TRIAL	Inclusion Criteria	STUDY GROUPS	MEDIAN FOLLOW-UP	ALL- CAUSE DEATH	CV DEATH	HHF	RENAL EFFECTS	OUTCOMES
SGLT2 inhibitors								
	Phase III Cardiovascular Outcome Trials							
EMPA-REG OUTCOME [1]	Age ≥18 years; Chronic HF, NHYA class II/III/IV; Preserved LVEF (EF > 40%); HF hospitalisation within 12 months; NT-proBNP ≥300 pg/ml without AF, >900 pg/ml with AF. Structural heart disease within 6 months or documented HF hospitalisation within 12 months. Stable dose of oral diuretics, if prescribed.	Empagliflozin (n=4,687) versus placebo (n=2,333) Mean patient age: 63.1 years Percentage female: 28%	3.1 years	3.8% versus 5.1%, p < 0.01	3.7% versus 5.9%, p < 0.001	2.7% versus 4.1%, p = 0.002	Incident or worsening nephropathy for empagliflozin versus placebo: 12.7% versus 18.8%, HR 0.61, 95% CI 0.53-0.70; p < 0.001. Doubling of serum creatinine: 1.5% versus 2.6%, p < 0.001. Progression to macroalbuminuria: 11.2% versus 16.2%, p < 0.001. Initiation of renal replacement therapy: 0.3% versus 0.6%, p = 0.04.	CV death, nonfatal MI, or stroke for empagliflozin versus placebo: 10.5% versus 12.1%, hazard ratio (HR) 0.86, 95% confidence interval 0.74-0.99, p < 0.001 for noninferiority; p = 0.04 for superiority.
CANVAS Program [2]	Patients with T2DM and high cardiovascular risk; ≥30 years of age and history of symptomatic atherosclerotic cardiovascular disease, or ≥50 years of age and 2+ of the following: T2DM duration >10 years, systolic BP >140 mm Hg on antihypertensive therapy, current smoking, albuminuria, or high-density lipoprotein cholesterol < 38.7 mg/dl.	Canagliflozin (n=5,795) versus placebo (n=4,347) Mean patient age: 63 years Percentage female: 36%	2.4 years	/	/	/	Progression of albuminuria: 89.4 participants per 1.000 patient-years versus 128.7 participants per 1,000 patient-years (p < 0.05).	Incidence of cardiovascular death, myocardial infarction, or stroke, occurred in 26.9 participants per 1,000 patient-years of the canagliflozin group versus 31.5 participants per 1.000 patient-years of the placebo group (p = 0.02 for superiority, p < 0.001 for noninferiority).

DECLARE-TIMI 58 [3]	Age ≥ 40 years and established CV disease or presence of multiple-risk factor.	Dapagliflozin (n=8,582) versus placebo (n=8,578) Mean patient age: 64.0 years Percentage female: 37%	4.2 years	6.2% versus 6.6%, p > 0.05		2.5% versus 3.3%, p < 0.005	> 40% decrease in GFR, end-stage renal disease, or death due to renal or CV causes: 4.3% versus 5.6%, p < 0.05	MACE for dapagliflozin versus placebo: 8.8% versus 9.4%, hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.84-1.03, p < 0.001 for noninferiority; p = 0.17 for superiority.
EMPEROR-PRESERVED [4]	Age ≥18 years; Chronic HF, NHYA functional class II/III/IV; Preserved LVEF (EF >40%); HF hospitalisation within 12 months; NT-proBNP ≥300 pg/ml without AF, >900 pg/ml with AF; Structural heart disease within 6 months or documented HF hospitalisation within 12 months; Stable dose of oral diuretics, if prescribed.	Empagliflozin (n=2,997) versus placebo (n=2,991) Mean patient age: 72 years Percentage female: 45%	26.2 months	13.4% versus 14.2% (HR 0.92, 95% CI 0.77-1.10, p > 0.05)	7.3% versus 8.2% (HR 0.91, 95% CI 0.76-1.09)	8.6% versus 11.8% (HR 0.71, 95% CI 0.60-0.83)	Change in mean eGFR slope/year: -1.25 versus -2.62 (p < 0.001).	CV death or HF hospitalisation, for empagliflozin versus placebo, was 13.8% versus 17.1% (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.69-0.90, p < 0.001).
DELIVER [5]	Men and women age ≥40 years; Documented diagnosis of symptomatic heart failure (NYHA class II–IV) at enrolment, and a medical history of typical symptoms/signs of heart failure ≥6 weeks before enrolment with at least intermittent need for diuretic treatment (requiring recurrent intermittent dosing); LVEF >40% and evidence of structural heart disease	Dapaglifozin 10 mg (3,131) versus Placebo (3,132) Mean patient age: 71.7 years Percentage female: 44%	2.3 years	CV death or HF hospitalisation: 4.9% versus 5.8%, p = 0.005	7.4% versus 8.3% (HR 0.88, 95% CI 0.74-1.05)	11.8% versus 14.5% (HR 0.79, 95% CI 0.69-0.91)	3.2% experienced a deterioration in eGFR to < 25 at least once during follow-up; the risk of the primary outcome was lower with dapagliflozin compared with placebo both among patients who did (HR 0.53, 95% CI 0.33-0.83) and did not (HR 0.78, 95% CI 0.72-0.86) experience renal function deterioration.	CV death or worsening HF for dapagliflozin versus placebo, was: 16.4% versus 19.5% (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.73-0.92, p < 0.001). Benefit is primarily driven by a reduction in HF hospitalisations, not mortality.
	Phase III HF Trials							
SOLOIST-WHF [6]	Acute HF; Treatment with diuretics; Stabilised, off oxygen, transitioned to oral diuretics; BNP ≥150 pg/ml (≥450 pg/ml if atrial fibrillation) or N-	Sotagliflozin (n=608) versus placebo (n=614)	9 months	/	CV deaths 10.6 versus 12.5 events/100 patient-years (p	Total hospitalisations: ≥1 hospitalisation for sotagliflozin	Change in eGFR: -0.34 versus -0.18 (p = 0.78).	CV death, hospitalisation for HF, or urgent visit for HF for sotagliflozin versus placebo, was 70 versus 98

	terminal pro–BNP ≥600 pg/ml (≥1800 pg/ml if atrial fibrillation); T2DM.	Mean patient age: 69 years Percentage female: 34%			= 0.36)	versus placebo: 38.5% versus 41.4% (p = 0.3); >1 hospitalisation: 16.3% versus 22.1% (p = 0.009).		events/100 patient-years (hazard ratio 0.67, 95% confidence interval [CI] 0.52-0.85, p = 0.0009).
Renin-Angiotensin System Inhibitors (RASI): ACEi, ARB and MRA								
CHARM-Preserved [7]	Age >18 years with symptomatic CHF corresponding to NHYA class II-IV, LVEF >40%, history of hospitalisation for a cardiac reason.	Candesartan (n=1514, target dose 32 mg once daily) versus placebo (n=1509) Mean patient age: 67 years Female: 40%	36.6 months (mean)	/	CV death did not differ between groups (170 versus 170); HR 0.99, p=0.918.	HF hospitalisations trended lower in the Candesartan group (HR 0.85, p=0.072; adjusted p=0.047).	/	CV death or admission to hospital for CHF: 0.89 [95% CI 0·77–1·03], p=0·118; covariate adjusted 0,86 [0·74–1·0], p=0·051.
TOPCAT [8]	Symptomatic CHF within 12 months, age ≥50 years, LVEF ≥45%, controlled systolic BP; serum potassium <5.0 mmol/L, stratified based on CHF hospitalisation within 12 months (stratum I), or elevated BNP/proBNP within 60 days (stratum II).	Spironolactone (n= 1.722, initiated at a dose of 15 mg/day and uptitrated to a maximum of 45 mg daily during the first 4 months) versus placebo (n = 1.723). Mean patient age: 69 years Percentage female: 52%	6 years (mean 3.3 years).	/	CV mortality was similar between the two groups. 9.3% versus 10.2%. p = 0.35.	CHF hospitalisations were lower in the Spironolactone group (12.0% versus 14.2%, p = 0.042)	Hyperkalaemia (18.7% versus 9.1%, p < 0.001) and renal failure were both significantly higher in the spironolactone arm.	The primary endpoint was similar between the spironolactone and placebo arms (18.6% versus 20.4%, hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.77-1.04, p = 0.14).
PARAMOUNT [9]	At least 40 years of age, LVEF ≥45%, NHYA class II-III, NT-proBNP >400 pg/ml, and an estimated glomerular filtration rate ≥30 with potassium ≤5.2 mmol/L.	Sacubitril/valsartan (n=149) titrated to 200 mg twice daily versus valsartan (n=152) titrated to 160 mg twice daily. Mean patient age: 71 years. Percentage female: 59%.	36 weeks	/	/	/	/	The change in NT-proBNP was greater with LCZ696 therapy compared with valsartan (ratio of change, 0.77 [0.64-0.92], p = 0.005) at 12 weeks, but was not significantly greater at 36 weeks (ratio of change, 0.88 [0.65-1.09], p = 0.20).
PARAGON-HF [10]	At least 50 years of age, NHYA class II-IV), LVEF ≥ 45%, elevated level of natriuretic peptides, structural heart disease (left atrial enlargement or LV hypertrophy).	Sacubitril/valsartan 97/103 mg twice daily (n = 2,419) versus valsartan 160 mg twice daily (n = 2.403). Percentage female:	35 months	/	The adjusted rate ratio for primary endpoint by subgroups, LVEF below the median value of 57% displayed a	/	There was less decline in renal function among the sacubitril/valsartan group: 1.4% versus 2.7% in the valsartan group (p < 0.05).	CV deaths or hospitalisations for HF was 12.8 events per 100 patient-years in the Sacubitril/valsartan group versus 14.6 events per 100 patient-years in the valsartan group (p =

		52% Percentage with diabetes: 44%			significant reduction of RR (HR 0.78, CI 0.64–0.95), consistent with PARADIGM HF trial.			not significant). Females displayed a better outcome (923/2479; RR 0.73, CI 0.59–0.90) than males (980/2317; RR 1.03, CI 0.85–1.25).
GLP1 receptor agonists								
LEADER [11]	**inclusion criteria**: DM2; Age ≥50 years and concomitant CV, cerebrovascular, or peripheral vascular disease or chronic renal failure or chronic heart failure OR age ≥60 years and other specified risk factors of vascular disease (microalbuminuria/proteinuria, hypertension, left ventricular [LV] hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9); Glycated haemoglobin ≥7.0%; Antidiabetic drug-naive or treated with one or more oral antidiabetic drugs or treated with human NPH insulin or long-acting insulin analogue or premixed insulin, alone or in combination with oral drugs.	Liraglutide (4668) versus placebo (4672). Mean patient age: 64 years Percentage female: 46%	51 months	8.2% versus 9.6%, p = 0.02	CV death: 4.7% versus 6.0%, p = 0.007.	4.7% versus 5.3%, p = 0.14	5.7% versus 7.2%, p = 0.003	CV death, nonfatal myocardial infarction (MI), or stroke for liraglutide versus placebo: 13.0% versus 14.9%, hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.78-0.97, p < 0.001 for noninferiority; p = 0.01 for superiority
STEP- HFpEF [12]	BMI ≥30.0 kg/m^2; NYHA Class II-IV; LVEF ≥ 45 %	Semaglutide 2.4 mg (529) versus placebo (529). Median patient age: 69 years Percentage female: 56.1%	5 weeks	/	/	1 versus 12 events (p < 0.05)	/	Change from baseline to week 52 in KCCQ-CSS: 16.6 versus 8.7 (p < 0.001), and percentage change in body weight: -13.3 versus -2.6 (p < 0.001).
STEP-HFpEF DM [13]	BMI greater than or equal to 30.0 kg/m^2; NYHA Class II-IV; LVEF ≥ 45 %; Diagnosed with T2D greater than or equal to 90 days prior to the day of screening; HbA1c of below or equal to 10.0% as measured at the screening visit.	Semaglutide 2.4 mg (617) versus placebo (617)	5 weeks	*Ongoing trial, no data still available*				

Supplementary Table 1. Important trials on RAASI , SGLT2i and GLP1 in HFpEF described in this review. NHYA = New York Heart Association; NTproBNP: *N-terminal pro–B-type natriuretic peptide*; *AF = atrial fibrillation; HF = heart failure; T2DM = type 2 diabetes mellitus*; *BP = blood pressure*; *AKI = acute kidney infection; CV = cardiovascular; MACE = major adverse cardiac events; BMI = body mass index; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalisation for heart failure.*

Source: Gori M, D'Elia E, Sciatti E, Senni M. Sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction: rationale for and practical use of a successful therapy. *Card Fail Rev* 2022;8:e26. https://doi.org/10.15420/cfr.2022.04; PMID: 35865457.

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