| Drug Class          | Metformin (MF) | Gliclazide (Diamicron, Glycin) | Glyburide (Diabeta) | Pioglitazone (Actos) | Rosiglitazone (Avandia) | Acarbose (Glucofage) | Repaglinide (Gliptin) | Nateglinide (Starlix) | Sulfonylureas |
|--------------------|----------------|-------------------------------|--------------------|----------------------|-------------------------|---------------------|----------------------|----------------------|----------------|---|
| TZDs               |                |                               |                    |                      |                         |                     |                      |                      |                 | |
| Meglitinides        |                |                               |                    |                      |                         |                     |                      |                      |                 | |
| Insulin in T2DM    |                |                               |                    |                      |                         |                     |                      |                      |                 | |
| Intensity: Less     |                |                               |                    |                      |                         |                     |                      |                      |                 | |
|                      |                |                               |                    |                      |                         |                     |                      |                      |                 | |
| Insulin in T2DM    |                |                               |                    |                      |                         |                     |                      |                      |                 | |
| Intensity: More     |                |                               |                    |                      |                         |                     |                      |                      |                 | |
|                      |                |                               |                    |                      |                         |                     |                      |                      |                 | |

**Major trials to support findings: Outcomes**

- **UKPDS-33, 34, 80** (ADOPT; some use in ADVANCE)
- **ADVANCE**
- **UKPDS-33, 80** (ADOPT)
- **ProACTIVE**
- **Meta-analysis. RECORD interim, ADOPT, DREAM** (prevention trial: Stop-NIDDM)
- **SAVOR-TIMI-33**
- **TEOS, EXAMINE, CARMELONA** (2018)
- **PAUROGUE** (2016)
- **ELDA LEADER SUSTAINING EXCEL** (2018)
- **REWIND** (2018)
- **T2DM UKPDS-33, 80, ADVANCE, ACCORD, VADT, ORIGIN**
- **Placebo group had > insulin use in LEADER**
- **T2DM: DCC/TEDC/ADOPT (Mali-khan et al., 2011:343-46679)**

**Outcomes**

- **L-BSP, L-1 Agonists (Subcut)**
- **DPP-4 Inhibitors**
- **GLP-1 Agonists (Subcut)**
- **SGLT-2 Inhibitors**

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**Effect on A1C**

- **Weight loss vs neutral vs gain**
- **Risk of Hypoglycemia**
- **Risk of HF / Edema**
- **Effect on GI tolerability**
- **Cost**
- **Other**

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**Overall**

- **An Advantage**
- **Neutral**
- **X**
- **A Disadvantage**
- **Unknown/Ongoing**

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**Intensities**

- **Less (NPH HS + MF)**
- **More (Multiple daily doses)**

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**Individualized approach considering balance of potential benefits & harms. Over-aggressive pursuit of targets can risk mortality.**

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**Footnotes**

- 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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**See full version of this ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table online for additional notes: [http://www.rxfiles.ca/rxfiles/upload/documents/Diabetes_Agents-Outcomes_Comparison-Summary-Table.pdf](http://www.rxfiles.ca/rxfiles/upload/documents/Diabetes_Agents-Outcomes_Comparison-Summary-Table.pdf)**

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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 \(\leq 1.3\)) vs comparator (typically placebo) in a RCT for all new agents in \(\uparrow\text{CV risk patients}\).  

2. Metformin vs conventional diet; obese \(\geq 1200\) kcal & small sample \(n=753\), \(\downarrow\text{all-cause mortality NNT}14/10.7\) yr, and \(\downarrow\text{MI NNT=14/10.7}\) yr.  

3. Intensive HbA1c target (including gliclazide) vs standard HbA1c target; MACE 10% vs 10.6% \(\uparrow\text{p=NS, all-cause mortality 8.9% vs 9.6% \(\uparrow\text{p=NS}\).}  

4. Intensive therapy (chlorpropamide, glibenclamide \(\uparrow\text{or insulin}\) vs conventional diet; all-cause mortality 17.9% vs 18.9% \(\uparrow\text{p=NS, MI 14.7% vs 17.4% \(\uparrow\text{p=NS, and stroke 5.6% vs 5% \(\uparrow\text{p=NS}\).}  

5. SU (2\text{nd} \text{or 3rd generation}) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, \(i^{2}=0.00\)), CV mortality OR 1.12 (0.87-1.42, \(i^{2}=12\)), MI OR 0.92 (0.76-1.12, \(i^{2}=\text{N/NR}\), stroke OR 1.16 (0.81-1.66, \(i^{2}=\text{N/NR}\)).  

6. Metformin vs glipizide; Chinese, small sample \(n=304\), & medically untreated 100% CAD, but \(\leq10\%\) taking ACE; Metformin \(\downarrow\text{MACE NNT=10/5.3}\).  

7. Pioglitazone vs placebo; T2DM & high CV risk; \(\downarrow\text{MACE NNT=50/2.9}\).  

8. Rosiglitazone vs placebo; \(\uparrow\text{MACE 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mos early.}\)  

9. SU (2\text{nd} or 3rd generation) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, \(i^{2}=0.00\)), CV mortality OR 1.12 (0.87-1.42, \(i^{2}=12\)), MI OR 0.92 (0.76-1.12, \(i^{2}=\text{N/NR}\), stroke OR 1.16 (0.81-1.66, \(i^{2}=\text{N/NR}\)).  

10. Liraglutide vs placebo; MACE 13% vs 14.9%, \(\uparrow\text{p=0.01, NNT=53/3.8}\), but results neutral in North America subgroup; \(\downarrow\text{CV death NNT=77/3.8}\) yr and \(\downarrow\text{all-cause mortality NNT=72/3.8}\) yr.  

11. Sitagliptin vs placebo; MACE 13.4% vs 13.2%, \(\downarrow\text{p=0.001, but not superior } (p=0.81)\).  

Death/MACE (MACE: Major adverse cardiovascular event)- cont’d

21. Greater insulin use (any & bolus) with intensive therapy vs standard therapy; \(\uparrow\text{MACE NNT=33/3.5}\) yr and \(\uparrow\text{CV death NNT=125/3.5}\) yr.  

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

A. Metformin: \(\downarrow\text{2.9 kg/yr } 1^\text{st}\) \(\text{ADOPT}\)  

B. Sulfonylureas: \(\uparrow\text{1.6 kg/yr } 1^\text{st}\) \(\text{ADOPT}\)  

C. Pioglitazone: \(\uparrow\text{3.6 kg/3 yr } 1^\text{st}\) \(\text{ADOPT}\)  

D. Rosiglitazone: \(\uparrow\text{4.8 kg/4 yr } 1^\text{st}\) \(\text{ADOPT}\)  

E. Alogliptin: \(\uparrow\text{1 kg/18 months } (\text{similar to placebo }) 1^\text{st}\) \(\text{ADOPT}\)  

F. Sitagliptin: \(\uparrow\text{0.5 kg/12 weeks} 1^\text{st}\) \(\text{ADOPT}\)  

G. GLP-1 agonists:

- exenatide \(\downarrow\text{2.8 kg/24-52 weeks} 1^\text{st}\) \(\text{ADOPT}\)  
- liraglutide \(\downarrow\text{2.3 kg/3.8 yr } 1^\text{st}\) \(\text{ADOPT}\)  
- dulaglutide \(\downarrow\text{1.3-3 kg/5-52 weeks} 1^\text{st}\) \(\text{ADOPT}\)  

H. SGLT2 inhibitors:

- canagliflozin \(\downarrow\text{2.6 kg/4-52 weeks} 1^\text{st}\) \(\text{ADOPT}\)  
- dapagliflozin \(\downarrow\text{2 kg/12-52 weeks} 1^\text{st}\) \(\text{ADOPT}\)  

I. Empaglifoxin \(\downarrow\text{1.5-2 kg/3.1 yr } 1^\text{st}\) \(\text{ADOPT}\)  

J. Azagluride: \(\downarrow\text{CV death NNT=22/1.3} 1^\text{st}\) \(\text{ADOPT}\)  

K. Sitagliptin: \(\downarrow\text{CV death NNT=5/2.9} 1^\text{st}\) \(\text{ADOPT}\)  

L. Ertugliflozin: \(\downarrow\text{CV death NNT=5/2.9} 1^\text{st}\) \(\text{ADOPT}\)  

M. Albiglutide: \(\downarrow\text{CV death NNT=5/2.9} 1^\text{st}\) \(\text{ADOPT}\)  

H/Edema

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

23. Retrospective cohort (n=10,920 patients hospitalized with HF); MF vs SU \(\downarrow\text{all-cause mortality aHR 0.85 (95% CI 0.75-0.98)}\), MF + SU vs MF \(\downarrow\text{all-cause mortality aHR 0.89 (95% CI 0.82-0.96)}\), MF + insulin vs neutral aHR 0.96 (95% CI 0.82-1.13), MF+SU insulin neutral aHR 0.94 (0.77-1.15).  

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

25. Glyburide vs rosiglitazone; \(\downarrow\text{HF (total events) NNT=67/3.5}\) yr.  

26. Pioglitazone vs placebo; \(\uparrow\text{hospitalization for HF NHH=50/2.9}\) yr (not adjudicated), \(\uparrow\text{edema (without HF) NHH=8/2.9}\) yr.  

27. Rosiglitazone + metformin or SU; \(\uparrow\text{hospitalization for HF or HF death NHH=69/5.5}\) yr.  

28. Acarbose vs placebo; \(\uparrow\text{impaired glucose tolerance; HF 0% vs 0.3% p=N/A} 1^\text{st}\) \(\text{ADOPT}\)  

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

30. Saxagliptin vs placebo; \(\uparrow\text{hospitalization for HF NHH=143/2.1}\) yr; however, subgroup without a history of HF at baseline \(\uparrow\text{hospitalization for HF NHH=147/2.1}\) yr, subgroup eGFR < 60 ml/min \(\uparrow\text{hospitalization for HF NHH=68/2.1}\) yr & no difference from 12 months on HR 1.05, 95% CI 0.81-1.35.  

31. Sitagliptin vs placebo; hospitalization for HF 3.9% vs 3.3% p=0.22; subgroup without a history of HF at baseline.\(\uparrow\text{hospitalization for HF NHH=111/1.5}\) yr.
39. FDA warnings for both saxagliptin & alogliptin.17
31. Basal insulin (glargine) 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 ELIKA
32. Canagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.20 EMPA-REG
33. Basal insulin (glargine) vs placebo; hospitalization for HF: 4.9% vs 5.5% p=N.S.21 ORIGIN
34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=N.S.22 ArthritisRheum1997

Other

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

- HF (see above)1 PROACTIVE, 2 RECORD, 3 DREAM, 4, 5
- fractures; pioglitazone vs placebo 5.1 vs 2.5%, calculated p=0.005 fractures; NNH=38.2/yr (unpublished data).6 Rosiglitazone vs MF ADAPT fractures; NNH=24/4 yr, rosiglitazone vs glyburide & fractures; NNH=17/4 yr.7 Post marketing data:

- pioglitazone exposure in women associated 0.8 excess fractures (distal upper and lower limbs)/100 patient-years vs comparator treated group. No ↑ risk in males.8,9
- diabetic macular edema: retrospective cohort, TZD users vs nonusers ↑ macular edema 1 yr follow up aOR 2.0 (1.5-3.6) & 10 yr follow up HR 2.3 (1.7-3.0).10 Cross-section of ACCORD ↑ macular edema aOR 0.97 (0.67-1.40).11 Note- only rosiglitazone has a warning.12

36. Pioglitazone & Rosiglitazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ↑ CV events- see MACE/mortality.10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22

37. Rosiglitazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ↑ HF risk with saxagliptin and alogliptin (see above).10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22

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

- ↑ HF risk with saxagliptin and alogliptin (see above).10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22

39. Incretin agents (DPP-4 inhibitors and GLP-1 agonists) ↑ pancreatic ↑ acute pancreatitis OR 1.79 (1.13-2.82) and ARI of 0.13% vs placebo.24, 25 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.26 FDA: 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

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, 25

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 agents: GI AE: tasgoplitazone once weekly 59% vs exenatide BID 35% (clinical development of tasgoplitazone has been stopped).31 GI AE: Exenatide once weekly 28% vs exenatide BID 48%, albglutide once weekly 29.8% vs liraglutide daily 52%, exenatide once weekly 19.1% vs liraglutide daily 44.5%.33 DURATION-6, 34 HARMONY-7, 35 DURATION-6

Other- continued

Neutral GI: dulaglutide once weekly 39.4% vs liraglutide daily 38.3%.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=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. “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; 15.4/1000ptyrs (Canagliflozin) vs 7.1/1000ptyrs (Liraglutide) incretin inhibitor effect is not lost; ~50% of fractures resulted in severe disability.41

- ↑ lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6yr; ↑ all amputation 6.3/1000ptyrs (Canagliflozin) vs 3.4/1000ptyrs (Liraglutide) (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below/above knee) 1.8/1000ptyrs (Canagliflozin) vs 0.3/1000ptyrs (Liraglutide) (HR 5.5/1000ptyrs).42, 43

- ↑ bladder infection; SGLT2 inhibitor vs placebo OR 1.34 (1.03-1.74, 95% CI 1.04-1.55), vs active agent: OR 1.42 (1.06-1.9, 95% CI 1.2-2.5).44

- ↑ UTI; SGLT2 inhibitor vs placebo OR 3.50 (2.46-4.99, 95% CI 1.04-1.55), vs active agent: OR 5.06 (3.44-7.45, 95% CI 1.04-1.55).44

- ↑ 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).45
References: Death/MAE


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

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