### Major trials to support findings/Outcomes*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Sulfonylureas</th>
<th>T2Ds</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>
<th>Intensity</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Less</td>
<td>More</td>
</tr>
</tbody>
</table>

### Risk of Death / Major CV1

<table>
<thead>
<tr>
<th>Risk on A1C**</th>
<th>Weight (loss vs neutral vs gain)</th>
<th>Risk of Hypoglycemia</th>
<th>Risk of HF / Edema</th>
<th>Effect on GI tolerability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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</tr>
</tbody>
</table>

### Other

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<thead>
<tr>
<th>May have to hold or double dose in acute illness</th>
<th>1st line for global T2DM (UKPDS 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose dysequilibrium or renal dysplasia (?)</td>
<td>Acidosis, may do 121</td>
</tr>
</tbody>
</table>
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. FDA

2. Metformin vs conventional diet; obese >120% BW & small sample n=753; ↓ all-cause mortality NNT 14/10.7 yr, and ↓ MI NNT=14/10.7 yr. [UKPDS-34] 10 yr observational follow-up ↓ all-cause mortality NNT=14/20 yr, and ↓ MI NNT=16/20 yr. [UKPDS-35] 3

3. Intensive HbA1c target (glarglizeid 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 (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. [UKPDS-23] 10 yr observational follow-up ↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=36/20 yr. [UKPDS-36] 3

5. SU (2nd or 3rd generation) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, 1p=0%), CV mortality OR 1.12 (0.87-1.42, 1p=12%), MI OR 0.92 (0.76-1.12, 1p=NR), stroke OR 1.16 (0.81-1.66, 1p=NR). 6

6. Metformin vs glipizide; Chinese, small sample n=304, & medically undertreated 100% CAD, but ≤10% taking ACEI; Metformin ↓ MACE NNT=10/5 yr. [SPREAD-DICARD]

7. Pioglitazone vs placebo; T2DM & high CV risk; ↓ MACE NNT=50/2.9 yr. [PROACTIVE] insulin resistance & recent TIA/stroke; ↓ MACE NNT=36/4.8 yr. [IRIS]

8. Rosiglitazone vs placebo; ↑ MACE 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mons early. [DREAM] ↑ MI NNN=167 & CV death 0.87% vs 0.39% p=0.06. [Rosiglitazone vs glyburide ↑ MACE NNN=63/4 yr. [ADOPT]

9. Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95% CI, 0.86-1.11, p=0.73. [ACE]

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 MACE 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, 0.93-1.06, 1p=0%). [17]

13. Lisinopril vs placebo; ↓ MACE 12.4% vs 12.1%, non-inferior (p<0.001), but not superior (p=0.74). [CARMELINA]

14. Dapagliflozin 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. [LEADER]

15. Semaglutide SC weekly vs placebo MACE; superior (nephropathy was better; however, retinopathy complications were worse). [SUSTAIN]

16. Lixisenatide vs placebo (post-ACS); MACE 13.4% vs 13.2%, non-inferior (p<0.001), 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 3.2 yr, non-inferior (p=0.001), but not superior (p=0.06). [EXSCEL]

18. Dulaglutide 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. [EMPA-REG]

19. Intensive insulin vs standard insulin; T1DM population: ~11 yr observational follow up ↓ MACE NNT=23/17 yr. [DCCT, 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%

Death/MACE (MACE: Major adverse cardiovascular event) - cont’d p=NS, and stroke 5.4% vs 5.0% p=NS. [UKPDS-33] 10 yr observational follow-up ↓ all-cause mortality NNT=29/20 yr, and ↓ MI NNT=36/20 yr. [UKPDS-80]

21. Greater insulin use (any & bolus) with intensive therapy vs standard therapy ↓ MACE NNT=33.5/yr and ↓ CV death NNT=125/3.5 yr. [ACCORD]

22. 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). [DEVOTE]

Weight (weight gain/loss variable, diabetic agents used in conjunction with dietary lifestyles as well as other concomitant medications)

A1. Metformin: ↓ 2.9 kg/4 yr 1 [ADOPT]

A2. Sulfonlyureas: ↑ 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 3 [STOP-NIDDM]

A6. Repaglinide: ↑ ~1.7 kg/12-24 wks; 4,5 nateglinide: ↑ 0.7-1/kg/16-24 wks 4,6

A7. DPP4-inhibitors (generally considered neutral) 5

- saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) 5 [SAVOR-TIM3]
- alogliptin ↑ 1 kg/18 months (similar to placebo) 5 [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 kg/4-52 weeks 15,16 [CANTATA-M]
- dapagliflozin ↓ 2 kg/12-52 weeks 17
- empagliflozin ↓ ~1.5 kg/3.1 yr 18 [EMPA-REG]

A10. Insulin

- intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 0.4 kg/3.5yr; 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

HF/Edeema

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 aHR 0.96 (95% CI 0.82-1.13), MF+SU+insulin neutral aHR 0.94 (0.77-1.15). 2

24. Intensive A1C target (included glarglizeide) vs standard A1C target; HF (HF death, HF hospitalization, worsening NYHA class) 3.9% vs 4.1% p=NS. 3 [ADVANCE]

25. Glyburide vs rosiglitazone; ↓ HF (serious events) NNT 167/3.5 yr. ↓ HF (total events) NNT=67/3.5 yr. 1 [ADOPT]

26. Pioglitazone vs placebo; ↓ hospitalization for HF NNN=50/2.9 yr (not adjudicated), ↑ edema (without HF) NNN=8/2.9 yr. 5 [PROACTIVE]

27. Rosiglitazone + metformin or SU vs control; ↑ hospitalization for HF or HF death NNN=69/5.5 yr. 6 [RECORD]

28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A. 5 [STOP-NIDDM]
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 NHN=38/2.9 yr (unpublished) 6 Rosiglitazone vs MF ↑ fractures NHN=24/4 yr, pioglitazone vs glyburide ↑ fractures NHN=17/4 yr 8 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. 9 No ↑ in males. 8, 9
   • ↑ 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). 10 Cross-section of ACCORD ↑ macular edema aOR, 0.97 (0.67-1.4). 11 Note- only rosiglitazone has a warning. 12

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

37. Rosiglitazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ↑ CV events- see MAE/mortality. 17, 21

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, 22
   • ↑ 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). 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. 24, 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
References: Death/MACE


References: Weight


8. www.cadth.ca


[ Grade Evidence Profiles of Long and Rapid Acting Insulin Analogues: http://cadth.ca/media/compass/reports/compass_Long-and-Rapid_Acting-Insulin-Analogues-Grade-Profile.pdf ]

References: HF/Edema


[ Grade Evidence Profiles of Long and Rapid Acting Insulin Analogues: http://cadth.ca/media/compass/reports/compass_Rapid-Acting-Insulin-Analogues-Grade-Profile.pdf ]