### Drug Class

<table>
<thead>
<tr>
<th>Generic BRAND</th>
<th>Metformin (MF)</th>
<th>Sulfonylureas</th>
<th>Glyburide</th>
<th>Glycine</th>
<th>Pioglitazone</th>
<th>Meglitinides</th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Agonists (Subcut)</th>
<th>SGLT-2 Inhibitors</th>
<th>Insulin in T2DM</th>
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<tr>
<td><strong>Sulfonylureas</strong></td>
<td>Glipizide</td>
<td>Diamicron</td>
<td><strong>GLUCOPLAG</strong></td>
<td>USA</td>
<td><strong>SPREAD-DIMACOL</strong></td>
<td>Nateglinide</td>
<td>Star D/C</td>
<td><strong>OSAXA</strong></td>
<td><strong>TANGLAY</strong></td>
<td><strong>EPERZAN</strong></td>
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<tr>
<td><strong>T2Ds</strong></td>
<td>Proactive</td>
<td>UKPDS-33, 80 (ADOPT)</td>
<td><strong>IRIS</strong></td>
<td><strong>ADVANCE</strong></td>
<td><strong>RECORD interimir, ADOPT, DREAM</strong></td>
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<td><strong>SAVOR-TIMI 53</strong></td>
<td><strong>EXCEL (2018)</strong></td>
<td><strong>REVIND, HARMONY (2018)</strong></td>
<td><strong>EXAMINE</strong></td>
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<tr>
<td><strong>Antidiabetic Agents</strong></td>
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<td><strong>VICTOZA</strong>, <strong>EXENATIDE</strong>, <strong>DUPLAGLUTIDE</strong>, <strong>LIXIENATE</strong></td>
<td><strong>SEMAGLUTIDE</strong>, <strong>ALBIGLUTIDE</strong></td>
<td><strong>empagliflozin</strong></td>
<td><strong>canagliflozin</strong>, <strong>dapagliflozin</strong></td>
<td><strong>Reflex, Edema</strong></td>
<td><strong>LACE</strong>, <strong>LACEMELA</strong></td>
<td><strong>MACE</strong></td>
<td><strong>MACE</strong></td>
<td><strong>MACE</strong></td>
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<td><strong>Intensification of Therapy</strong></td>
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<td><strong>NPH HS +</strong></td>
<td><strong>Multiple daily doses</strong></td>
<td><strong>More</strong></td>
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<td><strong>Outcomes</strong></td>
<td><strong>Major CV</strong></td>
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</table>

### Risk of Death / Major CV

- **β-Hex**: MACE vs MF NNH-10/5yr (SPREAD-DIMACOL)
- **β-MACE**: NNH-50/2.9yr, but 10 composite NS
- **β-ME**: IFG, NEACE 40/3.3yr

### Effect on A1C

1. **A**: X2
2. **A2**: X2
3. **A3**: X2
4. **A4**: X2
5. **A5**: X2
6. **A6**: X2
7. **A7**: X2
8. **A8**: X2
9. **A9**: X2
10. **A10**: X2

### Risk of HF / Edema

- 1st line in HF with eGFR >30 ml/min (CDAN13)

### Effect on Glucose Tolerance

- **Start low & titrate**
- **Rate of 1.8%/yr**

### Cost

- **Used in combination with metformin**
- **Price of insulin**

### Other

- **May have to hold or discontinue in acute illness/renal dysfunction**
- **Caution: renal function of older adults**
- **1st line for obese T2DM**

### Overall

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

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**Note:**
- **X** = X-ray
- **A** = Angiography
- **AA** = Angioplasty
- **C** = Coronary artery bypass grafting
- **M** = Mitral valve surgery
- **I** = Intracoronary stent placement
- **B** = Balloon angioplasty

**Disclaimer:**
- [RxFiles Diabetes Landmark Trials Summary](http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Summary.pdf)

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**Disclaimer:**

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**Individualized approach to consider balance of potential benefits & harms:**
- Our aggressive pursuit of targets can increase mortality.

**Additional notes:**
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% IW; & small sample n=753; ↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=14/10.7 yr.  
3. Intensive HbA1c target (included gliclazide) vs standard HbA1c target; MACE 10% vs 10.6% p=NS, all-cause mortality 8.9% vs 9.6% p=NS.  
4. Intensive therapy (chlorpropamide, glipizide, 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.  
5. SU (2nd or 3rd generation) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, p=0.0), CV mortality OR 1.12 (0.87-1.42, p=0.12), MI OR 0.92 (0.76-1.12, p=NR), stroke OR 1.16 (0.81-1.66, p=NR).  
6. Metformin vs gliclazide; Chinese, small sample n=304, & medically untreated 100% CAD, but ≤10% taking ACE; Metformin ↓ MACE NNT=10.5 yr.  
7. Pioglitazone vs placebo; T2DM & high CV risk; ↓ MACE NNT=50/2.9 yr.  
8. Rosiglitazone vs placebo; ↑ MACE 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mos early.  
9. Metformin vs conventional; recent TIA/stroke; ↓ MACE NNT=36/4.8 yr.  
10. Rosiglitazone vs placebo; ↑ MI NNT=167 & CV death 0.87% vs 0.39% p=0.06.  
11. Semaglutide vs placebo; MACE superior; (nephropathy was better; however, retinopathy complications were worse).  
12. Lixisenatide vs placebo; MACE 13.4% vs 13.2%, non-inferior (p=0.001), but not superior (p=0.81).  
13. Exenatide vs placebo; ↑ MI NNT=40/3.3 yr.  
14. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, non-inferior (p=0.001), but not superior (p=0.99).  
15. Alogliptin vs placebo; MACE 11.3% vs 11.8%, non-inferior (p=0.001), but not superior (p=0.32).  
16. Sitagliptin vs placebo; MACE 9.6% vs 9.6%, non-inferior (p=0.001), but not superior (p=0.65).  
17. Sitagliptin vs placebo; MACE RR 0.99 (95% CI, 0.93-1.06, p=0%).  
19. 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.  
20. 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.  
21. SGLT2 inhibitors; canagliflozin vs placebo; MACE 26.9/1000pts (2.7%/yr) vs 31.5/1000pts (3.15%/yr), superior (p=0.02, NNT=220/yr), f/u duration 3.6 yr, no significant difference in components of primary composite or death; ↑ MI in 1st 30 days (n=13 vs n=1, p=NS, non-dose related); ↓ MI (NS) after 30 days (HR 0.89, 95% CI 0.64, 1.25); numeric imbalance not present in non-CANVAS trials.   
23. 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.  
24. 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.  
25. EMPA-REG Canagliflozin vs placebo; MACE 26.9/1000pts (2.7%/yr) vs 31.5/1000pts (3.15%/yr), superior (p=0.02, NNT=220/yr), f/u duration 3.6 yr, no significant difference in components of primary composite or death; ↑ MI in 1st 30 days (n=13 vs n=1, p=NS, non-dose related); ↓ MI (NS) after 30 days (HR 0.89, 95% CI 0.64, 1.25); numeric imbalance not present in non-CANVAS trials.   
27. 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.  
28. 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.  
29. Intensive insulin vs standard insulin; TIDPM population; ~11 yr observational follow up ↓ MACE NNT=23/17 yr.  
30. Insulin bolus vs standard insulin; TIDPM population; ~11 yr observational follow up ↓ MACE NNT=23/17 yr.  
31. Insulin bolus vs standard insulin; TIDPM population; ~11 yr observational follow up ↓ MACE NNT=23/17 yr.  
32. UKPDS-33 10yr observational follow up↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=36/20 yr.
Other

35. Pioglitazone & Rosiglitazone FDA +/- - Health Canada warnings/label changes:
   - ?↑ HF (see above) 1 PROACTIVE, 2 RECORD, 3 DREAM, 4, 5
   - ?↑ fractures; pioglitazone versus placebo 5.1% vs 2.5%, calculated p=0.005 6 7
   - ?↑ fractures; pioglitazone vs placebo NNH=38/2.9 yr (unpublished data). 8 Rosiglitazone vs MF 12↑ fractures 9 NNH=24/4 yr, pioglitazone vs glyburide 13↑ fractures 10 NNH=17/4 yr. ADOPT Post-marketing data: pioglitazone exposure in women associated 0.8 excess fractures (distal upper and lower limbs)/100 patient-years vs comparator treated group. 11 No ↑ risk in males. 6, 7, 8, 9, 10, 11
   - ↑ 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). Cross-section of ACCORD ↑ macular edema aOR 0.97 (0.67-1.40). Note: only rosiglitazone has a warning. 14, 15

36. Piog: ↑ bladder cancer; France, retrospective observational cohort pioglitazone exposure versus other diabetic agent H1.22 (1.03-1.43), pioglitazone exposure cumulative dose > 28 000 mg vs other diabetic agent H1.75 (1.22-2.5), pioglitazone exposure >12 months vs other diabetic agent H1.28 (1.09-1.51). 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). FDA calculated pioglitazone >12 months associated 27.5 excess cases of bladder cancer /100 000 person-yr vs never exposed. 14, 15

37. Rosiglitazone FDA +/- - Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ↑ CV events; see MACE/mortality. 17, 18

38. DPP-4 inhibitors FDA +/- - Health Canada warnings/label changes:
   - ↑ HF risk with saxagliptin and alogliptin (see above). 10, 11 SAVOR-TIMI 53, 12, 13 EXAMINE, 16, 17, 18
   - ↑ 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). 20

39. Incretin agents (DDP-4 inhibitors and GLP-1 agonists) ↑ pancreatitis; 14 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. 5b, 21 US case control study; incretin agent (exenatide or sitagliptin) within 30 days aOR 2.24 (95% CI, 1.36-3.68). 22 FDA: n=30 cases of pancreatitis with exenatide of which n=21 cases hospitalized, n=3 cases reported positive rechallenge. 22 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 Listed adverse event for other agents (e.g., liraglutide) in product monograph.

40. Incretin agents (DDP-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). 20, 21

42. ↑↓ GI (nausea, diarrhea, vomiting) AE with long acting agents 21, 22; ↓ GI AE: taspoglitazone once weekly 59% vs exenatide BID 35% (clinical development of taspoglitazone has been stopped). 21 ↓ GI AE: Exenatide once weekly 28% vs exenatide BID 48%, albiglutide once weekly 29.8% vs liraglutide...
References:

References:

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