SUPPLEMENTARY MATERIAL

Methods for supplementary data

We conducted a dedicated search that was specifically aimed at reviewing the original reports or secondary analyses from published randomized controlled clinical trials that investigated medical therapy in patients with HFrEF and reported cardiovascular (CV) outcomes, specifically all-cause mortality and the combined endpoint of CV death and/or HF rehospitalization (or worsening HF). The HFrEF drug classes and related trials (see Supplementary Figure 1) that were evaluated included the more conventional treatment options (angiotensin converting enzyme inhibitors (ACEi), Angiotensin II receptor blockers (ARB), Mineralocorticoid Receptor Antagonists (MRA), Beta-Blockers, Digoxin, Ivabradine and Hydralazine-IsosorbideDinitrate (H-ISDN)) supplemented with newer and more recently investigated HFrEF treatments (Sacubitril/Valsartan, Sodium-glucose co-transporter-2 inhibitors (SGLT2i), Omecamtiv Mecarbil and Vericiguat).

We evaluated clinical outcomes according to baseline eGFR/creatinine clearance if reported and reviewed interaction analyses based on subgroups of CKD in the original report. Additionally, we searched for individual renal substudies of included randomized clinical trials for the treatment effect according to different subgroups of CKD (according to KDOQI CKD classes (Stage 1 (eGFR >90 mL/min/1.73m^2), Stage 2 (eGFR 60-89 mL/min/1.73m^2), Stage 3A (eGFR 45-59 mL/min/1.73m^2), Stage 3B (eGFR 30-44 mL/min/1.73m^2), Stage 4 (eGFR 15-29 mL/min/1.73m^2), and Stage 5 (eGFR <15 mL/min/1.73m^2 or dialysis)) for different clinical outcomes. If data was missing from the published reports for a specific study or drug or analysis we contacted the authors to provide additional information if possible. Measures of relative risk were extracted from these reports, as well as crude event numbers in each treatment arm from which the absolute risk reduction (ARR) was calculated for the end of the study. From these data, different figures (Supplementary Figure 4-6) were constructed to visualize the effect sizes of all drug classes according to individual studies and different clinical outcomes.

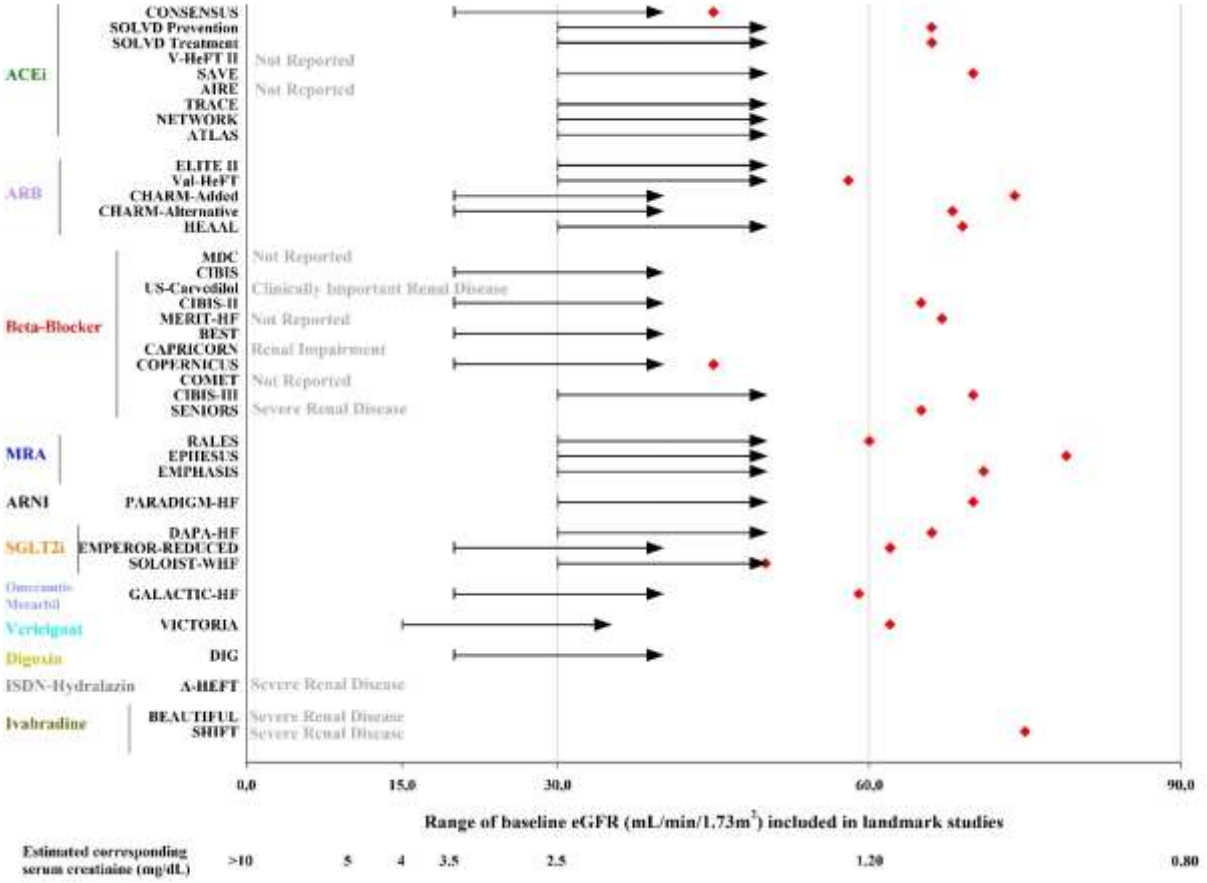
Supplementary Table 1. Renal function and electrolyte monitoring regimen of RCTs

Drug class	RCT (year)	Drug	Discontinuation	Downtitration/dose reduction	Restart	Renal function and electrolyte monitoring frequency
ACEi	CONSENSUS (1987)[20]	Enalapril 2.5mg, 10mg, 20mg or 40mg	NA	Symptoms of hypotension, other side effects	NA	Baseline, week 2,3, 6, 24
	SOLVD Treatment / Prevention (1991)[21,22]	Enalapril 5mg, 10g or 20mg	Significant hypotensive bout secondary to the active agent that cannot be controlled with other measures or if major changes in renal function are detected.	Symptomatic hypertension, angina, azotemia (increase in serum creatinine by 1.0 mg/dL or greater, not to exceed 4.0 mg/dL), hyperkalemia (serum potassium >5.5 mmol/L), proteinuria (appearance of two-plus protein in urine if previously absent or increase by two grades if already present).	As soon as possible in lower dose, preferably within 2 weeks	Baseline, week 2,4, 6, 8, Month 4, 8, 12 and every 4 months thereafter
	SAVE (1992)[38]	Captopril 6.25mg, 12.5mg, 25mg, 75mg or 150mg	NA	Marked, yet asymptomatic, reductions in blood pressure. Any adverse experience	NA	NA
	AIRE (1993)[39]	Ramipril 2,5mg, 5mg or 10mg	If refused or not tolerated by patient, if attending physician wished to use an open-label ACE inhibitor.	NA	NA	NA
	TRACE (1995)[40]	Trandolapril 1mg, 2mg, 4mg	NA	If patient did not tolerate high dose.	NA	NA
ARB	ValHeFT (2001)[24]	Valsartan 80mg, 160mg or 320mg	NA	Standing systolic blood pressure is <90 mmHg, serum creatinine level exceeds 2.0 mg/dL and is greater than 50% above baseline	NA	Baseline, week 2, 4, 6, Month 4, 6, 12 and every 6 months thereafter
	CHARM-Added [42](2003)	Candesartan 4mg, 8mg, 12mg, 16mg, 20mg, 24mg, 28mg or 32mg	No predefined absolute or relative cutoff for Hyperkalemia or plasma creatinine. Decision to reduce or discontinu study drug was left at the investigator discretion.		NA	Central: Baseline, week 6, Month 14 and 26 Local: Baseline, within 2 weeks of dose escalation or completion of dose titration and yearly thereafter
	CHARM-Alternative (2003)[43]					
	HEAAL (2009)[31]	Losartan 50mg or 150mg	NA	NA	NA	Baseline, Month 1, 4, 9, 12 and every 6 months thereafter
MRA	RALES (1999)[45]	Spironolactone 25mg or 50mg	Serious hyperkalemia (serum potassium >6.0	Development of hyperkalemia (serum potassium >5.5 mmol/L)	NA	Baseline, week 4, 8, 12, month 6, 12 and every 6

			mmol/L), serum creatinine of >4.0 mg/dL, intercurrent illness, or any condition in which such a course was deemed medically necessary to protect the patient's best interests			months thereafter
	EPHESUS (2003)[46]	Eplerenone 25mg or 50mg	Serious hyperkalemia (serum potassium >6.0 mmol/L)	Development of hyperkalemia (serum potassium >5.5 mmol/L)	If serum potassium concentration fell below 5.5 mmol/L	Baseline, 48 hours, week 1,4,5, 12 and every 3 months thereafter
	EMPHASIS-HF (2010)[47]	Eplerenone 25mg or 50mg	Serious hyperkalemia (serum potassium >6.0 mmol/L)	Development of hyperkalemia (serum potassium >5.5 mmol/L)	If potassium levels drop to <5.0 mmol/L	Potassium: Baseline, week 4, every 4 months thereafter Serum creatinine: Baseline, Month 5, 13 and every 5 months thereafter
BBL	US-Carvedilol (1996)[55]	Carvedilol 6.25mg, 12.5mg, 25mg, 50mg or 100mg	NA	Side effects that were thought to be related either to study drug itself	NA	NA
	CIBIS-II (1999)[59]	Bisoprolol 1.25mg, 2.50mg, 3.75mg, 5mg, 7.5mg or 10mg	In case of worsening chronic heart failure	Symptomatic bradycardia or hypotension or following adverse event or worsening chronic heart failure	Therapy may be resumed, if warranted, at one or two levels below the dose reached before discontinuation	NA
	MERIT-HF (1999)[58]	Metoprolol 12.5mg, 25mg, 50mg, 100mg or 200mg	According to judgment of investigator, intolerability of study drug	According to judgment of investigator, intolerability of study drug	According to judgment of investigator	No protocolized assessment of serum creatinine/potassium at follow up
	CAPRICORN (2001)[56]	Carvedilol 6.25mg, 12.5mg, 25mg, 50mg	Intolerability of study drug after dose-reduction	Intolerability of study drug, presence of adverse events, evidence of clinical heart failure, bradycardia (<50 bpm), systolic blood pressure <80 mmHg	NA	Safety laboratory tests at baseline, and every 6 months thereafter
	COPERNICUS (2001)[57]	Carvedilol 6.25mg, 12.5mg, 25mg, 50mg	Intolerability to lowest dose of study drug	Intolerability of study drug, presence of adverse events, evidence of clinical heart failure, bradycardia (<50 bpm), systolic blood pressure <80 mmHg	Investigators encouraged to rechallenge	NA
	BEST (2001)[66]	Bucindolol 3mg, 6.25mg, 12.5mg, 25mg, 50mg, 100mg, 200mg	At the discretion of the investigator, patients who develop worsening heart failure	At the discretion of the investigator, increase in heart failure symptoms, side effects of study medication such as impotence, dizziness, lightheadedness, nightmares	Encouraged as soon as the patient is clinically stable	Clinical Laboratory at Baseline, month 3 and 12

	SENIORS (2005)[60]	Nebivolol 1.25mg, 2.5mg, 5mg or 10mg	Depending on symptoms, possible side-effects, or at judgment of the local investigator	Depending on symptoms of intolerance (resting heart rate <50 bpm, systolic blood pressure <90 mmHg, drop in systolic blood pressure >30 mmHg on standing pressure, symptoms of postural hypertension or new symptoms of dizziness interfering with daily activities), possible side-effects, or at judgment of the local investigator	NA	Baseline, month 4, 6, 9, 12, 15, 24 and 30
ARNI	PARADIGM-HF (2014)[77]	Sacubitril/valsartan	Potassium >6.0 mmol/L immediately discontinue, potassium >5.5 and <6.0 mmol/L consider discontinuation	Potassium >5.3 but <5.5 mmol/L, potassium >5.5 and <6.0 mmol/L, Persisting symptomatic hypotension, clinically significant decrease in eGFR/increase in serum creatinine (eGFR decrease >40%, creatinine rises above 3mg/dL)	Every attempt should be made	Baseline, week 2, 4, Month 2, 4, 8, 12 and every 4 months thereafter
	PIONEER (2019)[81]	Sacubitril/valsartan	Pregnancy, any severe suspected drug related AE, angioedema	Depending on serum potassium, blood pressure, or eGFR	As soon as medically justified	Baseline, week 1, 2, 4, 8, 10, 12
SGLT2-i	DAPA-HF (2019)[82]	Dapagliflozin 5mg or 10mg	Diabetic ketoacidosis, pregnancy, use of other SGLT-2 or combined SGLT-1 inhibitors	Unexpected acute declines in eGFR, volume depletion/hypotension	Always encouraged	Baseline, week 2, Month 2, 4, 8, 12 and every 4th month thereafter
	EMPEROR-Reduced (2020)[83]	Empagliflozin 10mg	Diabetic ketoacidosis, pregnancy, use of other SGLT-2 or combined SGLT-1 inhibitors	Additional laboratory assessment if eGFR drops ≥40% or below 15 mL/min/1.73m2 (if eGFR ≥ 30 mL/min/1.73m2 at baseline) or below 10 mL/min/1.73m2 (if eGFR < 30 mL/min/1.73m2 at baseline)	Consider at every visit	Baseline, week 4, Month 3, 8, 12 and every 6 months thereafter
	SOLOIST-WHF (2020)[84]	Sotagliflozin 200mg or 400mg	Diabetic ketoacidosis, severe hypoglycemia, pregnancy, dialysis or renal transplantation, eGFR <15ml/min/1.73m2 (Twice measured), hospital admission for major surgical procedures, serious illness	Evidence of volume depletion, symptomatic hypotension (dizziness, lightheadedness), AEs intolerable to the patient (polyuria, nocturia), lower extremity complications (skin ulcers, infection, osteomyelitis, gangrene)	Early as possible	Baseline, week 2, Month 1, 4 and every 4 months thereafter

Supplementary Figure 1



Red diamond symbols show mean eGFR at baseline for the study population. The black arrow indicates the lower limit of inclusion and that there was no upper limit of eGFR for any trial. Abbreviations: ACEi: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin II Receptor Blocker, ARNI: Angiotensin Receptor blocker, Neprilysin Inhibitor, Beta-blocker: Beta-Blocker, CI: Confidence Interval, CV: Cardiovascular, eGFR: Estimated Glomerular Filtration Rate, H-ISDN: Hydralazine IsosorbideDinitrate, HR: Hazard Ratio, HF: Heart Failure, MRA: Mineralocorticoid Receptor Antagonist, SGLT2i: Sodium glucose co-transporter 2 inhibitor.

Study Acronyms

A-HEFT	African-American Heart Failure Trial
AIRE	Acute Infarction Ramipril Efficacy
ATLAS	Assessment of Treatment with Lisinopril and Survival
BEAUTIFUL	Morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction
BEST	Beta-Blocker Evaluation of Survival Trial
CAPRICORN	Carvedilol Post Infarct Survival Control in LV Dysfunction
CHARM-Added	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity Added trial
CHARM-Alternative	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity Alternative trial

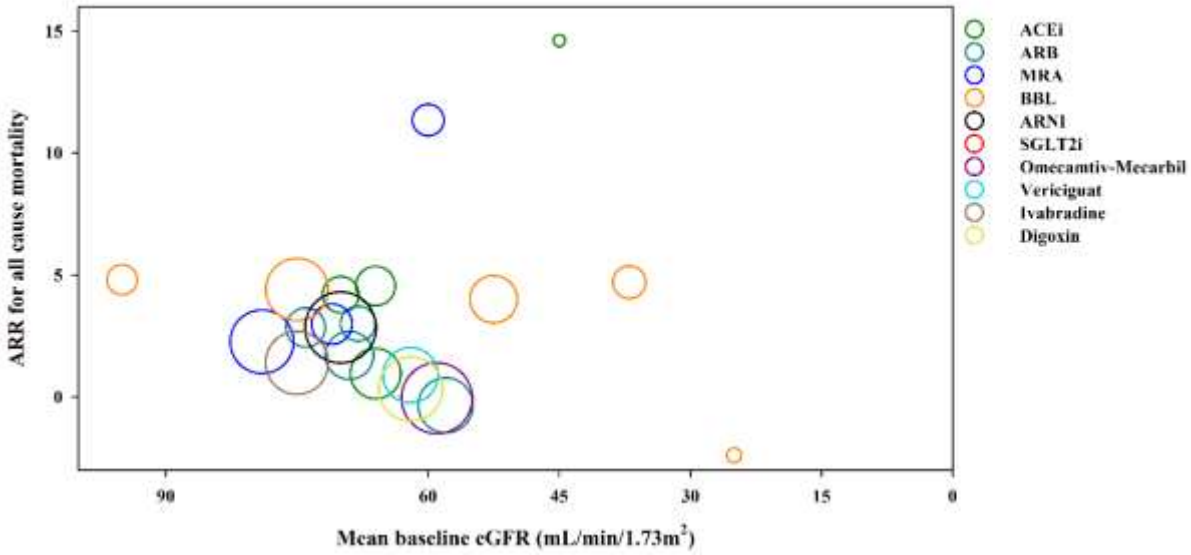
CIBIS	Cardiac Insufficiency Bisoprolol Study
CIBIS-II	Cardiac Insufficiency Bisoprolol Study II
COMET	Carvedilol Or Metoprolol European Trial
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure,
DIG	Digitalis Investigation Group
ELITE II	Evaluation of Losartan In The Elderly study II
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction
EMPHASIS	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
GALACTIC-HF	Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure
HEAAL	Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan
MDC	Metoprolol in Dilated Cardiomyopathy
MERIT-HF	Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure
PARADIGM-HF	Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure
RALES	Randomized Aldactone Evaluation Study
SAVE	Survival And Ventricular Enlargement
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure
SHIFT	Systolic Heart failure treatment with the If inhibitor ivabradine Trial
SOLOIST-WHF	The effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
SOLVD Prevention	Studies of Left Ventricular Dysfunction Prevention
SOLVD Treatment	Studies of Left Ventricular Dysfunction Treatment
TRACE	Trandolapril Cardiac Evaluation
US-Carvedilol	United States Carvedilol
Val-HeFT	Valsartan Heart Failure Trial
V-HEFT II	Vasodilator Heart Failure Trial II
VICTORIA	Vericiguat in the HFrEF population was the VerICguaT Global Study in Subjects with HFrEF

Supplementary Table 2. Summary of clinical interpretation of changes in renal function indices during initiation or uptitration of HFrEF drug classes

<table>
<tr><th colspan="5">Changes in renal function indices</th><th colspan="4">Evidence based HFrEF drug classes</th></tr>
<tr><th>Increase in serum creatinine (%)</th><th>Decrease in eGFR* (%)</th><th>Max serum creatinine (mg/dL)</th><th>Min eGFR mL/min/1.73 m^2</th><th>Max serum potassium (mmol/L)</th><th>ACEi/ARB/ARNI</th><th>MRA</th><th>SGLT2i#</th><th>Beta-Blocker</th></tr>
<tr><td>< 50</td><td>< 30</td><td>2.5</td><td>30</td><td>5.0</td><td>None, uptitrate and evaluate renal function and electrolytes</td><td>None, uptitrate and evaluate renal function and electrolytes</td><td>None, continue SGLT2i and reevaluate renal function regularly</td><td rowspan="4">Beta-Blockers do not cause a change in eGFR/serum creatinine. Revise clinical context, determine alternative cause of renal function worsening, including deterioration in clinical setting</td></tr>
<tr><td>50-100</td><td>30-50</td><td>3.5</td><td>20</td><td>5.5</td><td>Evaluate clinical status and other causes of WRF. Consider halving ACEi/ARB/ARNI and re-evaluate</td><td>Evaluate clinical status and other causes of WRF. Consider halving MRA and re-evaluate</td><td>Continue SGLT2i if eGFR/or serum creatinine are acceptable. Evaluate other causes in parallel.</td></tr>
<tr><td rowspan="2">> 100</td><td rowspan="2">> 50</td><td rowspan="2">> 3.5</td><td rowspan="2">< 20</td><td>> 5.5
(for ACEi / ARB / ARNI/SGLT2i)</td><td>Evaluate clinical status and other causes of WRF. Consider stopping ACEi/ARB/ARNI and re-evaluate</td><td></td><td>Such large increases in serum creatinine are unexpected with SGLT2i and should prompt further evaluation.
If deemed clinically appropriate, continue SGLT2i with close monitoring, if no other option, stop SGLT2i.</td></tr>
<tr><td>> 6.0
(For MRA)</td><td></td><td>Evaluate clinical status and other causes of WRF. Consider stopping MRA and re-evaluate</td><td></td></tr>
<tr><td colspan="9">Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function and/or potassium has improved</td></tr>
</table>

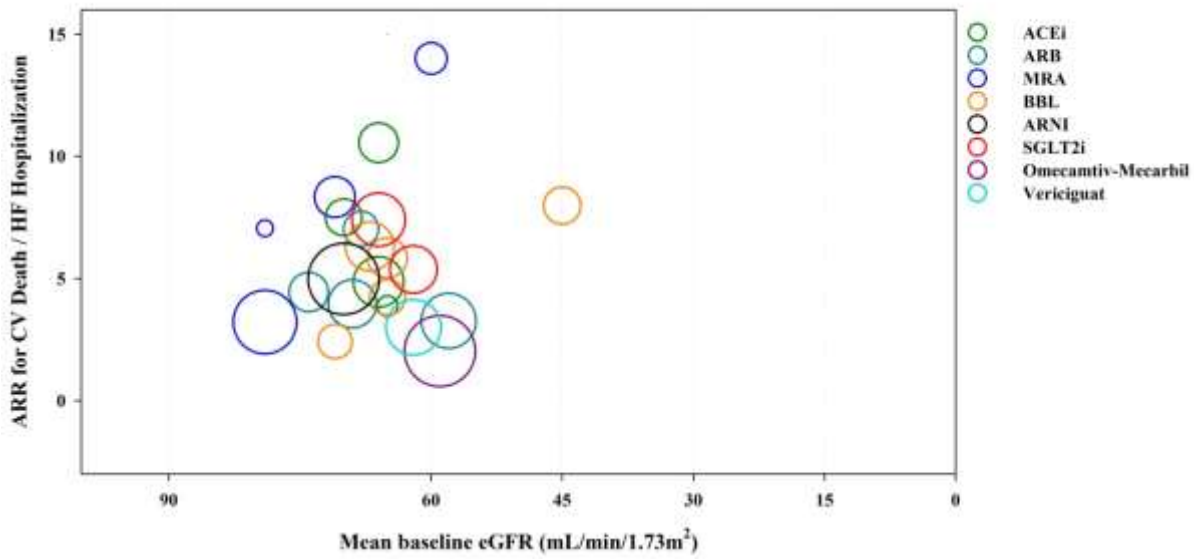
* arbitrary increase # clinical opinion in the absence of strong evidence

Supplementary Figure 2. Association between baseline eGFR and Absolute Risk Reduction of All-cause Mortality on study level



Shown are the mean baseline eGFR in relation to the absolute risk reduction in the overall individual study, or if available, data from specific subgroups of CKD in the individual studies. ARNI data represents PARADIGM-HF study, which had as active control enalapril. Area of the circle is proportional to the study size. Abbreviations: ACEi: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin II Receptor Blocker, ARNI: Angiotensin Receptor blocker, ARR: Absolute Risk Reduction, Neprilysin Inhibitor, Beta-blocker: Beta-Blocker, CI: Confidence Interval, CV: Cardiovascular, eGFR: Estimated Glomerular Filtration Rate, H-ISDN: Hydralazine IsosorbideDinitrate, HF: Heart Failure, MRA: Mineralocorticoid Receptor Antagonist, SGLT2i: Sodium glucose co-transporter 2 inhibitor.

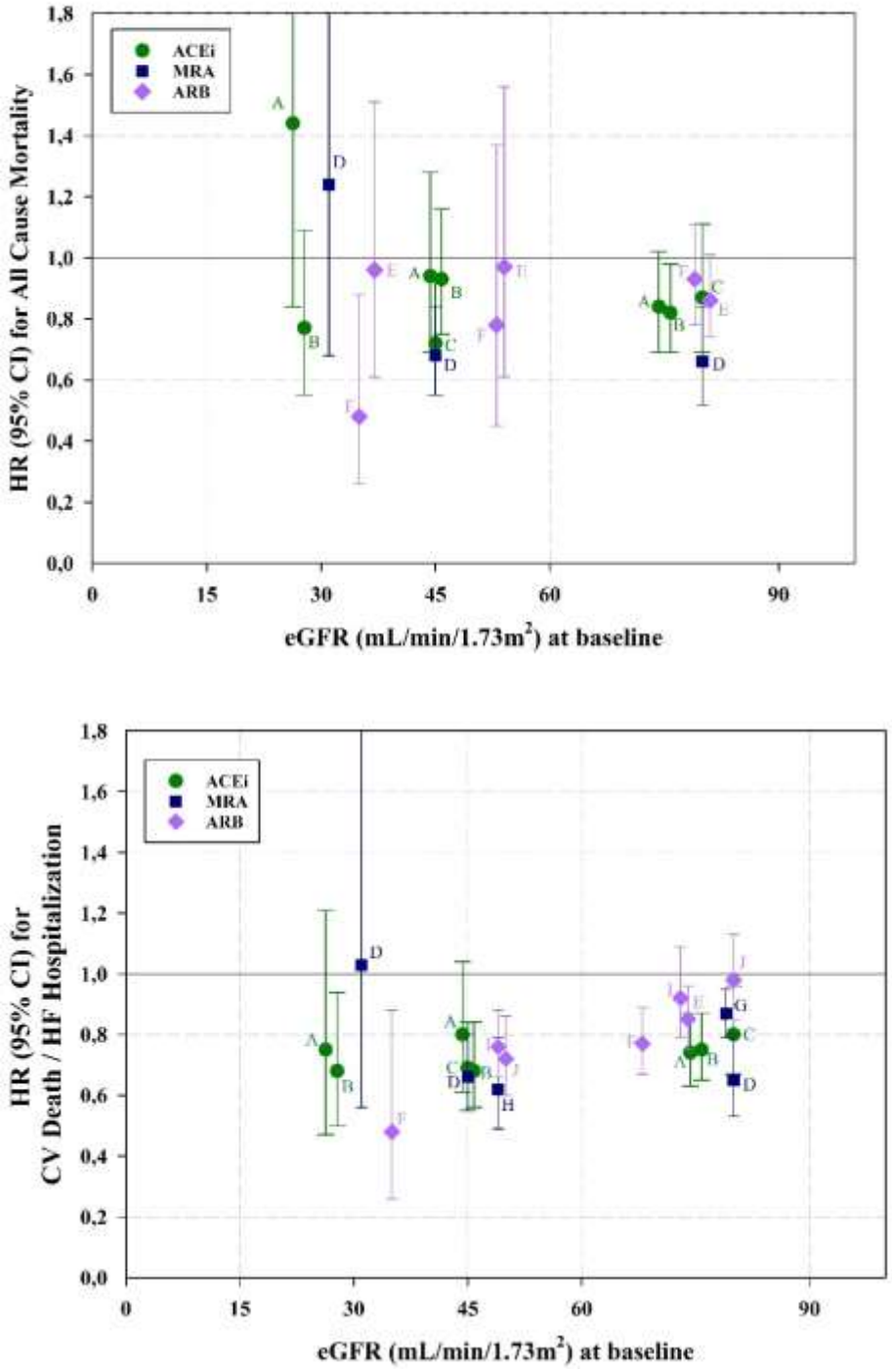
Supplementary Figure 3. Association between baseline eGFR and Absolute Risk Reduction of CV death or HF hospitalization on study level



Shown are the mean baseline eGFR in relation to the absolute risk reduction in the overall individual study, or if available, data from specific subgroups of CKD in the individual studies. ARNI data represents PARADIGM-HF study, which had as active control enalapril. Area of the circle is proportional to the study size. Abbreviations: ACEi: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin II Receptor Blocker, ARNI: Angiotensin Receptor blocker, ARR: Absolute Risk Reduction, Neprilysin Inhibitor, Beta-blocker: Beta-Blocker, CI: Confidence Interval, CV: Cardiovascular, eGFR: Estimated Glomerular Filtration Rate, H-ISDN: Hydralazine IsosorbideDinitrate, HF: Heart Failure, MRA: Mineralocorticoid Receptor Antagonist, SGLT2i: Sodium glucose co-transporter 2 inhibitor.

Supplementary Figure 4. Summary of effects of ACEi/ARB/MRA on clinical endpoints to CKD groups

A) **B)**



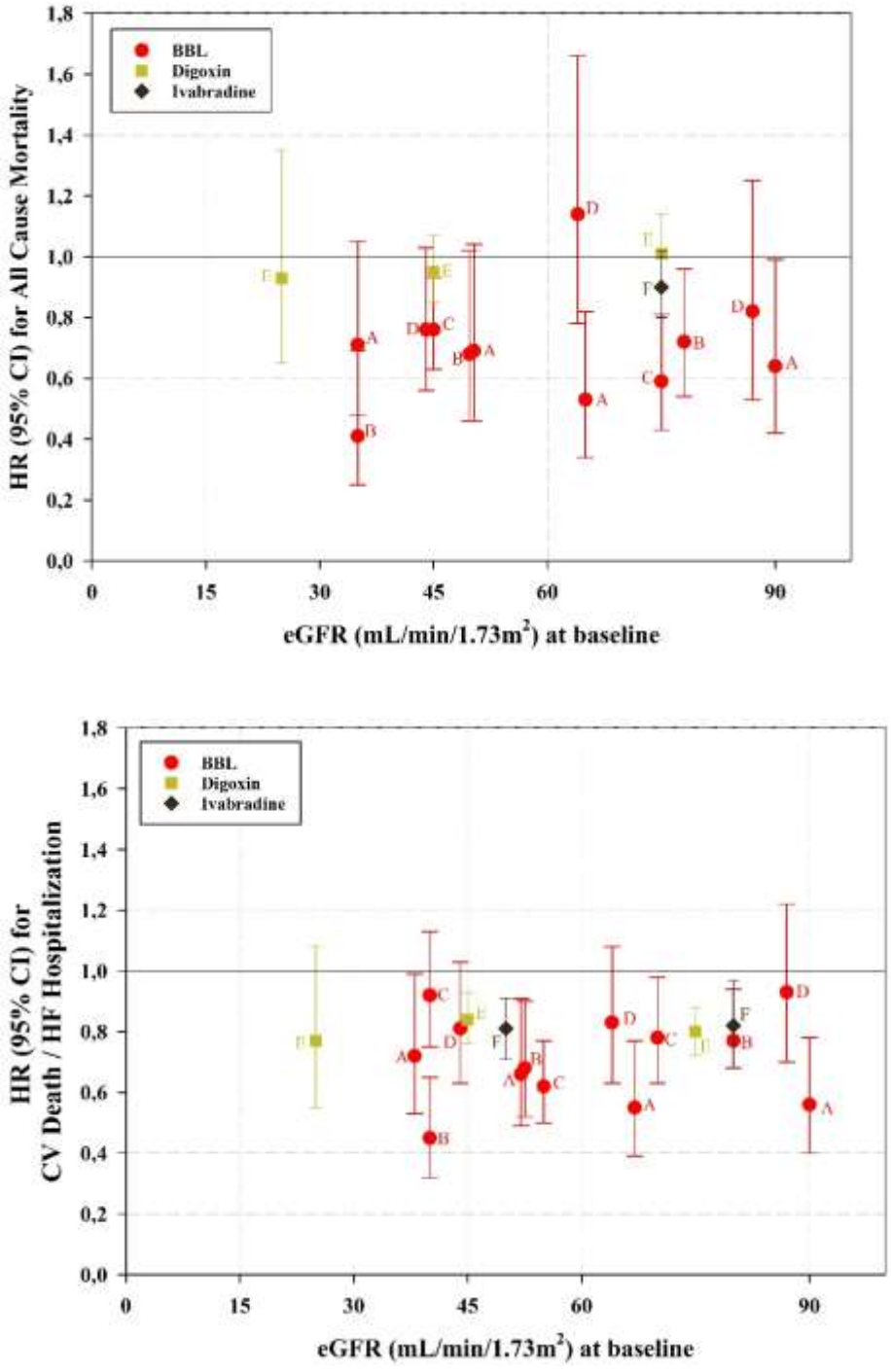
A) All Cause Mortality and B) CV Death / HF Hospitalization

Depicted are Hazard Ratio's and 95% Confidence Intervals for the treatment effect within CKD stages, or if not available the overall treatment effect at the study mean eGFR. Abbreviations: ACEi: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin II Receptor Blocker, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, HR: Hazard Ratio, MRA: Mineralocorticoid Receptor Antagonist.

A) SOLVD-Prevention[25-27,29]
B) SOLVD-Treatment[25-27,29]
C) SAVE[41]
D) RALES[50]
E) CHARM-Added[32]
F) CHARM-Alternative[32]
G) EPHESUS[51]
H) EMPHASIS-HF[48]
I) ValHeFT[33]
J) HEAAL[31]

Supplementary Figure 5. Summary of effects of Beta-blocker/Digoxin/Ivabradine on clinical endpoints according to CKD groups

A) **B)**



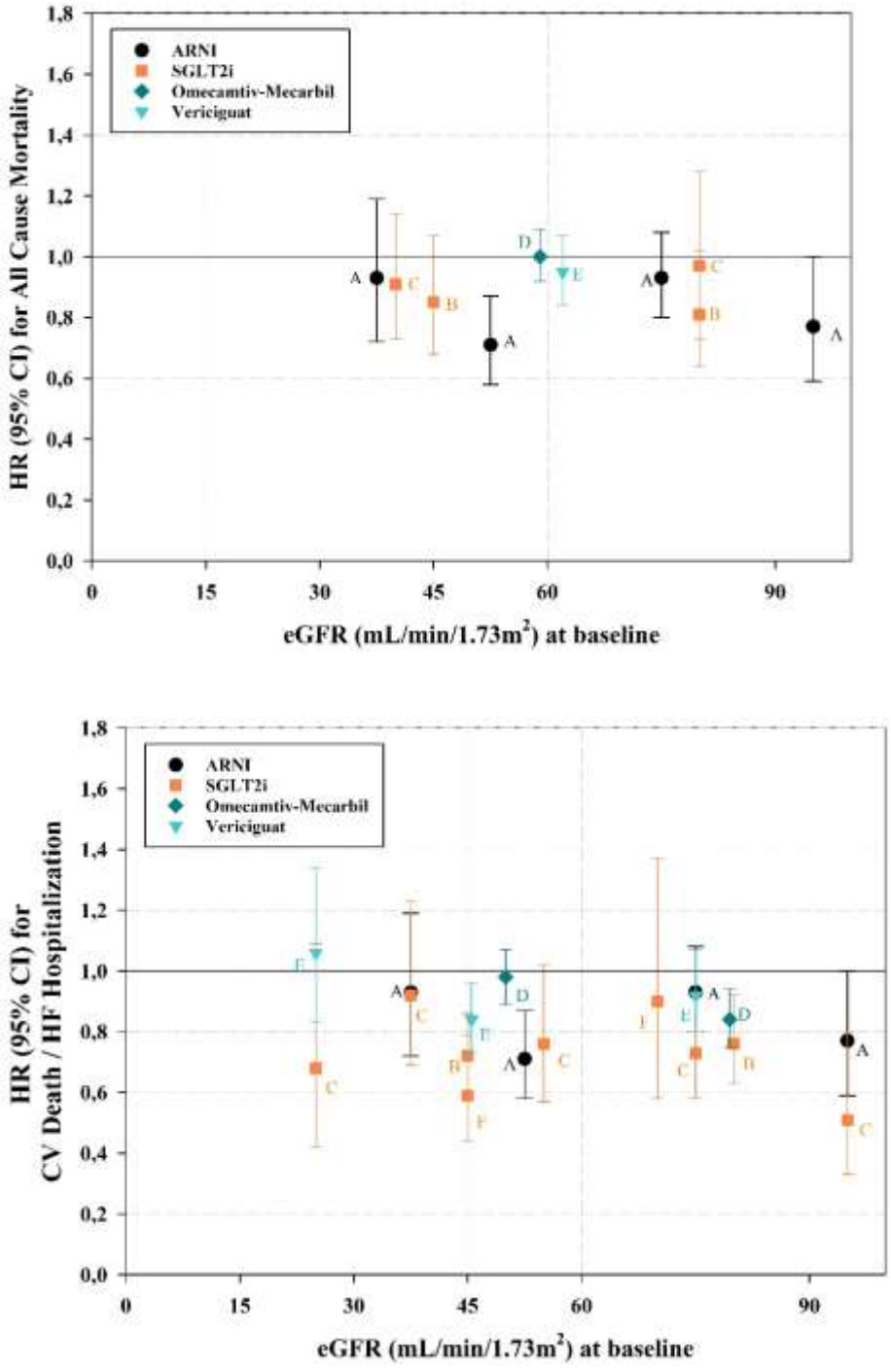
A) All Cause Mortality and B) CV Death / HF Hospitalization

Depicted are Hazard Ratio's and 95% Confidence Intervals for the treatment effect within CKD stages, or if not available the overall treatment effect at the study mean eGFR. Abbreviations: Beta-blocker: Beta-Blocker, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, HR: Hazard Ratio.

A) CIBIS-II[61]
B) MERIT-HF[63]
C) CAPRICORN/COPERNICUS[64]
D) SENIORS[65]
E) DIG[70]
F) SHIFT[68]

Supplementary Figure 6. Summary of effects of ARNI/SGLT2i/Vericiguat/Omecamtiv Mecarbil on clinical endpoints according to CKD groups

A) **B)**



A) All Cause Mortality and B) CV Death / HF Hospitalization

Depicted are Hazard Ratio's and 95% Confidence Intervals for the treatment effect within CKD stages, or if not available the overall treatment effect at the study mean eGFR. Abbreviations: ARNI: Angiotensin Receptor blocker Neprilysin Inhibitor, CI: Confidence Interval, eGFR: Estimated Glomerular Filtration Rate, HR: Hazard Ratio.

A) PARADIGM-HF[80]
B) DAPA-HF[86]
C) EMPEROR-Reduced[85]
D) GALACTIC-HF[97]
E) VICTORIA[96]
F) SOLOIST-WHF[84]