinical development of taspoglutide has been stopped). \( \text{32} \)
- GI 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%. \( \text{33, 34, 35, 36 AWARD-6} \)

43. SGLT-2 inhibitors FDA +/- Health Canada warnings/label changes:
- ↑ diabetic ketoacidosis; n=5 Canadian cases, 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. \( \text{37, 38} \)
- ↑ 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). \( \text{38} \)
- ↑ 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. \( \text{39, 40} \)
- ↑ fracture; canagliflozin 100 mg-300 mg vs placebo follow up 3.6 yr; 15.4/1000ptyrs (1.54/yr) vs 11.9/1000ptyrs (1.19/yr) NNT= 285/yr (HR 1.26, 95% CI 1.04-1.52), \( \text{CANVAS} \) ↑ bMD (total hips, lumbar spine, femoral neck, & distal forearm). \( \text{41} \)
- ↑ lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6 yr; ↑ all amputation 6.3/1000ptyrs (6.3%yr) vs 3.4/1000ptyrs (3.4%yr) NHR=345/yr (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below/above knee) 1.8/1000ptyrs (0.18%/yr) vs 0.9/1000ptyrs (0.09%/yr) NHR=1000/yr (HR 2, 95% CI 1.08-3.82). \( \text{CANVAS Other trials neutral.} \)

44. ↑ UTI; SGLT2 inhibitor vs placebo: OR 1.34 (1.03-1.74, I²=0%), vs active agent: OR 1.42 (1.06-1.9, I²=25%). ↑ genital tract infection; SGLT2 inhibitor vs placebo OR 3.50 (2.46-4.99, I²=0%), vs active agent: OR 5.06 (3.44-7.75, I²=0%). \( \text{44} \)

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). \( \text{46} \)

46. Canagliflozin vs placebo: ↓ primary composite outcome of ESKD, doubling of Scr & renal or CV death (NNT= 23/2.6 yrs)
hospitalized, n=3 cases reported positive rechallenge.20 FDA: n=88 cases of pancreatitis with sitagliptin


Summary Safety Review - SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin): Assessing the risk of the body producing high levels of acid in the blood (diabetic ketoacidosis).


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