Type 2 Diabetes Mellitus: Cardiovascular Outcome Trials (CVOTs) of Newer Antihyperglycemic Agents

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	Trial Characteristics	Population Baseline	Glycemic Intervention (added to usual T2DM care)	Final A1c	Macrovascular Outcome Summary: 1° outcome: MACE {Composite of CV death, non-fatal MI or non-fatal stroke}	Macrovascular Outcome Summary: 2° outcome: Hosp. for Heart Failure (HHF)	Macrovascular Outcome Summary: 2° outcomes: All-cause death CV death
DPP4 Inhibitors	**TECOS** 2015 ~ 3 yrs; n= 14,671	Established CVD (100%); 12 yr hx DM; Age: 66 A1c=7.2%; eGFR<50 (9.4%)	**Sitagliptin 100mg (50mg eGFR <50) po once daily** vs placebo	Mean ↓0.29% vs placebo	MACE + UA: **Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	**NS**	**NS**: All-cause death **NS**: CV death
	SAVOR-TIMI 53 '13 ~ 2.1 yrs; n= 16,492	CVD (79%) **or** ↑CVD risk; 10 yr hx DM; Age: 65 A1c=8.0%; eGFR<50 (15.6%)	**Saxagliptin 5mg (2.5mg eGFR <50) po once daily** vs placebo See RxFiles Trial Summary	7.7% vs 7.9%	Superiority for efficacy: **NS**	**NNH= 143/2.1yrs**	**NS**: All-cause death **NS**: CV death
	CARMELINA 2019 ~ 2.2 yrs; n= 6,979	CVD (57%) **&/or** ↑ renal risk 15 yr hx DM; Age: 66 A1c=8.0%; eGFR<60 (74%)	**Linagliptin 5mg po once daily** vs placebo	Not reported	**Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	**NS**	**NS**: All-cause death **NS**: CV death
	CAROLINA 2019 ~ 6.3 yrs; n= 6,033	CVD (42%) **or** ↑CVD risk 6 yr hx DM; Age: 64 A1c=7.2%	**Linagliptin 5mg po once daily** vs glimepiride 1-4mg daily	No mean difference	**Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	**NS**	**NS**: All-cause death **NS**: CV death
	EXAMINE 2013 ~ 1.5 yrs n= 5,380	Recent hosp for ACS (MI/UA) 7 yr hx DM; Age: 61 A1c=8.0%; eGFR<60 (29%)	**Alogliptin 25mg (12.5mg eGFR <60) po once daily** vs placebo	7.7% vs 8.1%	**Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	Post hoc FDA '15 (HR 1.19; 0.90-1.58)	**NS**: All-cause death **NS**: CV death
SGLT2 Inhibitors	**EMPA-REG** 2015 ~ 3.1 yrs; n= 7,020	Established CVD (100%) 10 yr hx DM; Age: 63 A1c=8.0%; eGFR=74 mL/min HF (10%); eGFR <60 (26%)	**Empagliflozin 10mg or 25mg po once daily** vs placebo *10mg same benefit as 25mg See RxFiles Trial Summary	mean ↓0.24% vs placebo	**Non-inferiority for safety: P<0.001 Superiority for efficacy: NNT = 63/3.1 yrs**	**NNT= 71/3.1 yrs**	All cause death: **NNT = 39/3.1 yrs** CV death: **NNT = 46/3.1 yrs**
	CANVAS 2017 ~ 3.6 yrs n= 10,142	CVD (66%) **or** ↑CVD risk 13.5 yr hx DM; Age: 63 A1c=8.2%; eGFR=77 mL/min HF (14%); eGFR <60 (20%)	**Canagliflozin 100mg or 300mg po once daily** vs placebo	mean ↓0.58% vs placebo	**Non-inferiority for safety: P<0.001 Superiority for efficacy: NNT = ~220/yr**	*Exploratory:** HR: 0.67 (0.52-0.87)	**NS**: All-cause death **NS**: CV death
	DECLARE-TIMI 2019 ~ 4.2 yrs n= 17,160	CVD (41%) **or** ↑CVD risk 11 yr hx DM; Age: 64 A1c=8.3%; eGFR=85 mL/min HF (10%); eGFR <60 (7%)	**Dapagliflozin 10mg po once daily** vs placebo See RxFiles DECLARE-TIMI Trial Summary	mean ↓0.42% vs placebo	Co-primary outcome: MACE **Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	Co-primary outcome: HHF **or** CV Death **NNT = 112/4.2 yrs** *Exploratory:** **NNT=125/4.2yrs**	**NS**: All-cause death **NS**: CV death
	CREDENCE 2019 n=4,401; ~2.6 yrs; **Population:** CVD (50%); 15.8 yr hx DM; Age: 63; A1c=8.3%; eGFR = 56 mL/min; HF (15%); eGFR <60 (60%) **Canagliflozin 100mg po once daily** vs placebo; **1° renal outcome** (ESRD, ↑SCr & renal or CV death): **NNT=23**/2.6 yrs; See RxFiles CREDENCE Trial Summary						
	DAPA-HF 2019 n=4,744; ~1.5 yrs; **Population:** NYHA Class II (67%), III (32%), IV (1%) and ↓EF ≤40%; T2DM (45%); previous HHF (47%); Age: 66; eGFR = 66mL/min **Dapagliflozin 10mg po once daily** vs placebo; **1° outcome- worsening HF (hosp. or need for IV HF therapy) or CV death: NNT=21**/1.5 yr; See RxFiles Trial Summary						
	VERTIS-CV Estimated completion 2020 **Population**: T2DM & established CVD; **Ertugliflozin 5mg or 15mg po once daily** vs placebo added to usual care; **1° endpoint**: MACE						
	Ongoing RCTs: **EMPEROR-Preserved & -Reduced** 2020 (HF ± T2DM); **EMPA-KIDNEY** 2022 (CKD ± T2DM); **Dapa-CKD** 11/20 (CKD ± T2DM)						
GLP1 Agonists	**EXSCEL** 2017 ~ 3.2 yrs n= 14,752	CVD (73%) **or** ↑CVD risk 12 yr hx DM; Age: 62 A1c=8.0%; eGFR=76 mL/min	**Exenatide ER 2mg SC once weekly** vs placebo	mean ↓0.53% vs placebo	**Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	**NS**	**NS**: All-cause death **NS**: CV death
	LEADER 2016 ~ 3.8 yrs n= 9,340	{CVD **or** CKD} (81%) **or** ↑CVD risk 13 yr hx DM; Age: 64 A1c=8.7%; eGFR<60 (23%)	**Liraglutide 1.8mg SC once daily** vs placebo See RxFiles LEADER Trial Summary	mean ↓0.40% vs placebo	**Non-inferiority for safety: P<0.001 Superiority for efficacy: NNT= 53/3.8yrs**	**NS**	All cause death: **NNT= 72/3.8 yrs** CV death: **NNT= 77/3.8 yrs**
	REWIND 2019 ~ 5.4 yrs n= 9,901	CVD (32%) **or** ↑CVD risk 10 yr hx DM; Age: 66 A1c=7.2%; eGFR=75mL/min HF=8.5%; eGFR<60 (22%)	**Dulaglutide 1.5mg SC once weekly** vs placebo	mean ↓0.60% vs placebo	**Superiority for efficacy: NNT= 72/5.4yrs**	**NS**	**NS**: All-cause death **NS**: CV death
	SUSTAIN-6 2016 ~ 2.1 yrs n= 3297	{CVD **or** CKD}(83%) **or** ↑CVD risk 14 yr hx DM; Age: 65 A1c=8.7%; eGFR<60 (29%)	**Semaglutide 0.5mg or 1mg SC once weekly** vs placebo	7.6% (0.5mg) & 7.3% (1mg) vs 8.3%	**Non-inferiority for safety: P<0.001 Superiority for efficacy: NNT= 44/2.1yrs**	**NS**	**NS**: All-cause death **NS**: CV death
	PIONEER-6 2019 ~ 1.3 yrs n= 3183	{CVD **or** CKD}(85%) **or** ↑CVD risk 15 yr hx DM; Age: 66 A1c=8.2%; eGFR=74mL/min	**Semaglutide 14mg po once daily** vs placebo	mean ↓1.0% vs ↓0.3% placebo	**Non-inferiority for safety: P<0.001** Not powered to test superiority	**NS**	*Exploratory*: All-cause death: **NNT= 72/1.3yrs**
	ELIXA 2015 ~ 2.1 yrs n= 6068	Recent hosp for ACS (MI/UA) 9 yr hx DM; Age: 60 A1c=7.7%; eGFR=76mL/min	**Lixisenatide 20mcg SC once daily** vs placebo	mean ↓0.27% vs placebo	MACE + UA: **Non-inferiority for safety: P<0.001** Superiority for efficacy: **NS**	**NS**	**NS**: All-cause death **NS**: CV death
	Ongoing RCTs: Exenatide mini-pump implant **FREEDOM CVO** (completed to show non-inferiority but not yet published), albiglutide (D/C) **HARMONY OUTCOMES**						
	*Exploratory 2° endpoints: 1° endpoint was not significant, therefore secondary endpoints are exploratory results only as they are not powered to test statistical significance						

Summary of RCT Evidence

Health Canada Approvals, Renal Outcomes

HC Approval	↓ MACE	↓ CV Death
Empagliflozin	X	✓T2DM + CVD
Canagliflozin	✓T2DM + CVD	X

Cardiovascular outcome summary: Zelniker et al 2019

Reduced MACE (HR 0.89) and CV Death (HR 0.84), effect only seen in patients with established CVD.

- Additional trials & head to head comparisons are needed as only 1 RCT per drug available for meta-analysis and CVD risk for patient populations at baseline variable.

HHF outcomes summary:

DAPA-HF: beneficial 1° endpoint outcomes for HF (see left). Meta-analysis suggests likely class effect (HR 0.69).Zelniker '19

Renal outcome summary:

Reduced progression of kidney disease (HR 0.55) in patients with and without established CVD. Zelniker et al 2019

- Less benefit in those with severe kidney disease

CREDENCE: first RCT to study renal outcomes as 1° endpoint

HC Approval	↓ MACE	↓ CV Death
Liraglutide	X	✓T2DM + CVD

Cardiovascular summary:

MACE superiority (lira-, dula- & sema-) was driven by a reduction in atherosclerotic events (MI & stroke).

- Most data from high CV risk patients except REWIND

Reduced MACE (HR 0.88), effect only seen in patients with established CVD (HR 0.87). Zelniker et al 2019

HHF summary:

- Incretin-based NS effect on HHF.

Microvascular summary: (No RCTs with this as 1° endpoint)

- Sema ↑ retinopathy: **NNH=83**/2.1 yrs SUSTAIN-6, FOCUS ongoing

Possible reno-protective class effect, however results exploratory (2° endpoints, short duration & minimal A1c separation):

- Lira- 2° renal endpoint: **NNT=67**/3.8yrs LEADER
- Sema- 2° renal endpoint: **NNT=43**/2.1 yrs SUSTAIN-6
- Dula- 2° microvascular (eye or renal): **NNT=45**/5.4yrs REWIND
- Meta-analysis: ↓progress of kidney dx HR 0.82 (0.75-0.89) Zelniker et al 2019

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