Supplementary Material Table 1: Trials design and key inclusion criteria

Trial	Drug and class	Key Inclusion Criteria
TD2		
EMPA-REG OUTCOME[3]	Empagliflozin SGLT2i	• T2D and ≥18 years old • HbA1c o≥7.0% and ≤10% and ≥12 weeks anti-diabetic background therapy or HbA1c ≥7.0% and ≤9.0% for drug-naïve patients • Established ASCVD: prior MI, CAD, stroke, UA or occlusive PAD • BMI ≤45 kg/m^2
CANVAS[4]	Canagliflozin SGLT2i	• T2D • HbA1c ≥7% and ≤10.5% who are drug-naïve or pre-treated with any background therapy • ≥30 years old with established ASCVD: prior MI, CAD, stroke, UA or occlusive PAD **or** • ≥50 years old without established ASCVD and ≥2 of the following risk factors: duration of T2D ≥ 0 years, SBP>140 mmHg on ≥1 anti-hypertensive drug, current cigarette smoker, micro- or macro-albuminuria, HDL-C <39 mg/dl • Postmenopausal women
DECLARE-TIMI 58[5]	Dapagliflozin SGLT2i	• T2D • ≥40 years old with established ASCVD: prior MI, CAD, stroke, UA or occlusive PAD **or** • Men >55 years old and women >60 years old without established ASCVD and ≥1 of the following risk factors: dyslipidemia (LDL-C >130 mg/dl within last year or on LLT), hypertension (BP >140/90 mmHg or on anti-hypertensive therapy), current cigarette smokers (≥1 year)
SCORED*[9]	Sotagliflozin SGLT2i and SGLT1i	• T2D and HbA1c ≥7% (53 mmol/mol) • CKD defined by eGFR ≥25 and ≤60 ml/min/1.73 m^2 (MDRD) • ≥18 years old with ≥1 of the major CV risk factors: HHF during previous 2 years, LVEF≤40%, LVH, coronary artery calcium score ≥300 Agatston Units, NT-pro-BNP ≥400 pg/ml, TnT-hs >15.0 pg/ml in men and >10.0 pg/ml in women, CRP-hs >3 mg/l, UACR ≥300 mg/g **or** • ≥55 years old with no major but with ≥2 minor CV risk factors: BMI ≥35 kg/m^2, dyslipidemia (LDL-C >130 mg/dl or HDL-C <40 mg/dl in men or <50 mg/dl in women on LLT), currently smoking tobacco, coronary artery calcium score >100 <300 Agatston Units, UACR ≥30 mg/g <300 mg/g, resistant hypertension (BP >140/90 mmHg on anti-hypertensive therapy), family history of premature CAD
LEADER[12]	Liraglutide GLP1-RA	• T2D and HbA1c ≥7% drug-naïve or pre-treated with any background antidiabetic therapy • ≥50 years old with previous CAD, or cerebrovascular disease, or PAD, or CKD stage 3 or greater, or chronic HF (NYHA II–III) **or** • ≥60 years old with ≥1 CV risk factor: microalbuminuria or proteinuria, hypertension and LVH, left ventricular systolic or diastolic dysfunction, or ankle-brachial index <0.9
REWIND[14]	Dulaglutide GLP1-RA	• T2D and HbA1c ≥6.5% and ≤9.5% drug-naïve or pre-treated with any background anti-diabetic therapy • ≥50 years old with established ASCVD: prior MI, CAD, stroke, UA or occlusive PAD **or** • ≥55 years old and ≥1 of the following: history of MI, >50% vascular stenosis, ankle-brachial index <0.9, eGFR<60 ml/minute/1.73m^2, hypertension and LVH, microalbuminuria or macroalbuminuria **or**

		• ≥60 years old and ≥2 CV risk factors as follows: current tobacco use, LDL-C ≥130 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women or triglycerides ≥200 mg/dl, hypertension on ≥1 anti-hypertensive drug or untreated BP ≥140/95 mmHg, waist-to-hip ratio >1.0 for men and >0.8 for women • BMI ≥23 kg/m^2
SUSTAIN-6[15]	Semaglutide GLP1-RA	• T2D and HbA1c ≥7% drug-naïve or pre-treated with any background antidiabetic therapy • ≥50 years old with previous CV disease, or cerebrovascular disease, or PAD, or CKD stage 3 or greater, or chronic HF (NYHA II-III) **or** • ≥60 years old with ≥1 CV risk factor: microalbuminuria or proteinuria, hypertension and LVH, left ventricular systolic or diastolic dysfunction, or ankle-brachial index <0.9
PREVENTION		
FOURIER[18]	Evolocumab PCSK9i	• ≥40 ≤85 years old • History of ASCVD: prior MI, non-haemorrhagic stroke, PAD • ≥1 major risk factor as follows: type 1 or 2 diabetes, ≥65 years old, MI or stroke within 6 months, ≥1 previous MI or stroke excluding qualifying event, current daily cigarette smoking, symptomatic PAD if eligible by MI or stroke **or** • ≥2 minor risk factors as follows: non-MI-related coronary revascularisation, residual CAD (stenosis ≥40% in ≥2 large arteries), HDL-C <40 mg/dl in men and <50 mg/dl in women, CRP-hs >2.0 mg/l, LDL-C ≥ 130 mg/dl or non-HDL-C≥ 160 mg/dl, metabolic syndrome • LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dl after ≥2 weeks of stable maximum-tolerated LLT • Triglycerides ≤400 mg/dl • eGFR ≥30 ml/min/1.73 m^2
ODYSSEY-OUTCOME[19]	Alirocumab PCSK9i	• ≥40 years old • Hospitalisation for ACS within 16 weeks • LDL-C ≥70 mg/dl, or non-HDL-C ≥100 mg/l or apolipoprotein B ≥80 mg/dl after ≥2 weeks stable maximum tolerated LLT • Triglyceride ≤400 mg/dl
ORION 10 and 11[22]	Inclisiran	• ≥18 years old • History ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, T2D, familial hypercholesterolaemia, 10-year risk of a CV event by Framingham Risk Score or equivalent with target LDL-C <100 mg/dl) • LDL-C ≥70 mg/dl and ASCVD or ≥100 mg/dl for ASCVD-risk equivalent group after ≥30 days of stable maximum-tolerated LLT • Triglycerides <400 mg/dl • eGFR ≥30 ml/min/1.73 m^2
REDUCE-IT[23]	Icosapent ethyl	• ≥45 years old and established ASCVD: prior MI, CAD, stroke, hospitalised for NSTEMI or PAD or carotid artery disease **or** • ≥50 years old with diabetes and ≥1 of the following: men ≥55 years old and women ≥65 years old, current cigarette smoker (or previous smoking within 3 months), resistant hypertension on anti-hypertensive medication, HDL-C ≤40 mg/dl for men or ≤50 mg/dl for women, CRP-hs >3.0 mg/l, CKD>30 and <60 ml/min, retinopathy, micro- or macroalbuminuria, ankle-brachial index <0.9. • Triglycerides ≥150 ≤499 mg/Dl and LDL-C >40 ≤100 mg/dl after ≥ 4 weeks of stable maximum-tolerated LLT

CLEAR HARMONY[26]	Bempedoic acid	• ≥18 years old • Established ASCD: prior MI, CAD, stroke, UA or occlusive PAD **and/or** • Heterozygous familial hypercholesterolaemia • LDL-C ≥70 mg/dl therapies after ≥4 weeks of stable maximum-tolerated LLT
CHRONIC HFrEF		
PARADIGM-HF[37]	Sacubitril/ Valsartan ARNI	• ≥18 years old • With or without T2D • NYHA II–IV for 6 months • LVEF ≤35% (≤40% in the original protocol) within last 6 months • BNP ≥150 or NT-pro-BNP ≥600 pg/ml or ≥100 or ≥400 pg/ml if HHF within the last 12 months • Optimized and stable (≥4 weeks) background SoC HFrEF treatment
DAPA-HF[38]	Dapagliflozin SGLT2i	• ≥18 years old • With or without T2D • NYHA II-IV for ≥ 2 months • LVEF ≤40% within last 12 months • NT-pro-BNP ≥ 600 pg/ml in sinus rhythm (or≥ 400 pg/ml if HHF within 12 months or ≥ 900 pg/ml if AF) • eGFR ≥30 ml/min/1.73 m^2 • Optimised and stable (≥4 weeks) background SoC HFrEF treatment
EMPEROR-REDUCED[41]	Empagliflozin SGLT2i	• **≥**18 years old • With or without T2D • NYHA II–IV for ≥ 3 months • LVEF ≤40% within last 12 months • NT-pro-BNP 3 different thresholds for 3 cut-offs of LVEF (higher in AF) without HHF, ≥600 pg/ml if HHF (≥1,200 pg/ml if also AF). • eGFR ≥20 ml/min/1.73 m^2 • Optimised and stable (≥4 weeks) background SoC HFrEF treatment
VICTORIA[70]	Vericiguat	• **≥**18 years old • With or without T2D • Chronic HF, NYHA II–IV before HF decompensation • LVEF <45% within last 12 months • BNP ≥300 pg/ml or NT-pro-BNP ≥1.000 pg/ml in sinus rhythm (BNP ≥500 pg/ml or NT-pro-BNP ≥1,600 pg/ml if AF) • Prior and recent HHF within 6 months or outpatient IV diuretic therapy for HF within 3 months before randomisation • Clinically stable (SBP ≥100 mmHg and no IV diuretics for 24h, no nitrates, no inotropes) • eGFR >15 ml/min/1.73m^2

		• OMT and stable (≥4 weeks) background SoC HFrEF treatment
GALACTIC-HF[76]	Omecamtiv Mecarbil	• ≥18 years ≤85 years old • With or without T2D • Chronic HF, NYHA II–IV for ≥4 weeks • A previous HHF or access to ED for HF within 12 months, or AHF (currently hospitalised for HF) • LVEF <35% within last 12 months • Clinically stable (no mechanical support or inotropes or IV drugs in the previous 12h, no mechanical ventilation) • BNP ≥125 pg/ml or NT-pro-BNP ≥400 pg/ml in sinus rhythm (≥375 pg/ml or ≥1200 pg/ml respectively if AF) • eGFR ≥20 ml/min/1.73m^2 • Optimised and stable (≥4 weeks) background SoC HFrEF treatment
CHRONIC HFmrEF and HFpEF		
PARAGON-HF[63]	Sacubitril/ Valsartan ARNI	• ≥50 years old • LVEF ≥45% by echocardiography within 6 months • Current NYHA II–IV and need of diuretics for ≥30 days • Structural heart disease evidenced ≥1 of the following at echocardiography: left atrium enlargement, LVH • HHF within 9 months **and/or** • NT-pro-BNP >300 pg/ml in sinus rhythm (>900 pg/ml if AF) • eGFR ≥30 ml/min/1.73 m^2
EMPEROR-PRESERVED[50]	Empagliflozin SGLT2i	• ≥18 years old • With or without T2D • NYHA II–IV for ≥3 months • LVEF >40% before enrolment (no prior LVEF ≤40%) • NT-pro-BNP >300 pg/ml in sinus rhythm (>900 pg/ml if AF) • Structural heart disease within 6 months (increase in left atrial size or left ventricular mass) on echocardiography or previous HHF within 12 months • eGFR ≥20 ml/min/1.73 m^2 • On stable dose of oral diuretics for 1week prior to randomisation
ACUTE HF		
SOLOIST-WHF[44]	Sotaglifozin SGLT2i and SGLT1i	• Currently hospitalised for AHF or urgent HF visit to ED, HF unit, or infusion center for WHF associated with intravascular volume overload • On treatment with intravenous diuretics • T2D

		• HF for ≥3 months before screening • Hemodynamically stable (SBP ≥100 mmHg, not receiving IV inotropes or vasodilators – except for nitrates – 48 h before randomisation, not on mechanical ventilation or O2-therapy 24 h before randomization) • BNP ≥ 150 pg/ml or NT-pro-BNP ≥600 pg/ml in sinus rhythm (or ≥ 1800 pg/ml if AF) • eGFR ≥30 ml/min/1.73 m^2 • No LVEF cut-off (HFrEF patients should be on ACEi/ARB/ARNI, BB, MRA as per local guidelines)
CHRONIC KIDNEY DISEASE		
CREDENCE[51]	Canaglifozin SGLT2i	• **≥**30 years old • CKD defined by eGFR ≥30 and <90 ml/min/1.73 m^2 (CKD-EPI) • T2D • HbA1c ≥6.5% and ≤12.0% • UACR >300 and < 5,000 mg/g • Optimised and stable (≥4 weeks) background SoC CKD treatment (ACEi/ARB)
DAPA-CKD[52]	Dapaglifozin SGLT2i	• ≥18 years old • CKD defined by eGFR ≥25 and ≤75 ml/min/1.73 m^2 (CKD-EPI) • With and without T2D • UACR ≥200 and ≤5,000 mg/g • Optimised and stable (≥4 weeks) background SoC CKD treatment (ACEi/ARB)

*Despite SCORED systematically studied a population with T2DM and CKD (as CREDENCE), we listed it among the trial dedicated to T2DM and not to CKD because the main end-points were the same as the other trials dedicated to prevention, differently from CREDENCE and DAPA-CKD.

ACS = acute coronary syndrome; ARNI = angiotensin receptor neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; BNP = brain natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; CRP-hs: = high-sensitivity C-reactive protein; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = cardiovascular; ED = emergency department; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalisation for heart failure; LDL-C: low-density lipoprotein cholesterol; LLT = lipid lowering treatment; LVH = left ventricular hypertrophy; MDRD = modification of diet in renal disease; NYHA = New York Heart Association; NT-pro-BNP = N-terminal pro-BNP; PAD = peripheral artery disease; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors; SBP = systolic blood pressure; SGLT2i = sodium-glucose co-transporter type 2 inhibitors; SoC = standard of care; TnT-hs = high-sensitivity troponin T; T2D: type 2 diabetes; UA = unstable angina; UACR = urinary albumin-to-creatinine ratio