

SUPPLEMENTARY DATA

Supplementary Table S1. Ongoing CVOTs

Trial	Intervention	Main Inclusion Criteria	Follow-Up (years)	Primary Endpoint	Key Secondary Endpoints	Year Started/ Expected Completion
CAROLINA (44) (n = 6,072)	Linagliptin/ glimepiride	Type 2 diabetes and pre-existing CVD or CV risk factors or age ≥ 70 years	8	3-point MACE	4-point MACE	2010/2019
CARMELINA (45) (n = 7003)	Linagliptin/ placebo	Type 2 diabetes and high CV risk (previous CVD and albuminuria, and/or proteinuria and renal compromise)	4.5	3-point MACE	Renal composite	2013/2017
CREDENCE (46) (n = 4,464)	Canagliflozin/ placebo	Type 2 diabetes and stage 2 or 3 CKD + macroalbuminuria	5.5	Composite of ESRD, doubling of creatinine, or renal/CV death	Composite of CV death or HF hospitalization	2014/2019
DECLARE-TIMI 58 (47) (n = 17,276)	Dapagliflozin/ placebo	Type 2 diabetes and high risk for CV events	6	3-point MACE; composite of CV death or HF hospitalization	Renal composite	2013/2019
VERTIS CV (48) (n = 8,000)	Ertugliflozin/ placebo	Type 2 diabetes and preexisting vascular disease	6.1	3-point MACE	4-point MACE; renal composite; composite of CV death or HF hospitalization	2013/2019
Dapa-HF (49) (n = 4,500)	Dapagliflozin/ placebo	Chronic HF and reduced ejection fraction	3	Composite of CV death, HF hospitalization, or urgent HF visit	Composite of CV death or HF hospitalization; renal composite	2017/2019
Dapa-CKD (50) (n = 4,000)	Dapagliflozin/ placebo	CKD (eGFR ≥ 25 and ≤ 75 mL/min/1.73 m ² by CKD-EPI formula) + macroalbuminuria	4	Composite of $\geq 50\%$ sustained decline in eGFR or reaching ESRD, CV death, or renal death	Renal composite; composite of CV death and HF hospitalization; all-cause mortality	2017/2020
EMPEROR-Reduced (51) (n = 2,850)	Empagliflozin/ placebo	Chronic HF and reduced ejection fraction	3.2	Composite of CV death or HF hospitalization	First or recurrent HF hospitalization; eGFR slope of change from baseline; sustained reduction of eGFR;	2017/2020

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					CV death; all-cause mortality	
EMPEROR-Preserved (52) (n = 4,126)	Empagliflozin/ placebo	Chronic HF and preserved ejection fraction	3.2	Composite of CV death or HF hospitalization	First or recurrent HF hospitalization; eGFR slope of change from baseline; sustained reduction of eGFR; CV death; all-cause mortality	2017/2020
FREEDOM-CVO (53)* (n = 4,156)	Exenatide continuous delivery/ placebo	Type 2 diabetes and coronary, cerebrovascular or peripheral artery disease	2 years	4-point MACE	Not specified	2013/2016
REWIND (54) (n = 9,901)	Dulaglutide/ placebo	Type 2 diabetes and preexisting vascular disease or ≥ 2 CV risk factors	6.5	3-point MACE	Composite of retinal and renal disease; hospitalization for unstable angina; HF hospitalization or urgent visit; all-cause mortality	2011/2018
HARMONY Outcomes (55) (n = 9,400)	Albiglutide/ placebo	Type 2 diabetes and established CVD	3–5 years	3-point MACE	Expanded MACE, including urgent revascularization for unstable angina; composite of CV death or HF hospitalization	2015/2018
PIONEER 6 (56) (n = 3,176)	Oral semaglutide/ placebo	Type 2 diabetes; existing CVD if age ≥ 50 years or ≥ 1 CV risk factor if ≥ 60 years	1.6	3-point MACE	Expanded MACE including hospitalization for unstable angina or HF; composite of all- cause mortality, nonfatal MI, and nonfatal stroke	2017/2018

*At the time of writing, this study had ended, and a new drug application had been submitted to the FDA, but full results were not yet published. CKD, chronic kidney disease; CKD-EPI, *Chronic Kidney Disease Epidemiology Collaboration*; ER, extended release;

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Supplementary Table S2. CVOTs Not Initiated as a Direct Result of the 2008 FDA Guidance

	DEVOTE (57) (n = 7,637)	ACE (58,61) (n = 6,522)	IRIS (39) (n = 3,876)
Intervention	Degludec/glargine	Acarbose/placebo	Pioglitazone/placebo
Main inclusion criteria	Type 2 diabetes; age ≥ 50 years + history of CVD and/or CKD; age ≥ 60 years + ≥ 1 CV risk factors	CHD and IGT (conducted in China)	Insulin resistance but not diabetes + ischemic stroke or TIA in 6 months before randomization
A1C inclusion criteria (%)	≥ 7.0 or < 7.0 + 20 units basal insulin/day	NA	NA
Mean age (years)	65	64.3	65.3
BMI (kg/m ²)	33.6	25.4	30
Diabetes duration (years)	16.4	NA	NA
Events planned/observed	633/681	728/949	—/403
Median follow-up (years)	1.99	5	4.8
Statin use (%)	79	93	82.5
Prior CVD/CHF (%)	83/—	100/3.7	—*
Baseline A1C/A1C change (%)	8.4/−0.9 (between-group treatment different of 0.01)	5.9/−0.07	5.8/—
Year started/reported	2013/2017	2009/2017	2005/2016
Primary outcome†	3-point MACE 0.91 (0.78–1.06)	5-point MACE (3-point MACE + hospitalization for HF or unstable angina) 0.98 (0.86–1.11)	Composite of fatal and nonfatal stroke and MI 0.76 (0.62–0.93)
Key secondary outcome†	Expanded MACE (3-point MACE plus hospitalization for unstable angina) 0.92 (0.80–1.05)	3-point MACE 0.95 (0.81–1.11)	Stroke; ACS; composite of stroke, MI, and HF leading to hospitalization or death
CV death†	0.96 (0.76–1.21)	0.89 (0.71–1.11)	—
MI†,‡	0.85 (0.68–1.06)	1.12 (0.87–1.46)	—
Stroke†,‡	0.90 (0.65–1.23)	0.97 (0.70–1.33)	0.82 (0.61–1.10)
HF hospitalization†	—	0.89 (0.63–1.24)	—§
Unstable angina hospitalization†	0.95 (0.68–1.31)	1.02 (0.82–1.26)	—
All-cause mortality†	0.91 (0.76–1.11)	0.98 (0.81–1.19)	0.93 (0.73–1.17)
Worsening nephropathy†	1.08 (0.88–1.32)	—	—

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*Data for overall CVD not reported; previous coronary artery disease was reported to be 12%, and previous stroke (required for inclusion) was 100%.

†Outcomes reported as HR (95% CI)

‡Reported as nonfatal events only in DEVOTE and as nonfatal and fatal events in ACE and IRIS.

§Adjudicated HF leading to death or hospitalization was 2.6% with pioglitazone compared to 2.2% with placebo.

Bold type indicates statistical significance; —, not assessed/reported; CHF, congestive heart failure; NA, not applicable.