SUPPLEMENTARY TABLE

Supplementary Table 1: Landmark studies demonstrating efficacy of angiotensin receptor/neprilysin inhibition (ARNI) in patients with heart failure and kidney disease.

Trial	Patients	intervention	Result of primary outcome	Secondary outcomes	Exclusion
PARADIGM-HF trial[44,59]	8,442 patients with NYHA class II-IV HF and LVEF ≤40%	Sacubitril + Valsartan (97 mg + 103 mg) twice daily vs enalapril 10 mg twice daily	Reduction in composite outcome of CV-death or hospitalization for HF by 20 % compared to enalapril monotherapy.	**Patients with HF:** QoL markers improved, death from any cause was lower in ARNI group. **Patients with CKD:** ARNI improved percentage decrease in eGFR annually compared to enalapril monotherapy.	eGFR < 30 ml/min/1.73 m^2, 25% decrease in eGFR between screening and randomization, hyperkalemia >5.2 mmol/l, symptomatic hypotension
PARAGON-HF trail[58,61]	4,822 patients with NYHA	Sacubitril +	Reduction in cumulative risk of CV-	**Patients with HF:**	Same as above

	class II-IV with LVEF >45%, elevated natriuretic peptides, and structural heart disease	Valsartan (97 mg + 103 mg) twice daily vs valsartan 160 mg twice daily	death HF hospitalizations by 13% compared to valsartan monotherapy, although results were statistically non-significant	QoL score and NYHA class from baseline have improved. **Patients with CKD:** ARNI reduced death from renal failure, progression to ESRD and > 50% decrease in eGFR annually by 50% compared to valsartan monotherapy	
UK HARP-III trial.[61]	414 CKD Patients with eGFR 20 to 60 ml/min/1.73 m^2	Sacubitril + Valsartan (97 mg + 103 mg) twice daily vs Irbesartan	Both treatment groups had similar effect on kidney function and albuminuria, ARNI use was not associated with serious or non-serious adverse events and hyperkalemia	ARNI treatment arm had an additional effect of lowering systolic and diastolic blood pressure by 5.4mm and 2.1mm respectively; levels of troponin I and N terminal-pro BNP were reduced by 16% and 18%	Hyperkalemia >5.5, ACS, stroke or TIA with in previous 3 months, Patients with kidney transplant or nephrotic syndrome or chronic liver disease

		300 mg once daily	compared to irbesartan group	respectively compared to irbesartan monotherapy	
Lee et al.[62]	501 patients with LVEF≤ 35% and anuric ESRD on HD or PD for 6 months	Retrospective single center study: 23 patients were switched to ARNI from ACEI or ARB	ARNI use resulted in significant improvement in LVEF from 29.7% to 40.8% in patients with ESRD	Cardiac biomarkers: highly sensitive troponin T and soluble suppression of tumorogenicity 2 levels were reduced significantly after treatment with ARNI during the study period	Patients on cardiac resynchronization therapy
Niu et al.[63]	49 patients with LVEF≤ 40 % and anuric	Sacubitril + Valsartan (27mg+26	ARNI treatment group had improvement in echocardiographic systolic parameters	ARNI treatment group had improvement in diastolic parameters compared to conventional treatment group.	Recent ACS and inadequate dialysis, CABG or coronary

	ESRD on HD or PD for 6 months	mg titrating to 97 mg + 103 mg) twice daily vs conventional therapy.	such as LVEF, LV end-systolic volume and LV internal diameter at end-systolic phase compared to conventional treatment group		angioplasty in the follow-up period.

Abbreviations: CKD-chronic kidney disease, CV-cardiovascular, eGFR-estimated glomerular filtration rate expressed in ml/min/1.73m^2, HF-heart failure, LVEF-left ventricular ejection fraction, QoL- quality of life, NYHA: New York Heart Association, UACR: Urine Albumin Creatinine Ratio, ACS: acute coronary syndrome, TIA: transient ischemic attack, ESRD: end stage renal disease, HD; hemodialysis, PD: peritoneal dialysis, CRT: cardiac resynchronization therapy, CABG: coronary artery bypass grafting.

Supplementary Table 2. Landmark studies evaluating efficacy of sodium glucose cotransporter-2 inhibitors in patients with heart failure or chronic kidney disease.

Trial	Patients	Intervention	Result of primary outcome	Secondary outcomes	Exclusion
EMPEROR Preserved[42]	5,988 patients with HF, NYHA classes II-IV and LVEF >40%	Empagliflozin 10 mg daily vs Placebo	Empagliflozin reduced the combined risk of CV-death or hospitalization for HF by 21 % compared to placebo	**Patients with HF:** QoL improved, NT-pro BNP levels improved, functional capacity improved, lower number of HF hospitalizations requiring intensive care, lower number of hospitalizations requiring a vasopressor or positive inotrope, and lower frequency of outpatient intensification of diuretics. **Patients with CKD:** Annual rate of decline in eGFR was lower with empagliflozin (-1.25) vs	Patients with recent CV events, heart transplant recipients, infiltrative or hypertrophic or obstructive cardiomyopathy, ICD or cardiac synchronization within 3 months, eGFR < 20 ml/min/1.73 m^2, or Hb<9 at screening.

				placebo (-2.62), also reduced CKD progression by 5%	
EMPEROR-Reduced[43]	3,730 HF patients with NYHA class II-IV and LVEF ≤40%	Empagliflozin 10 mg daily vs Placebo	Empagliflozin reduced the combined risk of CV-death or hospitalization for HF by 25%	**Patients with HF:** Lower number of HF hospitalizations by 31%, reduced all-cause death by 22%, and improvement in exercise capacity. **Patients with CKD:** Empagliflozin reduced CKD progression by 50%, HR: 0.50 (CI: 0.32-0.77)	Same as above.
DAPA-HF[45]	4,744 HF patients with NYHA class II-IV and LVEF ≤40%	Dapagliflozin 10 mg daily vs placebo	Dapagliflozin reduced the composite risk of CV-death or hospitalization/urgent care visit for HF by 26%	HF symptoms improved	Patients who had recent treatment with or unacceptable side effects associated with SGLT-2 inhibitors; type 1

					diabetics; eGFR <30 ml/min/1.73 m^2 BSA.
DELIVER[46]	6,263 patients with HF and LVEF >40%	Dapagliflozin 10 mg daily vs placebo	Dapagliflozin reduced the composite risk of CV-death or hospitalization/urgent care visit for HF by 18%	HF symptoms improved at 8 months from baseline	Type 1 diabetics, patients with eGFR < 25 ml/min/1.73 m^2, BMI >50 kg/m^2; Recent MI/ coronary revascularization, stroke/TIA, atrial fibrillation/flutter ablation; Infiltrative or hypertrophic obstructive or genetic cardiomyopathy; BMI >50 kg/m^2
SOLOIST-WHF[49]	1,222 diabetic patients hospitalized for	sotagliflozin 200-400	Sotagliflozin reduced the composite endpoint of CV-death or	HF symptoms, and QoL improved at week 12 and at week 28	HF class D, recent acute coronary syndrome, stroke, PCI or CABG

	worsening HF within the last 3 months	mg daily vs placebo	hospitalization/urgent care visit for HF by 33%		within 3 months; eGFR<30 ml/min/1.73 m^2; Infiltrative or hypertrophic obstructive cardiomyopathy
SCORED[47]	10,584 diabetic patients with CKD (eGFR 25-60) and CV risk	sotagliflozin 200-400 mg daily vs placebo	Sotagliflozin reduced the composite endpoint of CV-death or hospitalization/urgent care visit for HF by 26%	Lower number of HF hospitalizations, HR:0.67 (CI:0.55-0.82)	DKA or HHS in past 3 months; HF class D, planned coronary revascularization procedures, EP device/ mechanical support implantation or cardiac surgery after randomization. Allergic reaction to SGLT-2 inhibitor or sotagliflozin

CREDENCE [48]	4,401 diabetics with CKD (eGFR 30-90 and UACR 300-5,000) receiving a stable dose of ACE-I/ARB	Canagliflozin 100 mg daily vs placebo	Canagliflozin reduced the primary composite endpoint of CKD progression or CV-death by 30%	Empagliflozin reduced the risk of hospitalization for HF by 39%, reduced risk of CV-death or hospitalization for HF by 31%	Type 1 diabetics, history of DKA; Known non-diabetic renal disease; History of dialysis or kidney transplant or current immunosuppression for kidney disease
DAPA-CKD[50]	4,304 patients with CKD (eGFR 25-75 and UACR 200-5000	Dapagliflozin 10 mg daily vs placebo	Dapagliflozin reduced the primary composite outcome of CKD progression or CV-death by 39%	Dapagliflozin reduced the CV-death or hospitalization for HF by 29%, reduced all-cause mortality by 31%	type 1 diabetics, lupus nephritis, polycystic kidney disease, antineutrophilic cytoplasmic antibody-associated vasculitis; on immunotherapy, recent CV event

EMPA-KIDNEY[51]	6,609 patients with CKD (eGFR 20-45 or, with eGFR 45-90 + UACR ≥200) and receiving a stable dose of ACEi/ARB	Empagliflozin 10 mg daily vs placebo	Empagliflozin reduced the composite outcome of CKD progression or CV-death by 28%	Empagliflozin reduced all-cause hospitalization by 14%	Polycystic kidney disease, currently on/scheduled dialysis, functioning kidney transplant; Currently receiving SGLT-2 inhibitor or ACEi/ARB

Abbreviations: CKD-chronic kidney disease, CV-cardiovascular, eGFR-estimated glomerular filtration rate expressed in ml/min/1.73m^2, HF-heart failure, LVEF-left ventricular ejection fraction, QoL- quality of life, NT-peptide: N-teminal peptide, NYHA: New York Heart Association, UACR: Urine Albumin Creatinine Ratio.

Supplementary Table 3: Landmark studies demonstrating efficacy of GLP-1 agonists in chronic heart and kidney diseases.

Study	Patients	Intervention	Primary outcome	Secondary Outcome	Exclusion criteria
LEADER[52]	9,340 diabetics with high CV risk	Liraglutide 1.8 mg daily vs placebo	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke was reduced with treatment by 13%	All-cause death reduced by 15% and CKD progression reduced by 22%	Type 1 DM; Use of GLP-1 agonists, DPP-4 inhibitors, pramlintide or rapid acting insulin prior to screening; Family or personal history of medullary thyroid cancer or MEN-2; ACS or stroke/TIA within 14 days before screening; Current continuous renal replacement therapy
SUSTAIN-6[53]	3,297 diabetics with established	Semaglutide 0.5 mg-1 mg	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke	CKD onset or progression reduced by 36%	Treatment with DPP 4 inhibitor with in 30 days or with a GLP-1 agonists or

	CVD, HF, CKD stage 3-5, or with at least one CV risk factor	once weekly vs placebo	was reduced with treatment by 26%		insulin with in 90 days before screening; recent CV event; chronic dialysis
REWIND[54]	9,901 diabetics ≥50 years with prior CV event or with CV risk factor	Dulaglutide 1.5 mg weekly vs placebo	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke was reduced with treatment by 12%	Reduction in all-cause death by 15%, reduction in hospitalization for HF by 24%, reduction in CKD onset or progression by 15%	eGFR<15 ml/min/1.73 m^2 or on chronic dialysis at screening; Severe hyperglycemia, DKA in last years; recent CV event; Life expectancy < 1 year for any reason
EXSCEL[55]	14,752 diabetics	Exenatide 2mg weekly vs placebo	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke was non-inferior to placebo.	14% reduction in the risk of CKD onset or progression	Type 1 DM or DKA or > 2 hypoglycemia episodes in past; ESRD or eGFR <30 ml/min/1.73 m^2; Personal or family history of

					medullary thyroid cancer or MEN-2.
AMPLITUDE-0.[79]	4,076 Diabetics and with CVD or CKD with at least one CV risk factor.	Efpeglenatide 4 mg or 6 mg weekly subcutaneous injections vs placebo	The composite outcome of CV- death or non-fatal AMI or non-fatal stroke or death from undetermined causes was reduced with treatment by 27%	Efpeglenatide improved outcomes in a dose-response relationship and decrease in kidney function or microalbuminuria by 32%	Uncontrolled gastroparesis, reflux, prolonged nausea and vomiting, pancreatitis, severe retinal disease, eGFR < 25ml/min/m2 or use of GLP-1 receptor agonist or a DPP-4 inhibitor with in previous 3 months.

PIONEER 6 trial[75]	3,183 diabetics ≥50 years with CVD/CKD or, ≥60 years with CV risk factors	Semaglutide 14 mg oral once daily vs placebo	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke was non-inferior to placebo.	Reduction in HF readmissions and hospitalizations for unstable angina were not statistically significant	Use of GLP-1 agonists, DPP-4 inhibitors, pramlintide with in 90 days before screening, ESRD or eGFR <30 ml/min/1.73 m^2, recent CV event.
Heerspink et al.[77]	Post hoc analysis of SURPASS-4 trial: 2,002 diabetics with BMI>25 and CVD or risk factors	Tirzepatide 5 mg or 10 mg or 15 mg subcutaneous injection weekly vs titrated insulin glargine	Tirzepatide reduced risk of incident CKD with more pronounced renal benefits in subgroups with eGFR <60 (vs ≥60)	Tripeptide reduced the composite kidney endpoint of 40% decrease in eGFR from baseline, progression to ESRD, death from kidney failure or new onset macroalbuminuria by 42%.	Type 1 diabetes, history of acute or chronic pancreatitis, family or personal history of medullary thyroid cancer or MEN-2, recent CV event.

Abbreviations: AMI-acute myocardial infarction, BMI-body mass index in kg/m^2, CKD-chronic kidney disease, CV-cardiovascular, CVD-cardiovascular disease, HF-heart failure, HTN- hypertension, MEN- multiple endocrine neoplasm.

Supplementary Table 4: Landmark studies demonstrating efficacy of finerenone in chronic heart and kidney diseases.

Study	Patients	Intervention	Primary outcome	Secondary outcome	Exclusion criteria
FIDELIO-DKD trial.[85]	5734 diabetics with CKD (eGFR 25-60+ UACR: 30-300+ Diabetic retinopathy or eGFR 25-75 + UACR 300-5000)	Finerenone 10 mg or 20 mg once daily vs placebo	The composite outcome of death from renal causes, kidney failure and sustained decrease of at least 40% in eGFR from baseline was reduced with treatment by 18%.	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke or HF-hospitalization was reduced with treatment by 13% compared to placebo.	ACS, stroke or TIA with in the previous 30 days, severe hyperglycemia, uncontrolled hypertension, severe nondiabetic kidney disease, symptomatic hypotension, ESRD on dialysis or kidney transplant, chronic symptomatic HFrEF.
FIGARO-DKD trial.[86]	7437 diabetics with CKD (eGFR 25-90+ UACR: 30-300 or eGFR≥ 60 +	Finerenone 10 mg or 20 mg once daily vs placebo	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke or HF-hospitalization was reduced with treatment by 18%, majority of benefit	The composite outcome of death from renal causes, kidney failure and sustained decrease of at least 40% in eGFR from baseline was	same as above

	UACR 300-5000)		primarily driven by decrease in HF hospitalization by 29%.	reduced with treatment by 13%.	
The FIDELITY pooled analysis.[87]	13,026 diabetics with CKD at risk for HF.	Finerenone 10 mg or 20 mg once daily vs placebo	The composite outcome of CV-death, non-fatal AMI or non-fatal stroke or HF-hospitalization was reduced with treatment by 14% compared to placebo across the spectrum of CKD.	The composite outcome of death from renal causes, kidney failure and sustained decrease of at least 57% in eGFR from baseline was reduced with treatment by 23% compared to placebo.	Same as above

Abbreviations: ACS- acute coronary syndrome, AMI-acute myocardial infarction, eGFR-estimated glomerular filtration rate expressed in ml/min/1.73m^2, UACR: urinary albumin-creatinine ratio, CKD-chronic kidney disease, CV-cardiovascular, CVD-cardiovascular disease, ESRD- end stage renal disease, HF-heart failure, HTN- hypertension, HFrEF: Heart failure with reduced ejection fraction, TIA-transient ischemic attack.