ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table Glucose Lowering in T2DM

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Drug Class		Sulfonylureas		TZDs			Meglitinides	DDP-4 Inhibitors	GLP-1 Agonists (Subcut)	SGLT-2 Inhibitors	Insulin in T2DM	
Generic ⇨ Brand	Metformin (MF) Glucophage, Glycon	Gliclazide Diamicron	Glyburide Diabeta	Pioglitazone Actos	Rosiglitazone Avandia	Acarbose Glucobay	Repaglinide Gluconorm / Nateglinide Starlix D/C	Saxagliptin Onglyza Sitagliptin Januvia Alogliptin Nesina Linagliptin Trajenta	Liraglutide Victoza Exenatide Byetta Dulaglutide Trulicity Lixisenatide Lyxumia Semaglutide notCDN, Albiglutide Eperzan	Canagliflozin Invokana Dapagliflozin Forxiga / Farxiga Empagliflozin Jardiance Ertugliflozin	Intensity: Less (NPH HS + MF)	Intensity: More (Multiple daily doses)
		[Glipizide Glucotrol USA SPREAD-DIMCAD]										
Major trials to support findings/ Outcomes*	UKPDS-33,34,80 (ADOPT; some use in ADVANCE)	ADVANCE	UKPDS-33,80 (ADOPT)	ProACTIVE Ferwana M. Meta-analysis 2013. SR-Liao 2017; IRIS	Meta-analysis. RECORD interim, ADOPT, DREAM	(Prevention trial: Stop-NIDDM)	-	SAVOR-TIMI 53 TECOS, EXAMINE CARMELINA (2018) PROLOGUE (2016)	ELIXA LEADER SUSTAIN6 EXSCEL (2018), REWIND (2018), HARMONY (2019)	EMPA-REG CANVAS (2017), DECLARE (2019), VERTIS CV (2019)	T2DM UKPDS-33,80; ADVANCE, ACCORD, VADT, ORIGIN. Placebo group had ↑ insulin use in LEADER. (T1DM: DCCT/EDIC)(Also Boussageon et al Meta-analysis. BMJ 2011;343:d4169)	
↓ Risk of Death / Major CV[1]	✓✓✓[2] in obese, ↓ mortality NNT=14/10y ↓ MI NNT=14/10y (UKPDS-34)	✓[3,4,5] X?[5,6] glipizide ↑ MACE vs MF NNH=10/5y (SPREAD-DIMCAD)	✓[4,5]	✓✓[7] ↓ MACE NNT=50/ 2.9y , but 1° composite endpoint not significant (ProACTIVE)	X?[8]	✓✓[9] in IFG, ↓ MACE NNT=40/ 3.3y	?	✓[10] saxagliptin, alogliptin, sitagliptin ↔ non-inferior to placebo for MACE, *But see ?HF below* ?[11] (linagliptin ongoing). Sitagliptin no effect on intima-media thickness PROLOGUE	✓✓✓[12] liraglutide ↓ MACE NNT=53/3.8 y (North American subgroup neutral), ↓ mortality NNT=72/3.8 y (LEADER), semaglutide ↓MACE NNT=44/2 y (SUSTAIN-6) ✓[13] lixisenatide ↔ non-inferior to placebo for MACE (ELIXA) ?[14] (exenatide, dulaglutide, albiglutide ongoing)	✓✓✓[15] empagliflozin ↓ MACE NNT=63/3.1 y, ↓ mortality NNT=39/3.1 y (EMPA-REG) canagliflozin ↓ MACE NNT=334/3.6 y (CANVAS) but ↑ MACE in 1st 30 days (n=13 vs n=1, p=NS) interim analysis [16] (dapagliflozin, ertugliflozin ongoing)	✓[17,18]	✓[18,19,20] /X?[21] > insulin use with intensive target vs standard therapy, ↑ all-cause death NNH=95/3.5 y, & CV death NNH=125/3.5 y (ACCORD)
Effect on A1C**	✓✓✓	✓✓✓	✓✓✓	✓✓	✓✓	✓	✓✓ / ✓	✓	✓✓	✓✓	✓✓	✓✓✓
Weight (loss vs neutral vs gain)	✓✓✓[A1]	X[A2]	X[A2]	XX[A3]	XX[A4]	✓✓[A5]	X[A6]	✓[A7]	✓✓✓[A8]	✓✓✓[A9]	✓[A10]	XX[A10]
↓ Risk of Hypoglycemia	✓✓✓	✓ ? If less risk with MR formulation	X Severe, occurs at 1.4%/yr	✓✓ Low risk with monotherapy	✓	✓✓✓	✓ / ✓✓✓	✓✓?	✓✓?	✓✓ Risk when given with sulfonylurea or insulin	✓	XX Rate of 1.8%/yr
↓ Risk of HF / Edema	✓✓[22,23] 1st line in HF with eGFR >30 mL/min (CDA'13)	✓[23,24] (↑ CHF risk)	✓[23,25] (↑ CHF risk)	XX[26] ↑ HF NNH=50/2.9y, edema NNH=8/2.9 y	XX[25,27] ↑ HF NNH=69 /5.5y, (RECORD), ↑ HF NNH=250 /3y (DREAM)	✓[28]	✓[29]	X?[30] ↑ HF saxagliptin NNH=143/2.1 y (SAVOR), alogliptin (post hoc) (EXAMINE) sitagliptin HF neutral	✓[31] liraglutide (LEADER) and lixisenatide (ELIXA) neutral	✓[32] empagliflozin & canagliflozin neutral; (possible benefit: ↓hospitalizations)	✓[33,34] (↑ CHF risk)	✓[34] (↑ CHF risk)
Effect on GI tolerability	X Start low & titrate	✓✓	✓✓ rate of 1.8%/yr	✓✓	✓✓	XX	✓✓	✓✓	✓ Nausea, vomiting, diarrhea	✓ Nausea/diarrhea with dapaglifozin	✓✓✓	✓✓✓
Cost	✓✓✓	✓✓✓	✓✓✓	X	X	✓✓	✓✓	X	XX	X	✓	XX
Other	May have to hold or ↓ dose in acute illness/HF/ renal dysfx (? lactic acidosis); may ↓ B12. **1st line for obese T2DM (UKPDS-34)**	Used in combination with metformin (ADVANCE)	Caution: ↓ renal function (& older adults)	X FDA +/- HC warnings:[35] ?↑ HF *(see above)*, ?↑ fractures ♀ (NNH~30/~3.5 y) ?↑ macular edema (conflicting data) **Pio**:?↑ bladder ca >12 mos (27.5 excess /100,000 person yrs), avoid co-admin with dapagliflozin[36] **Rosi**: Restricted access in CDN (SK-EDS) (↑ **CV risk** concerns)[37]		✓✓ PPG, Possible benefit of laxative effect in some TID dosing	✓✓ PPG, flexibility with meals TID dosing	✓ PPG FDA +/- HC warning:[38] HF (saxa & alogliptin);arthralgia, hypersensitivity rx, ?↑ **pancreatitis (ARI 0.13%),**[39] **pancreatic cancer**[40] Linagliptin: no renal dose adjustment X **new agents – outcome & safety data still limited**	✓ PPG injection site irritation ?↑ **pancreatitis,**[39] **pancreatic cancer,**[40] ?↑ thyroid cancer (liraglutide)[41] (new *once weekly* agents may have ↓ GI adverse events)[42] ?gallbladder disease[46] X **new agents – outcome & safety data still limited**	X **new agents – outcome & safety data still limited** FDA +/- HC warning: ↑**ketoacidosis** (DKA); ↑AKI (caution: ↓ intravascular volume & ↓renal fnx Cana + Dapa), ↓BP; ↑(HR ~2) **limb amputations** Cana,[43] ↑urosepsis/pyelonephritis, (**UTI** OR 1.34 & **genital tract** infection OR 3.5 vs placebo);[44] ↑fracture (HR 1.3)/↓BMD Cana; **dapagliflozin** ?↑bladder/ breast cancer (avoid with pioglitazone)[45]	✓ Fear/ perception of insulin injections	✓✓PPG Fear/ perception of insulin injections
Overall	✓✓✓?	✓✓	✓	✓?	X?	✓	✓	✓?	? ✓✓ Liraglutide (CV+mortality benefit)	? ✓✓ Empaglifozin (CV+mortality benefit)	✓ / ✓✓	✓✓ / X?

*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-Agents-Outcomes-Comparison-Summary-Table.pdf

*See also: **RxFiles Diabetes Landmark Trials Summary** at:* http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf ***Diabetes Oral Agents Comparison Chart***: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-diabetes.pdf

Individualize approach considering balance of potential benefits & harms. Over-aggressive pursuit of targets can ↑mortality. ACCORD

An Advantage ✓✓✓	✓✓	Neutral ✓	X	A Disadvantage XX	Unknown/Ongoing ?

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.[1] FDA
2. Metformin vs conventional diet; obese >120% IBW & small sample n=753; **↓ all-cause mortality NNT 14/10.7 yr**, and **↓ MI NNT=14/10.7 yr**.[2] UKPDS-34 10 yr observational follow-up **↓ all-cause mortality NNT=14/~20 yr**, and **↓ MI NNT=16/~20 yr**.[3] UKPDS-80
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] ADVANCE
4. Intensive therapy (chlorpropamide, glipizide[USA], 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] UKPDS-33 10 yr observational follow-up **↓ all-cause mortality NNT=29/~20 yr**, and **↓ MI NNT=36/~20 yr**.[3] UKPDS-80
5. SU (2nd or 3rd generation) vs control (diet, placebo, other antihyperglycemic); all-cause mortality OR 1.12 (0.96-1.3, I^2=0%), CV mortality OR 1.12 (0.87-1.42, I^2=12%), MI OR 0.92 (0.76-1.12, I^2=NR), stroke OR 1.16 (0.81-1.66, I^2=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**.[7] SPREAD-DIMCAD
7. Pioglitazone vs placebo; T2DM & high CV risk; **↓ MACE NNT=50/2.9 yr**,[8] PROACTIVE insulin resistance & recent TIA/stroke; **↓MACE NNT=36/4.8 yr**.[9] IRIS
8. Rosiglitazone vs placebo; **↑ MACE** 2.9% vs 2.1% p=0.08 (NS), trial stopped 5 mons early,[10] DREAM ↑ MI NNH=167 & CV death 0.87% vs 0.39% p=0.06.[10] Rosiglitazone vs glyburide **↑ MACE NNH 63/4 yr**.[12] ADOPT
9. Acarbose vs placebo; impaired glucose tolerance; **↓ MACE NNT 40/3.3 yr**.[13] STOP-NIDDM
10. Saxagliptin vs placebo; MACE 7.3% vs 7.2%, **non-inferior** (p<0.001), but not superior (p=0.99).[14] SAVOR-TIMI 53 Alogliptin vs placebo; MACE 11.3% vs 11.8%, **non-inferior** (p<0.001), but not superior (p=0.32).[15] EXAMINE Sitaglipin MACE vs placebo; MACE 9.6% vs 9.6%, **non-inferior** (p<0.001), but not superior (p=0.65).[16] TECOS Meta-analysis(SAVOR-TIMI 53, EXAMINE, TECOS) MACE RR 0.99 (95% CI, 0.93-1.06, I^2=0%).[17]
11. Linagliptin CV trial ongoing, estimated completed 2018.[18] CARMELINA
12. 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**.[19] LEADER Semaglutide vs placebo; MACE **superior**; (nephropathy was better; however, retinopathy complications were worse).[20] SUSTAIN6
13. Lixisenatide vs placebo; MACE 13.4% vs 13.2%, **non-inferior** (p<0.001), but not superior (p=0.81).[21] ELIXA
14. Exenatide CV trial ongoing, estimated completed 2018.[22] EXSCEL Dulaglutide[USA] CV trial ongoing, estimated completed 2018.[23] REWIND Aliglutide CV trial ongoing, estimated completed 2019.[24] HARMONY
15. 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** 10.1% vs 9.8%, **superior** (p=0.02, **NNT=334/3.6 yr**), no signfigant 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.[26,27,27a] CANVAS
16. Dapagliflozin CV trial ongoing, estimated completed 2019.[28] DECLARE Ertugliflozin CV trial ongoing, estimated completed 2019.[29] VERTIS CV
17. 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.[30] ORIGIN
18. 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.[31]
19. Intensive insulin vs standard insulin; T1DM population; ~11 yr observational follow up **↓ MACE NNT=23/ ~17 yr**.[32] DCCT, [33] EDIC
20. Insulin basal/bolus vs conventional diet; all-cause mortality 18.6% vs 19.9% p=NS, MI 15.8% vs 17.9% p=NS, and stroke 5.4% vs 5.0% p=NS.[5] UKPDS-33 10 yr observational follow-up **↓ all-cause mortality NNT=29/~20 yr**, and **↓ MI NNT=36/~20 yr**.[3] UKPDS-80

HF/Edema- cont'd

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

21. Greater insulin use (any & bolus) with intensive therapy vs standard therapy; **↑ MACE NNT=33/3.5 yr** and **↑CV death NNT=125/3.5 yr**.[34] ACCORD
22. Insulin degludec vs insulin glargine (T2DM; ~50/50 split bolus vs bolus/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).[34a] DEVOTE

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 [3] STOP-NIDDM
A6. Repaglinide: ↑ ~1.7 kg/12-24 wks;[4,5] nateglinide: ↑ 0.7-1 kg/16-24 wks[4.6]
A7. DDP4-inhibitors (generally considered neutral)[7]
- saxagliptin ↓ 0.4 kg/2.1 year (similar to placebo) [8] SAVOR-TIMI 53
- 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/5-52 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/3.1 y[18] EMPA-REG

A10. Insulin
- intensive therapy vs standard therapy; avg weight ↑ 3.5 kg vs 0.4 kg/3.5 y; weight ↑ >10 kg 28% vs 14% p<0.00[19] ACCORD
- Note: detemir -1.27 to -0.8 kg vs NPH (glargine no difference vs NPH)[20]

HF/Edema

22. MF should be considered 1st line in HF patients with eGFR > 30 mL/min [Grade D, Consensus].[1] 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% 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 (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.**[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 +meformin or SU vs control; **↑ hospitalization for HF or HF death NNH=69/5.5 yr**.[6] RECORD Rosiglitazone vs placebo; **↑ HF NNT=250/3 yr**.[7] DREAM
28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A.[8] STOP-NIDDM
29. Repaglinide vs rosiglitazone: peripheral edema 0% vs 3.2%, p=N/A.[9]
30. Saxagliptin vs placebo; **↑ hospitalization for HF NNH=143/2.1 yr**; however, subgroup without a history of HF at baseline **↑ hospitalization for HF NNH=147/2.1 yr**, subgroup eGFR <60 mL/min **↑ hospitalization for HF NNH=68/2.1 yr** & no difference from 12 months on HR 1.05, 95% CI 0.81-1.35.[10, 11] SAVOR-TIMI 53 Alogliptin vs placebo; hospitalization for HF 3.9% vs 3.3% p=0.22; subgroup without a history of HF at baseline **↑ hospitalization for HF NNH=111/1.5 yr**.[12,13] EXAMINE Sitaglipin vs

Other- continued

Sitaglipin vs placebo; hospitalization for HF 3.1% vs 3.1% p=0.98; and neutral results when adjusted for baseline HF (aHR 1.00, 95% CI 0.83-1.20 [unpublished data]).[14,15] TECOS Meta-analysis[SAVOR-TIMI 53, EXAMINE, TECOS] HF admission RR 1.12 (95% CI, 1.00-1.25, I^2=42%).[16] FDA warnings for both saxagliptin & alogliptin.[17]

31. Liraglutide 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] ELIXA
32. Empagliflozin vs placebo; hospitalization for HF: 2.7% vs 4.1% p=0.002.[20] EMPA-REG Canagliflozin vs placebo; hospitalization for HF: 2.1% vs 2.8% (HR 0.67, 95% CI 0.52-0.87) but exploratory.[27a] CANVAS
33. Basal insulin (glargine) vs standard care; hospitalization for HF 4.9% vs 5.5% p=NS.[21] ORIGIN
34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS.[22] ArchInternMed1997

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=38/2.9 yr** (unpublished[PROACTIVE] data).[6] Rosiglitazone vs MF ↑ fractures ♀ **NNH=24/4 yr**, rosiglitazone vs glyburide ↑ fractures ♀ **NNH=17/4 yr**.[8] 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.[8] No ↑ risk 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 (0.67-1.40).[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), & piogltazone 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.[15,16]
37. Rosigltazone FDA +/- Health Canada warnings/label changes: restricted access- in Canada (SK-EDS) due to ?↑ CV events- see MACE/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 (DDP-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.[24a] 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] 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).[24,28]
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[30,31]: **↑ GI AE**: taspoglutide once weekly 59% vs exenatide BID 35% (clinical development of taspoglutide has been stopped).[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%.[33] DURATION-5,[34] HARMONY-7,[35] DURATION-6 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 15.4/1000 patient years vs 11.9/1000 patient years (HR 1.26, 95% CI 1.04-1.52). CANVAS ?↓BMD (total hips, lumbar spine, femoral neck, & distal forearm).[41]
    - ?↑ lower limb amputation; canagliflozin 100-300 mg vs placebo; ↑ all amputation 6.3/1000 patient years vs 3.4/1000 patients years (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below/above knee) 1.8/1000 patient years vs 0.9/1000 patient years (HR 2, 95% CI 1.08-3.82) .[CANVAS] Other trials neutral.[e.g.,CANVAS-R] [42,43] May2017 FDA: canaglifozin - increased risk of leg and foot amputations.
      https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
44. ?↑UTI; SGLT2 inhibitor vs placebo: **OR 1.34 (1.03-1.74, I^2=0%)**, vs active agent: OR 1.42 (1.06-1.9, I^2=25%). ↑ genital tract infection; SGLT2 inhibitor vs placebo **OR 3.50 (2.46-4.99, I^2=0%)**, vs active agent: OR 5.06 (3.44-7.45, I^2=0%).[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).

References: Death/MACE

1. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf (accessed July 12 2016).
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89.
4. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.
5. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.
6. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitão C, Gross JL. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. PLoS Med. 2016 Apr 12;13(4):e1001992.
7. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, Zhou Z, Tang W, Zhao J, Cui L, Zou D, Wang D, Li H, Liu C, Wu G, Shen J, Zhu D, Wang W, Shen W, Ning G; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11.
8. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O,Skrha J, Smith U, Taton J; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.
9. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP Jr, Berger L Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR; IRIS Trial Investigators. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016 Apr 7;374(14):1321-31.
10. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105.
11. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71. Epub 2007 May 21.
12. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care. 2002 Oct;25(10):1737-43.
13. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. Diabetes Care. 1998 Oct;21(10):1720-5.
14. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.
15. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35.
16. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42.
17. Barry AR, Turgeon RD. DPP-4 Inhibitors: The Seinfeld of Oral Antihyperglycemics. Can J Hosp Pharm. 2016 May-Jun;69(3):253-4.
18. Cardiovascular and Renal Microvascular Outcome study with Linagliptin in patients with Type 2 Diabetes Mellitus (CARMELINA). NCT01897532. Available: https://clinicaltrials.gov/ct2/show/NCT01897532. (Accessed July 16 2016).
19. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee on behalf of the LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jun 13.
20. Nainggolan L. Now Novo Says Semaglutide Cuts CV Risk: SUSTAIN-6 Top-line Data. http://www.medscape.com/viewarticle/862644 (accessed June 24, 2016).
21. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015 Dec 3;373(23):2247-57.
22. Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. NCT01144338. Available: https://clinicaltrials.gov/ct2/show/NCT01144338?term=EXSCEL&rank=1 (accessed July 21, 2016).
23. Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND). NCT01394952. Available: https://clinicaltrials.gov/ct2/show/NCT01394952?term=REWIND&rank=1 (accessed July 21, 2016).
24. Effect of Albiglutide, When added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus. NCT02465515. Available: https://clinicaltrials.gov/ct2/show/NCT02465515?term=HARMONY+and+albiglutide&rank=1 (accessed July 21, 2016).
25. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.
26. CANVAS- CANagliflozin cardiovascular Assessment Study. NCT01032629. Available: https://clinicaltrials.gov/ct2/show/NCT01032629?term=Canvas&rank=1 (accessed July 21 2016).
27. Center for Drug Evaluation and Research. Canagliflozin: Summary Review Available: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000SumR.pdf (accessed July 21 2016).
27a. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, et al. CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Jun 12.
28. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58). NCT01730534. Available: https://clinicaltrials.gov/ct2/show/NCT01730534?term=DECLARE+and+dapagliflozin&rank=1 (accessed July 21, 2016).
29. Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease, The VERTIS CV Study (MK-8835-004). NCT01986881. Available: https://clinicaltrials.gov/ct2/show/NCT01986881?term=Ertugliflozin+and+cardiovascular&rank=1 (accessed July 21 2016).
30. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012 Jul 26;367(4):319-28.
31. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Arch Intern Med. 1997 Jan 27;157(2):181-8.
32. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977- 86.
33. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care. 1999 Jan;22(1):99-111.
34. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.
34a. Marso SP, McGuire DK, Zinman Bet al. DEVOTE Study Group. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med. 2017 Jun 12.
35. Rodríguez-Gutiérrez R, Montori VM. Glycemic Control for Patients With Type 2 Diabetes Mellitus: Our Evolving Faith in the Face of Evidence. Circ Cardiovasc Qual Outcomes. 2016 Sep;9(5):504-12.

References: Weight

1. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care. 2002 Oct;25(10):1737-43.
2. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O,Skrha J, Smith U, Taton J; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.
3.Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. Diabetes Care. 1998 Oct;21(10):1720-5.
4. Rosenstock J, Hassman DR, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N, Hale PM; Repaglinide Versus Nateglinide Comparison Study Group. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. Diabetes Care. 2004 Jun;27(6):1265-70.
5. GlucoNorm ® (repaglinide tablets) Product Monograph. Novo Nordisk Canada Inc. ON, Canada. June 3, 2015
6. Starlix® (nateglinide tablets) Product Monograph. Novartis Pharmaceuticals Canada Inc. QB, Canada. June 10, 2011

6. Richard KR, Shelburne JS, Kirk JK. Tolerability of dipeptidyl peptidase-4 inhibitors: a review. Clin Ther. 2011 Nov;33(11):1609-29. doi:10.1016/j.clinthera.2011.09.028. Epub 2011 Nov 8.
7. Canadian Diabetes Association 2013 Clinical. Practice *Guidelines* for the Prevention and Management of Diabetes in Canada. Can J *Diabetes* 2013;37(suppl 1), pg S126-8.
8. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.
9. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35.
10. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007 Jan;61(1):171-80.
11. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ. 2012 Jan 10;344:d7771. doi:10.1136/bmj.d7771.
12. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee on behalf of the LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jun 13.
13. Edwards KL, Minze MG. Dulaglutide: an evidence-based review of its potential in the treatment of type 2 diabetes. Core Evid. 2015 Jan 9;10:11-21.
14. Scheen AJ. SGLT2 Inhibitors: Benefit/Risk Balance. Curr Diab Rep. 2016 Oct;16(10):92.
15. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol. 2014 Oct;70(10):1149-58.
16. Stenlöf K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, Tong C, Canovatchel W, Meininger G. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin. 2014 Feb;30(2):163-75.
17. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159:262–74.
18. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.
19. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.
20. Canadian Optimal Medication Prescribing & Utilization Service (**COMPUS**), 2008; Current Topics, Diabetes: http://cadth.ca/index.php/en/compus/current-topics/-dm1 (www.cadth.ca)
{Long-acting IAs: Metaanalysis of Clinical Outcomes: http://cadth.ca/media/compus/reports/compus_Long-Acting-Insulin-Analogs-Report_Clinical-Outcomes.pdf }
{Rapid Acting IAs: Metaanalysis of Clinical Outcomes: http://cadth.ca/media/compus/reports/compus_Rapid-Acting-Insulin-Analogues-Report_Clinical=Outcomes.pdf }
{Optimal Therapy Recommendations for Prescribing and Use of Insulin Analogues: http://cadth.ca/media/pdf/compus_IA_OT_rec_report.pdf Final Report: January 2009}
{Grade Evidence Profiles of Long and Rapid Acting Insulin Analogues: http://cadth.ca/media/compus/reports/compus_GRADE-REPORT.pdf }

References: HF/Edema

1. Canadian Diabetes Association 2013 Clinical. Practice *Guidelines* for the Prevention and Management of Diabetes in Canada. Can J *Diabetes* 2013;37(suppl 1), pg S126-8.
2. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jørgensen CH, Lange T, Abildstrøm SZ, Schramm TK, Vaag A, Køber L, Torp-Pedersen C, Gislason GH. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010 Dec;53(12):2546-53.
3. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2560-72.
4.Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care. 2002 Oct;25(10):1737-43.
5. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.
6. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes(RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 20;373(9681):2125-35.
7. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105.
8.Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. Diabetes Care. 1998 Oct;21(10):1720-5.
9. GlucoNorm ® (repaglinide tablets) Product Monograph. Novo Nordisk Canada Inc. ON, Canada. June 3, 2015
10. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.
11. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; SAVOR-TIMI 53 Steering Committee and Investigators. Heart Failure, Saxagliptin, and Diabetes Mellitus: Observations from the SAVOR-TIMI 53 Randomized Trial. Circulation. 2015 Oct 13;132(15):e198.
12. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35.
13. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015 May 23;385(9982):2067-76.
14. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42.
15. European Society of Cardiology Press Office. New TECOS analysis adds heart failure data for sitagliptin. http://www.escardio.org/The-ESC/Press-Office/Press-releases/Last-5-years/new-tecos-analysis-adds-heart-failure-data-for-sitagliptin (accessed July 16 2016).
16. Barry AR, Turgeon RD. DPP-4 Inhibitors: The Seinfeld of Oral Antihyperglycemics. Can J Hosp Pharm. 2016 May-Jun;69(3):253-4.
17. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Available: http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm (accessed July 16 2016).

18. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee on behalf of the LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jun 13.
19. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015 Dec 3;373(23):2247-57.
20. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.
21. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012 Jul 26;367(4):319-28.
22. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Arch Intern Med. 1997 Jan 27;157(2):181-8.

References: Other

1. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O,Skrha J, Smith U, Taton J; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.
2. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes(RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 20;373(9681):2125-35.
3. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105.
4. Manufacturers of Some Diabetes Drugs to Strengthen Warning on Heart Failure Risk-Companies Will Include Boxed Warning on Drug Label. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108966.htm (accessed July 21 2016).
5. Updated labelling for diabetes drug ACTOS and risk of heart failure. Available: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/13269a-eng.php (accessed July 21 2016).
Information for Healthcare Professionals Rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl). Available: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143406.htm#2007_7 (accessed July 21 2016).
6. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR; PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf. 2009;32(3):187-202.
7. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care. 2002 Oct;25(10):1737-43.
8. Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with ACTOSO (pioglitazone HOI) Tablets for Type 2 Diabetes Mellitus.
Available:http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153896.pdf (accessed July 21 2016).
9. Clinical Trial Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with Avandia® (rosiglitazone maleate) Tablets for Type 2 Diabetes Mellitus. Available:
http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153903.pdf (accessed July 21 2016).
10. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med. 2012 Jul 9;172(13):1005-11.
11. Ambrosius WT, Danis RP, Goff DC Jr, Greven CM, Gerstein HC, Cohen RM, Riddle MC, Miller ME, Buse JB, Bonds DE, Peterson KA, Rosenberg YD, Perdue LH, Esser BA, Seaquist LA, Felicetta JV, Chew EY; ACCORD Study Group. Lack of association between thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye substudy. Arch Ophthalmol. 2010 Mar;128(3):312-8.
12. Association of Avandia (rosiglitazone) and Avandamet (rosiglitazone/metformin) with new onset and/or worsening of macular edema-for health professionals. Available: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14308a-eng.php (accessed July 21 2016).
13. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 2012 Jul;55(7):1953-62.
14. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, Vaughn DJ, Nessel L, Selby J, Strom BL. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011 Apr;34(4):916-22.
15. ACTOS (pioglitazone hydrochloride) – Potential association with bladder cancer. Available: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/15854a-eng.php (accessed July 21 2016).
16. FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm (accessed July 21 2016).
17. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105.
18. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007 Jun 14;356(24):2457-71. Epub 2007 May 21.
19. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care. 2002 Oct;25(10):1737-43.
20. AVANDIA, AVANDAMET, AVANDARYL-Important New Restrictions on the Use of Rosiglitazone Products Due to Information on Cardiovascular Related Events: For Health Professionals.
Available: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2010/14591a-eng.php (accessed July 21 2016).
21. FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. Available http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm (accessed July 21 2016).
22. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Available: http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm (accessed July 21 2016).
23. FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. Available: http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm (accessed July 21 2016).
24. FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes
http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm (accessed July 21 2016).
24a. Tkáč I, Raz I. Combined Analysis of Three Large Interventional Trials With Gliptins Indicates Increased Incidence of Acute Pancreatitis in Patients With Type 2 Diabetes. Diabetes Care. 2017 Feb;40(2):284-286. doi: 10.2337/dc15-1707. Epub 2016 Sep 22.
25. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med. 2013 Apr 8;173(7):534-9.
26. Postmarket Drug Safety Information for Healthcare Professionals: Exenatide (marketed as Byetta)- 8/2008 update. Available: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713. htm (accessed July 21 2016).
27. Postmarket Drug Safety Information for Healthcare Professionals: Acute pancreatitis and sitagliptin (marketed as Januvia and Jaumet) Available:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htmhttp://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm (accessed July 21 2016).
28. Canadian Adverse Reaction Newsletter: Incretin-based therapies and the risk of pancreatic cancer. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htmIncretin-based therapies and the risk of pancreatic cancer. Canadian Adverse Reaction Newsletter 2014;24;4. Available: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v24n4-eng.php (accessed July 21 2016).
29. Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis. Available: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm (accessed July 12, 2016).
30. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. 2016 Apr;18(4):317-32.
31. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther Adv Endocrinol Metab. 2015 Feb;6(1):19-28.
32. Rosenstock J, Balas B, Charbonnel B et al. The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes. Diabetes Care 2013; 36: 498–504.
33. Blevins T, Pullman J, Malloy J etal. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; 96: 1301–1310.
34. Pratley RE, Nauck MA, Barnett AH etal. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately con- trolled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2: 289–297.
35. 31. Buse JB, Nauck M, Forst T et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381: 117–124.

36. Dungan KM, Povedano ST, Forst T etal. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 2014; 384: 1349–1357.
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). Available: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/sglt2-2-eng.php (accessed July 12, 2016).
38. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Available: http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm (accessed July 21 2016).
39. Summary Safety Review- SGLT2 Inhibitors INVOKANA (canagliflozin) and FORXIGA (dapagliflozin)- Evaluation of a Potential Risk of Acute Kidney Injury. Available: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/sglt2-eng.php (accessed July 21 2016).
40. FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Available: http://www.fda.gov/Drugs/DrugSafety/ucm505860.htm (accessed July 12, 2016).
41. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. Available: http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm (accessed July 21 2016).
42. FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. Available: http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm (accessed July 21 2016).
43. Drug safety update Canagliflozin (Invokana, Vokanamet): signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients. Avaliable: https://www.gov.uk/drug-safety-update/canagliflozin-invokana-vokanamet-signal-of-increased-risk-of-lower-extremity-amputations-observed-in-trial-in-high-cardiovascular-risk-patients (accessed July 21 2016).
44. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E,Sarigianni M, Matthews DR, Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013 Aug 20;159(4):262-74.
45. Lin HW, Tseng CH. A Review on the Relationship between SGLT2 Inhibitors and Cancer. Int J Endocrinol. 2014;2014:719578.
46. Faillie JL, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of Bile Duct and Gallbladder Diseases With the Use of Incretin-Based Drugs in Patients With Type 2 Diabetes Mellitus. JAMA Intern Med. 2016 Oct 1;176(10):1474-1481.