Table S1. RCTs on the use of mineralocorticoid receptor antagonists (MRAs)in HFpEF.

Trial	Design Study	Patients	Population Characteristics	LVEF	Groups of Treatment	Primary Endpoint (PE)	Results
			RANDOMIZED CLINICAL TRIALS				
							Adj. Mean Diff; (95% CI)
Aldo-DHF [125]	Multicenter, randomized, placebo-controlled, double-blinded trial	422	• HF NYHA II-III ambulatory	≥50%	Spironolactone 25 mg (n= 213) vs. placebo (n = 209)	Changes at 12 months FU E/e' andVO2 peak	−1.5; −2.0–0.9; p< 0.001
							HR; (95% CI)
TOPCAT-trial [98]	Multicenter, international, randomized, double-blind, placebo-controlled trial	3445	• HF NYHA II-III	≥45%		Composite ofCV mortality, aborted cardiac arrest, or HHF	0.89; 0.77–1.04; p = 0.14
			ONGOING CLINICAL TRIALS				
FINEARTS-HF (NCT04435626)	Multicenter, randomized, double-blind, parallel-group, placebo-controlled trial	6000	• HF NYHA class II-IV Ambulatory or hospitalized • On diuretics • Structural heart abnormalities: ○ LAD ≥3.8 cm ○ LAA ≥ 20 cm^2 ○ LAVI >30 mL/m^2 ○ LVMI ≥115 g/m^2 (♂)/95 g/m^2 (♀) ○ Septal thickness or posterior wall thickness ≥1.1 cm • NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL in sinus rhythm • NT-proBNP ≥900 pg/mL or BNP ≥300 pg/mL in AF	≥40%	Finerenone vs placebo	Rate of CV death and HF events (HHF or urgent HF visit)	Ongoing
MIRACLE (NCT04595370)	Phase-2b, randomized, double-blind, active-controlled, multicenterstudy		• HFNYHA II-III class • CKD with eGFR 20–60 mL/min/1.73 m^2	<60%	- Balcinrenone Dose A + dapagliflozin 10 mg - Balcinrenone Dose B + dapagliflozin 10 mg - Balcinrenone Dose C + dapagliflozin 10 mg - Dapagliflozin 10 m	Percent change from baseline in UACR at 12 weeks	Ongoing
SPIRIT-HF (NCT04727073)	Double-blind, randomized, placebo-controlled, parallel-group,interventional,phase-III study		• Symptomatic HF NYHA II-IV class	Mid-range (40–49%) or preserved (≥50%)	Spironolactone (25–50 mg) vs. placebo	Composite of recurrent HHF and CV death	Ongoing

SPIRRIT-HFpEF (NCT02901184)	Registry-randomized clinical trial	• Stable HF NYHA Class II-IV • NT-proBNP >300 ng/L (or BNP >100 pg/mL) in sinus rhythm • NT-proBNP >750 ng/L (or BNP >250 pg/mL) in AF • NT-proBNP >1200 ng/L (or BNP >400 pg/mL) within the last 12 months, even if most recent value is lower. • Regular use of LD	≥40%	Spironolactone vs. placebo	Primary outcome CV death or time to HHF	Ongoing

CV: cardiovascular; HHF heart failure hospitalizations; NYHA: New York Heart Association; HR: hazard ratio; CI: confidence interval; LAD: left atrial diameter; LAA: left atrial area; LAVI:left atrial volume index; LVMI: left ventricular mass index; NT-proBNP: n-terminal prohormone B-type natriuretic peptide; BNP: B-type natriuretic peptide;; AF: atrial fibrillation; CKD: chronic kidney disease; UACR: urine albumin-to-creatinine ratio; and LD: loop diuretics.

Table S2. RCTs on SGLT2i use in HFpEF.

	N° pt	DM	Follow-Up (Median)	Age	Sex (% Female)	LVEF*	Treatment	Primary Outcome	HR; (95% CI)
EMPEROR-PRESERVED [51] NCT03057951	5988	with or without DM	26.2 months	71.8	44.6%	54%	Empagliflozin	• CV deaths • HHF	0.79; (0.69–0.90I) *p* <0.001
PRESERVED-HF [133] NCT03030235	324	with or without DM	3.0 years	70.0	57%	60%	Dapagliflozin	• KCCQ-CS at 12 weeks after treatment initiation	68.6; (66.2, 71.0) *p* 0.001
DELIVER [52] NCT03619213.	6263		2.3 year	71.8	43.6%	54%	Dapagliflozin	• Composite of worsening HF or CV death*	0.82; (0.73–0.92) *p* <0.001
SOLOIST-WHF [134] NCT03521934.	1222	with DM and recent HF worsening	9.0 months	70	32.6%	20% with LVEF >50%	Sotagliflozin	• Total number of CV deaths HHF • HF urgent visits	0.67 (0.52–0.85); *p* <0.001
EMPERIAL-PRESERVED NCT03448406 [137]	315	with or without DM	12 weeks	73.5	43.2	53.1	Empagliflozin	• -6MWTD change in week 12	*p* =0.37
CHIEF-HF NCT04252287 [138]	476	with or without DM	2 weeks	63.4 ± 13.3	45%	50%(60%)	Canagliflozin (100 mg)	• Change in KCCQ TSS at 12 weeks	100 mg of canagliflozin or placebo
VERTIS CV NCT01986881 [139]	8246	with DM	3.5 years	64.4	30%	1007 patients with LVEF >45%)	Ertugliflozin	• CV death, nonfatal MI, nonfatal stroke	0.97 (0.85–1.11) *p*<0.001
SCORED [134].	10,584	with DM, CKD**	16 months	72	40%	>45%	Sotagliflozin	• risk of the composite of CV deaths, HHF	0.95 (0.86–1.05)
DECLARED-TIMI-58 [140]	17,160	with DM and CVD or multiple CVD risk factors	4.2 years	72	37%	1316 patients with 55%	dapagliflozin	• Primary safety outcome ○ Non-inferiority to placebo with respect to MACE	• Primary safety outcome: *p* <0.001 for noninferiority • Primary efficacy outcomes:

MUSCAT-HF NCT03315143 [141]	160 • Luseogliflozin(82) • Voglibose (83)	DM and HF	12 weeks			>45%	Luseogliflozin or voglibose	• Primary efficacy outcomes: ○ MACE: CV death, MI, or ischemic stroke ○ CV death or HHF • Difference in change in BNP from baseline to 12 weeks between the patients receiving luseogliflozin and those receivingvoglibose	• **MACE** 0.93; 0.84–1.03; p =0.17 • **CV death or HHF** 0.83; 0.73–0.95; p =0.005) 0.93; 0.78–1.10; p =0.26
CANDLE NCT03315143 [142]	253	DM and stable HF	24 weeks	68	25%	≥50%(71%)	canagliflozin 100 mg or glimepiride	Percentage change (post/pre −1) from baseline in NT-proBNP at week 24.	0.48; −0.13–1.59, p = 0.226

LVEF: left ventricle ejection fraction; DM: diabetes mellitus; CHD: chronic kidney disease;HHF heart failurehospitalizations; MACE:major adverse cardiovascular events; BNP: brain natriuretic peptide; and KCCQ TSS:Kansas City Cardiomyopathy Questionnaire Total Symptom Score.