Clinical trials in heart failure: The role of sodium-water homeostasis and heart failure chronicity

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Table of Contents

List of Tables

List of Figures

List of Publications

Yeoh SE, Osmanska J, Petrie MC, Brooksbank KJM, Clark AL, Docherty KF, Foley PWX, Guha K, Halliday CA, Jhund PS, Kalra PR, McKinley G, Lang NN, Lee MMY, McConnachie A, McDermott JJ, Platz E, Sartipy P, Seed A, Stanley B, Weir RAP, Welsh P, McMurray JJV, Campbell RT. Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics. Eur Heart J. 2023 Aug 14;44(31):2966-2977.

Yeoh SE, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Bengtsson O, Boulton DW, Greasley PJ, Langkilde AM, Sjöstrand M, Solomon SD, McMurray JJV. Relationship of Dapagliflozin With Serum Sodium: Findings From the DAPA-HF Trial. JACC Heart Fail. 2022 May;10(5):306-318.

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European Society of Cardiology Heart Failure Congress, May 2022 (Poster Presentation). **SE. Yeoh**, P. Jhund, K. Docherty, MC. Petrie, SE. Inzucchi, L. Kober, MN. Kosiborod, FA. Martinez, P. Ponikowski, MS. Sabatine, O. Bengtsson, AM. Langkilde, M. Sjostrand, SD. Solomon, JJV. McMurray. Outcomes related to hyponatraemia and effects of dapagliflozin: findings from DAPA-HF

American Heart Association Scientific Sessions, November 2020 (Poster Presentation). **Su Ern Yeoh**, Pooja Dewan, Pardeep Jhund, Silvio E Inzucchi, Lars Køber, Mikhail N Kosiborod, Felipe A Martinez, Piotr Ponikowski, Marc S Sabatine, Scott D Solomon, Olof Bengtsson, Mikaela Sjöstrand, Anna Maria Langkilde, John JV McMurray. Effect of Dapagliflozin According to Duration of Heart Failure: An Analysis of the DAPA-HF Trial

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I dedicate this thesis to my parents, my sister, and my partner Alistair who have been my unwavering source of strength and love, for which I am eternally grateful.

Author's Declaration

I confirm that the work presented in this thesis was carried out whilst I was registered as a postgraduate research (PGR) student at the University of Glasgow during which I was also a Clinical Research Fellow at the British Heart Foundation Centre of Research Excellence. I was supervised by Professor John McMurray and Dr. Ross Campbell.

I was involved in preparing the study protocols for DAPA-RESIST, designed the paperwork and electronic case report form, and obtained regulatory and ethical approval. I performed the screening, recruitment, study visits and follow-up of study participants in NHS Greater Glasgow and Clyde, as well as spearheaded the training for sites in other health boards. Analysis of lung ultrasound scans were performed in a blinded fashion by Dr. Ross Campbell and Dr. Elke Platz. Laboratory biobank samples were stored and processed by the Metabolic Medicine Biomarker Laboratory at Queen Elizabeth University Hospital, Glasgow, while laboratory samples as part of usual clinical care were processed by local NHS laboratories. Statistical analyses for trial outcomes were performed by Alex McConnachie and Bethany Stanley at the Robertson Centre for Biostatistics according to a pre-specified Statistical Analysis Plan which I designed.

Regarding the other submitted publications, I formulated the hypotheses tested in all these studies, did the analyses of the large datasets involved, drafted the manuscripts and saw these through to publication, including dealing with the comments from editors and reviewers.

I confirm that except where explicit reference is made to the contribution of others, this thesis is entirely my own work and has not been submitted for any other degree at the University of Glasgow or any other institution. The copyright of all six submitted publications belong to the first author and the University of Glasgow and were published as open access.

Su Ern Yeoh
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Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ADH	Anti-diuretic hormone
ADHF	Acute decompensated heart failure
ADVOR	Acetazolamide in Decompensated Heart Failure With Volume Overload
AF	Atrial fibrillation
AHF	Acute heart failure
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ASCEND-HF	Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure
AT	Angiotensin II
ATHENA-HF	Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure
BHF	British Heart Foundation
BMI	Body mass index
BNP	B-type natriuretic peptide
CANVAS	Canagliflozin Cardiovascular Assessment Study
CARRESS-HF	Cardiorenal Rescue Study in Acute Decompensated Heart Failure
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CLOROTIC	Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure
COPD	Chronic obstructive pulmonary disease
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

CRT	Cardiac resynchronization therapy
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DELIVER	Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
DOSE	Diuretic Optimization Strategies Evaluation
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EMPAG-HF	Empagliflozin in Acute Decompensated Heart Failure
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EMPULSE	EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart faiLure Who Have Been StabilisEd
ERA	Endothelin receptor antagonist
ESC	European Society of Cardiology
ET	Endothelin
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
Gal-3	Galectin-3
GDF-15	Growth differentiation factor-15
GI	Gastrointestinal
HbA1c	Glycated haemoglobin
HF	Heart failure

HFA	Heart Failure Association
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HPB	Hepatobiliary
HR	Hazard ratio
HRA	Health Research Authority
hs-TnT	high-sensitivity troponin-T
IGFBP7	Insulin-like growth factor-binding protein 7
IL	Interleukin
IQR	Interquartile range
ICD	Implantable cardioverter defibrillator
IV	Intravenous
JVP	Jugular venous pressure
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire–clinical summary score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire–total symptom score
KIM-1	Kidney injury molecule-1
LUS	Lung ultrasound
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MMP-2	Matrix metalloproteinase-2
MMP-9	Matrix metalloproteinase-9
MRA	Mineralocorticoid receptor antagonist
NHE1	Sodium-hydrogen exchanger 1
NHE3	Sodium-hydrogen exchanger 3
NP	Natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OAT	Organic anion transporter
PAD	Peripheral arterial disease

PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIIINP	Amino-terminal pro-peptide of type III procollagen
PPI	Proton pump inhibitor
RAAS	Renin–angiotensin–aldosterone system
RALES	Randomised Aldactone Evaluation Study
RCT	Randomised controlled trial
RCB	Robertson Centre for Biostatistics
REC	Research Ethics Committee
ROSE-AHF	Renal Optimization Strategies Evaluation in Acute Heart Failure
SBP	Systolic blood pressure
SD	Standard deviation
SECRET of CHF	Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure
SGLT2i	Sodium glucose cotransporter-2 inhibitor
SHIFT	Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial
SNRI	Serotonin norepinephrine reuptake inhibitor
SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
SSRI	Selective serotonin reuptake inhibitor
sST2	Soluble suppression of tumorigenicity-2
T2DM	Type 2 diabetes mellitus
TIMP-1	Tissue inhibitor of matrix metalloproteinase-1
UNLOAD	Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure
Val-HeFT	Valsartan Heart Failure Trial
ZENITH-CKD	Zibotentan and Dapagliflozin for the Treatment of Chronic Kidney Disease
3T Trial	Comparison of Oral or Intravenous Thiazides vs. tolvaptan in Diuretic Resistant Decompensated Heart Failure

Chapter 1 Introduction

1.1 Heart Failure Definition and Classification

Heart failure (HF) is universally defined as a clinical syndrome consisting of symptoms and/or signs of fluid overload due to a structural and/or functional abnormality of the heart, with elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.[1, 2] Broadly, heart failure can be classified according to left ventricular ejection fraction, the presence and severity of clinical symptoms, as well as the timescale/chronicity of symptoms. However, within these categories, despite the implementation of guideline-directed and evidence-based HF therapy, there exist a subset of HF patients with advanced HF which is characterised by persistent symptoms despite maximal conventional therapy.[3] Hence, patients with diuretic resistant HF are considered having advanced HF.

The classification of HF according to left ventricular ejection fraction (LVEF) comprises of heart failure with reduced ejection fraction (HFrEF) which are HF patients with LVEF ≤40%, heart failure with mildly reduced ejection fraction (HFmrEF) which are HF patients with LVEF between 41% and 49%, and heart failure with preserved ejection fraction (HFpEF), which are HF patients with LVEF ≥50%.[1, 2] Meanwhile, severity of HF symptoms is subjectively classified according to the New York Heart Association (NYHA) functional classification ranging from no limitation to physical activity (Class I) to symptoms at rest (Class IV). HF may also be classified according to the chronicity of symptom onset, i.e: acute heart failure (AHF) which refers to the rapid onset of HF symptoms and/or signs, whilst chronic heart failure (CHF) describes a more gradual onset of HF symptoms and/or signs. Patients with AHF may present as a first presentation i.e: new-onset HF or have an acute decompensation of CHF.[1] It is well-established that aggressive initiation and uptitration of guideline-directed HF therapy is crucial to improve mortality and morbidity outcomes, and prevent worsening HF and HF re-hospitalisations.[4, 5]

The primary mechanism driving congestion in the HF clinical syndrome, whether acute HF, acutely decompensated or chronic HF is sodium and water retention. Circulatory homeostasis is regulated by the cardio-renal axis via the natriuretic peptides (NP) system, the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system and the resulting effect on renal vasculature, glomerular filtration rate and renal sodium excretion. In healthy individuals, sodium and volume overload results in a rise in atrial blood volume and atrial stretch, which triggers a release in NPs which have both direct tubular and renal haemodynamic actions. NPs act on the renal tubules to increase sodium excretion (and thus, water excretion) and also increase glomerular filtration rate by afferent arteriole vasodilation, increase glomerular permeability, inhibit renin, angiotensin II and aldosterone secretion and act on the central nervous system to inhibit sympathetic activity.[6-9] The opposite occurs in a volume-depleted state, whereby reduced arterial stretch activates the RAAS and sympathetic nervous system which cause renal afferent and efferent vasoconstriction, sodium retention and sodium reabsorption, and cause vasopressin release by osmotic (i.e: central/hypothalamic) and non-osmotic (i.e: blood pressure and volume) pathways.[6, 9-12] In the HF clinical syndrome, impaired cardiac function and output result in a self-perpetuating vicious cycle of reduced arterial stretch leading to RAAS and sympathetic nervous system activation.[6, 9, 11, 12] Stimulation of renin release leads to angiotensin II production, which in turn causes intrarenal vasoconstriction, sodium retention in the proximal tubule and aldosterone release, and thus sodium reabsorption in the collecting duct and water retention. Furthermore, the activation of the sympathetic nervous system, vasopressin release and reduced NP responsiveness exacerbate these effects. [6, 9-14]

1.2 Heart Failure Therapies

Thus, the mainstay of initial AHF management is to achieve diuresis and natriuresis using diuretic therapy, primarily loop diuretics. Loop diuretics inhibit the sodium–potassium-chloride co-transporter in the thick ascending limb of the loop of Henle. Once in the bloodstream, loop diuretics are transported to their site of action which are the sodium–potassium-chloride co-transporters on the luminal side of the thick

ascending limb of the loop of Henle by being bound to plasma albumin. Due to the size of these loop diuretic-albumin molecules, they have to be actively secreted across the glomerular wall into the proximal tubule by the organic anion transporter (OAT).[6, 9, 15] Once the loop diuretics are delivered to their site of action, their mechanism of action is to block sodium reabsorption resulting in sodium excretion and the desired therapeutic effect of negative sodium balance and water excretion. In the majority of patients with AHF, loop diuretics at standard dosages will result in sufficient diuresis and natriuresis, resulting in the improvement of HF symptoms and signs of congestion. However, there are circumstances which may thwart this desired loop diuretic effect, leading to the diuretic resistance syndrome which will be discussed below.

Beyond diuretic therapy, current clinical guidelines advocate for the use of optimal pharmacotherapy i.e. the Four Pillars of HF therapy; with renin-angiotensin inhibitors (angiotensin-converting enzyme inhibitors, ACEi; or angiotensin receptor blockers, ARB) or angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRA), and sodium glucose cotransporter-2 inhibitors (SGLT2i) in patients with HF.[1] In these guidelines published by the European Society of Cardiology (ESC) in 2021, this quadruple therapy approach was firmly recommended as the foundational standard of medical therapy for patients with HFrEF, with softer recommendation for these therapies in patients with HFmrEF and HFpEF. It is noted that the results of the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) clinical trials, which demonstrated a significant risk reduction in cardiovascular death or worsening HF in patients with HFpEF and HFmrEF on empagliflozin and dapagliflozin respectively, were released after the publication of the 2021 ESC guidelines but were included in the ESC Focused Update in 2023.[16-18]

In patients with HF, there is overactivation – initially compensatory activation, which later progresses to pathologic activation – of the natriuretic peptides (NP) system,

the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system which leads to a vicious cycle of worsening sodium and water retention. Hence, RAAS blockers, neprilysin inhibition, and sympathetic nervous system antagonists were developed and utilised to counteract these deleterious actions. The angiotensin-converting enzyme (ACE) converts the inactive hormone Angiotensin I into the Angiotensin II which acts on the Angiotensin II (AT) receptor and has potent effects on vasoconstriction, sodium and water retention, and sympathetic nervous system activation.[19] Angiotensin II also stimulates aldosterone secretion by the adrenal cortex and anti-diuretic hormone (ADH) release from the pituitary gland, both of which result in further sodium and fluid retention. As its name suggests, ACE inhibitors inhibit the actions of ACE, thus reducing formation of Angiotensin II and it's downstream effects.[19] ARBs meanwhile, bind to the AT receptor, thus inhibiting the effects of Angiotensin II.[20] ARNIs consist of the ARB valsartan, coupled with the neprilysin inhibitor sacubitril. Neprilysin is an enzyme which degrades a variety of endogenous peptides, such as natriuretic peptides (NPs) and endothelin.[21] Neprilysin inhibition increases circulating levels of NPs which increase sodium and water excretion, thus preventing counterregulatory activation of the RAAS system. Endothelin (ET), namely ET-1, may also have diuretic and natriuretic effects by direct inhibition of renal sodium and water reabsorption.[22, 23] Combined inhibition of neprilysin and the renin-angiotensin system has been demonstrated to be superior to renin-angiotensin inhibition alone in patients with HF.[24-26] Aldosterone acts on the mineralocorticoid receptors in the renal tubules to promote sodium and thus, water retention with cross-influence from the sympathetic nervous system. MRAs inhibit the actions of aldosterone by binding to the mineralocorticoid receptor.[27] Meanwhile, beta-blockers reduce sympathetic nervous system activity, with direct cardiac benefits including reducing myocardial oxygen demand and reversing cardiac remodelling, but also has indirect benefits by suppressing renin release through inhibition of renal ß-adrenergic receptors.[28, 29]

SGLT2 inhibitors are the newest class of HF therapy. The sodium-glucose cotransporter 2 (SGLT2) is a member of the sodium glucose cotransporter family. SGLT2 is the major cotransporter involved in glucose reabsorption in the kidney at

the proximal renal tubule and normally reabsorbs about 97% of filtered glucose whereas SGLT1 normally reabsorbs the remainder.[30, 31] Inhibitors of SGLT2 decrease glucose reabsorption, thereby increasing urinary glucose excretion, leading to the initial discovery of SGLT2i as glucose-lowering, anti-diabetic agents. However, the ground-breaking and unexpected results of the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) clinical trial in patients with type 2 diabetes mellitus (T2DM) and cardiovascular disease has been reported.[32] This was the first large placebo-controlled SGLT2i clinical outcome trial and demonstrated significant reduction in cardiovascular outcomes, mortality and heart failure hospitalizations in the empagliflozin group. These findings were confirmed by the CANVAS Program (Canagliflozin Cardiovascular Assessment Study), which was another large-scale cardiovascular outcome trial studying canagliflozin in patients with T2DM and cardiovascular disease.[33] In addition, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trials demonstrated the benefits of SGLT2i on renal and cardiovascular outcomes in patients with chronic kidney disease (CKD).[34-37] More recently, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), DELIVER, EMPEROR-Reduced and EMPEROR-Preserved clinical trials have demonstrated the significant benefit of SGLT2i on preservation of renal function, and reduction in heart failure events and cardiovascular death in patients with chronic heart failure across the whole spectrum of ejection fraction, from reduced to preserved ejection fraction (HFrEF or HFpEF), whilst the EMPULSE (EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart faiLure Who Have Been StabilisEd) clinical trial demonstrated the benefits of the SGLT2i empagliflozin on all-cause mortality, heart failure events and quality of life in patients hospitalized for acute heart failure regardless of ejection fraction or diabetes status.[16, 17, 38-43]

Alongside the longer-term renal and cardiovascular benefits, the diuretic action of SGLT2i, as a result of its action on the proximal tubule to reduce glucose and sodium reabsorption, is likely to be advantageous in patients with acutely decompensated heart failure. The diuretic effect of SGLT2is appear to involve pathways beyond

urinary glucose excretion and osmotic diuresis.[31, 44] Most of the fluid and sodium reabsorption in the kidney occur in the proximal tubule by the sodium-hydrogen exchanger 3 (NHE3).[9] It has been postulated that SGLT2i inhibit proximal tubule NHE3 activity, thus reducing sodium and water reabsorption, but without systemic and intrarenal RAAS activation.[31, 45, 46] A small randomised controlled trial (RCT) in healthy subjects have shown the natriuretic effect of dapagliflozin and natriuretic synergy in combined dapagliflozin and bumetanide therapy.[47] Another small RCT in patients with type 2 diabetes mellitus (T2DM) showed that canagliflozin resulted in increased urine volume and natriuresis.[48] Other small RCTs in patients with T2DM and chronic heart failure have demonstrated varying natriuretic effects of SGLT2i, with one clinical trial showing the natriuretic benefit of empagliflozin, especially in combination with loop diuretics, whilst another clinical trial showed an increase in 24-hour urinary volume with empagliflozin (versus placebo) when added to loop diuretics, without an increase in natriuresis. [49, 50] More recently, the EMPAG-HF (Empagliflozin in Acute Decompensated Heart Failure) clinical trial demonstrated the diuretic benefit (increase in urine output and diuretic efficiency) of the early addition of empagliflozin onto standard diuretic therapy in patients with acute heart failure.[51]

Collectively, these findings suggest that SGLT2i may be effective in promoting diuresis in hospitalised heart failure patients with resistance to loop diuretics.

1.3 Diuretic Resistance

Diuretic resistance is a syndrome whereby patients with heart failure do not achieve the therapeutically desired diuresis despite high doses of loop diuretics, and is associated with worse clinical outcomes including prolonged hospital stay, increased risk of readmission after hospital discharge, and higher symptom burden and mortality.[6, 52-56] These patients are an important and difficult-to-treat/challenging cohort due to the complications of cardiorenal crosstalk and concomitant comorbidities, as well as the multiple intricacies and various metrics in accurate quantitative and qualitative assessment of fluid overload and congestion, both peripheral and pulmonary. Poor diuretic response (weight loss per 40 mg furosemide

or equivalent), low diuretic efficiency (net fluid loss per milligram of loop diuretic) and low urinary sodium excretion portend worse clinical outcomes.[57-62] However, at present, there is no single agreed universal metric definition of diuretic resistance, i.e: no specified amount weight or fluid loss, urinary sodium excretion, minimum daily furosemide dose or equivalents, or loop diuretic efficiency. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) position statement defines diuretic resistance as an "impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility to achieve euvolaemia".[63] However, a broadly accepted definition, which is the definition which we have used in the DAPA-RESIST clinical trial, is insufficient weight loss i.e: decrease <1kg in preceding 24 hours or absence of a negative fluid balance i.e: decrease <1 litre per 24 hours despite treatment with high dose intravenous (IV) loop diuretic (equivalent of ≥160mg IV furosemide) over the preceding 24 hours.[6, 9, 63]

The pathophysiology of diuretic resistance is multi-factorial and include homeostatic responses from the neurohormonal systems described above, in combination with the pharmacokinetics and pharmacodynamics of loop diuretic agents, renal factors such as alterations in renal haemodynamics (renal blood flow and glomerular filtration rate) and renal tubular remodelling, as well as biochemical factors which occur in patients with heart failure especially in the presence of renal dysfunction.[6, 9, 52] Firstly, diuretic agents require delivery from their mode of administration to their specific site of action at the renal tubules - loop diuretics inhibit the sodium-potassium-chloride co-transporter in the thick ascending limb of the loop of Henle. Loop diuretics administered via the oral route require absorption through the gut mucosa to enter the blood stream, a pathway which is impaired by the presence of gastrointestinal wall oedema or hypoperfusion which may occur in cardiac failure, hence reducing it's bioavailability.[6, 15] Intravenous administration of loop diuretics bypasses this issue. Next, loop diuretics have steep dose-response curves, with a logarithmic relationship between loop diuretic dose/concentration and drug response.[15, 55] Initially there is little therapeutic effect until a threshold dose is reached, beyond which the effect rapidly reaches a ceiling and plateaus. Alongside this, each individual has a natriuretic threshold whereby natriuresis depends on time

spent above the threshold. Hence, increasing loop diuretic doses beyond the ceiling will not achieve higher rates of natriuresis, but may maintain a longer diuretic steady-state concentration above the natriuretic threshold and increase overall natriuresis.[15, 55] In patients with heart failure, the dose-response curve is shifted downwards and to the right and the natriuretic threshold is increased. Once in the bloodstream, loop diuretics are transported to their site of action which are the sodium–potassium-chloride co-transporters on the luminal side of the thick ascending limb of the loop of Henle by being bound to plasma albumin. Due to the size of these loop diuretic-albumin molecules, they have to be actively secreted across the glomerular wall into the proximal tubule by the organic anion transporter (OAT).[6, 9, 15] This process is impaired in patients with hypoalbuminemia which is common in heart failure, with or without the presence of albuminuria. In albuminuria, the high levels of filtered albumin in the renal tubules bind to the loop diuretics and reduce their availability/prevent them from acting on the sodium-potassium-chloride co-transporter. However, there is little data to support the co-administration of albumin with loop diuretics in hypoalbuminemic patients.[64] Additionally, patients with heart failure especially with concomitant renal dysfunction often have high levels of organic acids and nitrogen-containing compounds such as urea and creatinine, also known as azotemia. These organic acids competitively inhibit the organic anion transporter (OAT) and reduce the secretion and hence, availability of loop diuretics at their site of action. Renal blood flow and glomerular filtration rate, which are often reduced in patients with heart failure, also affect the delivery of loop diuretics to the renal tubules, a cycle which loop diuretics themselves further potentiate and will be further discussed below. Once the loop diuretics are delivered to their site of action which is the sodium-potassium-chloride co-transporter in the thick ascending limb of the loop of Henle, their mechanism of action is to block sodium reabsorption resulting in sodium excretion and the desired therapeutic effect of negative sodium balance and water excretion. However, the resulting decrease in extracellular volume activates a homeostatic response from the RAAS and sympathetic nervous system which leads to increased sodium (and hence, water) reabsorption in other parts of the nephron which counterbalances the diuretic effect, also known as the ‘braking phenomenon’.[65, 66] Furthermore, prolonged loop diuretic use causes

increased sodium delivery downstream from the thick ascending limb of loop of Henle which results in distal convoluted tubular remodelling and hypertrophy of epithelial cells which increases sodium reabsorption. In addition to these tubular effects, loop diuretics also affect renal haemodynamics by reducing renal blood flow and glomerular filtration rate, which result in a reduction of filtered sodium and hence diminished ability of the kidney to excrete sodium.

1.4 Current approaches to treatment of diuretic resistance

Different treatment strategies have been proposed for these patients, including treatment with ultrafiltration, increasing doses of loop diuretics and a combination diuretic strategy. Ultrafiltration was investigated in the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) and UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) clinical trials. Meanwhile, increasing doses of loop diuretics and bolus versus continuous infusion of loop diuretic was studied in the DOSE (Diuretic Optimization Strategies Evaluation) trial. The combination diuretic strategy or sequential nephron inhibition, was widely investigated using various diuretic agents targeting different regions of the nephron. Namely, spironolactone in ATHENA-HF (Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure), nesiritide in the ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial, tolvaptan in the 3T Trial (Comparison of Oral or Intravenous Thiazides vs. tolvaptan in Diuretic Resistant Decompensated Heart Failure), EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial and the SECRET of CHF (Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure) trial, the carbonic anhydrase inhibitor acetazolamide in ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload) clinical trial, or most commonly, a thiazide or thiazide-like diuretic in combination with a loop diuretic in the CLOROTIC (Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure) trial and 3T Trial.[1, 63, 67-76] The rationale for combination diuretic strategies involves targeting the RAAS or different sites of action on the nephron for synergistic diuretic effect.

For example, mineralocorticoid receptor antagonists such as spironolactone bind to the mineralocorticoid receptor expressed in the distal nephron (distal convoluted tubules, connecting tubules and the cortical collecting duct), thus inhibiting the binding of aldosterone at these sites. The aldosterone-mineralocorticoid receptor complex activates two protein transporters, the basolateral Na+/K+ ATPase pump and the apical epithelial Na+ channel (ENaC), which function to increase sodium reabsorption and potassium excretion. Thus, inhibition of this complex results in sodium excretion without potassium loss.[77, 78] Dopamine regulates sodium balance by acting on dopamine receptors located throughout the nephron, both at a glomerular level to promote renal vasodilatation at dose-dependent levels, and at a tubular level, especially in the proximal tubules whereby the actions of dopamine on D1-like receptors inhibit the activity of both apical and basolateral sodium transporters thus inhibiting sodium reabsorption.[79] Nesiritide is a recombinant human B-type natriuretic peptide.[70] Tolvaptan is a vasopressin V2 receptor antagonist and acts on the distal nephron, primarily the collecting ducts, to mediate the renal actions of vasopressin (also known as antidiuretic hormone) which is often elevated in patients with heart failure.[73] Acetazolamide is a carbonic anhydrase inhibitor which acts in the proximal convoluted tubule to increase bicarbonate excretion and sodium reabsorption.[80, 81] Meanwhile, thiazide or thiazide-like diuretics act on the distal convoluted tubule and collecting duct by blocking sodium and chloride reabsorption downstream to the site of action of loop diuretics, thus further increasing the sodium and water excretion by preventing their distal renal tubular reabsorption.[6, 9] However, the data on the safety and efficacy of ultrafiltration on outcomes are unsettled, whilst the use of increasing doses of loop diuretic and the combination diuretic strategy also cause concerns which merit further attention.[67-69, 82] Namely, these strategies may be ineffective and/or cause worsening kidney function and electrolyte disturbances, especially hyponatraemia and hypokalaemia in the case of loop diuretics and thiazide or thiazide-like diuretics, and hyperkalaemia in the case of spironolactone, resulting in discontinuation of diuretic therapy, prolonged length of hospital stay, and worse mortality and heart failure (HF) rehospitalisation outcomes.[1, 63, 69-74, 83, 84] These clinical trials are summarised in Table 1.

Table 1 Summary of relevant acute decompensated heart failure clinical trials

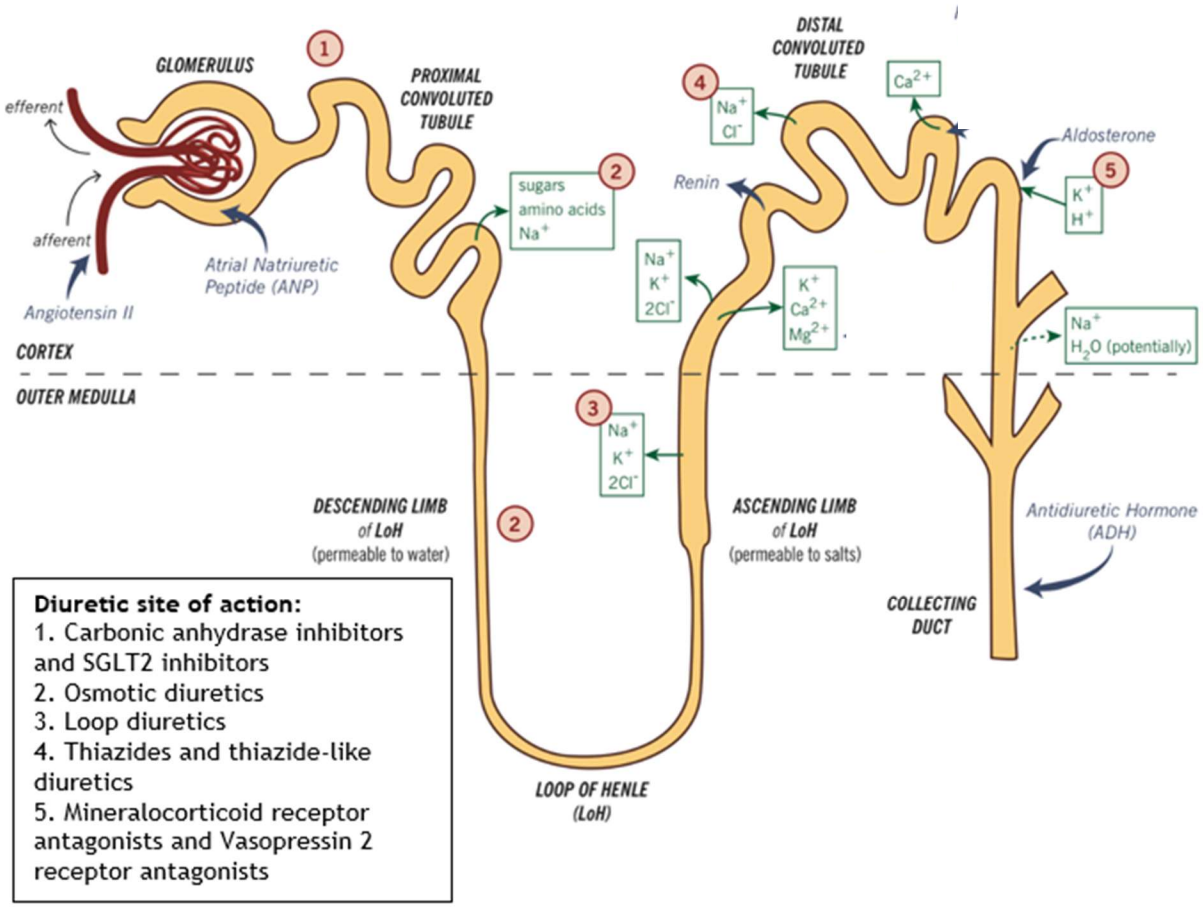
Study	Sample Size	Intervention	Patient Cohort	Primary Endpoint	Results
UNLOAD. Constanzo *et al*. (2007)	200	Ultrafiltration vs. IV loop diuretics	Patients hospitalised with ADHF	Change in weight and dyspnoea score at 48 hours	Ultrafiltration produces greater weight loss. No difference in dyspnoea score
CARRESS-HF. Bart *et al*. (2012)	188	Ultrafiltration vs. stepped diuretic therapy (IV loop diuretic ± Metolazone)	Patients hospitalised with ADHF and worsened renal function	Change in serum creatinine and change in weight at 96 hours	Ultrafiltration inferior to stepped diuretic therapy
DOSE. Felker *et al*. (2011)	308	Low-dose vs high-dose IV Furosemide vs IV Furosemide bolus every 12 hours vs. continuous IV infusion	Patients hospitalised with ADHF on 80-240 mg daily oral Furosemide or equivalent	Patient-reported global symptom assessment at 72 hours	No significant difference in global symptom assessment in low vs high-dose or in bolus vs continuous infusion
ATHENA-HF. Butler *et al*. (2017)	360	High-dose Spironolactone (100 mg) vs. placebo or 25 mg Spironolactone (usual care)	Patients hospitalised with ADHF on no or low-dose Spironolactone	Change in NT-proBNP levels at 96 hours	No significant difference in NT-proBNP reduction
ROSE-AHF. Chen *et al*. (2013)	360	Nesiritide vs. Dopamine	Patients hospitalised with ADHF and renal dysfunction	Cumulative urine volume and change in cystatin C at 72 hours	No significant effect or Dopamine or Nesiritide on urine volume or cystatin C
3T Trial. Cox *et al*. (2020)	60	Metolazone vs. Chlorothiazide vs. Tolvaptan	Patients hospitalised with ADHF and loop diuretic resistance	Change in weight at 48 hours	All 3 interventions significantly improved diuretic efficacy. No significant

					difference in weight loss between treatment groups
EVEREST. Konstam *et al*. (2007)	4133	Tolvaptan vs. placebo	Patients hospitalised with ADHF and LVEF ≤40%	All-cause mortality and CV death or HF hospitalisation	Tolvaptan has no effect on all-cause mortality or HF-related morbidity
SECRET of CHF. Konstam *et al*. (2017)	250	Tolvaptan vs. placebo	Patients hospitalised with ADHF and renal dysfunction, hyponatraemia or diuretic resistance	Change in dyspnoea score at 8 and 16 hours	No significant difference in dyspnoea reduction
ADVOR. Mullens *et al*. (2022)	519	Acetazolamide vs. placebo	Patients hospitalised with ADHF on >40mg daily oral Furosemide or equivalent	Successful decongestion at 3 days	Significantly greater incidence of successful decongestion with Acetazolamide
CLOROTIC. Trullàs *et al*. (2023)	230	Hydrochlorothiazide vs. placebo	Patients hospitalised with ADHF on 80-240 mg daily oral Furosemide or equivalent	Change in weight and dyspnoea at 72 hours	Significantly greater weight loss but no difference in dyspnoea with Hydrochlorothiazide

The sodium glucose cotransporter-2 inhibitor DAPAgliflozin versus thiazide diuretic in patients with heart failure and diuretic RESISTance (DAPA-RESIST) clinical trial was designed to assess whether dapagliflozin (in addition to intravenous loop diuretic) results in greater diuresis and decongestion compared to the standard practice of treatment with the thiazide-like diuretic metolazone (in addition to intravenous loop

diuretic) in patients hospitalised for heart failure and diuretic resistance. We included patients with diuretic resistant heart failure regardless of ejection fraction as they present the same management challenges and the study hypothesis and aims are as clinically relevant in patients with HFpEF and HFmrEF as in HFrEF.

Figure 1 Diuretics and their site of action



Adapted from McMaster Pathophysiology Review. Available at: http://www.pathophys.org/diuretics/

1.5 Overview of submitted publications

These six publications focus on key treatments for heart failure that have, in common, effects on sodium and water homeostasis. The most important paper describes the primary analyses of a clinical trial that I led using the SGLT2-inhibitor dapagliflozin in patients with heart failure (DAPA-RESIST). DAPA-RESIST was a multi-centre, open-label, randomised controlled trial comparing dapagliflozin with metolazone in patients with diuretic-resistant heart failure which was conducted by the Heart Failure Research Group at the University of Glasgow. I was involved in all aspects of this trial, including protocol design, trial set-up, patient recruitment, data management, interpretation of the results, writing of the manuscript and its publication.

I also include post hoc analyses of the DAPA-HF clinical trial which also uses the SGLT2i dapagliflozin, the PARADIGM-HF clinical trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) using the angiotensin receptor-neprilysin inhibitor sacubitril valsartan, and the RALES (Randomised Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trials which used mineralocorticoid receptor antagonists. In one of the DAPA-HF post hoc analyses, I studied the prognostic significance of hyponatraemia, the impact of baseline serum sodium on dapagliflozin efficacy and the effects of dapagliflozin on serum sodium in ambulatory patients with HFrEF. Understanding sodium status is crucial in the management of HF patients as abnormalities of sodium levels may develop secondary to the clinical congestive state of HF and/or as a result of HF therapy and portends a worse prognosis. It is important to understand of the effects of HF therapy on sodium status and vice versa. In another post-hoc analysis of DAPA-HF, I analysed the prognostic significant of Endothelin-1 (ET-1) on key study outcomes, the effect of dapagliflozin therapy on ET-1 levels, and the impact of ET-1 levels on the efficacy of dapagliflozin. As mentioned in an earlier section, endothelin is an endogenous peptide which may have diuretic and natriuretic effects by direct inhibition of renal sodium and water reabsorption but also with potent vasoconstrictive effects.[22, 23, 85] Hence, it's function and prognostic significant are less well understood. In a further

post hoc analysis of the DAPA-HF clinical trial, I sought to analyse the impact of chronicity of HF duration on patients' clinical outcomes, the effectiveness of dapagliflozin therapy, as well as the safety and tolerability of dapagliflozin. I studied the same question in a post hoc analysis of the PARADIGM-HF clinical trial, with sacubitril/valsartan instead of dapagliflozin. This is an important question to be studied, and provides insight into the progression of risk in the clinical course of HF, even in chronic stable patients. Secondly, this provides evidence for the utility and practicality of optimal HF therapy regardless of time from HF diagnosis – it's never too late to start HF therapy. Finally, I investigated the efficacy and safety of mineralocorticoid receptor antagonist therapy in a post hoc pooled analysis of patients in the RALES and EMPHASIS-HF clinical trials, focussing on patients with a diagnosis of chronic obstructive pulmonary disease (COPD) compared to those without COPD. The disease process of COPD, in itself, causes neurohormonal activation with sodium and water retention.[86] This congestive state is further exacerbated by the use of corticosteroids in many patients with COPD. Furthermore, patients with COPD may be on suboptimal HF therapy due to intolerance of beta-blocker therapy, especially non-cardioselective beta-blockers, in some patients. Hence, optimising the other pillars of HF therapy in COPD patients is of paramount importance.

Chapter 2 Dapagliflozin vs. Metolazone in Heart Failure Resistant to Loop Diuretics

2.1 Abstract

2.1.1 Background and Aims

To examine the decongestive effect of the sodium-glucose cotransporter 2 inhibitor dapagliflozin compared to the thiazide-like diuretic metolazone in patients hospitalized for heart failure and resistant to treatment with intravenous furosemide.

2.1.2 Methods and Results

A multi-centre, open-label, randomized, and active-comparator trial. Patients were randomized to dapagliflozin 10 mg once daily or metolazone 5–10 mg once daily for a 3-day treatment period, with follow-up for primary and secondary endpoints until day 5 (96 h). The primary endpoint was a diuretic effect, assessed by change in weight (kg). Secondary endpoints included a change in pulmonary congestion (lung ultrasound), loop diuretic efficiency (weight change per 40 mg of furosemide), and a volume assessment score. 61 patients were randomized. The mean (±standard deviation) cumulative dose of furosemide at 96 h was 977 (±492) mg in the dapagliflozin group and 704 (±428) mg in patients assigned to metolazone. The mean (±standard deviation) decrease in weight at 96 h was 3.0 (2.5) kg with dapagliflozin compared to 3.6 (2.0) kg with metolazone [mean difference 0.65, 95% confidence interval (CI) −0.12,1.41 kg; P = 0.11]. Loop diuretic efficiency was less with dapagliflozin than with metolazone [mean 0.15 (0.12) vs. 0.25 (0.19); difference −0.08, 95% CI −0.17,0.01 kg; P = 0.10]. Changes in pulmonary congestion and volume assessment score were similar between treatments. Decreases in plasma sodium and potassium and increases in urea and creatinine were smaller with dapagliflozin than with metolazone. Serious adverse events were similar between treatments.

2.1.3 Conclusion

In patients with heart failure and loop diuretic resistance, dapagliflozin was not more effective at relieving congestion than metolazone. Patients assigned to dapagliflozin received a larger cumulative dose of furosemide but experienced less biochemical upset than those assigned to metolazone.

2.2 Introduction

Patients with heart failure (HF) who do not achieve the therapeutically desired diuresis despite a high dose of a loop diuretic are said to have 'diuretic resistance' and this lack of response is associated with worse clinical outcomes including prolonged hospital stay, higher risk of readmission after hospital discharge, and greater symptom burden and mortality.[6, 52-56] The usual treatment for this problem is to add a different diuretic to simultaneously block sodium resorption in a separate segment of the nephron.[1, 63, 67-76] The commonest approach is to add a thiazide (or thiazide-like) diuretic acting in the distal convoluted tubule, although this can cause worsening kidney function, hyponatraemia, and hypokalaemia.[1, 63, 69-74, 83, 84] However, there has been recent interest in agents acting on the proximal tubule because most sodium is absorbed in this segment. One such treatment, acetazolamide, has been shown to enhance decongestion when added to an intravenous (IV) loop diuretic in a placebo-controlled trial, although this was associated with a small increase in creatinine.[75] The sodium-glucose cotransporter type 2 (SGLT2) is also responsible for sodium absorption in the proximal tubule and SGLT2 inhibitors might also augment the natriuretic and aquaretic action of loop diuretics.[30, 31] These agents are of particular interest as they are not known to cause electrolyte disturbances, as they have been postulated to lead to a smaller reduction in blood volume, relative to interstitial fluid volume, compared to loop diuretics, and because they improve outcomes in patients with HF.[87, 88] If correct, the latter difference might lead to less kidney dysfunction with an SGLT2 inhibitor compared to a conventional diuretic.

To test whether an SGLT2 inhibitor might be an alternative to a thiazide-like diuretic in the treatment of patients with loop diuretic resistance, we compared the addition

of dapagliflozin or metolazone to loop diuretic treatment in patients hospitalized with HF who remained congested despite treatment with a high dose of IV furosemide. Metolazone was chosen as the reference therapy because it is believed to be at least as potent as alternative thiazide diuretics, effective in patients with a low glomerular filtration rate, and is recommended in guidelines. We hypothesized that dapagliflozin would lead to greater decongestion than metolazone but cause less kidney dysfunction. The primary endpoint of this randomized trial was the diuretic effect, measured as the reduction in weight, over 5 days (96 h).

2.3 Methods

2.3.1 Study design

This was a multi-centre, open-label, randomized, active-comparator, controlled clinical trial designed, and conducted by the Heart Failure Research Group at the University of Glasgow, sponsored by NHS Greater Glasgow & Clyde and The University of Glasgow. The Clinical Trials Unit at the Robertson Centre for Biostatistics (RCB, University of Glasgow) was responsible for data management and statistical analysis. This study was performed according to the UK Policy Framework for Health and Social Care Research, The Medicines for Human Use (Clinical Trials) Regulations, and the Declaration of Helsinki, and was approved by the Research Ethics Committee (REC) and the Health Research Authority (HRA). All patients provided written informed consent. This trial is registered at ClinicalTrials.gov identifier: NCT04860011; EudraCT Number: 2020-004832-48.

2.3.2 Trial participants

Adult patients hospitalized for worsening HF (regardless of ejection fraction) with diuretic resistance defined as insufficient decongestion (decrease in weight <1 kg or negative fluid balance <1 L) over the prior 24 h despite treatment with high dose IV loop diuretic (equivalent to ≥160 mg IV furosemide in 24 h) were eligible.[15] Additional inclusion criteria were plasma B-type natriuretic peptide (BNP) ≥ 100 pg/mL or plasma N-terminal proBNP (NT-proBNP) ≥ 400 pg/mL, persisting congestion (defined as any of pitting peripheral oedema, ascites, elevated jugular venous pressure, or

radiographic or ultrasonic evidence of pulmonary congestion) and an expected hospital length of stay >3 days. Exclusion criteria included type 1 diabetes, an estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m2, and receipt of an SGLT2 inhibitor, thiazide, or thiazide-like diuretic in the 48 h before randomization. A full list of inclusion and exclusion criteria is given in Appendix 1.

2.3.3 Randomization and treatment allocation

Participants were randomized using an online web portal in a 1:1 ratio, to receive dapagliflozin or metolazone, employing a mixed minimization and randomization approach, designed to maintain a balance between treatment groups for left ventricular ejection fraction (LVEF) (≤40% and >40%), eGFR (≤30 mL/min/1.73 m2, > 30 mL/min/1.73 m2) and trial site. Participants had to be randomized within 24 h of screening, and the allocated study drug was administered within 1 h of randomization.

Patients were assigned to dapagliflozin 10 mg once daily or metolazone 5–10 mg once daily for up to three consecutive days. Treating physicians were permitted to select a dose of either 5 mg or 10 mg metolazone, according to their clinical judgement, as this reflects dosing with this agent in routine practice. Up-titration or down-titration of the dose of treatment was permitted at the discretion of the treating physician. The dose of dapagliflozin was fixed at 10 mg as this is the dose proven in HF trials and recommended in guidelines. Either of the randomized treatments could be stopped or continued (or the alternative treatment commenced), at the treating physician’s discretion after the 3-day trial period. No dose of loop diuretic was specified.

2.3.4 Follow-up and endpoints

Study participants were followed-up daily for 5 days (96 h) for all clinical endpoints, reviewed at hospital discharge, and reassessed 90 days after discharge. The randomisation day (0 h timepoint) was considered to be Day 1, the 24 h timepoint

considered to be Day 2 and so on, hence the Day 5 follow up was equivalent to the 96 h timepoint.

The primary endpoint was the diuretic effect, as assessed by mean change in weight, from randomization to 96 h. The secondary endpoints were the change in congestion, assessed using lung ultrasound (LUS), loop diuretic efficiency, and a volume assessment ('congestion') score, assessed over the same period.

Loop diuretic efficiency was defined as weight loss in kilograms divided by the equivalent of 40 mg of furosemide. LUS examinations were performed by trained investigators using a phased array transducer with a Philips Lumify handheld ultrasound machine and an eight-zone protocol (four zones on each hemithorax; 6 s video clips), in addition to an assessment of each hemidiaphragm, as described previously.[89, 90] LUS measures of congestion were: (1) the sum of B-lines in eight zones, and (2) pleural effusion size (the sum of pleural effusion scores from each hemidiaphragm), as described in Appendix 2 along with a description of the imputation procedures. LUS images were analysed in a core laboratory (www.ultrasoundcore.net) at the Brigham Women's Hospital, Boston, USA, blinded to clinical characteristics, treatment assignment, and outcomes.

The volume assessment score was a modification of the score used in the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial and a detailed description of this is provided in Table 2-1.[75]

Change in NT-proBNP was an exploratory endpoint, measured in a core laboratory, using automated measurements (e411, Roche Diagnostics).

Table 2-1 Modified ADVOR clinical congestion score

OEDEMA (by clinical exam)	No oedema (score 0)	Pitting oedema – ankle (score 2)	Pitting oedema – knee (score 3)	Pitting oedema – above knee (score 4)
PLEURAL EFFUSION (by ultrasound)	No pleural effusion (score 0)	Minor pleural effusion (score 2)	Major pleural effusion (score 3)	
ASCITES (by clinical exam)	No ascites (score 0)	Significant ascites (score 3)		

2.3.5 Safety assessments and adverse events

Safety endpoints included changes in kidney function, serum sodium, and potassium from randomization to 96 h. A clinically significant worsening in kidney function was defined as an increase in serum creatinine of >26.5 μmol/L (0.3 mg/dL) from baseline. Hypokalaemia and hyperkalaemia were defined as serum potassium ≤3.5 mmol/L and ≥5.5 mmol/L respectively, and hyponatraemia was defined as a serum sodium concentration ≤125 mmol/L.

The occurrence of adverse events was recorded daily from the date of randomization until the earliest of (a) 5 days post-completion of trial treatment, (b) the date of crossover to non-trial dapagliflozin or metolazone, or (c) the date of discharge. In addition, adverse events of interest were recorded at each study visit using a safety questionnaire.

2.3.6 Sample size calculation and statistical analysis

We estimated that 27 patients per treatment group (54 patients in total) would provide 90% power (α level = 0.05) to detect a clinically meaningful difference of 2 kg in mean weight change (≃2 L fluid) between the two groups at 96 h, assuming a standard deviation (SD) of 2.2 kg. A final sample size of approximately 60 participants was planned to account for potential dropouts.

The primary and secondary efficacy analyses were conducted according to the intention-to-treat principle (i.e. in all patients), and it was planned that safety analyses would be performed in patients taking at least one dose of randomized treatment (which, in the event, was also in all patients).

Baseline characteristics are summarized as mean ± SD or median (first and third quartile, Q1, Q3) for continuous variables and counts (percentages) for categorical variables. For the primary and secondary endpoint analyses, randomized groups were compared using a mixed effects linear regression model of endpoint measurements at all time points. The model included a random effect for participants. Fixed effects were included for time point, LVEF, eGFR, and trial site. To take account of possible differences in treatment time course, two models were fitted. In one, fixed effects were included for separate treatment effects at each post-baseline visit and, in the other, fixed effects were included for a treatment effect at 24 h, and a common treatment effect at 48, 72, and 96 h. Treatment effect estimates from both models are reported with 95% confidence intervals (CIs) and P-values. Model-predicted means from Model 2 at each time point are presented graphically with 95% CIs. For the safety outcome measures, Fisher's exact test, t-test, and Wilcoxon–Mann–Whitney tests were used to test for differences between groups. All analyses were performed using R (version 4.0.0).

2.4 Results

2.4.1 Patients

Between 05 May 2021 to 03 January 2023, 1651 patients with HF who were receiving ≥160 mg IV furosemide daily were screened, the most common reason for exclusion was absence of diuretic resistance (Figure 2-1). 61 patients were randomized at seven sites across the UK. All participants were included in the intention-to-treat analysis. One patient was randomized but withdrew consent before receiving investigational treatment (Figure 2-1). The remaining 60 participants had data on the primary endpoint available at all assessment points. Data on vital status were available for all participants. No patients crossed over between treatment groups during the 3 days

of study drug administration. Three patients in the metolazone arm were prescribed dapagliflozin between 72 and 96 h, and nine patients in the metolazone arm were prescribed dapagliflozin at discharge. Among the 30 patients initially assigned to dapagliflozin, two were prescribed metolazone between 72 and 96 h, and 4 prescribed metolazone at discharge.

Patients were randomized a median (Q1, Q3) of 6 (4, 11) days after admission. Their median age was 79 years, and 46% were men (Table 2-2). The median LVEF was 45% and the median NT-proBNP level was 4053 pg/mL. Overall, 44% of patients had an LVEF of ≤40%. Most patients had peripheral oedema (98%), pulmonary crepitations (93%), elevated jugular venous pressure (75%), and a third of patients had ascites (36%). The median (Q1, Q3) LUS B-line count was 12 (6, 18).

Comorbidities were common, in particular atrial fibrillation/flutter (67%), anaemia (61%), and type 2 diabetes (46%). Most participants had chronic kidney disease (CKD) (90%). The median eGFR was 41 mL/min/1.73 m2 at baseline, and 26% of patients had Grade 4 CKD (eGFR <30 mL/min/1.73 m2).

Patient characteristics were largely balanced between treatment groups at baseline, except for a higher proportion with type 2 diabetes and a higher median NT-proBNP in the dapagliflozin arm and some more evidence of congestion in the metolazone arm.

The rate of prescription of a renin-angiotensin system inhibitor was low (23%) although more patients were prescribed a beta- blocker (75%) and a mineralocorticoid receptor antagonist (MRA) (36%).

Figure 2-1 DAPA-RESIST Consort Diagram

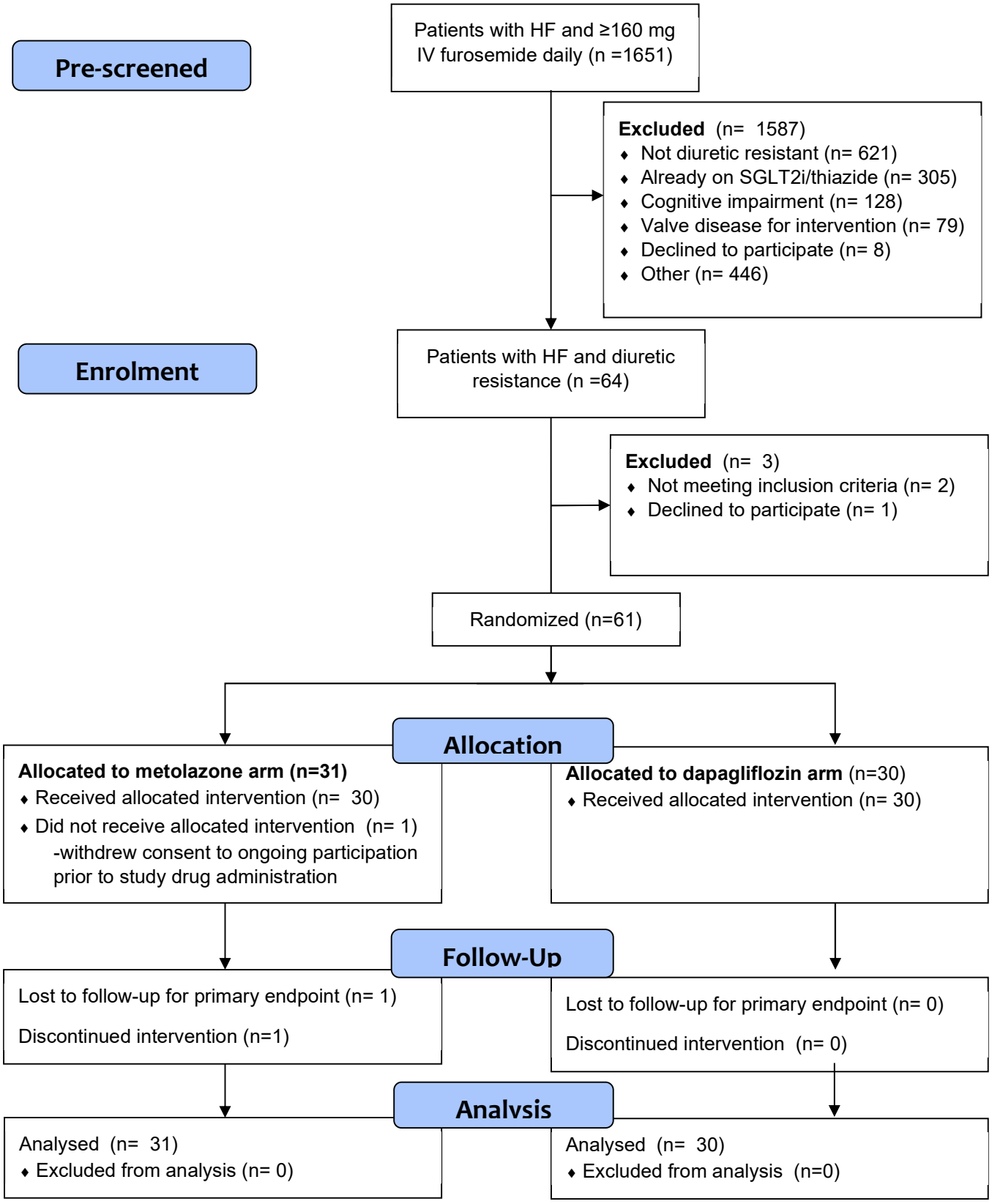


Table 2-2 Baseline characteristics according to treatment allocation

Characteristic	All (*n* = 61)	Dapagliflozin (*n* = 30)	Metolazone (*n* = 31)
Age (years)	79(71–85)	79 (73–86)	79 (68–84)
Male sex—*n* (%)	28 (46)	13 (43)	15 (48)
White race—*n* (%)	59 (97)	29 (97)	30 (97)
BMI (kg/m^2)	33 (27–37)	32 (27–36)	33 (28–38)
SBP (mmHg)	116 (106–128)	115 (104–128)	118 (109–127)
Heart rate (bpm)	72 (66–83)	71 (66–82)	72 (67–85)
HF history			
Ischaemic aetiology—*n* (%)	20 (33)	10 (33)	10 (32)
Valvular HF—*n* (%)	12 (20)	5 (17)	7 (23)
LVEF (%)	45 (35–55)	45 (35–55)	45 (35–55)
LVEF ≤40%—*n* (%)	27 (44)	13 (43)	14 (45)
Prior HF Hospitalization—*n* (%)	35 (57)	12 (40)	23 (74)
Past medical history—*n* (%)			
Type 2 diabetes	28 (46)	19 (63)	9 (29)
Myocardial infarction	21 (34)	9 (30)	12 (39)
Stroke	5 (8)	0	5 (16)
AF/flutter	41 (67)	18 (60)	23 (74)
Peripheral arterial disease	3 (5)	2 (7)	1 (3)
Chronic anaemia[a]	37 (61)	19 (63)	18 (58)
CKD[b]	55 (90)	28 (93)	27 (87)
Physical examination			
Elevated JVP (>4 cm)—*n* (%)	46 (75)	21 (70)	25 (81)
Pulmonary crepitations—*n* (%)	57 (93)	27 (90)	30 (97)
Peripheral oedema—*n* (%)	60 (98)	30 (100)	30 (97)
Ascites—*n* (%)	22 (36)	7 (23)	15 (48)
Modified ADVOR clinical congestion score	6.0 (5.0–9.0)	6.0 (5.5–8.0)	7.0 (5.2–9.0)
Pleural effusion[c]—*n* (%)	29 (48)	13 (43)	16 (52)
Pleural effusion size score	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (0.0–2.0)
B-lines (total number B-lines)	12.0 (5.8–18.0)	12.0 (6.2–18.2)	12.5 (3.5–17.8)
Baseline blood tests			
NT-proBNP (pg/mL)	4053 (1768–6461)	4855 (1792–9753)	3806 (1228–6140)

eGFR (mL/min/1.73 m2)	40.7 (32.4–54.4)	40.7 (34.1–50.7)	40.7 (29.2–59.1)
eGFR <30 mL/min/ 1.73 m^2—*n* (%)	14 (26)	7 (25)	7 (26)
Sodium (mmol/L)	138 (135–140)	138 (133–139)	139 (137–141)
Potassium (mmol/L)	4.0 (3.8–4.3)	4.1 (3.8–4.4)	4.0 (3.8–4.2)
Urea (mmol/L)	12.4 (8.3–17.2)	12.4 (9.6–15.9)	12.2 (7.8–18.7)
Creatinine (µmol/L)	130 (101–172)	131 (101–168)	130 (101–172)
HbA1c (mmol/mol)	43.5 (37.0–51.2)	44.5 (37.0–56.5)	40.0 (37.8- 50.0)
Treatment before admission—*n* (%)			
ACEi/ARB/ARNI	19 (31)	12 (40)	7 (23)
Beta-blocker	45 (74)	25 (83)	20 (65)
MRA	22 (36)	11 (37)	11 (35)
Loop diuretic	54 (89)	26 (87)	28 (90)
Thiazide or thiazide-like diuretic	8 (13)	3 (10)	5 (16)
SGLT2i	2 (3)	2 (7)	0
ICD/CRT	3 (5)	1 (3)	2 (6)
Treatment at randomization—*n* (%)			
ACEi/ARB/ARNI	14 (23)	10 (33)	4 (13)
Beta-blocker	46 (75)	24 (80)	22 (71)
MRA	22 (36)	10 (33)	12 (39)
Total daily loop diuretic dose at randomization – mean (SD)			
Total daily loop diuretic dose at randomization (mg)	244 (120)	260 (139)	229 (99)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ADVOR, Acetazolamide in Decompensated Heart Failure with Volume Overload; AF, atrial fibrillation; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; ICD, implantable cardioverter defibrillator; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Values expressed as *n* (%) or median (quartile 1–quartile 3), or mean (SD).
[a]Female Hb <120 g/L; Male Hb <130 g/L.
[b]eGFR <60 mL/min/1.73 m2.
[c]Assessed clinically.

2.4.2 Loop diuretic use after randomization

The mean (SD) cumulative dose of furosemide administered over the 96 h after randomization was 977 (492) mg in the dapagliflozin group and 704 (428) mg in patients assigned to metolazone and (P = 0.02). The mean (SD) daily dose of furosemide was 255 (120) mg in the dapagliflozin group and 185 (115) mg in the metolazone group. The mean dose of furosemide per day is shown in Table 2-3. The mean (SD) daily dose of dapagliflozin and metolazone used over the three days of study treatment was 10 (0) mg and 5.4 (1.3) mg, respectively.

Table 2-3 Cumulative furosemide dose per day

	Dapagliflozin (n=30)	Metolazone (n=30)	p value
Total cumulative furosemide dose, mg			
24 hours	253 (106)	221 (98)	0.61
48 hours	520 (238)	412 (197)	0.19
72 hours	756 (360)	566 (313)	0.04
96 hours	977 (493)	704 (427)	0.02
Daily furosemide dose, mg			
24 hours	253 (106)	229 (90)	0.77
48 hours	266 (140)	198 (115)	0.11
72 hours	245 (145)	163 (134)	0.05
96 hours	228 (163)	152 (135)	0.14

Values expressed as mean (standard deviation)

2.4.3 Primary efficacy endpoint

Weight loss was numerically but not statistically significantly smaller in patients treated with dapagliflozin compared with metolazone (Table 2-4 and Figure 2-2).
The mean (SD) decrease in weight with dapagliflozin at 24, 48, 72, and 96 h with dapagliflozin was −1.2 (1.2) kg, −2.2 (1.3) kg, −2.6 (1.8) kg, and −3.0 (2.5), respectively compared to −1.8 (1.1) kg, −2.6 (1.5) Kg, −3.2 (1.8) kg, and −3.6 (2.0)

kg, respectively, with metolazone. The modelled mean (95% CI) differences in change in weight at 24, 48, 72, and 96 h were 0.55 (−0.22, 1.31) kg (P = 0.17), 0.46 (−0.31, 1.22) kg (P = 0.25), 0.59 (−0.18, 1.35) kg (P = 0.14), and 0.65 (−0.12, 1.41) kg (P = 0.11), respectively.

In the alternative model, the estimated mean (95% CI) difference in change in weight was 0.55 (−0.22, 1.31) kg at 24 h (P = 0.17) and 0.56 (−0.06, 1.19) kg over 48–96 h (P = 0.08).

In a post hoc sensitivity analysis, we also adjusted the treatment effect for type 2 diabetes (yes/no), baseline NT-proBNP level, and ascites (yes/no). This did not meaningfully change the results (Table 2-5 and Figure 2-3).

Table 2-4 Primary and secondary efficacy endpoints

	Dapagliflozin (*n* = 30)		**Metolazone (*n* = 31)**		**Between-group difference (95% CI)[a]**	***P*-value**
Primary endpoint	***n*=**		***n*=**			
Weight at baseline (kg)	30	87.6 (20.2)	31	91.7 (23.1)		
Change from baseline (kg)						
24 h	30	−1.2 (1.2)	30	−1.8 (1.1)	0.55 (−0.22, 1.31)	0.17
48 h	30	−2.2 (1.3)	30	−2.6 (1.5)	0.46 (−0.31, 1.22)	0.25
72 h	30	−2.6 (1.8)	30	−3.2 (1.8)	0.59 (−0.18, 1.35)	0.14
96 h	30	−3.0 (2.5)	30	−3.6 (2.0)	0.65 (−0.12, 1.41)	0.11
48–96 h	—	—	—	—	0.56 (−0.06, 1.19)	0.08

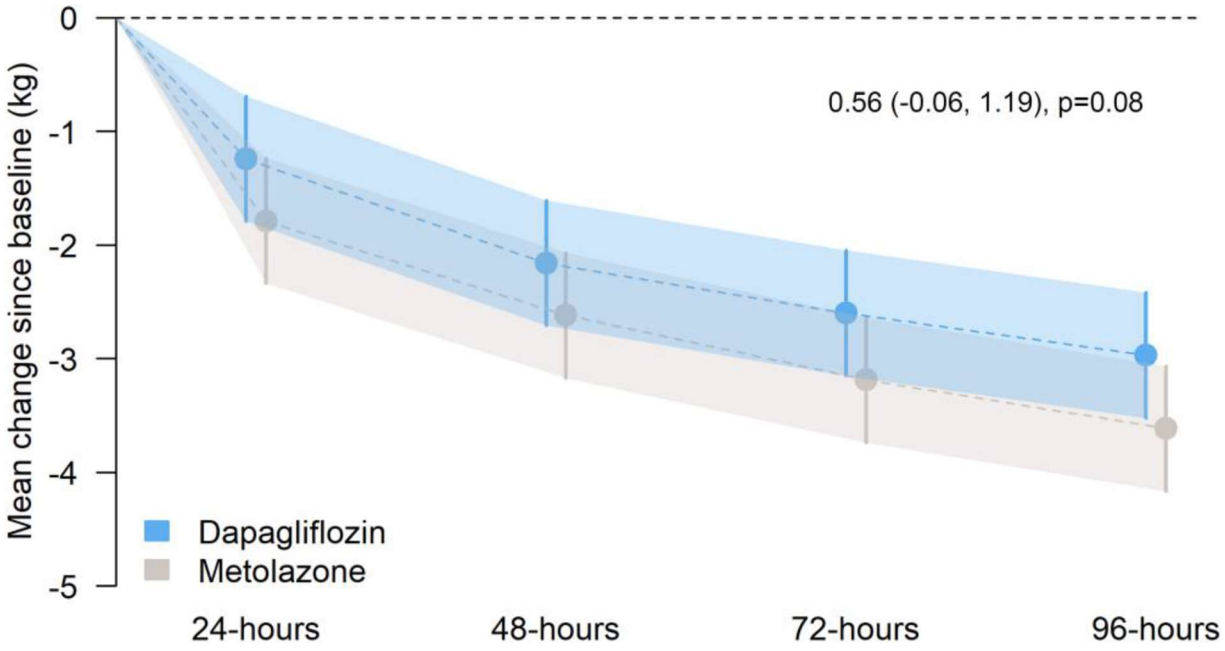
Secondary endpoints						
Sum of B-lines on LUS (eight zones) at baseline	26	12.0 (5.8, 18.0)	30	12.5 (3.5, 17.8)	—	—
Change from baseline						
24 h	23	−2.0 (−3.5, 0.5)	29	−2.0 (−5.0, 2.0)	0.54 (−1.56, 2.64)	0.62
48 h	25	−3.0 (−5.0, 2.0)	25	−3.0 (−6.0, 0.0)	0.28 (−1.85, 2.41)	0.80
72 h	25	−3.0 (−5.0, 0.0)	27	−1.0 (−6.5, 1.5)	−0.24 (−2.35, 1.87)	0.83
96 h	24	−3.0 (−5.2, -0.8)	29	−1.0 (−6.0, 1.0)	−1.16 (−3.27, 0.94)	0.29
48–96 h	—	—	—	—	−0.38 (−2.09, 1.32)	0.67
Total pleural effusion score at baseline	30	2.5 (1.6, 3.5)	31	1.9 (1.0, 2.7)	—	—
Change from baseline						
24 h	29	−0.6 (−1.2, −0.2)	30	−0.1 (−0.7, 0.5)	−0.39 (−1.05, 0.26)	0.24
48 h	29	−0.8 (−1.4, −0.2)	30	−0.5 (−1.0, −0.1)	−0.24 (−0.93, 0.46)	0.50
72 h	29	−1.0 (−1.7, −0.3)	30	−0.7 (−1.3, −0.1)	−0.19 (−0.98, 0.60)	0.63
96 h	29	−1.1 (−1.9, −0.3)	30	−0.7 (−1.4, −0.1)	−0.26 (−1.04, 0.52)	0.50
48–96 h	—	—	—	—	−0.23 (−0.88, 0.42)	0.48
Loop diuretic efficiency						
24 h	30	0.23 (0.22)	29	0.34 (0.24)	−0.11 (−0.20, −0.01)	0.03
48 h	30	0.19 (0.13)	30	0.30 (0.23)	−0.09 (−0.18, 0.00)	0.07
72 h	30	0.17 (0.13)	30	0.27 (0.22)	−0.08 (−0.17, 0.01)	0.10

96 h	30	0.15 (0.12)	30	0.25 (0.19)	−0.08 (−0.17, 0.01)	0.10
48–96 h	—	—	—	—	−0.08 (−0.17, 0.00)	0.07
Modified ADVOR score at baseline	30	5.8 (5.0, 6.6)	31	6.3 (5.4, 7.2)	—	—
Change from baseline						
24 h	29	−0.8 (−1.4, −0.2)	30	−0.9 (−1.5, −0.2)	−0.04 (−0.85, 0.77)	0.92
48 h	29	−1.4 (−2.1, −0.8)	30	−1.7 (−2.3, −1.0)	0.10 (−0.75, 0.96)	0.81
72 h	29	−1.9 (−2.6, −1.1)	30	−2.3 (−3.0, −1.5)	0.29 (−0.57, 1.15)	0.51
96 h	29	−2.2 (−3.0, −1.5)	30	−2.6 (−3.3, −1.9)	0.22 (−0.63, 1.08)	0.60
48–96 h	—	—	—	—	0.21 (−0.48, 0.89)	0.56

Baseline data are presented as mean (SD) or median (Q1, Q3). Change from baseline data are presented as mean (SD) or median (Q1, Q3).

[a]Between-group difference presented as mean difference (95% CI) from a mixed effects linear regression model measured at all visit time points including a random effect for the subject and fixed effects for the visit time point, baseline LVEF, baseline eGFR, and study site.

Figure 2-2 Mean change in weight (kg) from randomization to 48, 72, and 96 h in dapagliflozin vs. metolazone groups



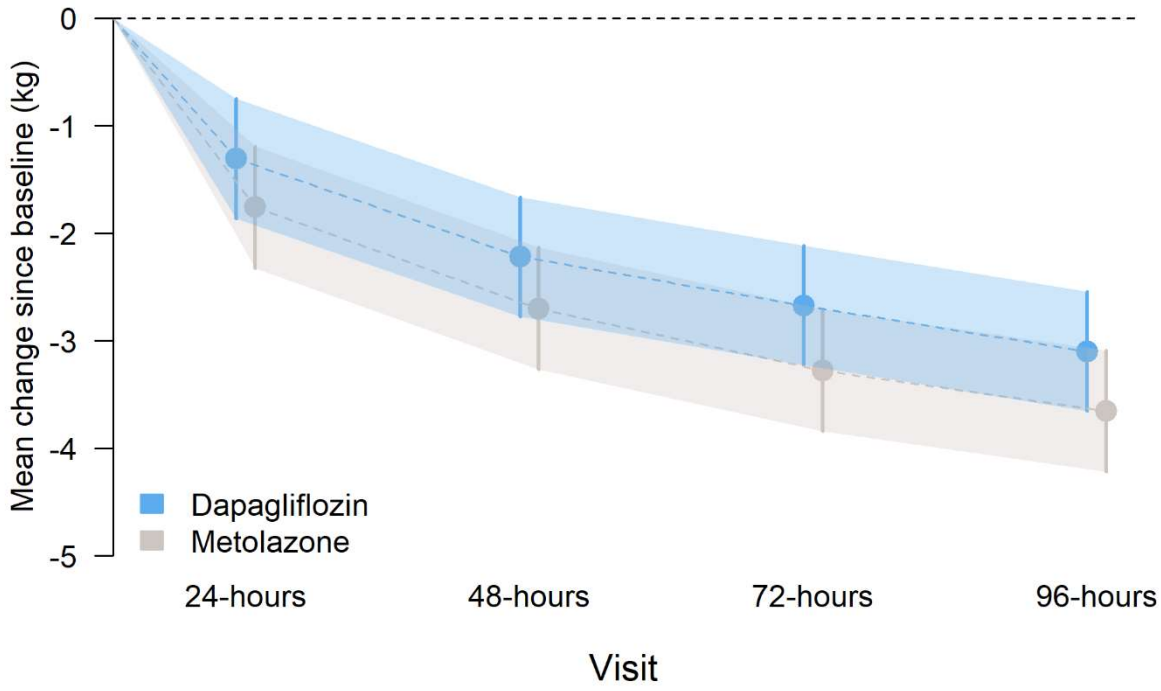
Model-predicted mean change in weight from baseline with 95% confidence intervals at each time point.

Table 2-5 Primary Outcome - Sensitivity Analysis

Randomised treatment groups compared using a mixed effects linear regression model of weight measured at all visit time points.
Two models have been fitted, each including a random effect for subject and fixed effects for visit time point, baseline LVEF, baseline eGFR, study site, type 2 diabetes, baseline NT-proBNP and presence of ascites at baseline.
- Model 1 includes a treatment effect at 24-hours and a common treatment effect at 48, 72 and 96-hours.
- Model 2 includes a separate treatment effect at each post-baseline visit.
Intervention (Dapagliflozin) group treatment effect estimate presented with 95% confidence interval and p-value, at each post-baseline visit and for the combined 48, 72 and 96-hour visits. Metolazone is the reference group for all treatment effect estimates.
The likelihood ratio test p-value assesses whether the treatment effect changes between 48 and 96-hours.

Time Point	**Intervention effect estimate, 95% CI and p-value**
Model 1:	
24-hours	0.45 (-0.32, 1.23), p=0.264
Combined 48 to 96-hours	0.55 (-0.09, 1.18), p=0.098
Model 2:	
24-hours	0.45 (-0.32, 1.23), p=0.266
48-hours	0.48 (-0.29, 1.26), p=0.236
72-hours	0.60 (-0.17, 1.38), p=0.137
96-hours	0.56 (-0.22, 1.33), p=0.172
Likelihood Ratio Test p-value = 0.952	

Figure 2-3 Mean change in weight (kg) from randomization to 48,72 and 96 hours in dapagliflozin vs metolazone groups – sensitivity analysis



Model-predicted mean change in weight from baseline with 95% confidence intervals at each time point. Model have been fitted including a random effect for subject and fixed effects for visit time point, baseline LVEF, baseline eGFR, study site, type 2 diabetes, baseline NT-proBNP and presence of ascites at baseline.

2.4.4 Secondary efficacy endpoints

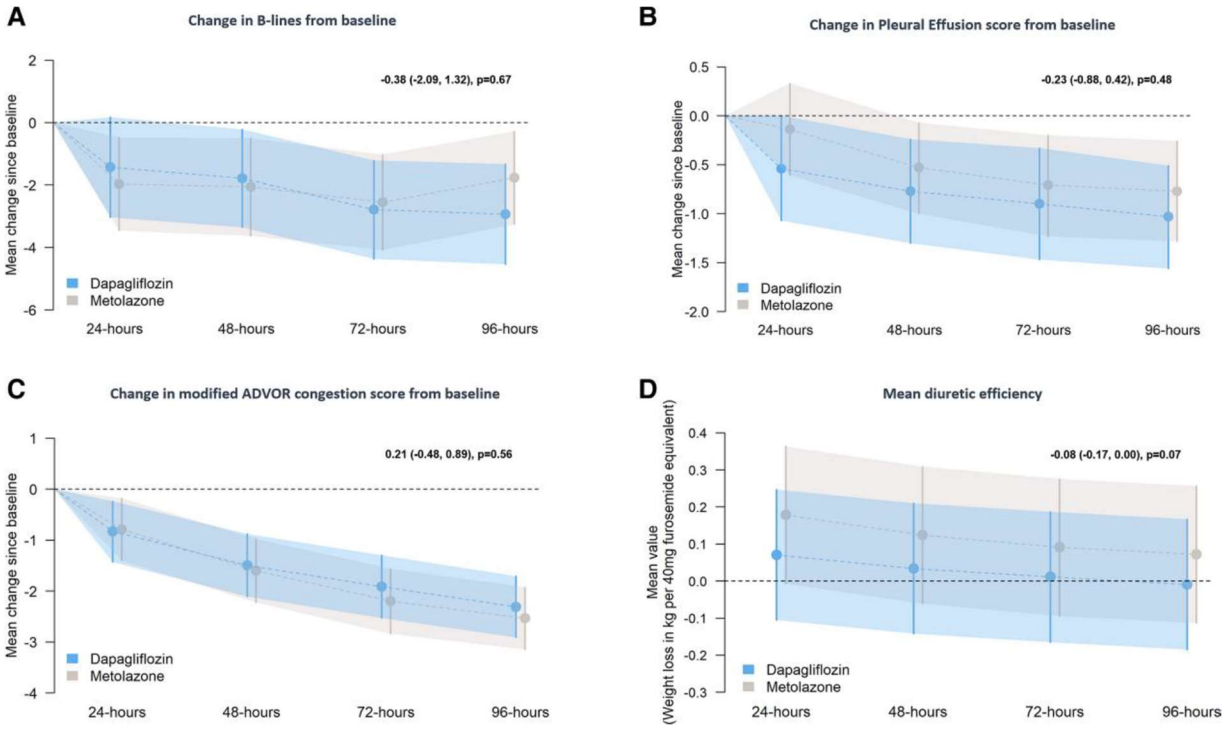
The mean decrease in B-line count over 96 h was similar in patients assigned to dapagliflozin and metolazone (Table 2-4 and Figure 2-4A).

Overall, 17 patients assigned to dapagliflozin and 11 assigned to metolazone had a pleural effusion at baseline. Effusion score decreased similarly in the two treatment groups (Table 2-4 and Figure 2-4B).

The mean (95% CI) change in modified ADVOR volume assessment score at 24, 48, 72, and 96 h after randomization was also similar between treatment groups (Table 2-4 and Figure 2-4C).

Loop diuretic efficiency, defined as the change in weight (kg) per 40 mg of furosemide administered, was smaller with dapagliflozin than with metolazone at each time point after randomization although the difference was only significant at 24 h (Table 2-4 and Figure 2-4D).

Figure 2-4 Secondary endpoints

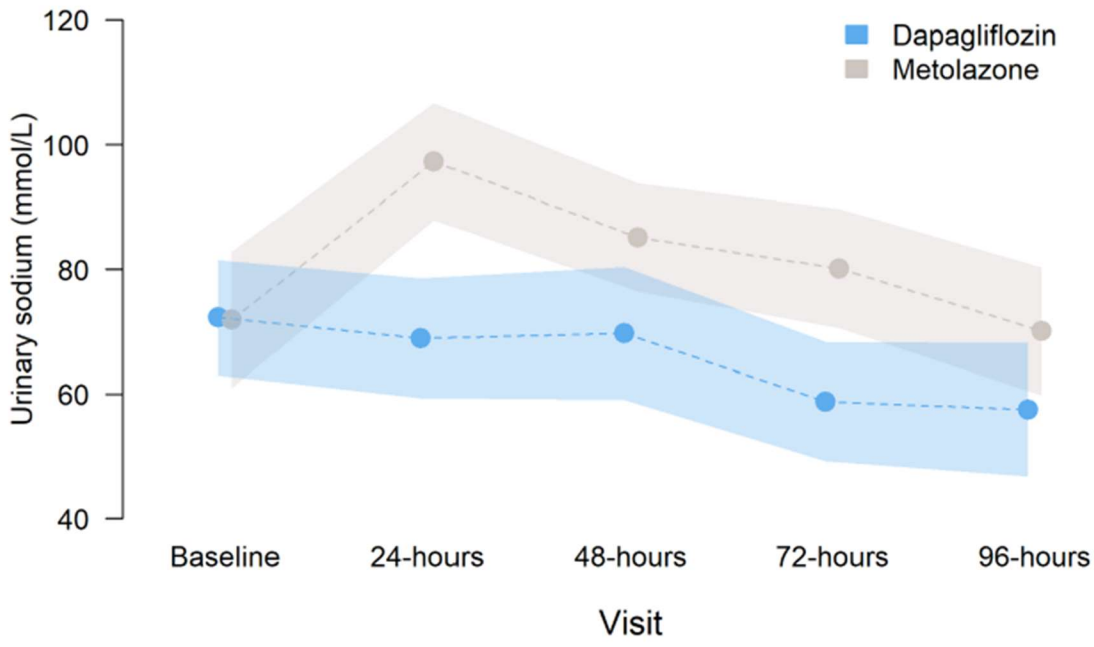


Mean change in B-lines (panel A), pleural effusion score (panel B), and congestion score (panel C), from randomization to 48, 72, and 96 h. Mean diuretic efficiency (panel D) was calculated at 24, 48, 72, and 96 h. Model-predicted mean change from baseline with 95% confidence intervals at each time point. The treatment effect estimate displayed in the text represents the between-group difference (dapagliflozin vs. metolazone) in the common effect estimate between 48 and 96 h.

2.4.5 Exploratory efficacy endpoints

The median (Q1, Q3) decreases in NT-proBNP in the dapagliflozin group at 24, 48, 72, and 96 h were 27 (−770, 429), −91 (−1676, 184), −361 (−1308, −52), and −436 (−1758, 76) pg/mL, respectively. The corresponding decreases in the metolazone group were 138 (−232, 1347) P = 0.19, 16 (−442, 1240) P = 0.23, −223 (−854, 826) P = 0.18, and −341 (−819, 481) P = 0.26 pg/mL. Urinary spot sodium was greater at all time points in the metolazone group (Figure 2-5). Daily urine output and cumulative net fluid balance were similar between groups (Figures 2-6 and 2-7).

Figure 2-5 Spot urinary sodium (mmol/L) per study day



Absolute values summarised at each time point with shaded 95% confidence interval area, by randomised treatment group.

Figure 2-6 Cumulative fluid balance (ml) per study day

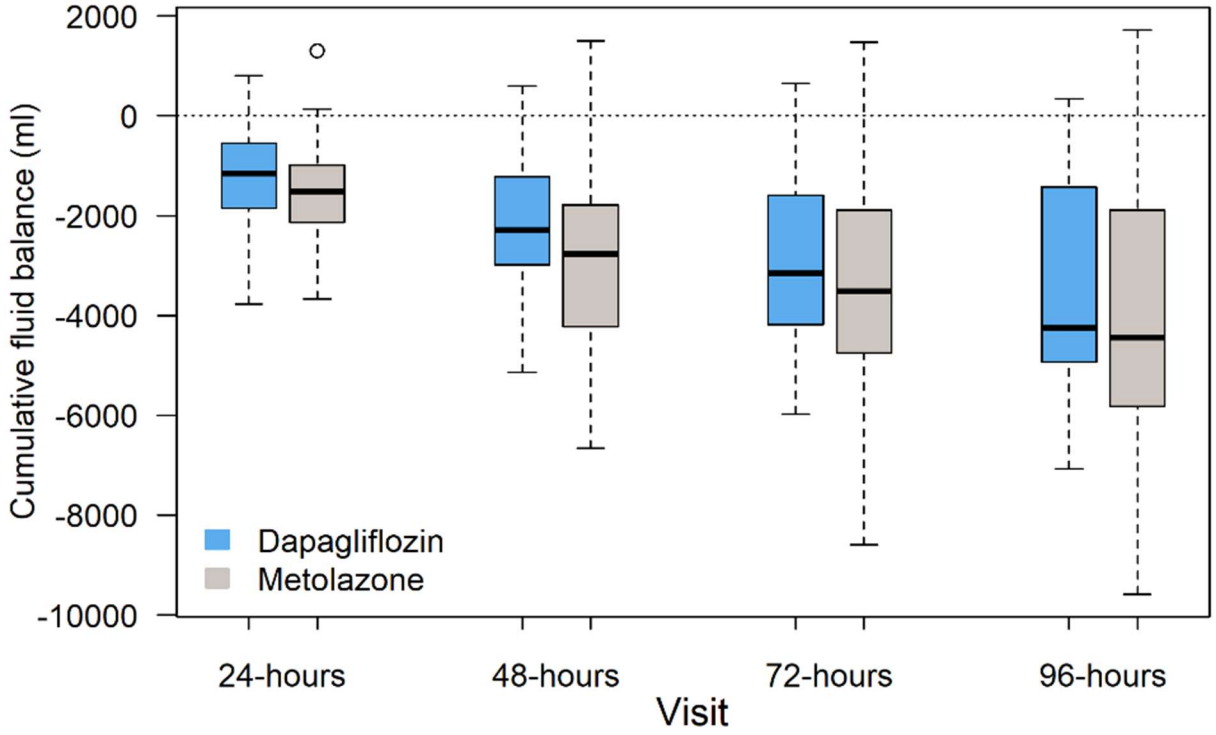
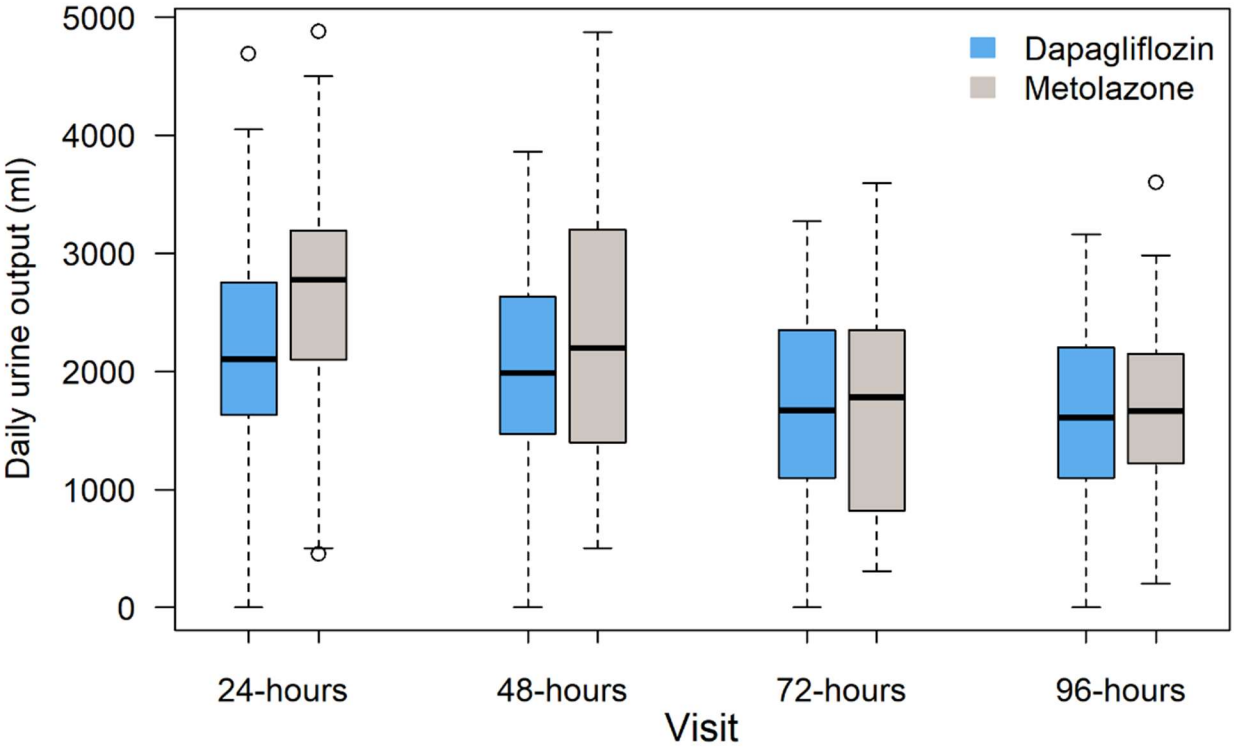


Figure 2-7: Urine output (ml) per study day



2.4.6 Safety endpoints and adverse events

The prespecified laboratory safety assessments and adverse events of interest are shown in Table 2-6.

Table 2-6 Safety assessments and adverse events of interest

	n=	Dapagliflozin (*n* = 30)	*n*=	Metolazone (*n* = 31)	*P*-value
Change in serum urea from baseline, mmol/L					
24 h	30	−0.0 (1.4)	29	0.6 (1.5)	0.26
48 h	30	−0.0 (1.9)	29	1.9 (2.7)	<0.01
72 h	28	0.1 (3.0)	29	3.7 (3.9)	<0.01
96 h	30	−0.0 (3.7)	29	4.4 (5.0)	<0.01
Change in eGFR from baseline, mL/min/1.73 m^2					
24 h	30	−3.0 (−5.8, −0.9)	30	−2.5 (−4.6, 0.3)	0.83
48 h	30	−3.0 (−6.2, −0.1)	30	−5.2 (−9.9, −2.5)	0.02
72 h	28	−3.7 (−7.5, 1.5)	30	−8.9 (−13.6, −3.4)	0.01
96 h	30	−5.9 (−9.4, −0.8)	30	−7.3 (−12.3, −4.9)	0.09
Change in serum creatinine from baseline, µmol/L					
24 h	30	8.4 (14.6)	30	6.9 (13.1)	0.67
48 h	30	10.4 (18.7)	30	20.8 (18.9)	0.04
72 h	28	11.2 (28.2)	30	29.3 (26.9)	0.02
96 h	30	16.5 (32.5)	30	29.7 (29.7)	0.11
Impaired renal function[a]					
Increase in serum creatinine concentration of >26.5 µmol/L	30	14 (47)	30	15 (50)	1.00
eGFR decrease > 50%	30	2 (7)	30	0	0.49
Change in serum potassium from baseline, mmol/L					
24 h	29	0.0 (−0.4, 0.2)	28	0.3 (−0.5, −0.1)	0.02
48 h	29	−0.2 (−0.4, 0.0)	28	−0.3 (−0.6, 0.0)	0.29
72 h	28	0.0 (−0.6, 0.4)	29	−0.3 (−0.5, −0.1)	0.30
96 h	29	−0.1 (−0.4, 0.2)	28	−0.3 (−0.4, 0.0)	0.43
Hypokalemia/hyperkalemia[a]					
Serum potassium ≤3.0 mmol/L	30	1 (3)	30	3 (10)	0.61
Serum potassium ≤3.5 mmol/L	30	15 (50)	30	19 (63)	0.44
Serum potassium ≥5.5 mmol/L	30	1 (3)	30	0	1.00
Change in serum sodium from baseline, mmol/L					
24 h	30	1.0 (−1.0, 2.8)	30	−1.0 (−2.0, 0.0)	<0.01
48 h	30	1.0 (−1.0, 2.0)	30	−2.0 (−3.0, 0.0)	<0.01

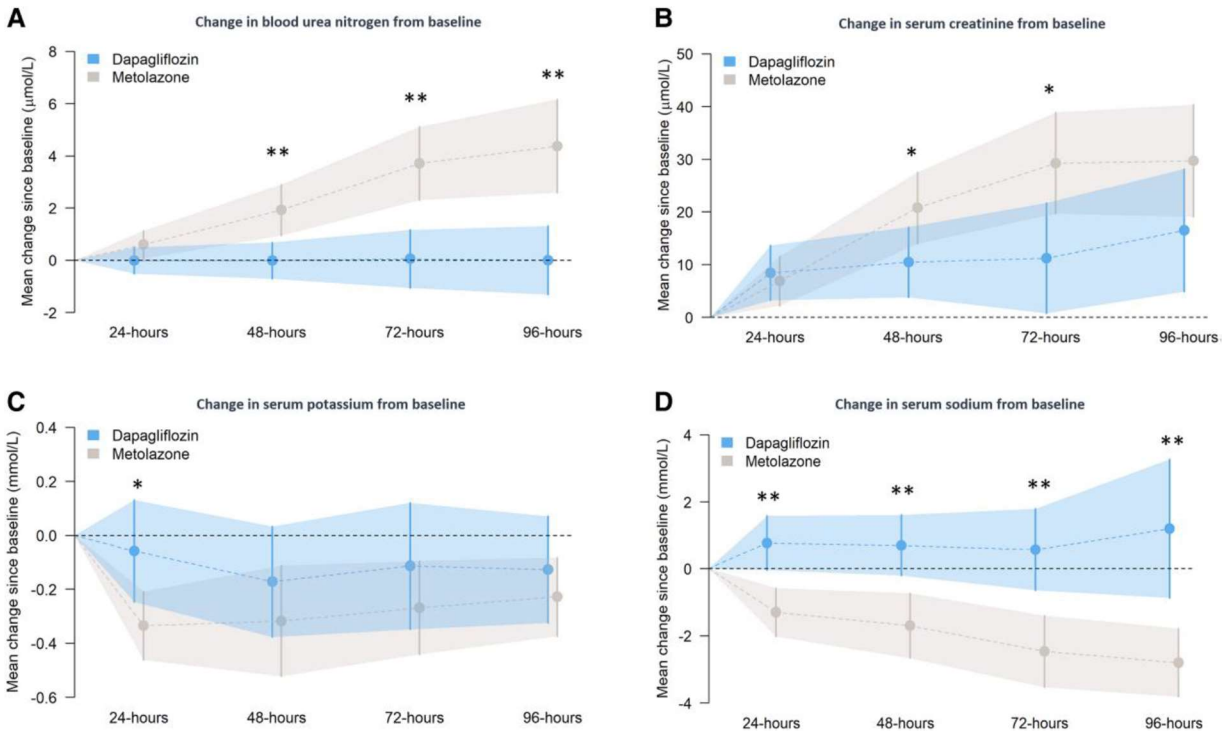
72 h	28	1.0 (−2.0, 2.2)	30	−2.0 (−5.0, −1.0)	<0.01
96 h	30	0.5 (−1.0, 2.0)	30	−3.0 (−4.8, −1.2)	<0.01
Hyponatraemia[a]					
Serum sodium ≤125 mmol/L	30	1 (3)	30	0	1.00
Serum sodium ≤130 mmol/L	30	5 (17)	30	4 (13)	1.00
AE of special interest—	30	—	30	—	—
Symptoms of hypotension/volume depletion	—	0	—	4 (13)	0.11
Urinary tract infections		0		1 (3)	1.00
Genital infections		0		0	n/a
Ketoacidosis		0		0	n/a
Hepatic injury		0		0	n/a
Clinically meaningful escalation of loop diuretic therapy[b]		0		0	n/a
New utilization/escalation of vasoactive therapy		0		1 (3)	1.00
Renal replacement therapy		0		0	n/a
Worsening HF		0		1 (3)	1.00

Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; n/a, not applicable.

[a]At any time point between baseline and 96 h assessment.

[b]Defined as >50% increase in daily dose.

Figure 2-8 Safety endpoints



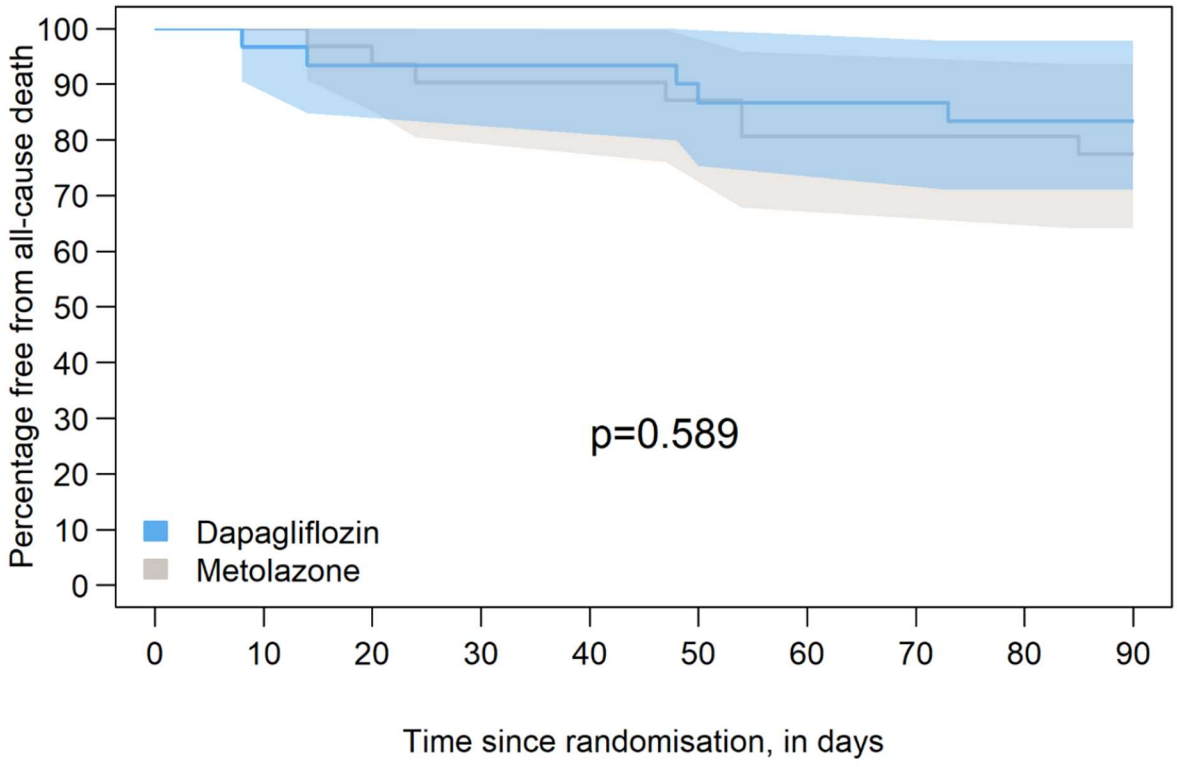
Mean change in blood urea nitrogen (panel A), creatinine (panel B), serum potassium (panel C), and serum sodium (panel D) from baseline with 95% confidence intervals at each time point.
*P < 0.05;
**P < 0.01.

Serum sodium and potassium decreased more and urea and creatinine increased more, with metolazone compared to dapagliflozin, although only differences in urea and sodium were significant (Table 2-6 and Figure 2-8). However, there was no difference between treatments in the proportion of patients crossing the predefined thresholds for worsening kidney function, hyponatraemia, or hypokalaemia.

There was no significant difference in adverse events of interest between metolazone and dapagliflozin although a higher proportion of patients (13%) treated with metolazone experienced symptoms of hypotension/volume depletion compared to those treated with dapagliflozin (0%) (P = 0.11).

Median (Q1, Q3) length of stay was similar between dapagliflozin and metolazone groups, at 20 (13, 32) and 19 (12, 26) days (P = 0.41), respectively. Mortality was similar between groups at all time points (Figure 2-9), with two (7%) in-hospital deaths in the dapagliflozin group compared to 4 (13%) in the metolazone group. By 90 days, five patients (17%) in the dapagliflozin group and seven (23%) patients in the metolazone group had died. Time to first HF hospitalization and time to first HF hospitalization/all-cause mortality were similar between treatment groups (Figures 2-10 and 2-11).

Figure 2-9 Kaplan-Meier survival plot of time from randomisation until all-cause death, by randomised treatment group



Solid line presents the survival probability estimate and the dotted lines give the upper and lower 95% confidence interval. The p-value presented is from the log-rank test comparing the survival curve of each randomised treatment group.

Figure 2-10 Kaplan-Meier survival plot of time from randomisation until first heart failure re-hospitalisation, by randomised treatment group

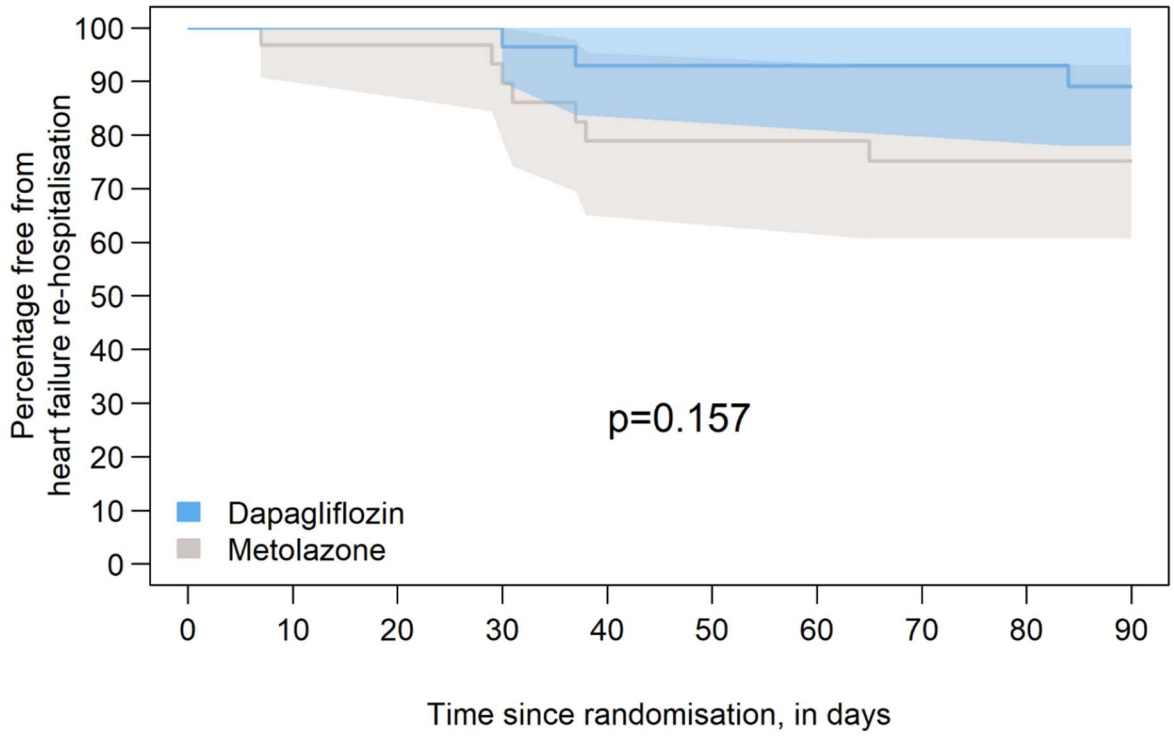
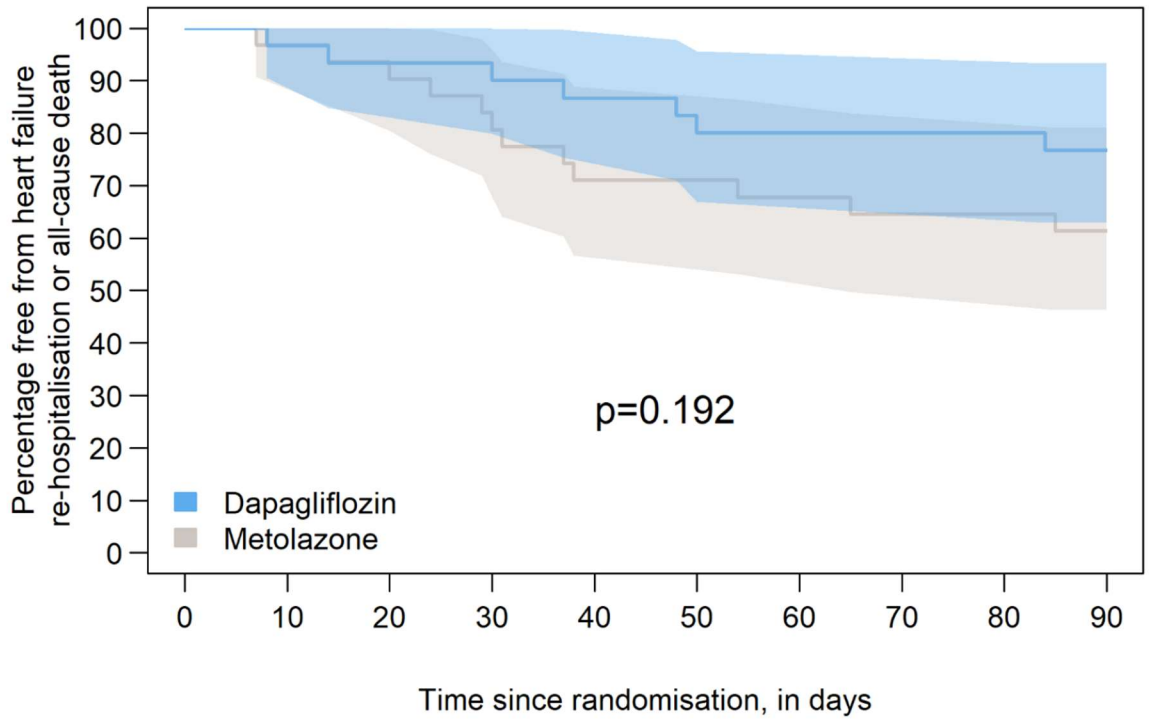


Figure 2-11 Kaplan-Meier survival plot of time from randomisation until first HF re-hospitalisation or all-cause death, by randomised treatment group



2.5 Discussion

Some patients admitted to the hospital with worsening HF and congestion do not respond adequately to an IV loop diuretic. Guidelines recommend concomitant administration of another diuretic acting at a different site in the nephron to overcome this resistance and relieve persisting congestion. Usually, a thiazide diuretic or metolazone is recommended although there has also been recent interest in the use of acetazolamide. Like acetazolamide, SGLT2 inhibitors act in the proximal tubule and may augment the action of a loop diuretic.[87, 91, 92] Because most sodium absorption takes place in the proximal tubule, we hypothesized that an agent acting in this segment of the nephron would lead to greater decongestion than one acting distally. However, the primary outcome of weight loss, a measure of decongestion, was not significantly different between patients randomly assigned to the SGLT2 inhibitor dapagliflozin compared to metolazone: mean (SD) decrease in weight at 96 h −3.0 (2.5) kg vs. −3.6 (2.0) kg, respectively, mean (95% CI) difference between groups 0.65 (−0.12, 1.41) (P = 0.11). The prespecified secondary outcomes which also reflected congestion, including the number of B-lines and size of pleural effusions on LUS, and the modified ADVOR volume assessment score, also decreased to a similar extent in each treatment group. Although these data collectively suggested equivalent decongestion in the two randomized treatment groups, this required a higher total dose of furosemide in the dapagliflozin group, with a mean total cumulative dose of 977 mg at 96 h, compared to 704 mg in the metolazone group. As a result, diuretic efficiency (kilogram of weight loss per 40 mg of furosemide), the final secondary endpoint, was lower in the dapagliflozin group compared to the metolazone group, suggesting a more modest natriuretic action of SGLT2 inhibitors than anticipated. However, despite the use of more furosemide, decongestion in the dapagliflozin group was achieved with smaller decreases in plasma sodium and potassium, and smaller increases in urea (blood urea nitrogen) and creatinine than in the metolazone group, in keeping with our hypothesis that SGLT2 inhibition would cause less kidney dysfunction and electrolyte disturbance than metolazone.

The present findings can be compared to those from other recent trials of combination diuretic therapy in patients hospitalized with worsening HF, albeit not specifically with diuretic resistance. In the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial, the median (interquartile range) weight loss over 72 h in patients randomly assigned to placebo in addition to IV furosemide was 1.5 (0.0–3.2) kg and 2.0 (2.1–4.6) kg in those assigned to hydrochlorothiazide, giving an adjusted placebo-corrected difference of 1.14 (0.42–1.84) kg.[13] The total mean dose of furosemide administered from enrolment to 72 h was 375 mg in the placebo group and 340 mg in the hydrochlorothiazide group (compared with 756 mg in the dapagliflozin group and 566 mg in the metolazone group in the present trial). The greater diuretic effect of hydrochlorothiazide was achieved at the expense of worse renal function and more hypokalaemia.

Perhaps of more interest, is the ADVOR trial, given the proximity of site of action of both dapagliflozin and acetazolamide in the proximal tubule although neither directly inhibits sodium-hydrogen exchanger 3 which accounts for most sodium reabsorption in this segment of the nephron.[75, 93] In addition, acetazolamide appears to have relatively more effect on sodium compared to water excretion than SGLT2 inhibitors. The estimated mean decrease in weight in the placebo group by day 3 was 1.64 kg compared to 3.31 kg on acetazolamide, giving a placebo-corrected difference of approximately 1.68 kg. In the current trial, the mean (SD) decrease in weight at 72 h was 3.2 (1.8) kg in patients randomized to metolazone, consistent with the greater weight loss observed with combination diuretic therapy in ADVOR (and CLOROTIC). By comparison, the mean weight loss in patients assigned to dapagliflozin was 2.6 (1.8) kg which was not significantly different from the decrease in weight with metolazone. Although acetazolamide has not been compared directly to metolazone or a thiazide diuretic, its use in ADVOR led to a small but significant increase in creatinine, like that seen in previous studies with metolazone and thiazide diuretics. Potassium appeared to be lower with acetazolamide compared to placebo in ADVOR and acetazolamide has been reported to cause a reduction in potassium in other studies. Compared to values at admission (day 3 vs. day 0), serum potassium levels declined by 0.4 ± 0.3 mmol/L in the acetazolamide arm and 0.2 ± 0.2 mmol/L in the

placebo arm (P = 0.022).[94] However, on day 3, mild hypokalaemia (3–3.5 mmol/L) was not significantly more frequent with acetazolamide (P = 0.061).

Collectively, these trials show that each of a thiazide/thiazide-like diuretic, acetazolamide, and an SGLT2 inhibitor augments decongestion in patients already receiving IV loop diuretic. Because the patients studied in each trial were different, the treatments were not compared directly, and the dose of loop diuretic varied between treatment groups, it is not possible to draw firm conclusions about the relative efficacy of each therapy (or strategy). Moreover, in some countries, the selective vasopressin receptor 2 antagonist tolvaptan is another agent that can be used to augment diuresis.[72]

There is now irrefutable evidence of the benefit of SGLT2 inhibitors in HF, and guidelines recommend their initiation in the hospital, but, as with other therapies, once patients are 'stabilized'. The present data suggest that SGLT2 inhibitors can be started earlier, if needed, to facilitate decongestion. More research into the treatment of diuretic resistance is needed and future investigation should focus on the safety and efficacy of adding a thiazide/thiazide-like diuretic or acetazolamide, and perhaps tolvaptan, in patients with persisting congestion despite treatment with a loop diuretic and SGLT2 inhibitor (and in patients with HF with reduced/mildly reduced ejection fraction, an MRA).

2.6 Limitations and strengths

The present trial was unblinded which may have led to bias. This was a pragmatic trial in which the clinicians responsible for the care of the participating patients were free to adjust the dose of furosemide as they thought appropriate. We did not attempt to mandate usual care and we do not believe that there is any universally agreed and routinely used furosemide-dosing protocol. Effectively, the comparison was of two decongestion strategies- one using furosemide plus metolazone and another using furosemide plus dapagliflozin. The latter resulted in the use of more furosemide than the former but, as we found, with less biochemical disturbance. The

sample size was small but a post hoc power calculation showed sufficient power to detect a difference between treatments of 1 kg in weight. Nevertheless, in a larger trial, some of the differences between treatments, such as in diuretic efficiency, may have become statistically significant. There were some imbalances in patient characteristics between the treatment groups at baseline. Strengths of this trial include the use of LUS to assess congestion and the relatively large proportion of women included.

2.7 Conclusions

In hospitalized patients with HF and loop diuretic resistance, we did not prove that dapagliflozin was more effective at relieving congestion than metolazone. Patients assigned to dapagliflozin received a larger cumulative dose of furosemide but experienced less biochemical upset than those assigned to metolazone.

Chapter 3 Relationship of Dapagliflozin With Serum Sodium: Findings From the DAPA-HF Trial

3.1 Abstract

3.1.1 Objectives

This study aimed to assess the prognostic importance of hyponatremia and the effects of dapagliflozin on serum sodium in the DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) trial.

3.1.2 Background

Hyponatremia is common and prognostically important in hospitalized patients with heart failure with reduced ejection fraction, but its prevalence and importance in ambulatory patients are uncertain.

3.1.3 Methods

We calculated the incidence of the primary outcome (cardiovascular death or worsening heart failure) and secondary outcomes according to sodium category (≤135 and >135 mmol/L). Additionally, we assessed: 1) whether baseline serum sodium modified the treatment effect of dapagliflozin; and 2) the effect of dapagliflozin on serum sodium.

3.1.4 Results

Of 4,740 participants with a baseline measurement, 398 (8.4%) had sodium ≤135 mmol/L. Participants with hyponatremia were more likely to have diabetes, be treated with diuretics, and have lower systolic blood pressure, left ventricular ejection fraction, and estimated glomerular filtration rate. Hyponatremia was associated with worse outcomes even after adjustment for predictive variables (adjusted HRs for the primary outcome 1.50 [95% CI: 1.23-1.84] and all-cause death 1.59 [95% CI: 1.26-2.01]). The benefits of dapagliflozin were similar in patients with

and without hyponatremia (HR for primary endpoint: 0.83 [95% CI: 0.57-1.19] and 0.73 [95% CI: 0.63-0.84], respectively, P for interaction = 0.54; HR for all-cause death: 0.85 [95% CI: 0.56-1.29] and 0.83 [95% CI: 0.70-0.98], respectively, P for interaction = 0.96). Between baseline and day 14, more patients on dapagliflozin developed hyponatremia (11.3% vs 9.4%; P = 0.04); thereafter, this pattern reversed and at 12 months fewer patients on dapagliflozin had hyponatremia (4.6% vs 6.7%; P = 0.003).

3.1.5 Conclusions

Baseline serum sodium concentration was prognostically important, but did not modify the benefits of dapagliflozin on morbidity and mortality in heart failure with reduced ejection fraction. (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]: NCT03036124).

3.2 Introduction

Hyponatremia is common in patients hospitalized with decompensated heart failure (HF), occurring in 20% to 30% of such individuals.[95-98] In these patients, hyponatremia is an established predictor of adverse outcomes, associated with both inpatient and longer-term mortality.[95-98] The causes of hyponatremia in HF are complex, but they can be simplified into those causing impaired water excretion and those increasing sodium loss (both reduced water excretion and increased sodium loss can contribute to hyponatremia).[98-101] Renin-angiotensin-aldosterone system and sympathetic nervous system activation lead to a nonosmotically mediated release of arginine vasopressin which inhibits free-water excretion and stimulates thirst, leading to increased water intake.[98-101] Reduced glomerular filtration (and as a result, renal tubular flow) leads to an impaired ability of the kidney to excrete free water.[98-101] Large doses of diuretic agents may lead to excessive sodium loss, especially if coupled with restriction of sodium intake; thiazide diuretic agents may also inhibit urinary dilution.[98-101] Whether hyponatremia is causally related to mortality or is simply a marker of the severity of HF remains unknown, although low serum sodium

concentration remains an independent predictor of mortality in adjusted models incorporating other prognostic variables.[98-100, 102]

Much less is known about the prevalence or the prognostic significance of hyponatremia in ambulatory patients with heart failure and reduced ejection fraction (HFrEF), especially in such individuals receiving contemporary treatments.[103-105] Sodium glucose cotransporter 2 (SGLT2) inhibitors have been recently introduced as a treatment for HFrEF.[38, 40, 106] SGLT2 inhibitors inhibit proximal renal tubular reabsorption of glucose, coupled with sodium, leading to an initial osmotic diuresis and natriuresis. The effects of these agents (added to conventional diuretic agents and mineralocorticoid receptor antagonists) on serum sodium concentration in HFrEF are unknown and probably complex. Therefore, we investigated the effect of dapagliflozin on serum sodium in the DAPA-HF (Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure; "Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure") trial.[38] We also examined whether sodium concentration at baseline modified the effects of dapagliflozin on clinical outcomes in the DAPA-HF trial.

3.3 Hypothesis

This study was designed to investigate the prognostic significance of hyponatremia in ambulatory patients with HFrEF, the efficacy of dapagliflozin according to baseline serum sodium concentration, and the effect of dapagliflozin on serum sodium in the DAPA-HF trial.

3.4 Methods

DAPA-HF was a prospective, randomized, double-blind, controlled trial in patients with HFrEF, which evaluated the efficacy and safety of dapagliflozin 10 mg once daily, compared with matching placebo, added to standard care.[38] The ethics

committees at each of the 410 participating institutions (in 20 countries) approved the protocol, and all patients gave written informed consent.

3.4.1 Study patients

Patients ≥18 years of age in New York Heart Association (NYHA) functional class II-IV with a left ventricular ejection fraction (LVEF) ≤40% and an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were eligible if receiving optimal pharmacological and device therapy.[38] The main exclusion criteria included type 1 diabetes mellitus, symptomatic hypotension/systolic blood pressure (SBP) <95 mm Hg, and estimated glomerular filtration rate (eGFR) <30 mL/min/ 1.73 m^2. There was no serum sodium concentration inclusion or exclusion criterion.

3.4.2 Measurement of serum sodium (creatinine and other electrolytes)

Blood samples were obtained at randomization 14 days, 2, 4, 8, and 12 months, and every 4 months thereafter.

3.4.3 Prespecified trial outcomes

The primary outcome of DAPA-HF was the composite of worsening HF (HF hospitalization or urgent visit for HF requiring intravenous therapy) or cardiovascular death, whichever occurred first. Prespecified secondary endpoints included HF hospitalization or cardiovascular death, HF hospitalizations (first and recurrent), and cardiovascular deaths. The change from baseline to 8 months in Kansas City Cardiomyopathy Questionnaire–total symptom score (KCCQ-TSS) was an additional secondary endpoint, with the proportion having a 5-point or more increase or decrease in their score at 8 months determined as previously described. There was also a prespecified secondary renal composite outcome, but this was not evaluated further in this study because of the small number of events.

3.4.4 Serum sodium, definition of hyponatremia, and clinical outcomes

Hyponatremia was defined as serum sodium concentration ≤135 mmol/L.7 Sodium concentration and sodium category (normal or reduced, ie, >135 mmol/L vs ≤135 mmol/L) were defined at baseline and each follow-up visit to 1 year. The association between baseline sodium category and subsequent clinical outcomes was also analyzed, along with the effects of dapagliflozin on clinical outcomes according to baseline sodium concentration, as described in the statistical analysis section below.

3.4.5 Statistical analysis

Baseline characteristics were summarized as mean ± SD, median (IQR), or percentages. We used the Kaplan-Meier estimate and Cox proportional hazards models, stratified by diabetes status, and adjusted for history of HF hospitalization (except for all-cause death) and treatment-group assignment to examine the primary and secondary outcomes, with further models adjusted for known predictors of risk in patients with HF, including: age, sex, race, geographic region, HF duration, heart rate, SBP, body mass index, NYHA functional class, LVEF, eGFR, serum haemoglobin, NT-proBNP, aetiology of HF, history of atrial fibrillation, history of chronic obstructive pulmonary disease, use of loop diuretic therapy, use of other diuretics, and use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor–neprilysin inhibitors. Effect modification of treatment effect by baseline hyponatremia status was assessed by a likelihood ratio test. The differences between treatment groups in the proportion of patients with a clinically significant (≥5 points) improvement or deterioration in KCCQ-TSS at 8 months was analyzed using the methods described previously and presented as an odds ratio for each baseline sodium category.[38] Safety analyses were performed in randomized patients who had received at least 1 dose of dapagliflozin or placebo. The interaction between baseline sodium category and randomized treatment on the occurrence of the prespecified safety outcomes was tested in a logistic regression model.

The relationship between baseline sodium as a continuous variable (adjusted for randomized treatment and history of HF hospitalization [apart from all-cause death]

with stratification by diabetes status) and the risk of the primary outcome, its composite, and all-cause death was examined as a restricted cubic spline.[107] This was repeated with additional adjustment for the known HF risk predictors listed above. The effect of dapagliflozin compared with placebo on each of the major clinical endpoints over baseline sodium as a continuous variable was modelled as a fractional polynomial. Changes in serum sodium, SBP, eGFR and haematocrit were analyzed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient).

All analyses were conducted using Stata version 16.0 (StataCorp) and SAS version 9.4 (SAS Institute). A value of $P < 0.05$ was considered statistically significant. All of the analyses was performed by myself using Stata statistical software except for the KCCQ-TSS analysis, which was analysed by the 2nd author (Docherty KF) using SAS software.

3.5 Results

A baseline serum sodium measurement was available in 4,740 patients and showed a normal distribution (Figure 3-1); 398 (8.4%) participants had a value ≤135 mmol/L (Table 3-1), of which 379 participants (8.0%) had a baseline serum sodium of 130 to 135 mmol/L, 16 (0.34%) with baseline sodium of 125 to 129 mmol/L, and 3 (0.06%) with baseline sodium <125 mmol/L. There were many statistically significant differences between the 2 groups. Participants with hyponatremia were more likely to have diabetes (58.3% vs 43.9%), compared to those with serum sodium >135 mmol/L. Patients with a serum sodium ≤135 mmol/L had a lower SBP (118 ± 16 mm Hg vs 122 ± 16 mm Hg), lower LVEF (29.8 ± 7.2% vs 31.2 ± 6.7%), and lower eGFR (63.2 ± 19.0 mL/min/1.73 m2 vs 66.0 ± 19.4 mL/min/1.73 m2). Other differences between patients with and without hyponatremia included a lower body mass index and lower hemoglobin in the former group; patients with hyponatremia had a borderline higher NT-proBNP than those with sodium >135 mmol/L (Table 3-1). Patients with

hyponatremia were more often treated with a diuretic, mineralocorticoid receptor antagonist (MRA), and digoxin compared to those with sodium >135 mmol/L.

The baseline characteristics independently associated with hyponatremia are shown in Table 3-2. Geographic region (North America and South America), lower SBP, body mass index, and hemoglobin level were each associated with hyponatremia, as was treatment with an MRA and a non-loop diuretic. The baseline characteristics of patients treated with loop diuretic, other (mainly thiazide) diuretics, both types of diuretic, or no diuretic (including concomitant MRA use) are shown in Table 3-3.

Figure 3-1 Baseline serum sodium distribution in DAPA-HF

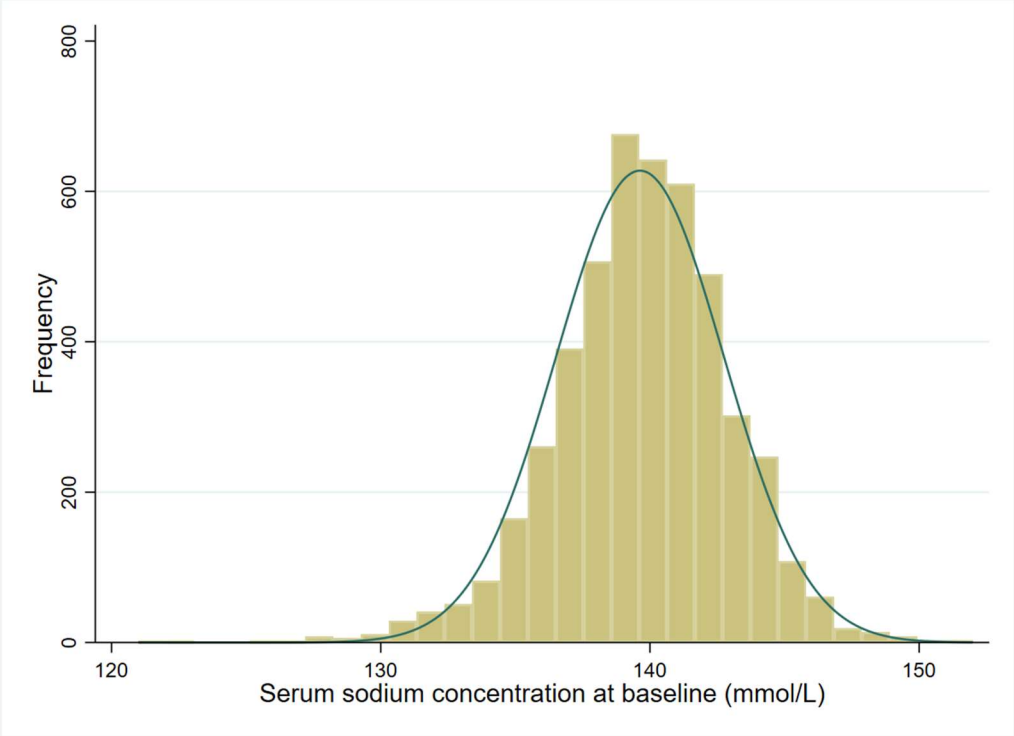


Table 3-1 Patient Characteristics According to Baseline Sodium Category

	Baseline Sodium		P Value
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	**Na^+ >135 mmol/L (n = 4,342, 91.6%)**	
Age, y	66.1 ± 10.6	66.4 ± 10.9	0.61
Age >75 y	73 (18.3)	928 (21.4)	0.31
Female	82 (20.6)	1,027 (23.7)	0.17
Race or ethnic group			0.009
White	266 (66.8)	3,063 (70.5)	
Black	17 (4.3)	209 (4.8)	
Asian	102 (25.6)	1,014 (23.4)	
Other	13 (3.3)	56 (1.3)	
Region			<0.001
North America	74 (18.6)	601 (13.8)	
Latin America	90 (22.6)	727 (16.7)	
Europe	135 (33.9)	2,017 (46.5)	
Asia Pacific	99 (24.9)	997 (23.0)	
SBP, mm Hg	118 ± 16	122 ± 16	<0.001
Heart rate, beats/min	72 ± 12	71 ± 12	0.31
BMI, kg/m^2	27.1 ± 5.4	28.3 ± 6.0	<0.001
Classification			0.027
Obesity (≥30)	116 (29.1)	1,554 (35.8)	

	Baseline Sodium		P Value
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	**Na^+ >135 mmol/L (n = 4,342, 91.6%)**	
Overweight (25-29.9)	147 (36.9)	1,573 (36.2)	
Normal weight (18.5-24.9)	126 (31.7)	1,135 (26.2)	
Underweight (<18.5)	9 (2.3)	78 (1.8)	
Hemoglobin, g/L	132.6 ± 16.3	135.8 ± 16.2	<0.001
Hematocrit, %	40.7 ± 5.2	41.5 ± 5.0	0.002
HbA1c, %	7.3 ± 2.2	6.4 ± 1.2	<0.001
Serum creatinine, µmol/L	111.0 ± 35.5	103.8 ± 29.8	<0.001
Serum sodium, mmol/L	133.4 ± 2.1	140.2 ± 2.5	<0.001
Serum urea, mg/dL	26.2 ± 13.4	23.0 ± 9.7	<0.001
eGFR, mL/min/1.73 m^2	63.2 ± 19.0	66.0 ± 19.4	0.005
Clinical HF features			
Ischemic cardiomyopathy	233 (58.5)	2,438 (56.1)	0.36
LVEF, %	29.8 ± 7.2	31.2 ± 6.7	<0.001
NT-proBNP, pg/mL	1,531 (891–3,019)	1,431 (853–2,626)	0.055
NYHA functional class			0.85
II	265 (66.6)	2,934 (67.6)	
III	130 (32.7)	1,368 (31.5)	
IV	3 (0.8)	40 (0.9)	
KCCQ-TSS (baseline)	73.2 ± 22.5	73.7 ± 21.7	0.67

	Baseline Sodium		P Value
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	**Na^+ >135 mmol/L (n = 4,342, 91.6%)**	
Medical history			
Hypertension	287 (72.1)	3,233 (74.5)	0.31
Diabetes	232 (58.3)	1,907 (43.9)	<0.001
Atrial fibrillation (history)	145 (36.4)	1,673 (38.5)	0.41
Atrial fibrillation/flutter (ECG)	100 (25.1)	1,028 (23.7)	0.52
Prior HF hospitalization	185 (46.5)	2,062 (47.5)	0.70
MI	180 (45.2)	1,910 (44.0)	0.63
Stroke	47 (11.8)	419 (9.6)	0.17
COPD	47 (11.8)	537 (12.4)	0.75
CKD (eGFR<60 mL/min/1.73 m^2)	183 (46.0)	1,741 (40.1)	0.022
Anemia[a]	144 (36.5)	1,157 (26.8)	<0.001
Treatments at randomization			
ACEi	221 (55.5)	2,438 (56.1)	0.81
ARB	105 (26.4)	1,200 (27.6)	0.59
ACEi/ARB/ARNI	366 (92.0)	4,072 (93.8)	0.15
Beta blocker	376 (94.5)	4,178 (96.2)	0.085
Any diuretic	354 (88.9)	3,651 (84.1)	0.01

	Baseline Sodium		P Value
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	**Na^+ >135 mmol/L (n = 4,342, 91.6%)**	
Loop diuretic	332 (83.4)	3,490 (80.4)	0.14
Other diuretic	65 (16.3)	447 (10.3)	<0.001
Digitalis	97 (24.4)	790 (18.2)	0.002
MRA	313 (78.6)	3,056 (70.4)	<0.001
Anticoagulant	169 (42.5)	1,800 (41.5)	0.70
Antiplatelet	228 (57.3)	2,361 (54.4)	0.26
Statin	271 (68.1)	2,903 (66.9)	0.62
SSRI/SNRI	26 (6.5)	187 (4.3)	0.04
PPI	139 (34.9)	1,263 (29.1)	0.015
ICD/CRT-D	108 (27.1)	1,132 (26.1)	0.64
CRT-P/CRT-D	34 (8.5)	320 (7.4)	0.39

Values are mean ± SD, n (%), or median (IQR).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D or P, cardiac resynchronization therapy with defibrillator or pacemaker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb1Ac, hemoglobin A1c; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire–total symptom score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PPI, proton pump inhibitor; SBP, systolic blood pressure; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Anaemia: Haemoglobin <130 g/L in males and haemoglobin <120 g/L in females.

3.5.1 Cardiovascular outcomes according to baseline serum sodium - Primary and secondary trial outcomes related to hyponatremia

Incidence rates of the primary and secondary outcomes of the trial were substantially higher in patients with hyponatremia at baseline, compared to those without (Table 3-4, Figure 3-2, Figure 3-3). The elevated risk associated with hyponatremia persisted after comprehensive adjustment for other predictors of worse outcomes, including NT-proBNP, with an adjusted HR for the primary outcome of 1.50 (95% CI: 1.23-1.84). The adjusted HR for all-cause death (compared to patients with normal serum sodium) was 1.59 (95% CI: 1.26-2.01)

Table 3-2 Baseline characteristics independently associated with hyponatremia (sodium ≤135 mmol/L)

Baseline variable	Odds ratio	P-value
Region (North America)	1.96	<0.001
Region (South America)	1.64	0.003
Systolic BP <121 mmHg	1.45	0.002
BMI 25.0-29.9 Kg/m^2	1.40	0.016
BMI 18.5-24.9 Kg/m^2	1.77	0.001
BMI <18.5 Kg/m^2	2.18	0.049
Hemoglobin <136 g/L	1.38	0.047
QRS duration ≥114 msec	1.31	0.022
MRA treatment	1.65	<0.001
Other diuretic	1.96	<0.001

Table 3-3 Patient characteristics according to baseline diuretic category

Baseline characteristic	Baseline Diuretics				
	No Diuretic	**Other Diuretic* Only**	**Loop Diuretic Only**	**Loop and Other diuretics**	***P*-value**
No. (%)	736 (15.5)	183 (3.9)	3,496 (73.7)	329 (6.9)	
Baseline sodium – mmol/L	139.7 ± 2.9	139.3 ± 3.3	139.7 ± 3.1	139.0 ± 3.4	<0.001
Baseline hyponatremia (Na^+ ≤135mmol/L) – no. (%)	44 (6.0)	22 (12.0)	289 (8.3)	43 (13.1)	<0.001
Age – years	67.3 ± 10.6	68.1 ± 10.5	66.1 ± 10.9	66.2 ± 11.2	0.004
Female sex – no. (%)	166 (22.6)	52 (28.4)	790 (22.6)	101 (30.7)	0.003
Race or ethnic group – no. (%)					<0.001
- White	490 (66.6)	132 (72.1)	2,483 (71.0)	228 (69.3)	
- Black	11 (1.5)	5 (2.7)	189 (5.4)	21 (6.4)	
- Asian	225 (30.6)	39 (21.3)	776 (22.2)	76 (23.1)	
- Other	10 (1.4)	7 (3.8)	48 (1.4)	4 (1.2)	
Region – no. (%)					<0.001
- North America	150 (20.4)	19 (10.4)	479 (13.7)	29 (8.8)	
- Latin America	150 (20.4)	51 (27.9)	569 (16.3)	47 (14.3)	
- Europe	218 (29.6)	75 (41.0)	1,684 (48.2)	177 (53.8)	
- Asia Pacific	218 (29.6)	38 (20.8)	764 (21.9)	76 (23.1)	
Systolic BP - mmHg	124 ± 17	129 ± 20	121 ± 16	122 ± 18	<0.001
Heart rate – bpm	70 ± 12	71 ± 12	72 ± 12	73 ± 12	<0.001
BMI - kg/m^2	26.7 ± 5.0	27.3 ± 4.5	28.4 ± 6.1	29.3 ± 6.7	<0.001
- BMI classification					<0.001
• Obesity (BMI≥30)	176 (23.9)	59 (32.2)	1,299 (37.2)	138 (41.9)	
• Overweight (BMI 25-29.9)	295 (40.1)	77 (42.1)	1,242 (35.5)	108 (32.8)	
• Normal weight (BMI 18.5-24.9)	249 (33.9)	46 (25.1)	888 (25.4)	78 (23.7)	
• Underweight (BMI<18.5)	15 (2.0)	1 (0.5)	66 (1.9)	5 (1.5)	

Hemoglobin – g/L	136.0 ± 15.8	136.1 ± 13.2	135.6 ± 16.3	133.5 ± 17.1	0.11
Hematocrit - %	41.5 ± 4.8	41.1 ± 4.1	41.5 ± 5.0	41.0 ± 5.3	0.21
HbA1c – %	6.2 ± 1.2	6.3 ± 1.2	6.5 ± 1.4	6.7 ± 1.6	<0.001
Serum Creatinine – µmol/L	95.8 ± 26.3	100.8 ± 32.9	105.5 ± 30.1	114.4 ± 35.3	<0.001
eGFR - mL/min/1.73m^2	70.4 ± 18.6	67.0 ± 19.6	65.3 ± 19.5	59.8 ± 18.2	<0.001
Clinical HF features					
- Ischemic cardiomyopathy – no. (%)	424 (57.6)	107 (58.5)	1,957 (56.0)	186 (56.5)	0.80
- LVEF - %	32.1 ± 6.3	33.3 ± 6.0	30.6 ± 6.9	31.9 ± 6.7	<0.001
- Median NT-proBNP (IQR) – pg/mL	1168 (732 - 1823)	1034 (704 - 1908)	1535 (907 - 2812)	1815 (987 - 3478)	<0.001
NYHA Class – no. (%)					<0.001
- II	588 (79.9)	146 (79.8)	2,280 (65.2)	189 (57.4)	
- III	142 (19.3)	37 (20.2)	1,180 (33.8)	139 (42.2)	
- IV	6 (0.8)	0 (0)	36 (1.0)	1 (0.3)	
KCCQ-TSS (baseline)	80.6 ± 18.9	79.1 ± 19.7	72.3 ± 21.9	68.6 ± 23.1	<0.001
Medical History – no. (%)					
- Hypertension	506 (68.8)	147 (80.3)	2,597 (74.3)	272 (82.7)	<0.001
- Diabetes	255 (34.6)	72 (39.3)	1,634 (46.7)	178 (54.1)	<0.001
- Atrial Fibrillation (History)	217 (29.5)	56 (30.6)	1,399 (40.0)	146 (44.4)	<0.001
- Prior HF hospitalization	271 (36.8)	78 (42.6)	1,737 (49.7)	165 (50.2)	<0.001
- MI	375 (51.0)	78 (42.6)	1,503 (43.0)	136 (41.3)	<0.001
- Stroke	65 (8.8)	18 (9.8)	347 (9.9)	36 (10.9)	0.72
- COPD	75 (10.2)	19 (10.4)	457 (13.1)	34 (10.3)	0.08
- CKD (eGFR<60 mL/min/1.73m^2)	216 (29.4)	76 (41.5)	1,465 (41.9)	169 (51.4)	<0.001

- Anemia†	181 (24.8)	42 (23.1)	976 (28.2)	103 (31.4)	0.055
Treatments at randomization – no. (%)					
- ACEi	388 (52.7)	95 (51.9)	2,019 (57.8)	159 (48.3)	<0.001
- ARB	218 (29.6)	72 (39.3)	895 (25.6)	122 (37.1)	<0.001
- ACEi/ARB/ARNI	690 (93.8)	173 (94.5)	3,269 (93.5)	310 (94.2)	0.91
- Beta-blocker	695 (94.4)	170 (92.9)	3,376 (96.6)	317 (96.4)	0.006
- Digitalis	80 (10.9)	27 (14.8)	717 (20.5)	63 (19.1)	<0.001
- MRA	425 (57.7)	91 (49.7)	2,623 (75.0)	231 (70.2)	<0.001
- Anticoagulant	241 (32.7)	55 (30.1)	1,524 (43.6)	149 (45.3)	<0.001
- Antiplatelet	463 (62.9)	108 (59.0)	1,851 (52.9)	170 (51.7)	<0.001
- Statin	501 (68.1)	128 (69.9)	2,325 (66.5)	222 (67.5)	0.68
- SSRI/SNRI	30 (4.1)	6 (3.3)	165 (4.7)	12 (3.6)	0.59
- PPI	184 (25.0)	41 (22.4)	1,071 (30.6)	106 (32.2)	0.002
- ICD/CRT-D	167 (22.7)	28 (15.3)	973 (27.8)	74 (22.5)	<0.001
- CRT-P/CRT-D	46 (6.3)	11 (6.0)	266 (7.6)	31 (9.4)	0.25

*Other Diuretics comprise predominantly of thiazides/thiazide derivatives

† Anemia: Hemoglobin <130 g/L in males and hemoglobin <120 g/L in females

Table 3-4 Event Rate (Per 100 Person-Years) and Hazard Ratios for Trial Outcomes According to Baseline Sodium Category

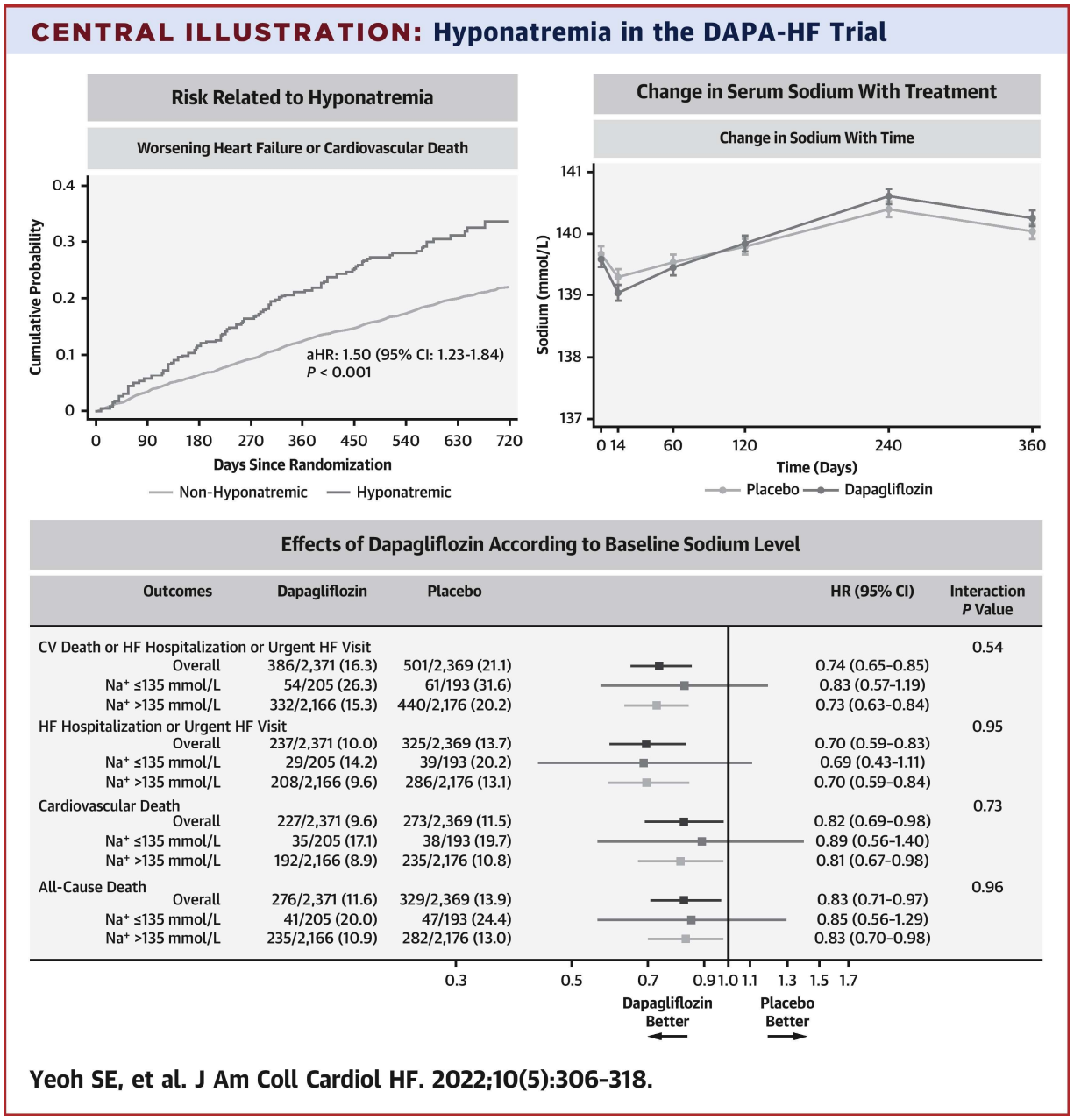
	Baseline Sodium		P Value
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	**Na^+ >135 mmol/L (n = 4,342, 91.6%)**	
Primary endpoint (worsening HF or cardiovascular death)	115 (28.9)	772 (17.8)	
Event rate per 100 person-y (95% CI)	22.2 (18.5-26.7)	13.0 (12.1-13.9)	<0.001
Unadjusted HR (95% CI)	1.63 (1.34-1.99)	1.00 (ref)	<0.001
Adjusted HR (95% CI)	1.50 (1.23-1.84)	1.00 (ref)	<0.001
Hospitalization or urgent visit for HF	68 (17.1)	494 (11.4)	
Event rate per 100 person-y (95% CI)	13.1 (10.4-16.7)	8.3 (7.6-9.1)	<0.001
Unadjusted HR (95% CI)	1.49 (1.16-1.93)	1.00 (ref)	0.002
Adjusted HR (95% CI)	1.36 (1.05-1.77)	1.00 (ref)	0.022
Cardiovascular death	73 (18.3)	427 (9.8)	
Event rate per 100 person-y (95% CI)	12.9 (10.3-16.3)	6.8 (6.2-7.5)	<0.001
Unadjusted HR (95% CI)	1.81 (1.41-2.33)	1.00 (ref)	<0.001
Adjusted HR (95% CI)	1.52 (1.18-1.97)	1.00 (ref)	0.001
All-cause mortality, number of events	88 (22.1)	517 (11.9)	
Event rate per 100 person-y (95% CI)	15.6 (12.6-19.2)	8.2 (7.6-9.0)	<0.001

	Baseline Sodium		P Value
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	**Na^+ >135 mmol/L (n = 4,342, 91.6%)**	
Unadjusted HR (95% CI)	1.81 (1.45-2.28)	1.00 (ref)	<0.001
Adjusted HR (95% CI)	1.59 (1.26-2.01)	1.00 (ref)	<0.001

Values are n (%) or HR (95% CI). ref = reference value

Models for death/hospitalization outcomes adjusted for age; sex; treatment arm; race; region; duration of HF; previous HF hospitalization; heart rate; SBP; BMI; NYHA functional classification; LVEF; eGFR; etiology of HF; history of atrial fibrillation, diabetes, and chronic obstructive pulmonary disease; serum hemoglobin; NT-proBNP; and use of loop diuretic therapy, other diuretic therapy, beta-blocker therapy, and ACEi or ARB or ARNI.

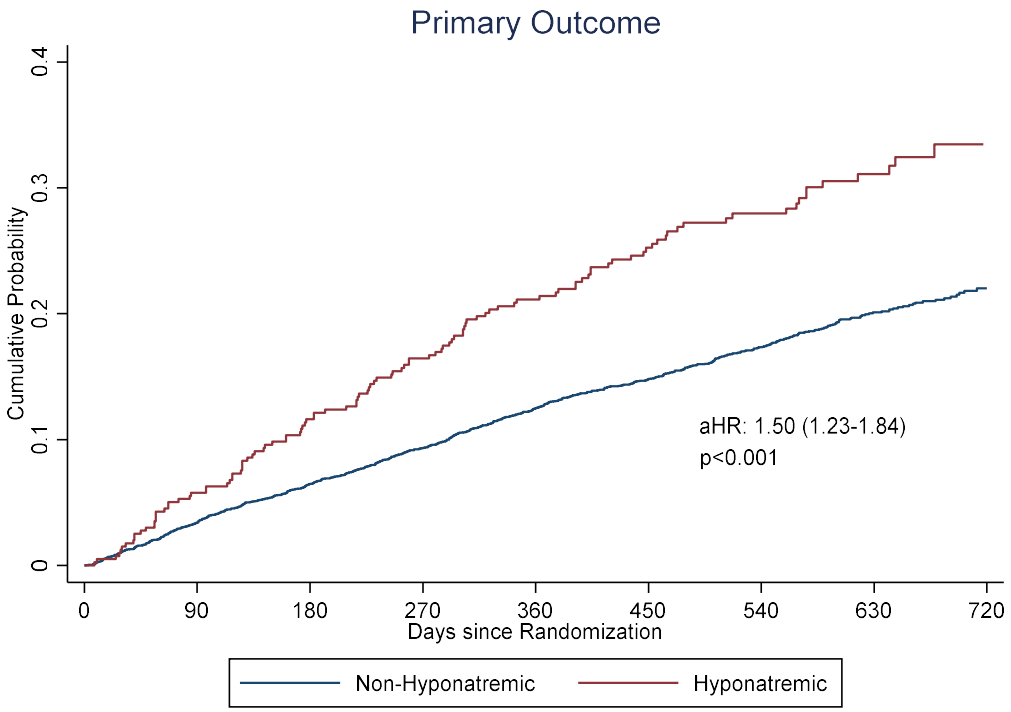
Figure 3-2 Central Illustration



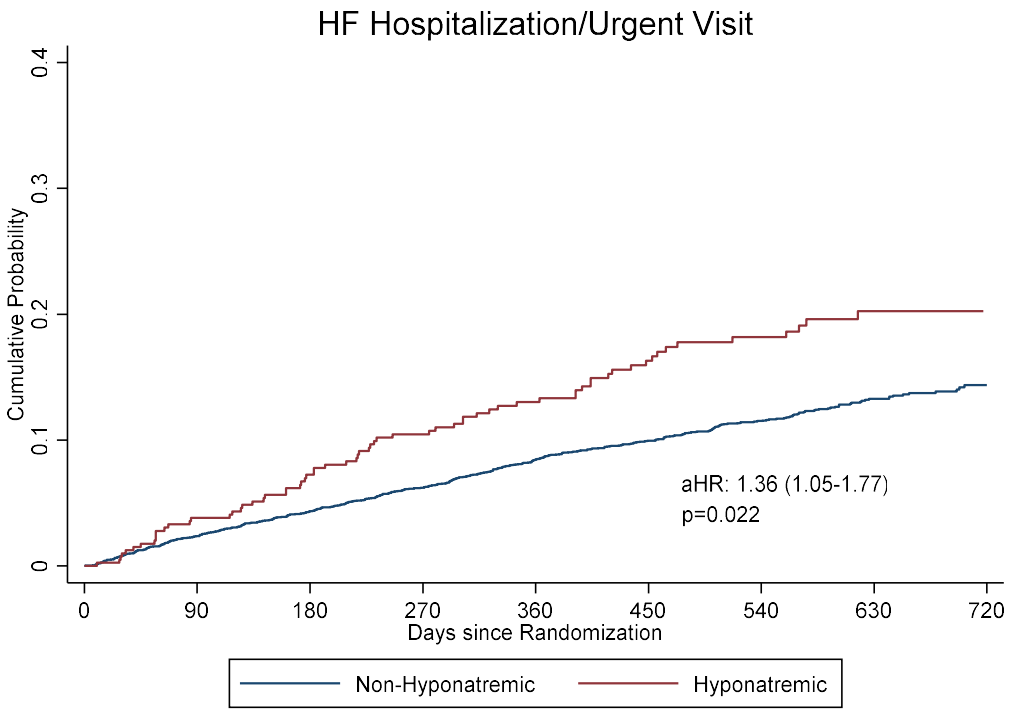
Relationship of dapagliflozin with serum sodium based on findings from the DAPA-HF trial. aHR = adjusted hazard ratio; CV = cardiovascular; HF = heart failure.

Figure 3-3 Primary and secondary outcomes. Kaplan-Meier curves showing outcomes in patients with and without hyponatremia at baseline. Hyponatremia was defined as baseline sodium ≤135mmol/l

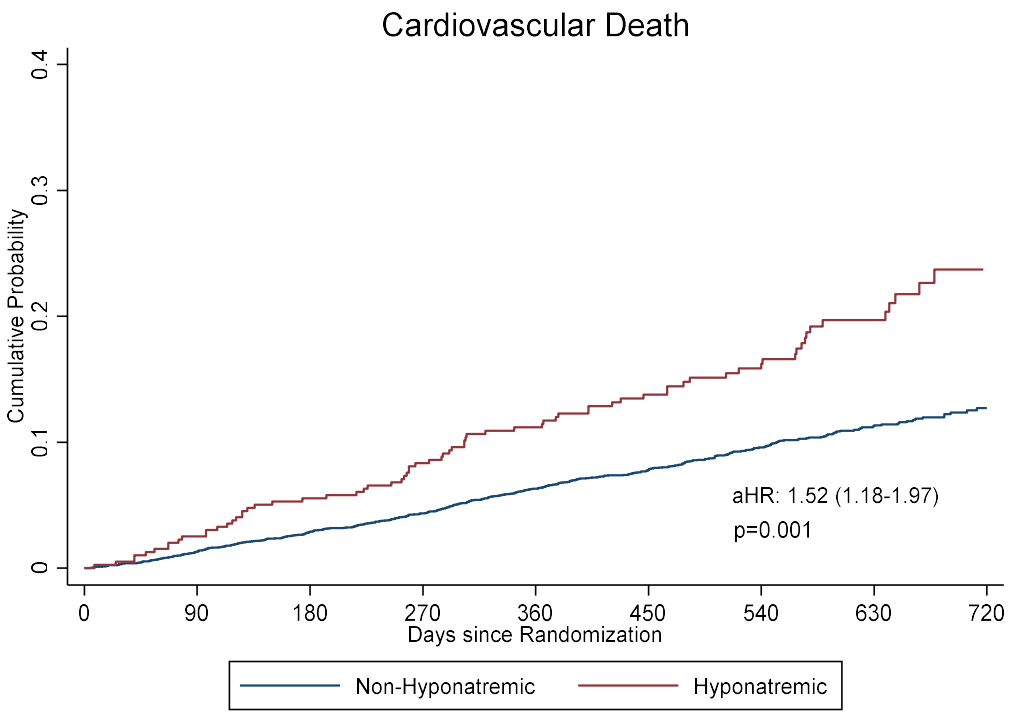
(a)



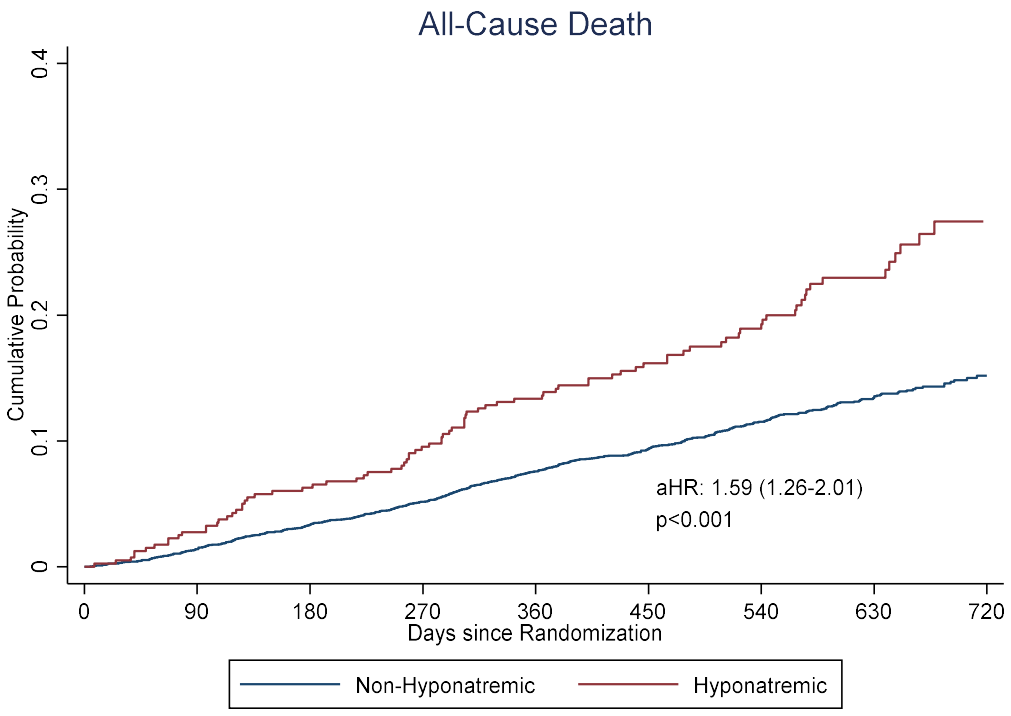
(b)



(c)



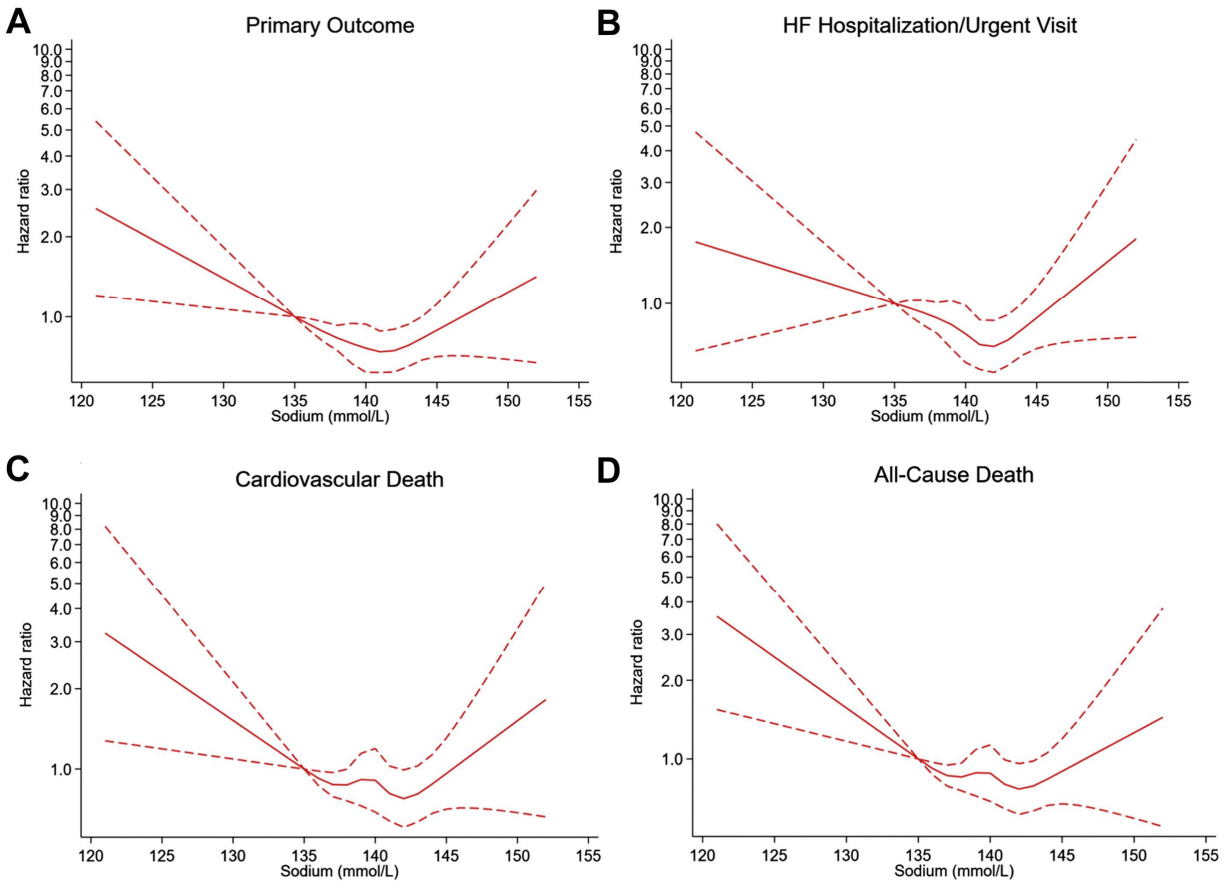
(d)



aHR: adjusted hazard ratio, HF: heart failure

Analyses using baseline sodium as a continuous variable showed that the nadir in event rates for all the outcomes of interest was around a sodium concentration of approximately 141 mmol/L to 142 mmol/L (Figures 3-4 and 3-5). There was a linear increase in event rates as sodium concentration decreased below this level. The increase in risk per 1 mmol/L decrease in sodium below 142 mmol/L was 5% for the primary endpoint and 6% for each of cardiovascular and all-cause mortality. Inspection of the restricted cubic spline Figures also suggested the possibility of a J-shaped relationship, where high sodium concentration was also associated with worse outcomes, but this was not statistically significant for any of the prespecified endpoints.

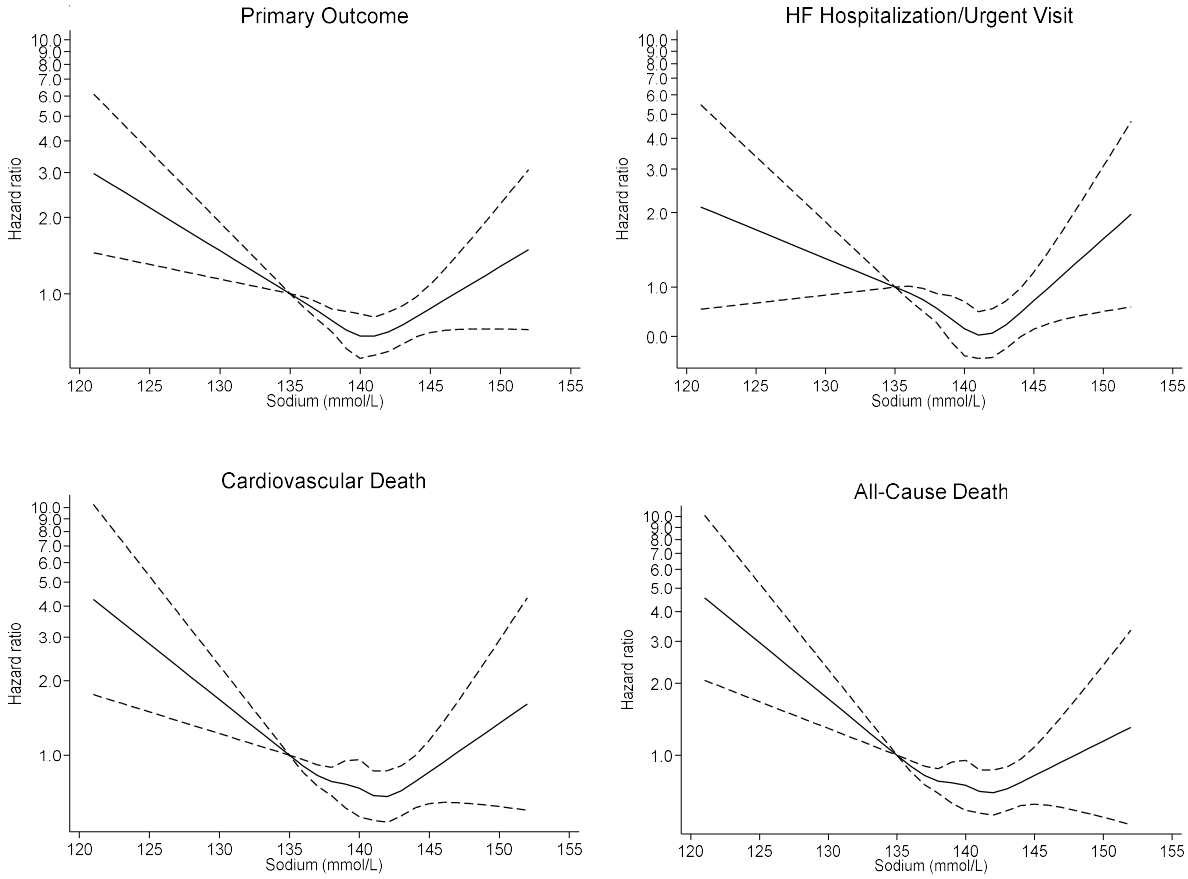
Figure 3-4 Key Trial Outcomes According to Baseline Serum Sodium Concentration (adjusted)



These restricted cubic splines show the risk of each outcome modeling serum sodium concentration as a continuous variable, adjusted for prognostic variables. The dashed lines represent corresponding 95% CIs (reference sodium level = 135 mmol/L).

Figure 3-5 Key Trial Outcomes According to Baseline Serum Sodium Concentration (unadjusted)

These restricted cubic splines demonstrate the unadjusted risk of each outcome modelling serum sodium concentration as a continuous variable. The interrupted lines represent corresponding 95% confidence intervals (reference sodium level = 135mmol/L).



3.5.2 Effect of dapagliflozin on primary and secondary trial outcomes according to baseline sodium concentration

The efficacy of dapagliflozin in preventing the primary outcome of cardiovascular death or worsening HF did not differ between those with hyponatremia and those without (P for interaction = 0.54). The efficacy of dapagliflozin in preventing cardiovascular death, HF hospitalizations, or urgent HF visits and all-cause death also did not differ by sodium group (Table 3-5, Figure 3-6). The results were similar when serum sodium was treated as a continuous variable (P for interaction = 0.96 for the primary outcome) (Figure 3-7).

Table 3-5 Effect of Dapagliflozin on the Primary and Secondary Outcomes According to Baseline Sodium Category

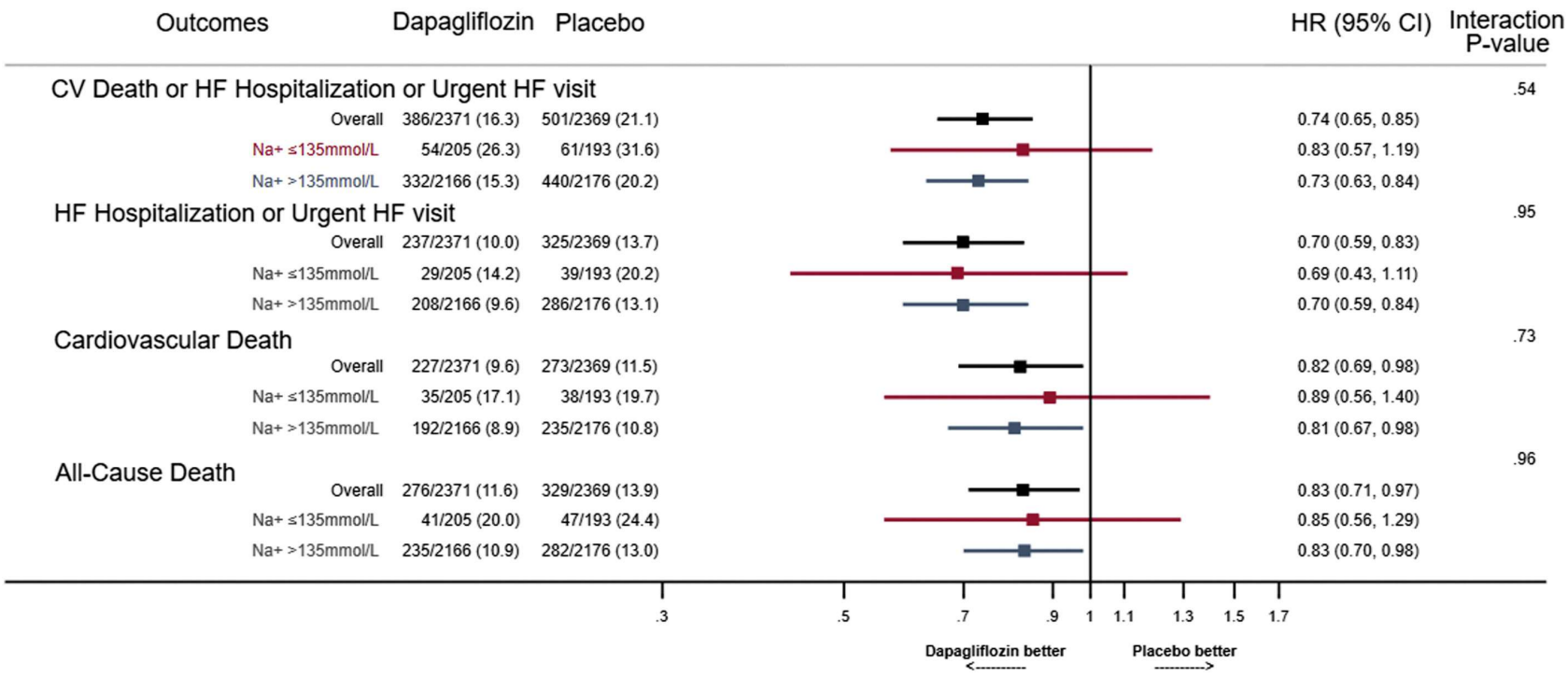
	Na^+ ≤135 mmol/L		Na^+ >135 mmol/L		*P* for Interaction
	Placebo (n = 193)	Dapagliflozin (n = 205)	Placebo (n = 2,176)	Dapagliflozin (n = 2,166)	
Primary endpoint (worsening HF or cardiovascular death)					
n (%)	61 (31.6)	54 (26.3)	440 (20.2)	332 (15.3)	0.54
Rate per 100 person-y (95% CI)	24.6 (19.1-31.6)	20.1 (15.4-26.2)	15.0 (13.7-16.5)	11.0 (9.9-12.3)	
HR (95% CI)	0.83 (0.57-1.19)		0.73 (0.63-0.84)		
Hospitalization or urgent visit for HF					
n (%)	39 (20.2)	29 (14.2)	286 (13.1)	208 (9.6)	0.95
Rate per 100 person-y (95% CI)	15.7 (11.5-21.5)	10.8 (7.5-15.5)	9.8 (8.7-11.0)	6.9 (6.0-7.9)	
HR (95% CI)	0.69 (0.43-1.11)		0.70 (0.59-0.84)		
Cardiovascular death					
n (%)	38 (19.7)	35 (17.1)	235 (10.8)	192 (8.9)	0.73

	Na^+ ≤135 mmol/L		Na^+ >135 mmol/L		*P* for Interaction
	Placebo (n = 193)	**Dapagliflozin (n = 205)**	**Placebo (n = 2,176)**	**Dapagliflozin (n = 2,166)**	
Rate per 100 person-y (95% CI)	13.8 (10.1-19.0)	12.1 (8.7-16.8)	7.5 (6.6-8.5)	6.1 (5.3-7.0)	
HR (95% CI)	0.89 (0.56-1.40)		0.81 (0.67-0.98)		
All-cause death					
n (%)	47 (24.4)	41 (20.0)	282 (13.0)	235 (10.9)	0.96
Rate per 100 person-y (95% CI)	17.1 (12.9-22.8)	14.1 (10.4-19.2)	9.0 (8.0-10.1)	7.5 (6.6-8.5)	
HR (95% CI)	0.85 (0.56-1.29)		0.83 (0.70-0.98)		
Significant worsening in KCCQ-TSS (≥5) at 8 months					
Proportion ± SE	0.39 ± 0.04	0.27 ± 0.03	0.32 ± 0.01	0.25 ± 0.01	0.55
OR (95% CI)	0.78 (0.63-0.98)		0.84 (0.78-0.90)		
Significant improvement in KCCQ-TSS (≥5) at 8 months					
Proportion ± SE	0.46 ± 0.04	0.57 ± 0.04	0.51 ± 0.01	0.58 ± 0.01	0.52
OR (95% CI)	1.23 (0.99-1.51)		1.15 (1.07-1.22)		

OR = odds ratio

KCCQ-TSS data was analysed by the 2nd author (Docherty KF) using SAS software

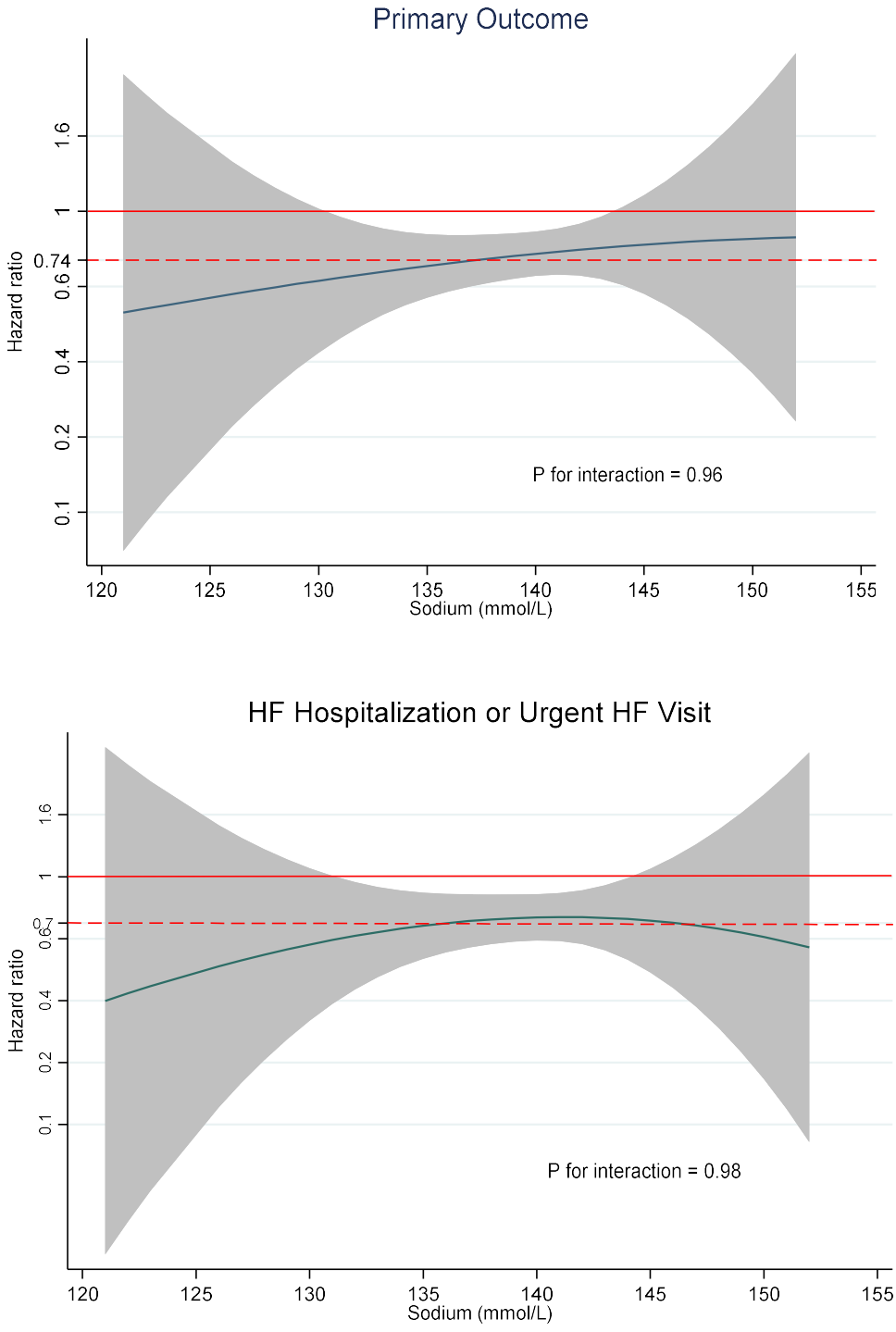
Figure 3-6 Dapagliflozin Treatment Effect

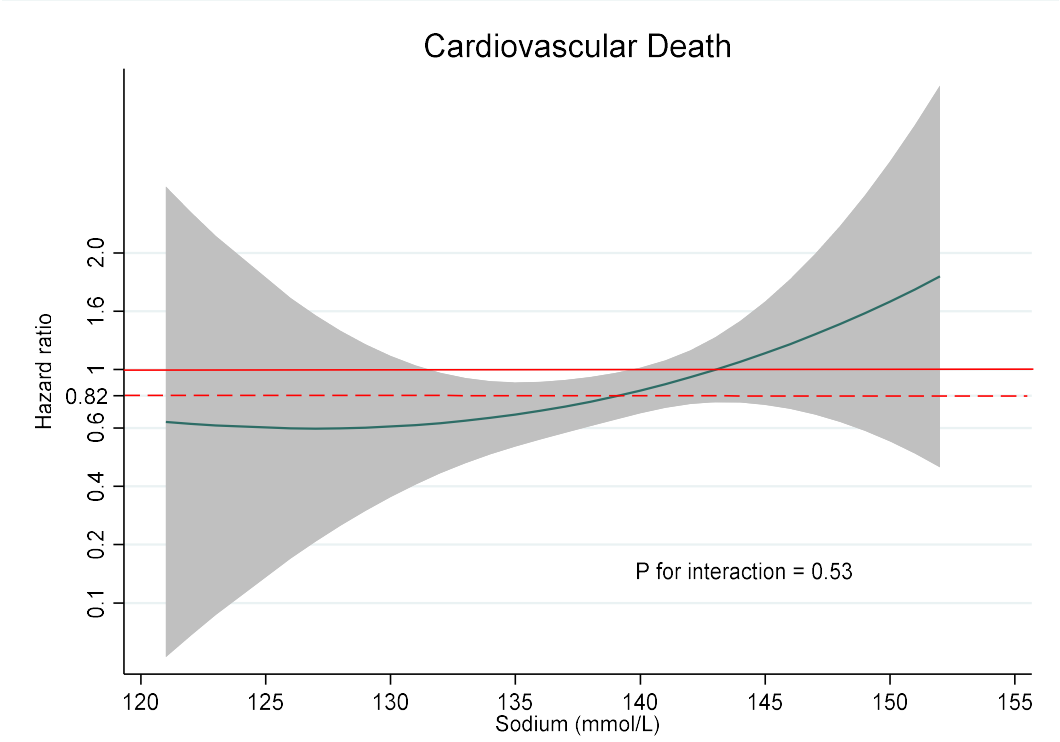


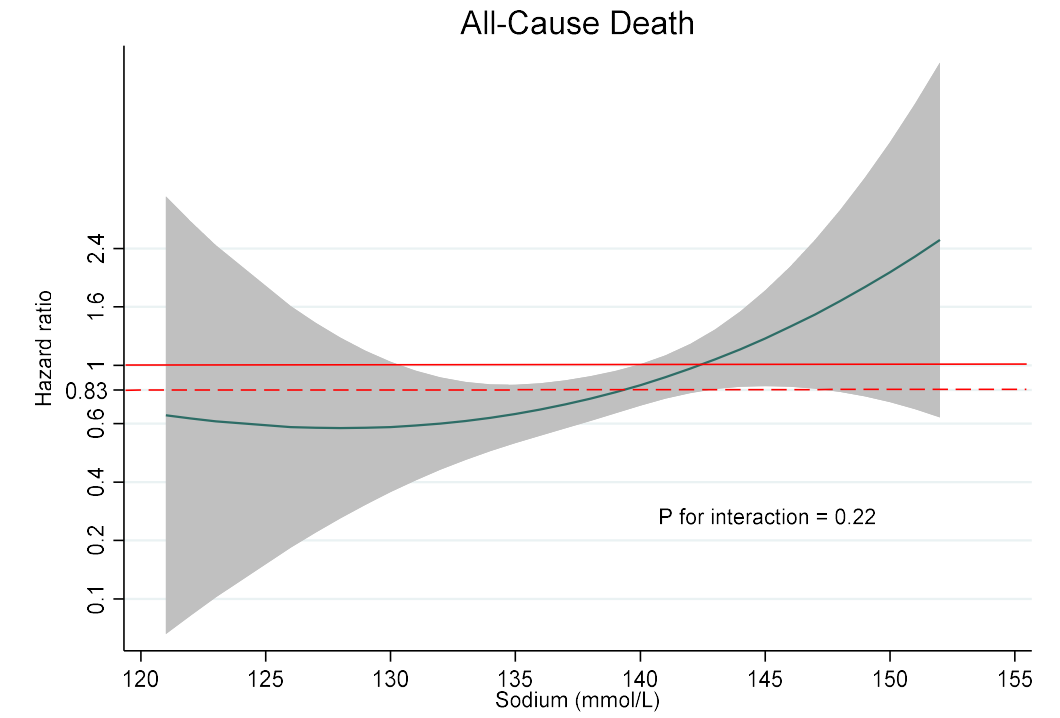
Effect of dapagliflozin on key outcomes in patients with and without hyponatremia at baseline.

Figure 3-7 Effect of dapagliflozin on the primary outcome according to baseline serum sodium in DAPA-HF

The blue line represents a continuous hazard ratio. The grey area represents the 95% confidence interval. The overall hazard ratio for the effect of dapagliflozin is given by the dashed red line. The solid red line is a HR of 1 (unity), indicating no difference between treatments.



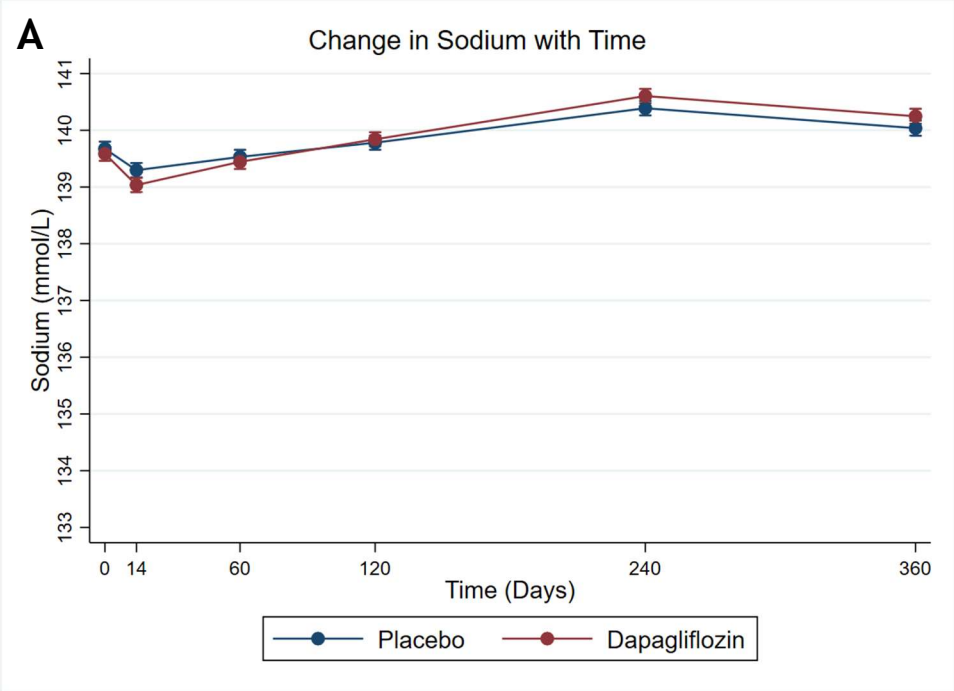

Cardiovascular Death
Hazard ratio
0.1
0.2
0.4
0.6
0.82
1
1.6
2.0
P for interaction = 0.53
120
125
130
135
140
145
150
155
Sodium (mmol/L)

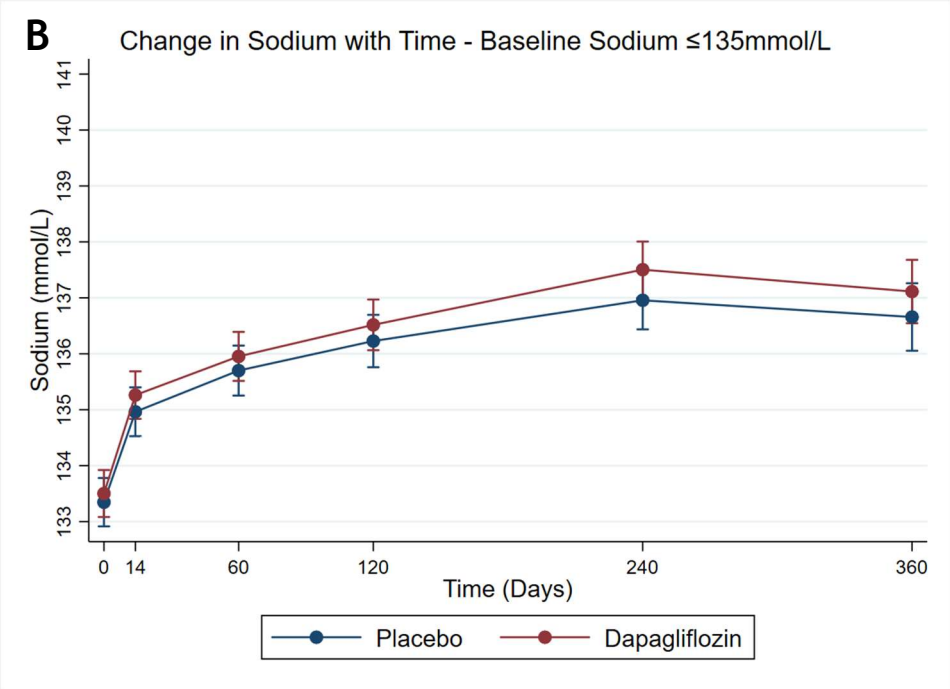

All-Cause Death
Hazard ratio
0.1
0.2
0.4
0.6
0.83
1
1.6
2.4
P for interaction = 0.22
120
125
130
135
140
145
150
155
Sodium (mmol/L)

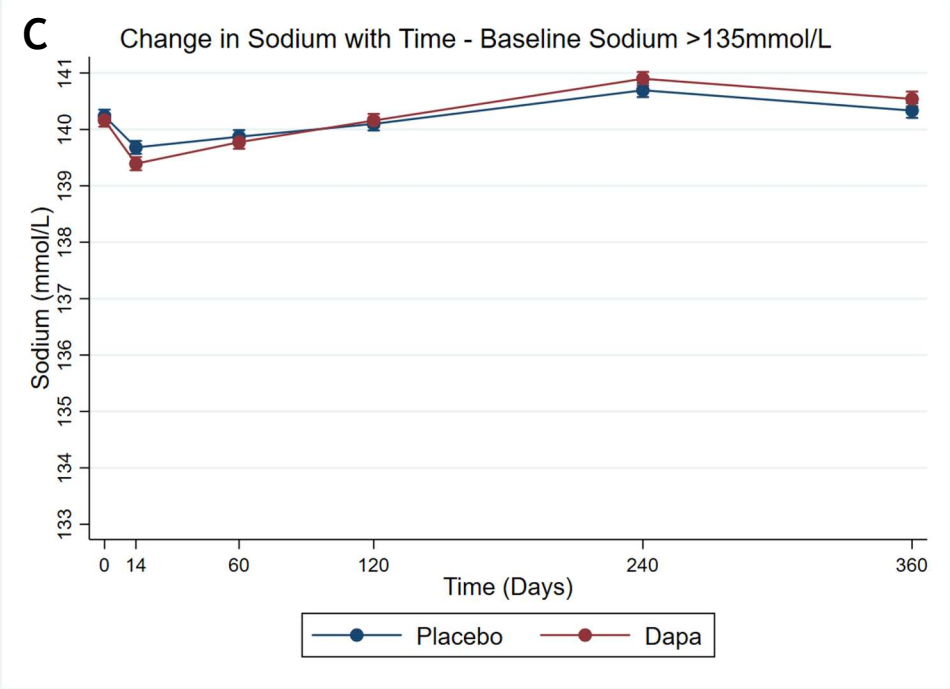
3.5.3 Effect of dapagliflozin on serum sodium - Mean serum sodium concentration

There was a small and transient decline in mean sodium concentration between baseline and 14 days in both treatment groups which was slightly greater in the dapagliflozin, compared with the placebo group (-0.55 mmol/L vs -0.38 mmol/L; P = 0.042). Thereafter, sodium tended to be slightly higher in the dapagliflozin group, but again the differences were small and although statistically significant were clinically negligible (Figure 3-8). For example, the change in sodium concentration from baseline to 8 months was +1.01 mmol/L in the dapagliflozin group vs +0.71 mmol/L in the placebo group (P = 0.001). Looking specifically at participants with hyponatremia at baseline, the effects of dapagliflozin on improvement in sodium levels were more marked, with consistently higher sodium concentration at all follow-up timepoints from baseline.

Figure 3-8 Effect of Dapagliflozin on Serum Sodium Concentration Between Baseline and 12 Months







(A) Overall. (B) Patients with baseline sodium ≤135 mmol/L. (C) Patients with baseline sodium >135 mmol/L.

3.5.4 Development of hyponatremia (in participants with normal baseline sodium)

Between baseline and day 14, 159 of 2,104 participants (7.6%) in the dapagliflozin group with sodium measurements had developed transient hyponatremia compared with 120 of 2,118 participants (5.7%) in the placebo group (P = 0.013) (Table 3-6). After day 14, the opposite pattern was observed and by 12 months, 48 of 1,870 surviving participants (2.6%) in the dapagliflozin group with sodium measurements had new hyponatremia compared with 89 of 1,848 participants (4.8%) in the placebo group (P < 0.001) (Table 3-6).

Table 3-6 Proportion of Patients Showing Resolution of Baseline Hyponatremia (Na^+ ≤135 mmol/L) After Randomization or Developing New Hyponatremia After Baseline

Visit	Resolution of Hyponatremia			New Hyponatremia		
	Dapagliflozin	Placebo	*P* Value	Dapagliflozin	Placebo	*P* Value
14 d	99/200 (49.5)	92/190 (48.4)	0.83	159/2104 (7.6)	120/2118 (5.7)	0.013
2 mo	117/190 (61.6)	108/184 (58.7)	0.57	118/2048 (5.8)	108/2076 (5.2)	0.43
4 mo	113/186 (60.8)	105/174 (60.3)	0.94	78/2033 (3.8)	103/2021 (5.1)	0.052
8 mo	134/177 (75.7)	111/165 (67.3)	0.084	50/1954 (2.6)	74/1938 (3.8)	0.025
12 mo	126/171 (73.7)	102/147 (69.4)	0.40	48/1870 (2.6)	89/1848 (4.8)	<0.001
16 mo	109/138 (79.0	86/124 (69.4)	0.074	51/1563 (3.3)	48/1554 (3.1)	0.78
Values are n/N (%). The analysis was truncated at 16 months because there were fewer than 100 people in one or both treatment groups among those who had hyponatremia at baseline.						

3.5.5 Resolution of hyponatremia (in participants with baseline hyponatremia)

Nearly half of patients showed rapid resolution of baseline hyponatremia by 14 days with 99 of 200 (49.5%) surviving patients with sodium measurements in the dapagliflozin group and 92 of 190 (48.4%) in the placebo group (P = 0.83); the proportions were much larger among survivors at 1 year with 126 of 171 (73.7%) in the dapagliflozin group and 102 of 147 (69.4%) in the placebo group (P = 0.40) (Table 3-6).

The net result of these changes was that more patients in the dapagliflozin group had hyponatremia (n = 260, 11.3%) than in the placebo group (n = 218, 9.4%) at 14 days (P = 0.04), whereas by 12 months the opposite was true, with 93 cases (4.6%) in the dapagliflozin group and 134 cases (6.7%) in the placebo group (P = 0.003).

3.5.6 Change in SBP, eGFR, and hematocrit according to baseline hyponatremia status

The pattern and extent of change in SBP, eGFR, and hematocrit with dapagliflozin were similar in patients with and without hyponatremia at baseline (Figures 3-9 and 3-10). Participants in the dapagliflozin group showed a sustained and statistically significant increase in hematocrit levels from baseline to all follow-up timepoints regardless of baseline hyponatremia status, whereas there was no significant change in hematocrit for participants in the placebo group. For example, the change in hematocrit from baseline to 14 days was +0.7% in the dapagliflozin group vs -0.15% in the placebo group (P < 0.001), with the difference increasing to +2.4% in the dapagliflozin group vs -0.15% in the placebo group from baseline to 4 months (P < 0.001), and levels in both groups remaining relatively stable thereafter.

Figure 3-9 Effect of Dapagliflozin on Hematocrit

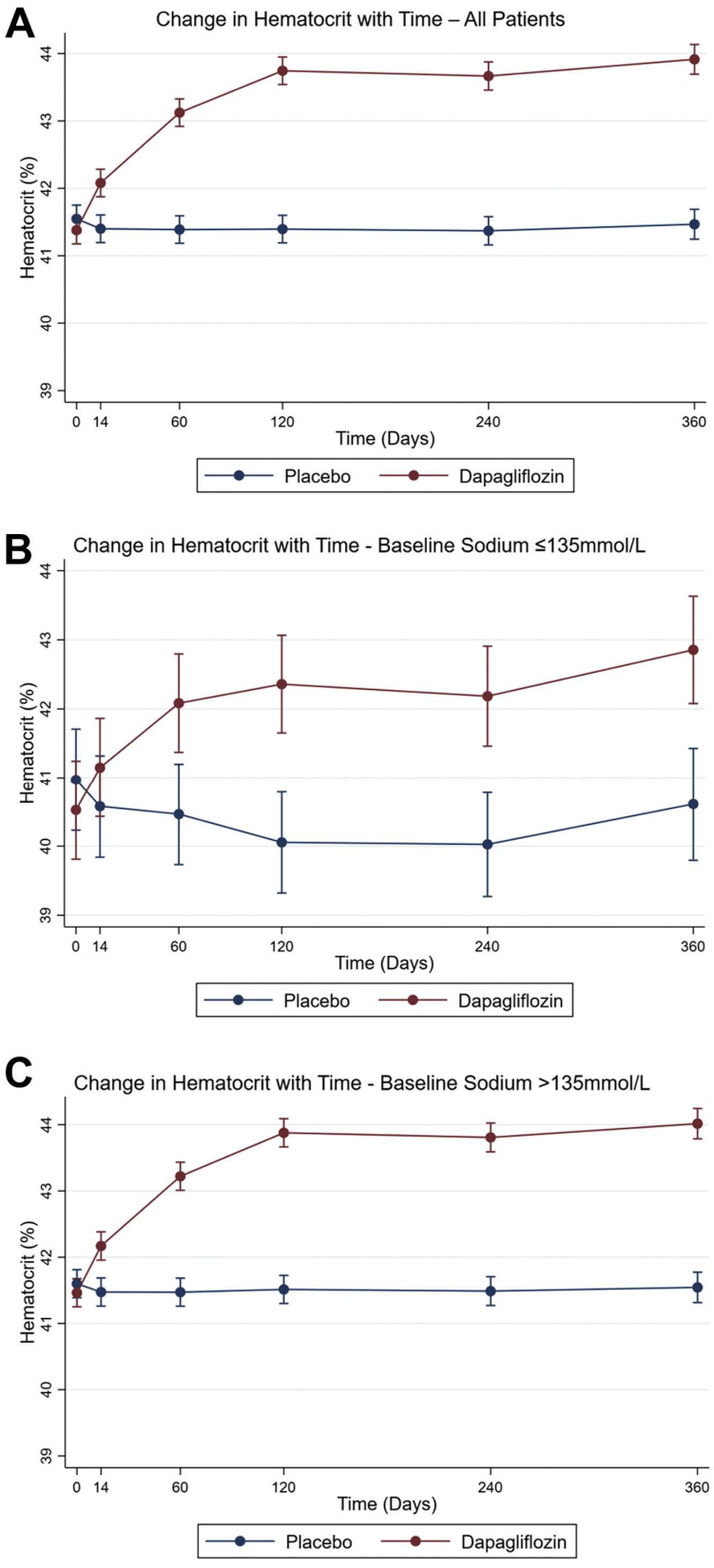
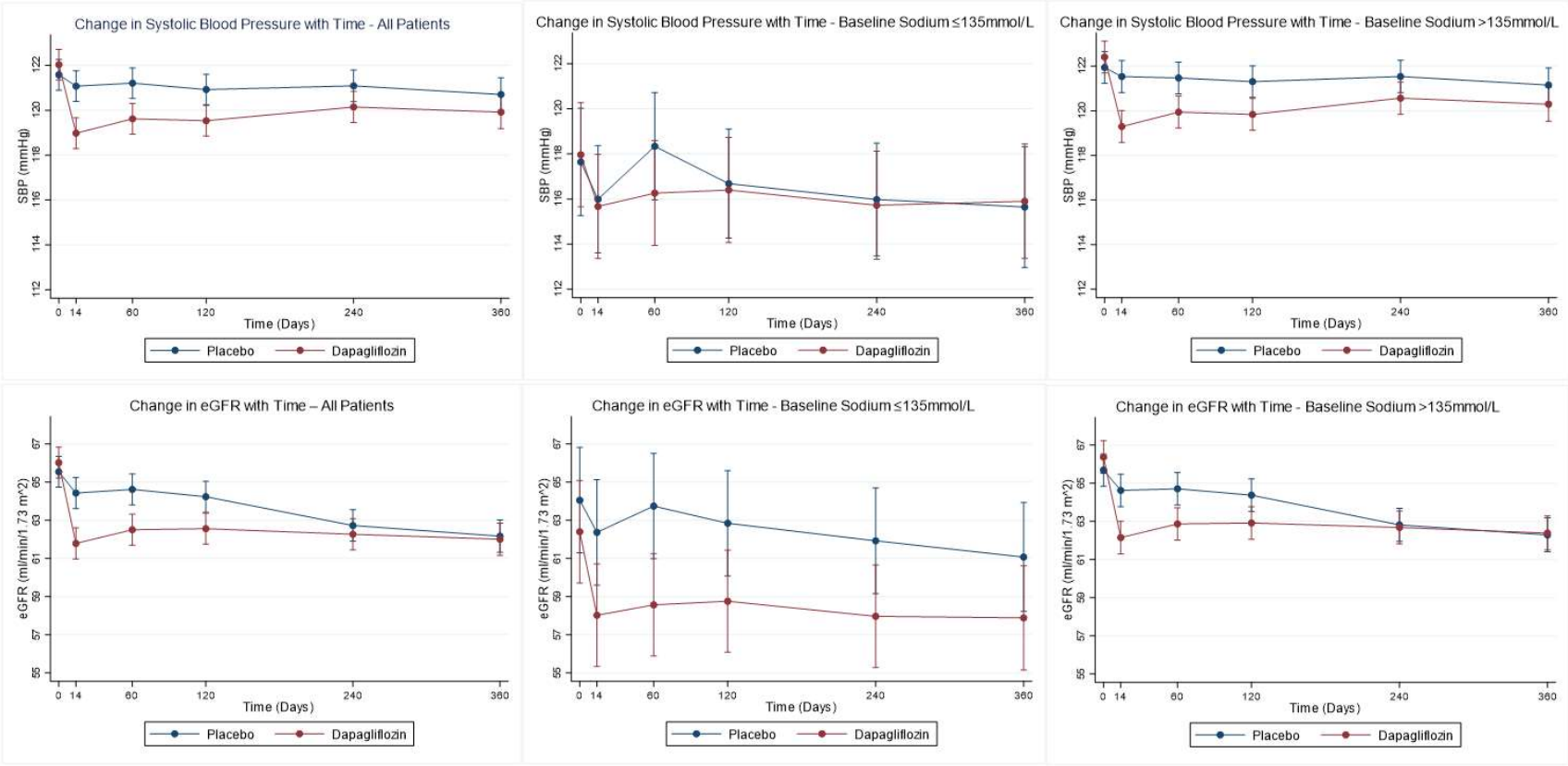


Figure 3-10 Effect of dapagliflozin on systolic blood pressure and eGFR

The graphs indicate the effect of dapagliflozin on all patients, patients with baseline sodium ≤135 mmol/L and patients with baseline sodium >135 mmol/L.



3.5.7 Safety and adverse events

Each of the adverse events of interest was uncommon. There was a higher rate of adverse events related to volume depletion and renal dysfunction in the low-sodium group compared with the normal-sodium group (Table 3-7). The other adverse events of interest were very infrequent in each sodium subgroup. Baseline serum sodium did not notably modify the rate of adverse events in patients assigned to either placebo or dapagliflozin (Table 3-7).

Table 3-7 Adverse Events Related to Randomized Therapy According to Baseline Sodium Category

	Na^+ ≤135 mmol/L		Na^+ >135 mmol/L		*P* for Interaction[a]
	Placebo (n = 193)	Dapa (n = 205)	Placebo (n = 2,174)	Dapa (n = 2,161)	
Any discontinuation	27 (14.0)	31 (15.1)	231 (10.6)	217 (10.0)	0.61
Discontinuation due to AE	11 (5.7)	11 (5.4)	105 (4.8)	100 (4.6)	0.97
Adverse events					
Volume depletion	19 (9.8)	20 (9.8)	143 (6.6)	158 (7.3)	0.74
Renal	20 (10.4)	20 (9.8)	150 (6.9)	133 (6.2)	0.85
Fracture	6 (3.1)	4 (2.0)	44 (2.0)	45 (2.1)	0.46
Amputation	1 (0.5)	1 (0.5)	11 (0.5)	12 (0.6)	0.94
Major hypoglycemia	1 (0.5)	0 (0)	3 (0.1)	4 (0.2)	—

Values are n (%). The safety analysis included only patients who took at least one dose of randomized treatment.

Abbreviations: AE = adverse event; Dapa = dapagliflozin.

[a]Interaction between sodium category and effect of randomized treatment.

3.6 Discussion

In a contemporary, well-treated ambulatory cohort of patients with HFrEF, most of whom had mild symptoms, the prevalence of hyponatremia was low (8.4%) and there were few cases of severe hyponatremia (0.06%). However, hyponatremia remained an independent predictor of outcomes despite adjustment for other prognostic variables, including NT-proBNP. The benefit of dapagliflozin was consistent across the range of sodium concentrations measured at baseline. Dapagliflozin had a small biphasic effect on serum sodium concentration. Initially, compared with placebo, dapagliflozin led to a small, although statistically significant, decrease in sodium. However, after 2 weeks, the opposite pattern was observed.

Although hyponatremia is recognized as the most common electrolyte disorder among hospitalized patients with HF, there are few reports of the prevalence of hyponatremia in ambulatory patients with HFrEF and none in patients comprehensively managed with contemporary guideline-recommended medical therapy.[103-105] Even accounting for different definitions, the prevalence of hyponatremia in our outpatient cohort (8.4%) was less than half that reported in hospitalized patients (generally 20% to 25%).[95-98]

Although most cases of hyponatremia in the DAPA-HF trial were mild, low sodium still predicted worse outcomes. This excess risk persisted despite adjustment for other recognized prognostic variables, many of which showed an imbalance between patients with and without hyponatremia. Indeed, we know of no prior study where such extensive adjustment was made, including for natriuretic peptide level, in ambulatory patients.[103-105] Moreover, most studies to date have only reported the association between hyponatremia and all-cause mortality, whereas we have also shown that low sodium was independently predictive of worsening HF events (principally HF hospitalization) and symptoms.[108, 109]

The prognostic importance of a single sodium measurement was remarkable given the rapid and frequent resolution of hyponatremia on rechecking blood chemistry. In the placebo group, almost half of cases of hyponatremia had resolved at the 2-week measurement after randomization and about two-thirds of cases had resolved by 8 months. This substantial recategorization occurred because the initial measurement was only slightly below normal in many patients. However, almost as many people in the placebo group developed new hyponatremia at each timepoint during follow-up as showed resolution of hyponatremia. Dapagliflozin had a surprising, previously unrecognized, biphasic effect on new hyponatremia. The incidence of hyponatremia was increased during the first 14 days after randomization but was decreased thereafter in patients treated with dapagliflozin compared to placebo. The explanation for this pattern is uncertain. The initial osmotic and natriuretic diuresis induced by SGLT2 inhibitors causes an increase in vasopressin secretion and a reduction in free-water clearance, experimentally and clinically, which might account for the early transient reduction in serum sodium concentration.[50, 110-112] The subsequent effects on serum sodium concentration are harder to predict given the direct effects of SGLT2 inhibitors and the compensatory responses to these. The diuresis induced by SGLT2 inhibitors is believed to lead to a reduction in intravascular volume and blood pressure, and the increased delivery of sodium to the distal nephron results in a decline in eGFR by inducing tubuloglomerular feedback.[49, 113-115] However, it has been hypothesized that SGLT2 inhibitors reduce blood volume less than conventional diuretics.[87] Although the initial decrease in sodium mirrors the early decline in eGFR after starting dapagliflozin, subsequently, serum sodium concentration increased more in the dapagliflozin group than the placebo group, to the extent that the mean concentration was eventually significantly higher in the dapagliflozin group. Although the initial decrease in eGFR also partially recovers, eGFR does not recover back to the same level as in the placebo group (as is also observed in other trials and real-world data over the same period) and eGFR does not crossover as for sodium.[36, 116] So, it seems unlikely that the effect of SGLT2 inhibitors of eGFR alone explain the early effect on sodium, although it might explain the longer-term effect if there is a relative increase in free-water clearance with these agents (as seems likely) and sodium excretion is maintained (and sodium retention

does not occur), which may be the case if eGFR is maintained. The complexity of these effects is reflected in the seeming paradox of the early decline in serum sodium concentration occurring contemporaneously with an increase in hematocrit, questioning whether the latter can be wholly explained by volume contraction. Although detailed analyses of change in hemoglobin have been reported in other trials, the effect of other SGLT2 inhibitors on serum sodium has not been reported.[117] Irrespective of the possible mechanisms, the important overarching finding was that after 14 days, patients treated with dapagliflozin were less likely to develop new hyponatremia and more likely to show resolution of existing hyponatremia than individuals treated with placebo, which may be a favorable effect of SGLT2 inhibition in HF. The benefits of dapagliflozin on the primary and secondary cardiovascular outcomes were consistent in patients with and without hyponatremia (and across the range of serum sodium concentration at baseline), despite the initial transient small decline in serum sodium concentration. Indeed, the absolute risk reduction with dapagliflozin was 1.5- to 2.0-fold greater in patients with hyponatremia than in those without. Similarly, dapagliflozin was also well-tolerated in patients with hyponatremia, and the safety of dapagliflozin was similar in patients with and without hyponatremia.

3.7 Study limitations

Analysis of the effect of dapagliflozin on outcomes according to baseline sodium concentration was not a prespecified outcome, although assessment of the effect of dapagliflozin on sodium level was a prespecified safety outcome. Measurement of urinary sodium and water excretion, along with osmolality, might have suggested possible mechanisms underlying the biphasic effect of dapagliflozin on serum sodium concentration. The low prevalence of hyponatremia in DAPA-HF may have reflected the enrollment of relatively low-risk patients as a result of the specific inclusion and exclusion criteria used in the trial. Our patients were ambulatory, and understanding of the effects of SGLT2 inhibitors on sodium status in patients hospitalized with worsening HF would be of interest.

3.8 Conclusions

Hyponatremia predicts worse clinical outcomes in patients with HFrEF. Compared with placebo, dapagliflozin improved mortality and worsening HF events and symptoms, regardless of serum sodium concentration. Dapagliflozin led to a small early and transient increase in the risk of hyponatremia but a long-term sustained decrease in this risk.

Chapter 4 Endothelin-1, Outcomes in Patients With Heart Failure and Reduced Ejection Fraction, and Effects of Dapagliflozin: Findings From DAPA-HF

4.1 Abstract

4.1.1 Background

ET-1 (endothelin-1) is implicated in the pathophysiology of heart failure and renal disease. Its prognostic importance and relationship with kidney function in patients with heart failure with reduced ejection fraction receiving contemporary treatment are uncertain. We investigated these and the efficacy of dapagliflozin according to ET-1 level in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure).

4.1.2 Methods

We investigated the incidence of the primary outcome (cardiovascular death or worsening heart failure), change in kidney function, and the effect of dapagliflozin according to baseline ET-1 concentration, adjusting in Cox models for other recognized prognostic variables in heart failure including NT-proBNP (N-terminal pro-B-type natriuretic peptide). We also examined the effect of dapagliflozin on ET-1 level.

4.1.3 Results

Overall, 3048 participants had baseline ET-1 measurements: tertile 1 (T1; ≤3.28 pg/mL; n=1016); T2 (>3.28–4.41 pg/mL; n=1022); and T3 (>4.41 pg/mL; n=1010). Patients with higher ET-1 were more likely male, more likely obese, and had lower left ventricular ejection fraction, lower estimated glomerular filtration rate, worse functional status, and higher NT-proBNP and hs-TnT (high-sensitivity troponin-T). In the adjusted Cox models, higher baseline ET-1 was independently associated with

worse outcomes and steeper decline in kidney function (adjusted hazard ratio for primary outcome of 1.95 [95% CI, 1.53–2.50] for T3 and 1.36 [95% CI, 1.06–1.75] for T2; both versus T1; estimated glomerular filtration rate slope: T3, –3.19 [95% CI, –3.66 to –2.72] mL/min per 1.73 m2 per y, T2, –2.08 [95% CI, –2.52 to –1.63] and T1 –2.35 [95% CI, –2.79 to –1.91]; P=0.002). The benefit of dapagliflozin was consistent regardless of baseline ET-1, and the placebo-corrected decrease in ET-1 with dapagliflozin was 0.13 pg/mL (95% CI, 0.25–0.01; P=0.029).

4.1.4 Conclusions

Higher baseline ET-1 concentration was independently associated with worse clinical outcomes and more rapid decline in kidney function. The benefit of dapagliflozin was consistent across the range of ET-1 concentrations measured, and treatment with dapagliflozin led to a small decrease in serum ET-1 concentration.

4.2 Introduction

The endothelins are a family of 21 amino acid vaso-active peptides consisting of 3 isoforms (ET [endothelin]-1, ET-2, and ET-3) encoded by separate genes.[22, 118-120] ET-1 is the most abundant and best-characterized isoform.[22, 118-120] ET-1 is produced in small amounts mainly in endothelial cells in blood vessels and primarily acts as a local paracrine and autocrine mediator. However, under pathophysiological conditions, increased ET-1 production is stimulated in other cell types, including vascular smooth muscle cells, cardiac myocytes, and inflammatory cells.[118] The effects of ET-1 are mediated by ETA and ETB receptors, which usually have opposing actions. ETA receptors function to promote vasoconstriction and inflammation, whereas ETB receptors produce vasodilation and natriuresis and inhibit inflammation. ET-1 may have diuretic and natriuretic effects in the kidney, mediated predominantly by ETB receptors, leading to inhibition of sodium and chloride reabsorption, suppression of Na+/K+ ATPase activity, and inhibition of vasopressin-induced water reabsorption in the collecting duct.[22, 23, 119-121] Recently, a possible role for the endothelins in the progression of kidney dysfunction was suggested by the beneficial effect of the selective ETA receptor antagonist atrasentan in patients with diabetic

nephropathy.[122] These actions are plausibly relevant in heart failure (HF) given the strong bidirectional links between chronic kidney disease and HF. Indeed, circulating ET-1 levels are often elevated in patients with this condition.[123-125] Moreover, the circulating level of ET-1 is associated with the severity of HF and, in some studies, the risk of HF hospitalization and mortality.[126-129] However, the relationship between ET-1 levels and serial changes in kidney function in HF has not been reported.

SGLT-2 (sodium-glucose cotransporter-2) is also expressed in the proximal renal tubule, and SGLT-2 inhibitors have demonstrated important cardiovascular and kidney benefits in multiple recent clinical trials, including slowing the rate of decline in estimated glomerular filtration rate (eGFR) in patients with HF.[16, 36-38, 40, 42] Intriguingly, the SGLT-2 inhibitor empagliflozin has recently been shown to inhibit basal and IL-1ß (interleukin-1ß)–induced ET-1 expression in 2 independent human proximal tubular cell lines under normoglycemic conditions, raising the potential for an interaction between the endothelin system and SGLT-2 inhibitors in patients with HF.[130]

We examined the role of serum ET-1 concentration as a prognostic biomarker in a contemporary population with HF and reduced ejection fraction (HFrEF), including its value when added to other established biomarkers, evaluated the relationship between serum ET-1 and decline in kidney function in HFrEF, and investigated whether ET-1 modifies the response to SGLT-2 inhibition in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure).[38]

4.3 Methods

DAPA-HF was a prospective, randomized, double-blind, controlled trial that evaluated the efficacy and safety of 10 mg of dapagliflozin once daily, compared with placebo, added to standard care in 4744 patients with HFrEF followed up for a median of 18.2 months.[38] Ethics committees at each participating institution approved the protocol, and all patients gave written informed consent. Participation in a prospective biomarker substudy was offered to all enrolled patients in countries where regulations allowed it. The first authors had full access to the data in the study

and take responsibility for its integrity and the data analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

4.3.1 Study Patients

Patients ≥18 years of age were eligible if they were in New York Heart Association functional class II to IV, had a left ventricular ejection fraction ≤40%, and were optimally treated with pharmacological and device therapy for HFrEF.[38] Study participants were also required to have an elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide) level (ie, NT-proBNP ≥600 pg/mL or ≥400 pg/mL if hospitalized for HF within the previous 12 months or ≥900 pg/mL if there was concomitant atrial fibrillation or flutter, irrespective of history of HF hospitalization).

The main exclusion criteria included type 1 diabetes, symptomatic hypotension or systolic blood pressure <95 mm Hg and eGFR <30 mL/min per 1.73 m2 or rapid decline in renal function. Patients were also excluded if they had current acute decompensated HF or HF hospitalization within 4 weeks before enrollment, or recent myocardial infarction or coronary revascularization in the preceding 12 weeks.

4.3.2 Measurement of Serum ET-1 and Other Biomarkers

Venous blood samples were taken at randomization and at 12 months. ET-1 samples were collected in serum tubes, whereas other biomarkers were collected in EDTA anticoagulant tubes. Isolated serum (ET-1) and plasma (other biomarkers) were stored at −20°C or colder until shipped on dry ice to the central repository, where they were stored at −80°C or colder until assayed. ET-1 was measured (TIMI Clinical Trials Laboratory, Boston, MA) using a microfluidics immunoassay on the Ella system (ProteinSimple). The limit of quantitation of the assay is 0.25 pg/mL, with a normal range of 0.92 to 1.58 pg/mL. There were only 5 ET-1 values lower than the limit of quantitation, so no imputation was made. hs-TnT (high-sensitivity troponin-T) was measured (TIMI Clinical Trials Laboratory, Boston, MA) at baseline and 12 months with an Elecsys immunoassay on the Cobas E601 analyzer (Roche Diagnostics).[131] The limit

of quantitation of the assay is 6 ng/L, and the 99th percentile upper reference limit used in the laboratory is 14 ng/L. For analyses as a continuous variable, patients with hs-TnT concentrations <6 ng/L were assigned a value of half the limit of quantitation (ie, 3 ng/L). NT-proBNP was measured at baseline and at 8 months in a central laboratory (Covance) using an Elecsys immunoassay (Roche Diagnostics).[132]

4.3.3 Prespecified Trial Outcomes

The primary outcome of DAPA-HF was the composite of worsening HF (HF hospitalization or urgent visit for HF) or cardiovascular death, whichever occurred first. Prespecified secondary end points included: HF hospitalization or cardiovascular death; HF hospitalizations (first and recurrent) and cardiovascular deaths; all-cause death; and a change in KCCQ-TSS (Kansas City Cardiomyopathy Questionnaire-total symptom score) from baseline to 8 months. For the KCCQ-TSS, higher scores reflect better health status, and the proportion having a ≥5-point increase or decrease in score at 8 months was determined as previously described.[38] There was also a prespecified secondary renal composite outcome, but this was not evaluated further in this analysis because of the small number of events.

In addition to these prespecified outcomes, the post hoc outcome of the slope of change in eGFR over time according to baseline ET-1 tertile was calculated as described in the Statistical Analysis section.

4.3.4 Statistical Analysis

Baseline characteristics were summarized according to baseline ET-1 tertile as mean (SD) or median (interquartile range) for continuous variables and count (percentage) for categorical variables. Differences in the baseline characteristics between tertiles were evaluated with a Wilcoxon-type test for trend.[133]

We analyzed the association between baseline ET-1 tertile and key clinical outcomes, the relationship between change in ET-1 from baseline to 12 months with the primary outcome, the association of ET-1 concentration with changes in renal function, and

the efficacy of dapagliflozin according to baseline ET-1 concentrations. In addition, we further investigated the risk of primary and key secondary outcomes according to ET-1 groups by studying the inflexion points in restricted cubic splines. This resulted in 3 ET-1 groups: group 1 (≤4 pg/mL; n=1724), group 2 (>4–7 pg/mL; n=1145), and group 3 (>7 pg/mL; n=179).

Time-to-event end points were analyzed using Kaplan-Meier estimate and Cox proportional-hazards models, with ET-1 modeled as both a categorical variable (tertiles and groups) and continuous variable and stratified according to diabetes status, history of HF hospitalization (except for all-cause death), and treatment group assignment, as described in the trial statistical analysis plan. We further adjusted these estimates using Cox models with known predictors of risk in patients with HF, including age, sex, race, geographic region, duration of HF, heart rate, systolic blood pressure, body mass index, New York Heart Association functional classification, left ventricular ejection fraction, eGFR, etiology of HF, history of atrial fibrillation and NT-proBNP, a model with adjustment for baseline hs-TnT as an additional covariate, as well as an additional model adjusting for baseline use of an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor–neprilysin inhibitor, or mineralocorticoid receptor antagonist. Proportionality of hazards for these models was confirmed visually using log(−log) plots and testing Schoenfeld residuals.

The relationships between baseline ET-1 and risks of key clinical end points were displayed using both unadjusted and adjusted restricted cubic splines with 5 knots. In addition, we described the incidence of the primary outcome according to tertiles of baseline ET-1, tertiles of baseline hs-TnT, and tertiles of baseline NT-proBNP. We then plotted the incidence of the primary outcome according to tertiles of baseline ET-1 versus tertiles of baseline hs-TnT and tertiles of baseline ET-1 versus tertiles of baseline NT-proBNP. The association between change in ET-1 from baseline to 12 months and risk of subsequent outcomes was analyzed in a landmark analysis of patients who were alive at 12 months with available ET-1 data. Hazard ratios (HRs)

and 95% CIs for the primary outcome according to the log2-transformed ratio of 12 months to baseline ET-1 were modeled using restricted cubic spline analysis adjusted for log-transformed baseline ET-1, randomized treatment, history of HF hospitalization, and stratified by diabetes status. A repeated-measures mixed-effect model was used to examine the slope of change in eGFR over time and the interaction between treatment and visit, as well as the interaction between baseline ET-1 concentration and visit, with a random intercept and slope per patient as previously described.[42] The effect of the randomized treatment on change in ET-1 from baseline to 12 months was also examined using an ANCOVA model adjusted for baseline value.

The effect of dapagliflozin compared with placebo on each outcome was calculated as HR and 95% CI derived from Cox proportional-hazards models adjusted for a history of hospitalization for HF and treatment assignment and stratified by baseline diabetes status, as prespecified in the statistical analysis plan for the main trial. The effect of baseline ET-1 concentration on the treatment effect of dapagliflozin compared with placebo was assessed by the inclusion of ET-1 tertile*treatment interaction term in the model, and an interaction P value was calculated using a likelihood ratio test. The proportion of patients with a clinically significant (≥5 points) improvement or deterioration in KCCQ-TSS at 8 months was analyzed as previously described and presented as an odds ratio for each ET-1 tertile.[38]

All analyses were conducted using Stata version 16.0 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant. As before, all of the analyses was performed by myself using Stata statistical software except for the Schoenfeld residual test and KCCQ-TSS analysis, which was analysed by the 2nd author (Docherty KF) using SAS software.

4.4 Results

Baseline serum ET-1 was measured in 3048 patients, and 12-month serum ET-1 was measured in 2436 patients. The median baseline ET-1 concentration was 3.81 pg/mL

(25th to 75th percentile, 3.03–4.80), with tertile 1 ≤3.28 pg/mL (n=1016), tertile 2 >3.28 to 4.41 pg/mL (n=1022), and tertile 3 >4.41 pg/mL (n=1010).

4.4.1 Baseline Characteristics

Baseline characteristics according to ET-1 tertiles are summarized in Table 4-1. Patients with higher baseline ET-1 concentrations were more likely to be male, non-Asian, and obese, with more comorbidities, especially diabetes, atrial fibrillation, and chronic obstructive pulmonary disease (Table 4-1). They also had worse kidney function, lower left ventricular ejection fraction, and poorer functional status, with a higher proportion of patients with New York Heart Association class III or IV symptoms and lower (worse) KCCQ-TSS (each P<0.001). Patients with higher baseline ET-1 were more often treated with a diuretic, an angiotensin receptor–neprilysin inhibitor, digoxin, and devices but less often with a mineralocorticoid receptor antagonist.

Table 4-1 Patient Characteristics According to Baseline ET-1 Tertile

Baseline characteristic	Baseline ET-1 (3048 patients) – pg/mL			*P*-trend
	Tertile 1 (≤3.28 pg/mL)	**Tertile 2 (>3.28-4.41 pg/mL)**	**Tertile 3 (>4.41 pg/mL)**	
Age – years	66.4 ± 10.8	68.0 ± 10.0	67.2 ± 10.5	0.29
Age >75 years – no. (%)	220 (21.7)	236 (23.1)	218 (21.6)	0.75
Female sex – no. (%)	259 (25.5)	227 (22.2)	178 (17.6)	<0.001
Race or ethnic group – no. (%)				<0.001
- White	753 (74.1)	817 (79.9)	812 (80.4)	
- Black	16 (1.6)	30 (2.9)	39 (3.9)	
- Asian	245 (24.1)	172 (16.8)	152 (15.0)	
- Other	2 (0.2)	3 (0.3)	7 (0.7)	
Region – no. (%)				<0.001
- North America	114 (11.2)	190 (18.6)	205 (20.3)	
- Latin America	86 (8.5)	88 (8.6)	85 (8.4)	
- Europe	575 (56.6)	578 (56.6)	573 (56.7)	
- Asia Pacific	241 (23.7)	166 (16.2)	147 (14.6)	
Systolic BP – mmHg	122 ± 15	124 ± 16	121 ± 16	0.059
Heart rate – bpm	70 ± 10	70 ± 11	73 ± 12	<0.001
BMI – kg/m^2	27.6 ± 5.5	28.7 ± 6.0	29.3 ± 6.0	<0.001
- BMI classification				<0.001
• Obesity (BMI≥30)	327 (32.2)	404 (39.6)	441 (43.7)	

• Overweight (BMI 25-29.9)	363 (35.8)	360 (35.3)	348 (34.5)	
• Normal weight (BMI 18.5-24.9)	309 (30.4)	239 (23.4)	207 (20.5)	
• Underweight (BMI<18.5)	16 (1.6)	18 (1.8)	14 (1.4)	
Hemoglobin – g/L	135.6 ± 14.7	135.6 ± 15.8	136.2 ± 17.2	0.30
Hematocrit - %	41.2 ± 4.5	41.3 ± 4.7	42.0 ± 5.6	0.002
HbA1c – %	6.3 ± 1.1	6.4 ± 1.2	6.6 ± 1.4	<0.001
Serum Creatinine – µmol/L	97.7 ± 25.8	105.2 ± 30.4	111.8 ± 33.6	<0.001
Serum Urea – mg/dL	21.6 ± 7.7	23.8 ± 9.8	25.6 ± 12.9	<0.001
eGFR – mL/min/1.73m^2	69.4 ± 19.1	64.3 ± 18.3	61.8 ± 18.3	<0.001
Clinical HF features				
- Ischemic cardiomyopathy – no. (%)	594 (58.5)	597 (58.4)	616 (61.0)	0.25
- LVEF - %	31.9 ± 6.3	31.4 ± 6.7	30.2 ± 7.3	<0.001
NYHA Class – no. (%)				<0.001
- II	748 (73.6)	737 (72.1)	613 (60.7)	
- III	265 (26.1)	283 (27.7)	392 (38.8)	
- IV	3 (0.3)	2 (0.2)	5 (0.5)	
KCCQ-TSS (baseline)	78.7 ± 19.1	76.0 ± 21.2	69.1 ± 21.5	<0.001
Median Biomarkers (IQR)				
- NT-proBNP – pg/mL	1069 (681 – 1782)	1283 (813 – 2219)	2288 (1317 – 4144)	<0.001
• NT-proBNP if history of AF – pg/mL	1316 (851-2135)	1519 (990-2465)	2472 (1507-4375)	<0.001
• NT-proBNP if no history of AF – pg/mL	966 (626-1572)	1164 (719-1921)	2043 (1125-3891)	<0.001
- hs-TnT – ng/L	15.8 (11.1 – 24.5)	19.6 (14.2 – 28.2)	25.5 (17.3 – 38.6)	<0.001
- Gal-3 – pg/mL	11240 (9218 – 13453)	11504 (9523 – 13941)	11765 (9457 – 14400)	0.001
- GDF-15 – pg/mL	1541 (1103 – 2212)	1876 (1341 – 2575)	2378 (1692 – 3543)	<0.001
- sST2 – ng/mL	26.9 (20.3 – 36.7)	29.9 (22.0 – 40.3)	37.5 (27.1 – 53.8)	<0.001
- IGFBP7 – ng/mL	170 (146 – 209)	189 (156 – 236)	230 (185 – 293)	<0.001
- PIIINP – ug/L	7.1 (5.7 – 9.2)	7.8 (6.3 – 10.1)	8.5 (6.7 – 10.9)	<0.001
Medical History – no. (%)				
- Hypertension	738 (72.6)	794 (77.7)	800 (79.2)	<0.001
- Diabetes	383 (37.7)	456 (44.6)	536 (53.1)	<0.001

- Atrial Fibrillation (History)	316 (31.1)	424 (41.5)	504 (49.9)	<0.001
- Atrial Fibrillation/Flutter (ECG)	167 (16.4)	254 (24.9)	318 (31.5)	<0.001
- Prior HF hospitalization	471 (46.4)	467 (45.7)	448 (44.4)	0.37
- MI	475 (46.8)	483 (47.3)	495 (49.0)	0.31
- Stroke	89 (8.8)	94 (9.2)	116 (11.5)	0.039
- COPD	85 (8.4)	147 (14.4)	164 (16.2)	<0.001
- CKD (eGFR<60 mL/min/1.73m^2)	323 (31.8)	415 (40.7)	495 (49.0)	<0.001
- Anemia*	251 (25.0)	271 (26.7)	293 (29.2)	0.034
Treatments at randomization – no. (%)				
- ACEi	629 (61.9)	585 (57.2)	510 (50.5)	<0.001
- ARB	269 (26.5)	264 (25.8)	261 (25.8)	0.75
- ARNI	65 (6.4)	121 (11.8)	179 (17.7)	<0.001
- Beta-blocker	972 (95.7)	989 (96.8)	956 (94.7)	0.26
- Digitalis	109 (10.7)	161 (15.8)	195 (19.3)	<0.001
- Diuretic	817 (80.4)	855 (83.7)	913 (90.4)	<0.001
- MRA	765 (75.3)	718 (70.3)	686 (67.9)	<0.001
- Anticoagulant	370 (36.4)	475 (46.5)	532 (52.7)	<0.001
- Antiplatelet	592 (58.3)	558 (54.6)	507 (50.2)	<0.001
- Statin	705 (69.4)	687 (67.2)	685 (67.8)	0.45
- ICD/CRT-D	257 (25.3)	333 (32.6)	367 (36.3)	<0.001
- CRT-P/CRT-D	69 (6.8)	92 (9.0)	95 (9.4)	0.034

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, CRT with defibrillator; CRT-P, CRT with pacemaker; eGFR, estimated glomerular filtration rate; ET, endothelin; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; HF, heart failure; hs-TnT, high-sensitivity troponin-T; ICD, implantable cardioverter defibrillator; IGFBP7, insulin-like growth factor-binding protein 7; IQR, interquartile range; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire-total symptom score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PIIINP, amino-terminal pro-peptide of type III procollagen; and sST2, soluble suppression of tumorigenicity-2.

*Anemia: hemoglobin <130 g/L in males and hemoglobin <120 g/L in females.

4.4.2 Relationship Between ET-1 and Clinical Outcomes

Incidence rates of the primary and secondary outcomes increased with increasing ET-1 tertile, with the difference most marked for the outcome of worsening HF (Table 4-2; Figure 4-1). The elevated risk for the primary end point remained significant after comprehensive adjustment for prognostic variables, including NT-proBNP, with an adjusted HR (aHR) of 1.36 (95% CI, 1.06–1.75) for tertile 2 and 1.95 (95% CI, 1.53–2.50) for tertile 3, compared with tertile 1. This higher risk was driven by the risk of worsening HF, with an aHR of 1.54 (95% CI, 1.10–2.18) and 2.54 (95% CI, 1.82–3.53) for tertiles 2 and 3, respectively. However, the risk relationship with death was attenuated by adjustment, and the aHR for all-cause mortality was 1.08 (95% CI, 0.80–1.45) and 1.45 (95% CI, 1.09–1.93) for tertiles 2 and 3, respectively. This pattern of risk was maintained after additional adjustment for baseline hs-TnT (Table 4-2).

Inspection of the restricted cubic spline models suggested a linear increase in the risk of the primary and secondary outcomes from an ET-1 concentration >4 pg/mL which, when log-transformed, equates to log ET-1 >1.39 pg/mL (Figure 4-2; Figure 4-3). Analysis of the primary and secondary outcomes according to the ET-1 group (group 1: 0–4 versus group 2: >4–7 versus group 3: >7 pg/mL) showed a more graduated increase in risk compared with an analysis by tertiles (Table 4-3; Figure 4-4) with an HR for the primary outcome, adjusted for predictive variables including baseline NT-proBNP and hs-TnT, of 1.51 (95% CI, 1.24–1.83) for group 2 and 2.28 (95% CI, 1.68–3.11) for group 3 compared with group 1, and an aHR for all-cause mortality of 1.28 (95% CI, 1.01–1.62) and 1.57 (95% CI, 1.08–2.28) for groups 2 and 3, respectively.

Table 4-2 Event Rate (per 100 Person-Years) and Hazard Ratios for Trial Outcomes According to Baseline ET-1 Tertile

	Tertile 1	Tertile 2	Tertile 3	*P-Trend*
Primary Endpoint (Worsening HF or cardiovascular death) – no. (%)	**102 (10.0)**	**157 (15.4)**	**302 (29.9)**	**<0.001**
- Event rate per 100 person-years (95% CI)	6.9 (5.7-8.3)	10.8 (9.3-12.7)	23.6 (21.1-26.4)	
- Unadjusted HR (95% CI)	1.00 (ref)	1.55 (1.21-2.00)	3.32 (2.65-4.16)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.36 (1.06-1.75)	1.95 (1.53-2.50)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.31 (1.02-1.69)	1.80 (1.41-2.31)	
- Adjusted HR (95% CI)‡	1.00 (ref)	1.31 (1.02, 1.69)	1.79 (1.40, 2.29)	
Hospitalization or urgent visit for HF – no. (%)	**52 (5.1)**	**95 (9.3)**	**213 (21.1)**	**<0.001**
- Event rate per 100 person-years (95% CI)	3.5 (2.7-4.6)	6.6 (5.4-8.0)	16.7 (14.6-19.0)	
- Unadjusted HR (95% CI)	1.00 (ref)	1.85 (1.32-2.60)	4.62 (3.40-6.26)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.54 (1.10-2.18)	2.54 (1.82-3.53)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.51 (1.07-2.12)	2.37 (1.70-3.30)	
- Adjusted HR (95% CI)‡	1.00 (ref)	1.50 (1.07–2.12)	2.34 (1.68–3.25)	
Cardiovascular death – no. (%)	**66 (6.5)**	**86 (8.4)**	**163 (16.1)**	**<0.001**
- Event rate per 100 person-years (95% CI)	4.3 (3.4-5.5)	5.7 (4.6-7.0)	11.4 (9.8-13.3)	

- Unadjusted HR (95% CI)	1.00 (ref)	1.27 (0.92-1.76)	2.50 (1.87-3.33)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.13 (0.82-1.57)	1.39 (1.01-1.92)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.08 (0.78-1.50)	1.27 (0.92-1.74)	
- Adjusted HR (95% CI)‡	1.00 (ref)	1.08 (0.78–1.50)	1.26 (0.92–1.74)	
All-cause mortality (no. of events) – no. (%)	**83 (8.2)**	**102 (10.0)**	**196 (19.4)**	**<0.001**
- Event rate per 100 person-years (95% CI)	5.5 (4.4-6.8)	6.7 (5.6-8.2)	13.8 (12.0-15.8)	
- Unadjusted HR (95% CI)	1.00 (ref)	1.20 (0.90-1.61)	2.40 (1.85-3.11)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.08 (0.80-1.45)	1.45 (1.09-1.93)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.03 (0.77-1.39)	1.33 (1.00-1.77)	
- Adjusted HR (95% CI)‡	1.00 (ref)	1.03 (0.77–1.39)	1.33 (1.00–1.77)	
Overall eGFR slope – slope per mL/min/1.73m^2 per year	-2.35 (-2.79 to -1.91)	-2.06 (-2.51 to -1.62)	-3.19 (-3.66 to -2.72)	0.002§
eGFR slope from baseline to Day 14 – slope per mL/min/1.73m^2 over 14 days	-2.61 (-3.10 to -2.12)	-2.58 (-3.07 to -2.09)	-2.30 (-2.79 to -1.80)	0.6339§
eGFR slope from Day 14 to Day 720 – slope per mL/min/1.73m^2 per year	-1.83 (-2.28 to -1.37)	-1.46 (-1.93 to -1.00)	-2.59 (-3.08 to -2.10)	0.004§

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ET, endothelin; HF, heart failure; and HR, hazard ratio.

* Model 1 was adjusted for death/hospitalization outcomes adjusted for age, sex, treatment arm, race, region, duration of heart failure, previous heart failure hospitalization, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, pathogenesis of heart failure, history of atrial fibrillation, diabetes, and NT-proBNP (N-terminal pro-B-type natriuretic peptide).

† Model adjusted as for model 1, with additional adjustment for baseline high-sensitivity troponin-T.

‡ Model adjusted as for model 1, with additional adjustment for angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/mineralocorticoid receptor antagonist/angiotensin receptor–neprilysin inhibitor use.

§ *P* value for joint difference in slopes between ET-1 tertiles.

Figure 4-1 Kaplan-Meier curves showing key trial outcomes according to baseline ET-1 (endothelin-1) tertile

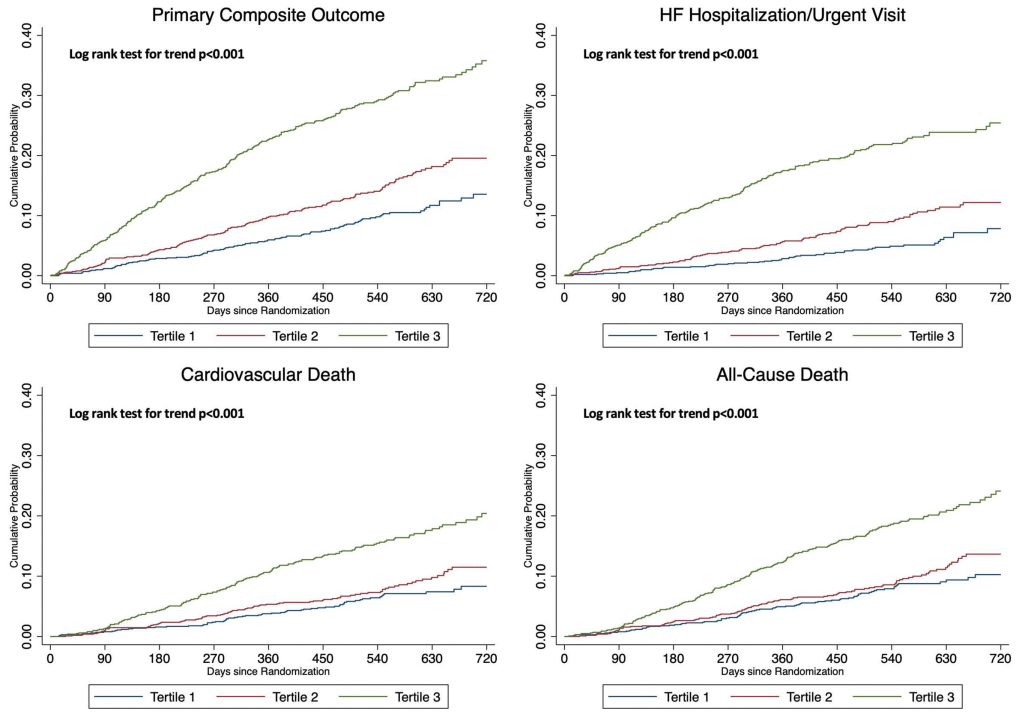
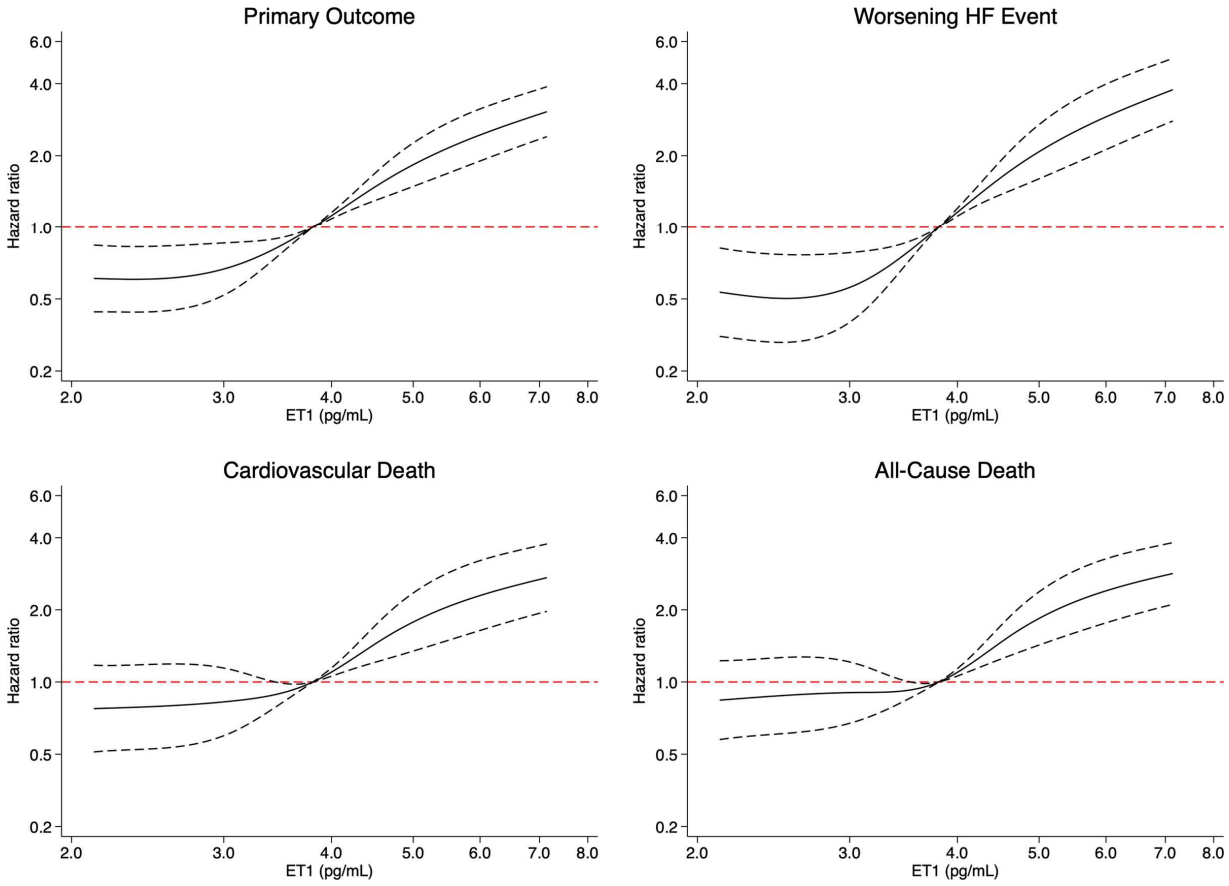


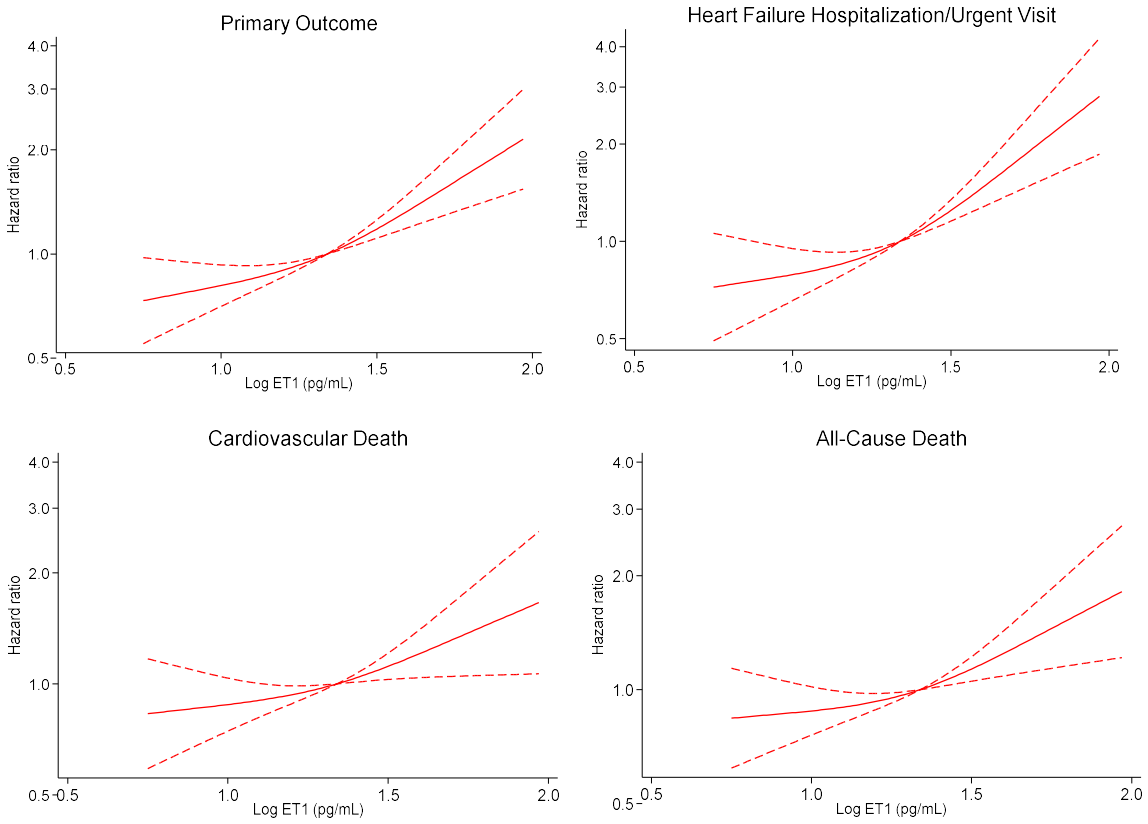
Figure 4-2 Key trial outcomes according to baseline ET-1 levels (unadjusted)



These restricted cubic splines demonstrate the unadjusted risk of each outcome modeling baseline log-transformed ET-1 levels as a continuous variable. The interrupted lines represent corresponding 95% CIs.

Abbreviations: ET-1, endothelin-1; HF, heart failure.

Figure 4-3 Key trial outcomes according to baseline ET-1 levels (adjusted)



These restricted cubic splines demonstrate the risk of each outcome modeling baseline ET-1 concentration as a continuous variable, adjusted for prognostic variables. The interrupted lines represent corresponding 95% confidence intervals.

Table 4-3 Event rate (per 100 person-years) and hazard ratios for trial outcomes according to baseline ET-1 group

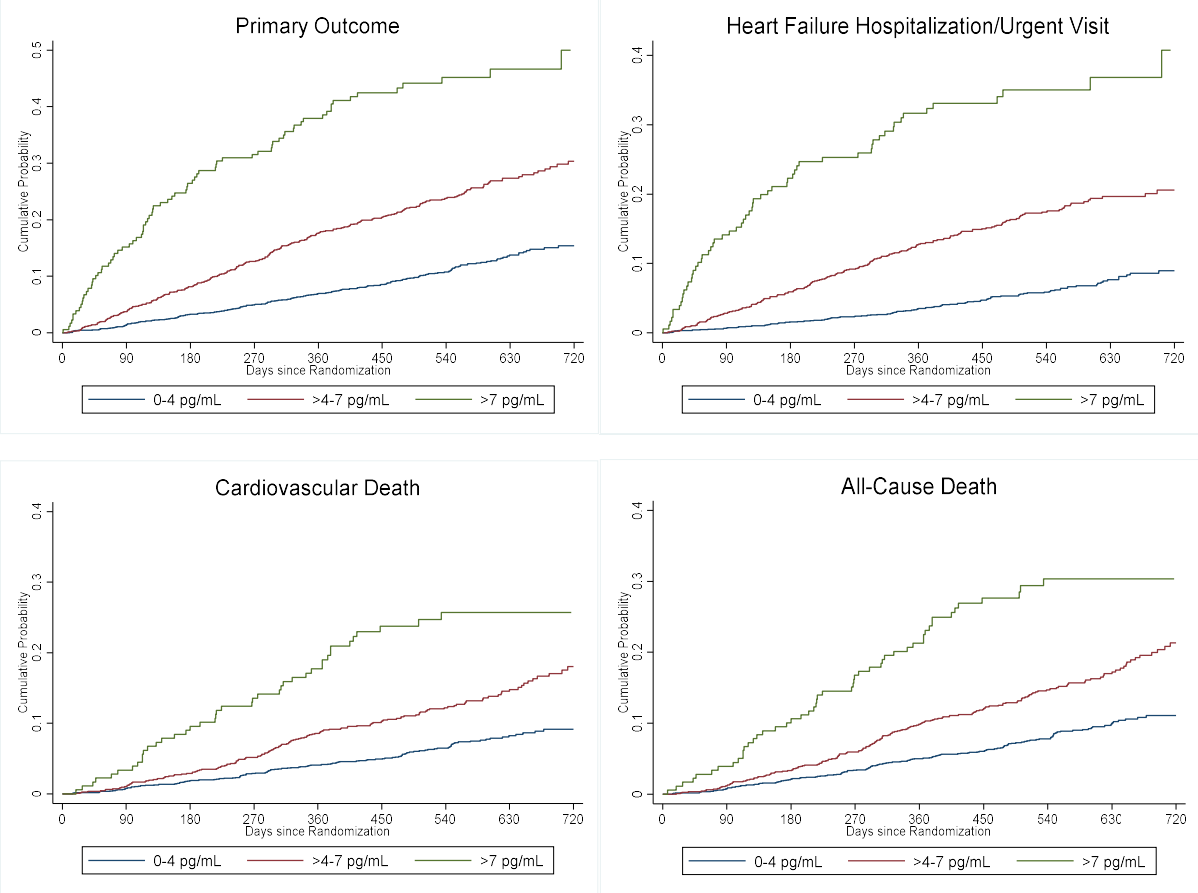
	Group 1 (0-4 pg/mL) N=1,724	Group 2 (>4-7 pg/mL) N=1,145	Group 3 (>7 pg/mL) N=179	*P-Trend*
Primary Endpoint (Worsening HF or cardiovascular death) - no. (%)	**202 (11.7)**	**280 (24.5)**	**79 (44.1)**	**<0.001**
- Event rate per 100 person-years (95% CI)	8.0 (7.0-9.2)	18.5 (16.5-20.8)	42.6 (34.2-53.1)	
- Unadjusted HR (95% CI)	1.00 (ref)	2.26 (1.88-2.71)	5.08 (3.91-6.60)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.61 (1.32-1.95)	2.44 (1.79-3.32)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.51 (1.24-1.83)	2.28 (1.68-3.11)	
Hospitalization or urgent visit for HF - no. (%)	**109 (6.3)**	**191 (16.7)**	**60 (33.5)**	**<0.001**
- Event rate per 100 person-years (95% CI)	4.3 (3.6-5.2)	12.6 (11.0-14.5)	32.4 (25.1-41.7)	
- Unadjusted HR (95% CI)	1.00 (ref)	2.87 (2.27-3.64)	7.10 (5.17-9.76)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.98 (1.54-2.55)	3.41 (2.33-4.99)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.88 (1.45-2.42)	3.24 (2.22-4.75)	
Cardiovascular death - no. (%)	**121 (7.0)**	**152 (13.3)**	**42 (23.5)**	**<0.001**
- Event rate per 100 person-years (95% CI)	4.7 (3.9-5.6)	9.3 (7.9-10.9)	18.3 (13.5-24.7)	
- Unadjusted HR (95% CI)	1.00 (ref)	1.91 (1.50-2.43)	3.74 (2.63-5.32)	

- Adjusted HR (95% CI)*	1.00 (ref)	1.33 (1.03-1.72)	1.46 (0.97-2.21)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.22 (0.94-1.59)	1.34 (0.88-2.02)	
All-cause mortality (no. of events) – no. (%)	**148 (8.6)**	**182 (15.9)**	**51 (28.5)**	**<0.001**
- Event rate per 100 person-years (95% CI)	5.7 (4.9-6.7)	11.1 (9.6-12.8)	22.2 (16.9-29.2)	
- Unadjusted HR (95% CI)	1.00 (ref)	1.88 (1.51-2.34)	3.74 (2.72-5.15)	
- Adjusted HR (95% CI)*	1.00 (ref)	1.37 (1.09-1.73)	1.71 (1.18-2.48)	
- Adjusted HR (95% CI)†	1.00 (ref)	1.28 (1.01-1.62)	1.57 (1.08-2.28)	

*Models for death/hospitalization outcomes adjusted for age, sex, treatment arm, race, region, duration of heart failure, previous heart failure hospitalization, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, etiology of heart failure, history of atrial fibrillation, diabetes and NT-proBNP.

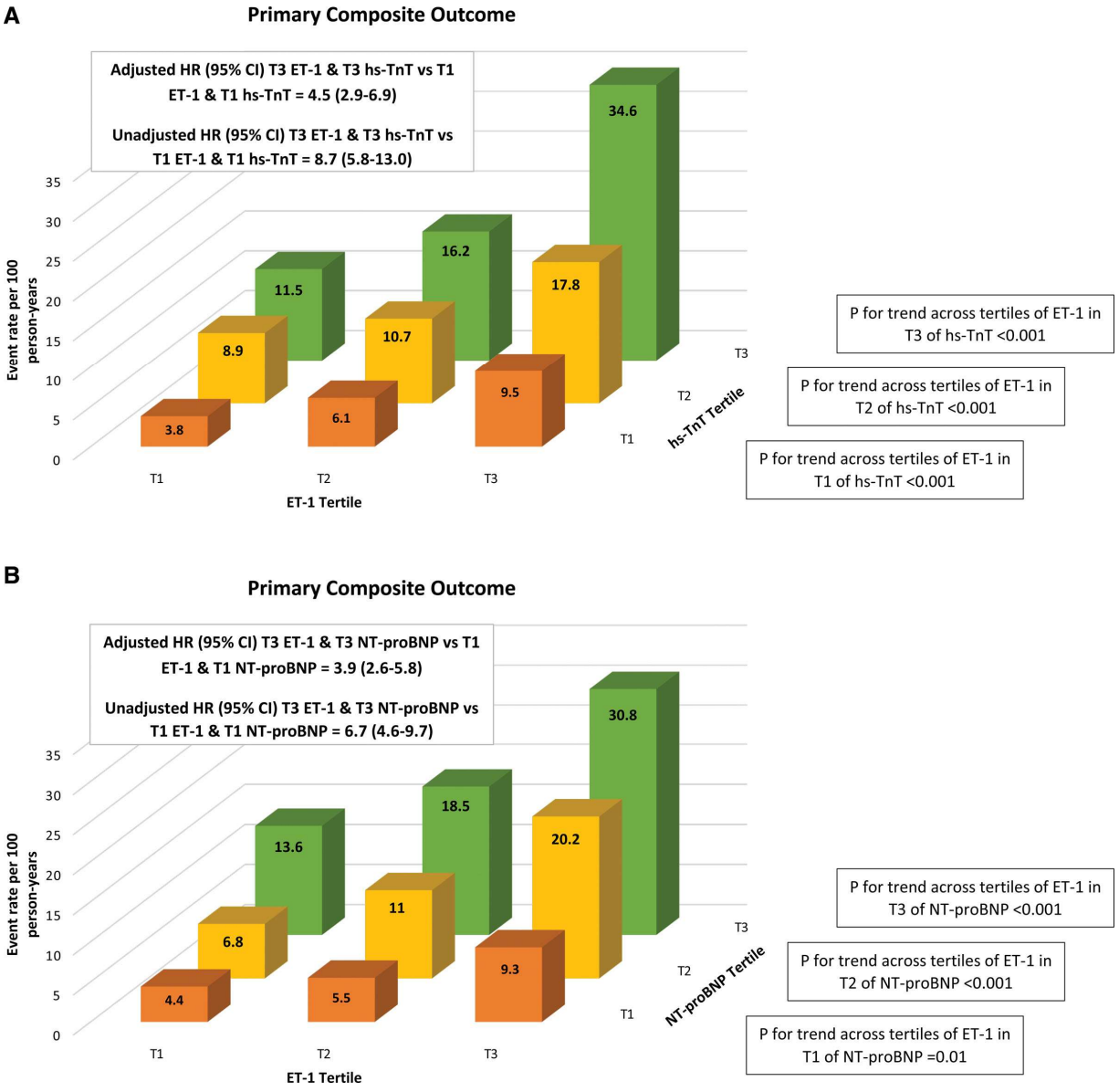
† Model adjusted as for model * with additional adjustment for baseline high-sensitivity Troponin T

Figure 4-4 Kaplan-Meier curves showing key study outcomes according to baseline ET-1 group (group 1: 0-4 vs group 2: >4-7 vs group 3: >7 pg/mL)



The additive risk of ET-1 and hs-TnT is illustrated in Figure 4-5A, which shows a >8-fold higher risk for patients in tertile 3 for both ET-1 and hs-TnT compared with those in tertile 1 for both peptides (event rate per 100 person-years, 34.6 versus 3.8). A similar pattern was seen when baseline ET-1 was analyzed together with baseline NT-proBNP, with a >6-fold higher risk for patients in tertiles 3 of both ET-1 and NT-proBNP compared with patients in tertile 1 for both biomarkers (event rate per 100 person-years, 30.8 versus 4.4; Figure 4-5B).

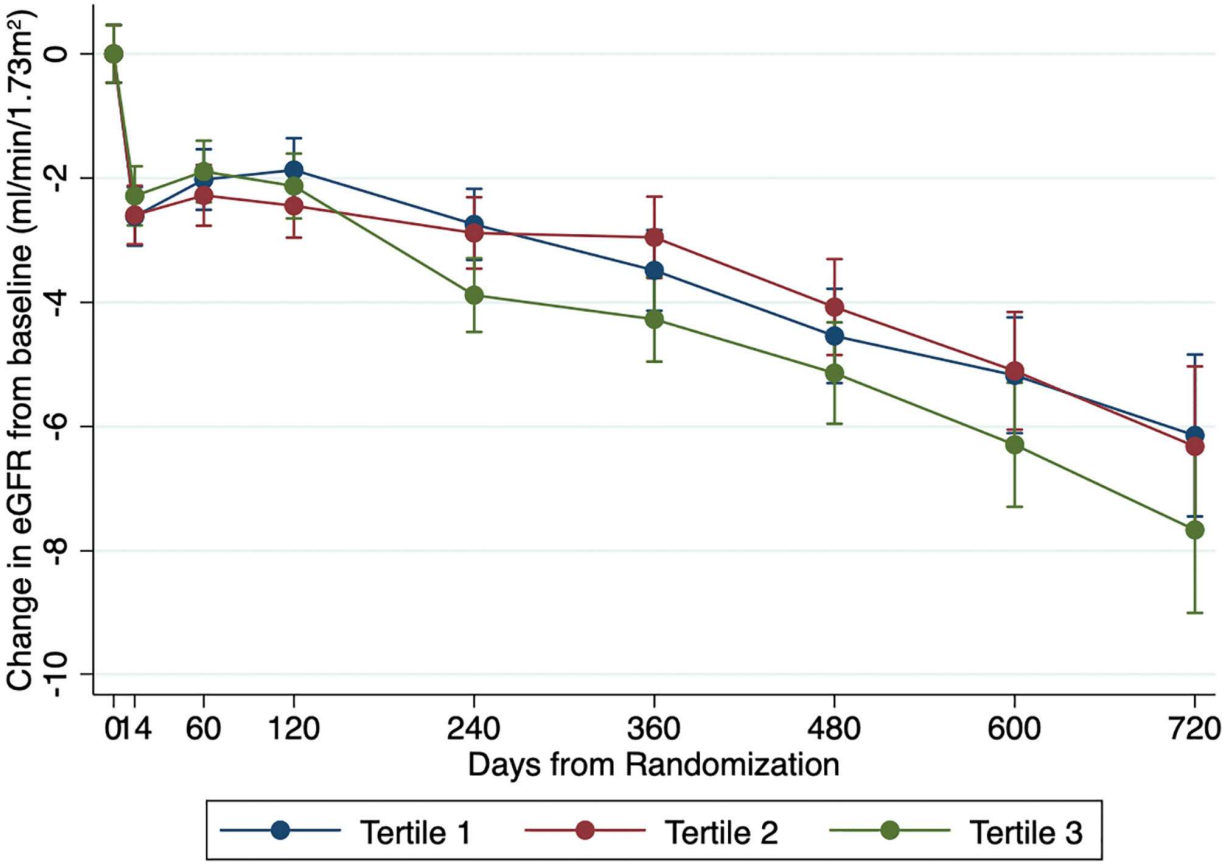
Figure 4-5 Event rates for the primary outcome according to baseline ET-1, hs-TnT, and NTproBNP



4.4.3 Relationship Between Baseline ET-1 and Change in Kidney Function

Overall, kidney function declined during follow-up in DAPA-HF. The steepest rate of decline in eGFR was in ET-1 tertile 3. The overall eGFR slope, measured as mL/min per 1.73 m2 per year, was -2.35 (95% CI, -2.79 to -1.91) in tertile 1, -2.08 (95% CI, -2.52 to -1.63) in tertile 2, and -3.19 (95% CI, -3.66 to -2.72) in tertile 3 (P=0.002; Table 4-2, Figure 4-6).

Figure 4-6 Change in eGFR from baseline in DAPA-HF according to baseline ET-1 (endothelin-1) tertile



The change in eGFR from baseline at each time point is displayed as mean with 95% CI.

4.4.4 Effect of Dapagliflozin on Primary and Secondary Trial Outcomes According to Baseline ET-1 Concentration

Of the 3048 patients with baseline ET-1 measurements, dapagliflozin reduced the primary outcome of cardiovascular death or worsening HF by 22% (HR, 0.78 [95% CI, 0.66–0.92]). The efficacy of dapagliflozin in preventing the primary end point was consistent regardless of baseline ET-1 concentration, whether analyzed according to tertiles (P-interaction=0.47) or as a continuous variable (P-interaction=0.10; Table 4-4; Figure 4-7). Similarly, there was no difference in the treatment effect of dapagliflozin on preventing HF hospitalizations or urgent HF visits, cardiovascular death, and all-cause deaths according to baseline ET-1 tertiles.

Figure 4-7 Kaplan-Meier curves showing the effect of treatment group on the primary outcome according to ET-1 tertile

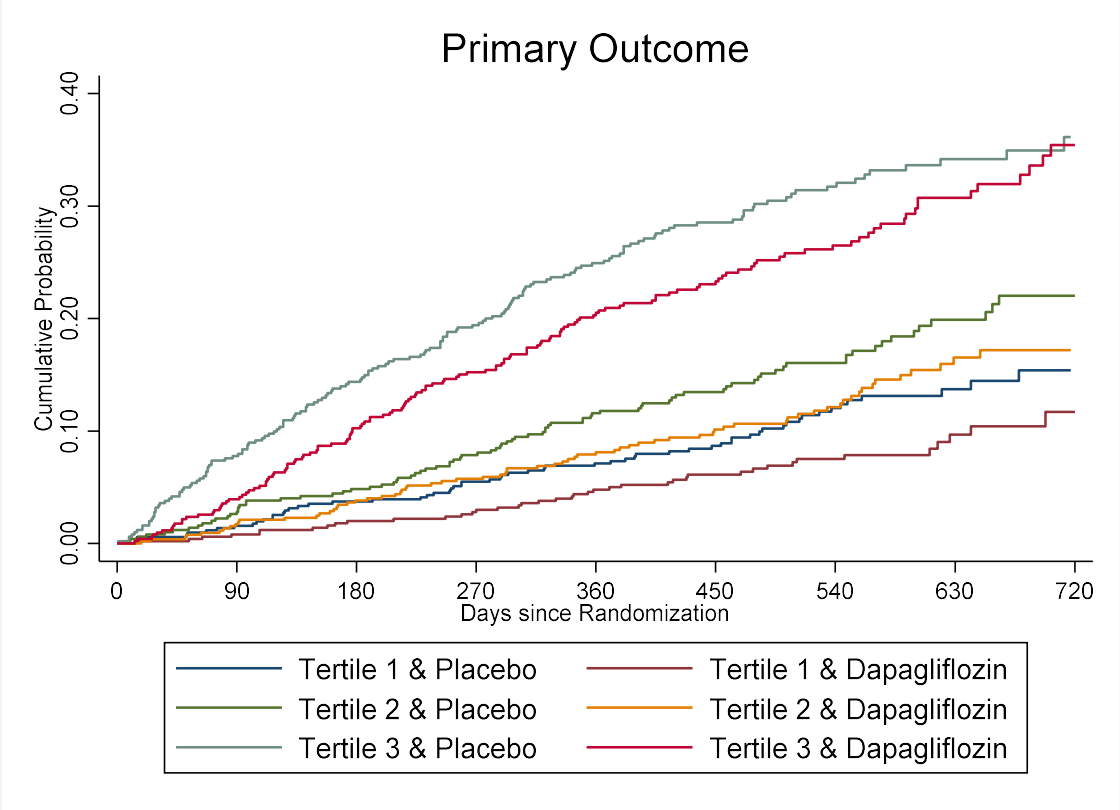


Table 4-4 Effect of Dapagliflozin on the Primary and Secondary Outcomes According to Baseline ET-1 Tertile

Outcome	Tertile 1		Tertile 2		Tertile 3		P-value for interaction
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	
Primary endpoint (worsening HF or cardiovascular death)							
No. (%)	41 (8.1)	61 (11.9)	70 (13.4)	87 (17.5)	142 (28.0)	160 (31.8)	0.47
Rate per 100 person-years (95% CI)	5.5 (4.0-7.4)	8.3 (6.4-10.7)	9.3 (7.4-11.8)	12.5 (10.1-15.4)	21.6 (18.3-25.4)	25.8 (22.1-30.1)	
HR (95% CI)	0.65 (0.44-0.96)		0.73 (0.54-1.01)		0.85 (0.68-1.06)		
Hospitalization or urgent visit for HF							
No. (%)	24 (4.8)	28 (5.5)	40 (7.6)	55 (11.0)	95 (18.7)	118 (23.5)	0.80
Rate per 100 person-years (95% CI)	3.2 (2.1-4.8)	3.8 (2.6-5.5)	5.3 (3.9-7.2)	7.9 (6.1-10.3)	14.4 (11.8-17.6)	19.0 (15.9-22.8)	
HR (95% CI)	0.83 (0.48-1.43)		0.66 (0.44-0.99)		0.77 (0.59-1.01)		
Cardiovascular death							
No. (%)	25 (5.0)	41 (8.0)	42 (8.0)	44 (8.8)	78 (15.4)	85 (16.9)	0.30
Rate per 100 person-years (95% CI)	3.3 (2.2-4.9)	5.4 (4.0-7.4)	5.4 (4.0-7.3)	6.0 (4.5-8.1)	10.9 (8.7-13.6)	12.0 (9.7-14.9)	
HR (95% CI)	0.58 (0.36-0.96)		0.89 (0.58-1.35)		0.92 (0.67-1.25)		
All-cause death							
No. (%)	32 (6.3)	51 (10.0)	49 (9.4)	53 (10.6)	96 (18.9)	100 (19.9)	0.22
Rate per 100 person-	4.2	6.7	6.3	7.2	13.4	14.1	

years (95% CI)	(3.0-5.9)	(5.1-8.9)	(4.8-8.3)	(5.5-9.5)	(11.0-16.4)	(11.6-17.2)	
HR (95% CI)	0.60 (0.39-0.94)		0.86 (0.58-1.27)		0.96 (0.72-1.27)		
Significant worsening in KCCQ-TSS (≥5) at 8 months							
% (95% CI)	20.8 (16.9-24.6)	31.3 (27.1-35.6)	27.7 (23.8-31.7)	32.2 (27.9-36.5)	28.0 (24.0-31.9)	34.6 (30.3-38.9)	0.92
OR (95% CI)	0.76 (0.65-0.90)		0.91 (0.78-1.04)		0.86 (0.75-0.98)		
Significant improvement in KCCQ-TSS (≥5) at 8 months							
% (95% CI)	60.2 (55.5-64.9)	51.8 (47.3-56.3)	56.5 (52.1-61.0)	49.8 (45.2-54.5)	54.5 (50.0-58.9)	49.8 (45.3-54.4)	0.76
OR (95% CI)	1.18 (1.03-1.35)		1.14 (1.00-1.30)		1.10 (0.96-1.25)		

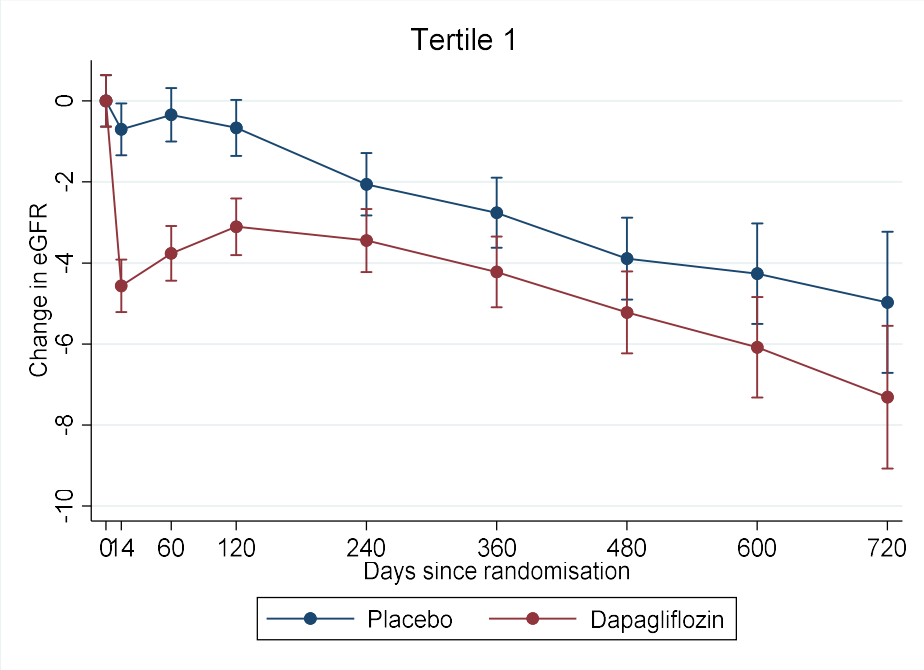
Abbreviations: Heart failure (HF), confidence interval (CI), hazard ratio (HR), Kansas City Cardiomyopathy Questionnaire-total symptom score (KCCQ-TSS), standard error (SE), odds ratio (OR)

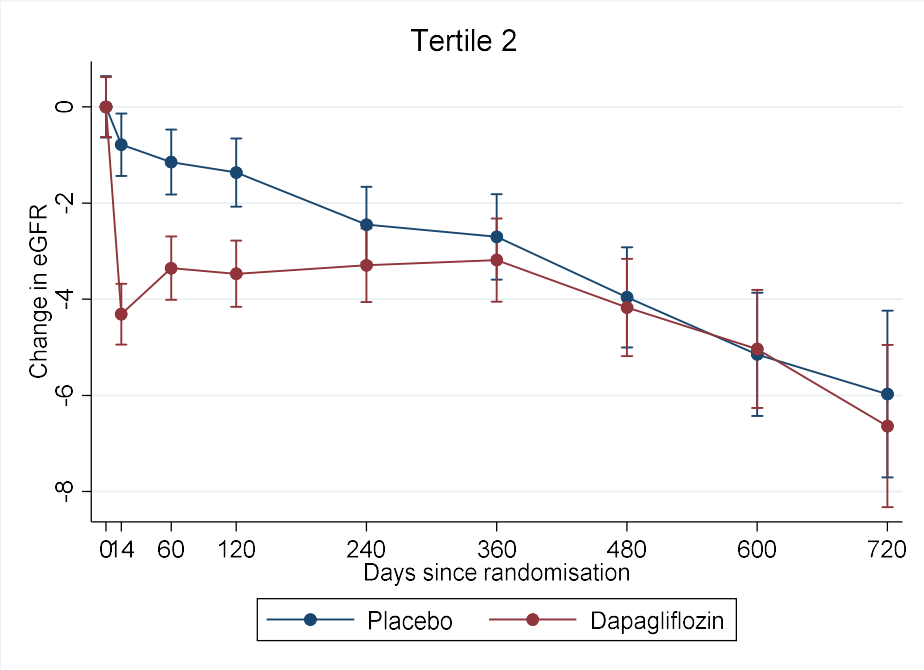
KCCQ-TSS data was analyzed by the 2nd author (Docherty KF) using SAS software

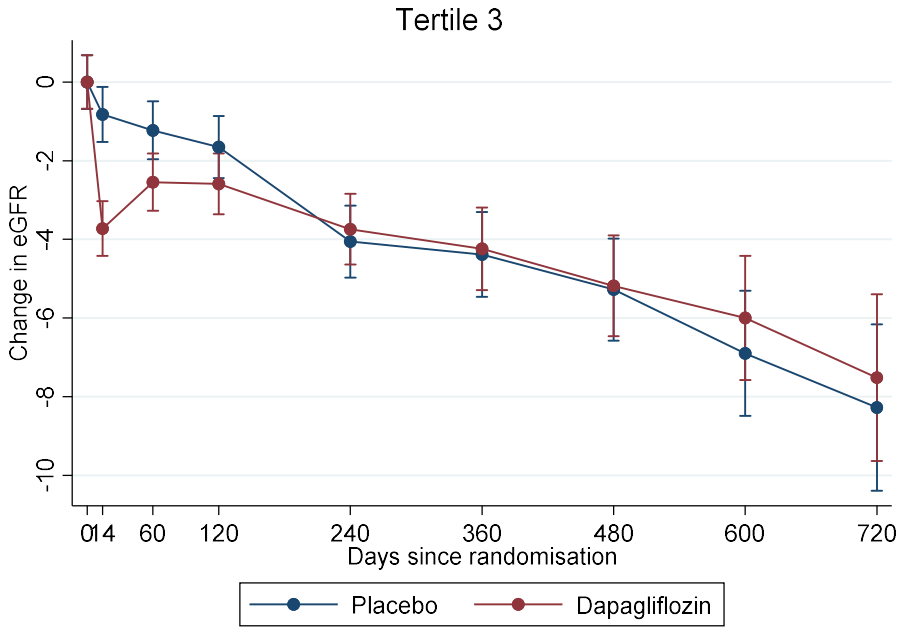
4.4.5 Effect of Dapagliflozin on eGFR Slope According to Baseline ET-1 Concentration

Compared with placebo, dapagliflozin resulted in an initial decrease in eGFR overall, from baseline to day 14, and this was similar across all ET-1 tertiles. Thereafter, the rate of decline in eGFR was steeper in the placebo group than in the dapagliflozin group overall. This pattern was also the case across each tertile of ET-1, with the fastest rate of decline in the third of patients with the highest ET-1 level at baseline (Figure 4-8). For ET tertile 1, the change in eGFR in the dapagliflozin group between day 14 and day 720 was -1.11 (95% CI, -1.72 to -0.50) mL/min per 1.73 m2 per year compared with -2.53 (95% CI, -3.14 to -1.92) in the placebo group (P for difference=0.0013). For tertile 2, change in eGFR was -0.55 (95% CI, -1.14 to 0.05) in the dapagliflozin group versus -2.43 (95% CI, -3.05 to -1.82) in the placebo group (P for difference<0.001). For tertile 3, change in eGFR was -1.75 (95% CI, -2.52 to -0.97) in the dapagliflozin group versus -3.62 (95% CI, -4.41 to -2.83) in the placebo groups (P for difference=0.0009). The interaction P value between ET-1 tertile and treatment group was 0.12.

Figure 4-8 Effect of dapagliflozin (vs. placebo) on change in eGFR from baseline, according to baseline ET-1 tertiles




Tertile 2
Change in eGFR
0
-2
-4
-6
-8
0 14 60 120 240 360 480 600 720
Days since randomisation
Placebo
Dapagliflozin


Tertile 3
Change in eGFR
0
-2
-4
-6
-8
-10
0 14 60 120 240 360 480 600 720
Days since randomisation
Placebo
Dapagliflozin

4.4.6 Change in ET-1 Concentration Between Baseline and 12 Months

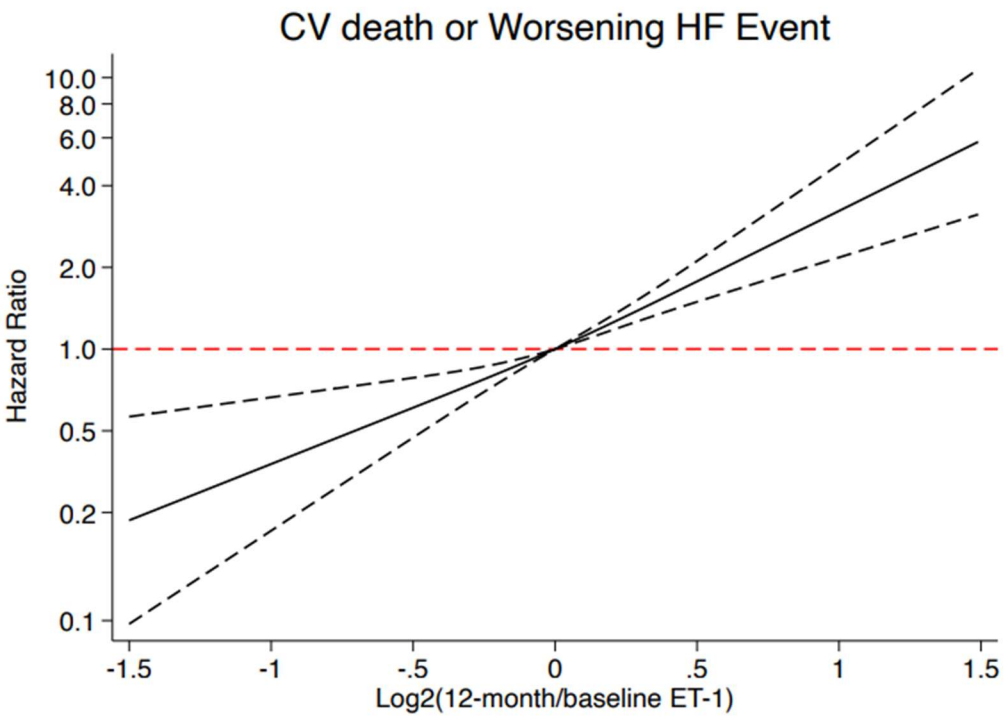
Compared with placebo, there was a reduction in ET-1 level at 12 months with dapagliflozin (difference –0.13 pg/mL [95% CI, –0.25 to -0.01]; P=0.029]. In the placebo group, ET-1 level increased (0.10 pg/mL [95% CI, 0.003–0.20]) from baseline to 12 months, whereas in the dapagliflozin group, ET-1 decreased (–0.04 pg/mL [95% CI, –0.13 to 0.05]).

Figure 4-9 displays the association between change in ET-1 assessed as a continuous variable and subsequent outcomes: a doubling of ET-1 from baseline to 12 months was associated with an HR, for the primary composite of 3.23 (95% CI, 2.18–4.79). Conversely, a halving of ET-1 from baseline was associated with an HR of 0.38 (95% CI, 0.21–0.66).

4.4.7 Safety and Adverse Events

Inspection of the placebo group suggested that the rate of discontinuation of randomized treatment increased as ET-1 increased, as did the frequency of renal adverse events. No other adverse event appeared to show any association with ET-1 level at baseline. Generally, there was no clear difference between placebo and dapagliflozin for any adverse event according to ET-1 tertile (Table 4-5).

Figure 4-9 Association between change in ET-1 from baseline to 12 months and subsequent risk of the primary outcome



This figure displays the subsequent risk of the primary composite outcome according to the change in ET-1 concentration from baseline to 12 months. HR for the primary outcome according to the log2-transformed ratio of 12 months to baseline ET-1 were modelled using restricted cubic spline analysis adjusted for log-transformed baseline ET-1, randomised treatment, history of heart failure hospitalization and stratified by diabetes status. The referent point is patients with no change in ET-1. The dotted lines represent 95% CIs of the HR estimates. A value of 1.0 and -1.0 on the X-axis represents a doubling and halving in ET-1 from baseline to 12 months, respectively.

Table 4-5 Adverse events related to randomized therapy, according to baseline ET-1 tertile

	Tertile 1		Tertile 2		Tertile 3	
	Dapagliflozin	**Placebo**	**Dapagliflozin**	**Placebo**	**Dapagliflozin**	**Placebo**
Any discontinuation – no. (%)	57 (11.3)	32 (6.3)	52 (9.9)	63 (12.7)	61 (12.1)	70 (13.9)
Discontinuation due to AE – no. (%)	27 (5.4)	13 (2.5)	18 (3.4)	28 (5.6)	29 (5.7)	35 (7.0)
Adverse events – no. (%)						
Volume depletion	26 (5.2)	36 (7.1)	42 (8.0)	26 (5.2)	46 (9.1)	40 (8.0)
Renal	17 (3.4)	22 (4.3)	35 (6.7)	28 (5.6)	34 (6.7)	45 (9.0)
Fracture	10 (2.0)	12 (2.4)	10 (1.9)	8 (1.6)	17 (3.4)	16 (3.2)
Amputation	2 (0.4)	4 (0.8)	5 (1.0)	0 (0)	3 (0.6)	4 (0.8)
Major hypoglycemia	0 (0)	2 (0.4)	1 (0.2)	0 (0)	1 (0.2)	0 (0)

The safety analysis included only patients who took at least one dose of randomized treatment and patients with baseline ET-1 (3046 patients). Abbreviations: AE, adverse event.

4.5 Discussion

We believe that this is the largest-ever study of the association between circulating ET-1 and a range of outcomes in HFrEF.[134] We confirmed the prognostic importance of this peptide in a well-treated, contemporary population, provided novel information about the incremental predictive value of ET-1 when added to NT-proBNP and hs-TnT (particularly for HF hospitalization), and showed a previously unknown association between ET-1 and progressive worsening of kidney function over time in patients with HFrEF. We also showed that despite a potential interaction between ET-1 and SGLT-2 in the proximal renal tubule, the benefits of dapagliflozin were consistent across the range of serum ET-1 concentrations measured in DAPA-HF.

Although discovered in 1988, less is known about the clinical importance of ET-1 than most other neurohumoral biomarkers in HF.[135] By far, the largest previous report about this peptide in patients with chronic HFrEF was from the neurohumoral substudy of the Val-HeFT (Valsartan Heart Failure Trial), which included 1934 participants enrolled in the United States.[136] Although details of baseline treatment were not provided in this report, in the parent trial, conducted between 1997 and 2000, just more than one-third of patients were treated with a beta-blocker, and ≈4% were treated with a mineralocorticoid receptor antagonist.[137] Although this and some other studies included natriuretic peptides, none reported measurement of ET-1 and troponin, which has emerged as another incrementally important prognostic marker in contemporary trials.[131, 138] In Val-HeFT, a baseline ET-1 level ≥1.50 pmol/L was a univariate predictor of morbidity and mortality, although its prognostic value in a multivariable model was not reported. In our larger study of patients receiving contemporary therapy, serum ET-1 concentration was associated with the primary composite outcome, its components, and all-cause mortality, both in univariate and multivariate analyses. Importantly, ET-1 remained independently associated with these outcomes, even in models including NT-proBNP and the combination of NT-proBNP and hs-TnT in addition to other prognostic clinical variables, an attribute shared by few if any other biomarkers.[139, 140] Speculatively, ET-1 might be associated with worse outcomes given that it is a much more potent vasoconstrictor than angiotensin II, on a molar basis, and a powerful mitogen known to cause hypertrophy

and fibrosis.[22, 118-120, 123, 124] The vasoconstrictor actions of ET-1, mediated by the ETA receptor, may be most pronounced in the pulmonary circulation, and endothelin receptor antagonists have been developed as an important treatment for patients with primary pulmonary hypertension.[22, 118-120] These ET-1 mechanisms may in part explain the strong association we observed with HF hospitalization, through the worsening of symptoms. Unfortunately, endothelin receptor antagonists have not been effective in patients with HFrEF. Indeed, in virtually all placebo-controlled trials, endothelin receptor antagonists caused worsening HF symptoms and signs.[141-143] This unexpected outcome has never been adequately explained. However, these agents cause fluid retention with the postulated mechanism being cross-talk between ETA and ETB receptors, resulting in a degree of ETB receptor blockade even with specific ETA blockers, and this adverse effect may be dose related and differ by receptor antagonist selectivity.[144, 145]

Although endothelin receptor antagonists were not beneficial in HF, the selective ETA antagonist atrasentan has recently been shown to slow the rate of decline in kidney function in patients with diabetes and chronic kidney disease.[122] Consequently, we also examined the relationship between serum ET-1 concentration and the rate of decline in eGFR over time among patients included in DAPA-HF. Patients in the highest ET-1 tertile in DAPA-HF had a significantly greater rate of decrease in eGFR compared with patients in tertile 1, suggesting that ET-1 might also play a role in the progressive decline in kidney function that occurs in many patients with HF.[146] Ongoing clinical trials in patients with chronic kidney disease will define the future position of endothelin receptor antagonists in the management of chronic kidney disease.[147, 148]

Because of the known potent vasoconstrictor properties of ET-1, the focus of the potential actions of this peptide in the kidney has been on renal blood flow and glomerular haemodynamics. However, as alluded to above, ET-1 also plays a role in sodium and water homeostasis, and ET-1 levels correlate with markers of congestion in patients with HF.[23, 149, 150] These findings, along with the fact that ET-1 acts in the proximal renal tubule and experimental evidence that SGLT-2 inhibition reduces ET-

1 expression in human proximal tubular cell lines, raised the possibility of an interaction between ET-1 level and the effects of dapagliflozin in patients with HFrEF.[130] However, we did not find evidence for this in DAPA-HF. The benefit of dapagliflozin was consistent across the range of ET-1 concentrations measured. Nevertheless, there is interest in the combination of an SGLT-2 inhibitor (causing diuresis and a rise in haematocrit) and endothelin receptor antagonists (causing fluid retention and a decrease in haematocrit) because of their complementary actions.[151]

The modest reduction in ET-1 levels at 12 months with dapagliflozin was notable, although the explanation for this effect is unknown. It might be indirect, with a secondary reflex reduction caused by overall improvement in HF status, or reflect a direct action of SGLT-2 inhibition on the secretion of ET-1 from the blood vessel wall or elsewhere. This finding raises the possibility that some of the renal and even other benefits of SGLT-2 inhibition might be a result of a reduction in ET-1.

4.6 Limitations

This was not a prespecified analysis of the DAPA-HF trial. Because of the inclusion and exclusion criteria, these findings cannot be generalized to patients with mildly reduced and preserved ejection fraction and patients with severely reduced eGFR. We had only one follow-up measurement of ET-1 12 months after randomization, meaning that we could not look at short-term changes in ET-1, and the 12-month measurement was, by definition, in a survivor cohort. The interpretation of systemic circulating ET-1 levels is difficult because ET-1 is a locally secreted and acting peptide, and blood levels reflect “spill-over” from tissues. Measurement of big ET-1 as well as ET-1 would have provided additional pathophysiological insights including secretion of the precursor peptide and endothelin-converting enzyme activity.

4.7 Conclusions

Elevated serum ET-1 concentration was associated with worse clinical outcomes in a contemporary, well-treated cohort of patients with HFrEF, independently of other

prognostic variables including NT-proBNP and hs-TnT. Baseline ET-1 concentration was also associated with a more rapid decline in kidney function. The benefit of dapagliflozin was consistent across the range of ET-1 concentrations measured, and treatment with dapagliflozin led to a small reduction in ET-1.

Chapter 5 Patient Characteristics, Clinical Outcomes, and Effect of Dapagliflozin in Relation to Duration of Heart Failure: Is It Ever Too Late to Start a New Therapy?

5.1 Abstract

5.1.1 Background

The impact of heart failure (HF) duration on outcomes and treatment effect is largely unknown. We aim to compare baseline patient characteristics, outcomes, and the efficacy and safety of dapagliflozin, in relation to time from diagnosis of HF in DAPA-HF trial (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure).

5.1.2 Methods

HF duration was categorized as ≥2 to ≤12 months, >1 to 2 years, >2 to 5 years, and >5 years. Outcomes were adjusted for prognostic variables and analyzed using Cox regression. The primary end point was the composite of worsening HF or cardiovascular death. Treatment effect was examined within each duration category and by duration threshold.

5.1.3 Results

The number of patients in each category was: 1098 (≥2–≤12 months), 686 (>1–2 years), 1105 (>2–5 years), and 1855 (>5 years). Longer-duration HF patients were older and more comorbid with worse symptoms. The rate of the primary outcome (per 100 person-years) increased with HF duration: 10.2 (95% CI, 8.7–12.0) for ≥2 to ≤12 months, 10.6 (8.7–12.9) >1 to 2 years, 15.5 (13.6–17.7) >2 to 5 years, and 15.9 (14.5–17.6) for >5 years. Similar trends were seen for all other outcomes. The benefit of dapagliflozin was consistent across HF duration and on threshold analysis. The hazard ratio for the primary outcome ≥2 to ≤12 months was 0.86 (0.63–1.18), >1 to 2 years 0.95 (0.64–1.42), >2 to 5 years 0.74 (0.57–0.96), and >5 years 0.64 (0.53–0.78), P

interaction=0.26. The absolute benefit was greatest in longest-duration HF, with a number needed to treat of 18 for HF >5 years, compared with 28 for ≥2 to ≤12 months.

5.1.4 Conclusions

Longer-duration HF patients were older, had more comorbidity and symptoms, and higher rates of worsening HF and death. The benefits of dapagliflozin were consistent across HF duration.

5.2 Introduction

The DAPA-HF trial (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) demonstrated clinical benefits of the SGLT2i (sodium-glucose cotransporter 2 inhibitor) dapagliflozin, when added to standard therapy, in patients with heart failure (HF) and reduced ejection fraction (HFrEF), independently of diabetes status.[38] Further subgroup analyses demonstrated consistent benefit, irrespective of age, ejection fraction, and background HF therapy, among others. However, whether the benefit of dapagliflozin varies by duration of HF is unknown. In fact, few studies have reported any data on the relationship between duration of HF and patient characteristics or whether duration of HF modifies the efficacy and safety of therapy.[152, 153] Complex and potentially competing factors are at play in relation to duration of HF. On the one hand, longer duration might be expected to be associated with more advanced disease, as HF is a progressive condition. On the other hand, by definition, patients with longer-standing HF are a survivor cohort. Longer-duration also means more opportunity to optimize pharmacological and device therapy, although disease progression might also lead to the development of intolerance of certain pharmacological agents because of problems such as hypotension and kidney dysfunction. Ultimately, the physician may be left with the question whether is still worthwhile starting a new treatment in a patient who has already survived for an extended time? Therefore, we have investigated these questions further in this post hoc analysis of DAPA-HF. Specifically, our aims were to compare patient demographics, comorbidities, HF characteristics, and background therapy according to duration of HF, as well as outcomes in relation to time from diagnosis of HF. We

also analyzed the effects of dapagliflozin, compared with placebo, according to duration of HF.

5.3 Methods

DAPA-HF was a randomized, double-blind, placebo-controlled, event-driven, trial in patients with HFrEF who were enrolled between February 2017 and August 2018. The efficacy and safety of dapagliflozin 10 mg once daily, added to standard care, was compared with matching placebo. The design, baseline characteristics, and primary results are published.[38, 154, 155] The Ethics Committee of the 410 participating institutions (in 20 countries) approved the protocol, and all patients gave written informed consent.

5.3.1 Study Patients

Patients aged ≥18 years with HF were eligible if they were in New York Heart Association functional class II to IV for ≥2 months and had a left ventricular ejection fraction (LVEF) ≤40%, an elevated natriuretic peptide level and were receiving optimal HFrEF pharmacological and device therapy, according to local guidelines.

Key exclusion criteria included symptomatic hypotension or systolic blood pressure <95 mm Hg, estimated glomerular filtration rate <30 mL/(min·1.73 m2), or rapid decline in renal function and type 1 diabetes.

5.3.2 Trial Outcomes

The primary trial outcome was the composite of worsening HF (HF hospitalization or urgent visit attributed to HF requiring intravenous therapy) or cardiovascular death, whichever occurred first. Prespecified secondary end points included HF hospitalization or cardiovascular death; HF hospitalizations (first and recurrent) and cardiovascular deaths; change from baseline to 8 months in the total symptom score of the Kansas City Cardiomyopathy Questionnaire; the incidence of a composite worsening renal function outcome and all-cause death. Because of the small number of renal events overall, this end point was not examined in the present analysis of

subgroups. Prespecified safety analyses included any serious adverse event, adverse events leading to discontinuation of trial treatment, adverse events of interest (ie, volume depletion, renal events, major hypoglycemic events, bone fractures, diabetic ketoacidosis, amputation), and any diagnosis of Fournier gangrene, as well as laboratory findings of note.

5.3.3 Duration of HF

Time from diagnosis of HF was collected in the following categories: ≤3 months, >3 to 6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, and >5 years. Due to inclusion criteria of the DAPA-HF trial, the ≤3 months category only includes patients with HF duration of 2 to 3 months. In this analysis, we combined the first three categories to form the HF duration ≤1-year group (ie, patients with HF duration of ≥2 months–1 year), to ensure adequate numbers for analysis in each category. However, all predefined categories were used in the threshold analysis (see below).

5.3.4 Statistical Analysis

Baseline characteristics are summarized as frequencies with percentages for categorical variables and means ± SD for all continuous variables, except NT-proBNP (N-terminal pro-B-type natriuretic peptide) which is reported as medians and interquartile ranges. A Wilcoxon-type test for trend was used to compare baseline characteristics between groups.[133]

Time-to-event hospitalization/death end points were evaluated using Kaplan-Meier estimates and Cox proportional-hazards models to estimate hazard ratios with 95% CIs and treatment effect. Along with crude hazard ratios, which had history of prior HF hospitalization and assigned treatment group as fixed-effect factors and stratified by diabetes status, we report adjusted hazard ratios from models including the aforementioned factors along with age, region, gender, race, heart rate, systolic blood pressure, body mass index, New York Heart Association class, LVEF, estimated glomerular filtration rate, history of myocardial infarction, history of atrial fibrillation, NT-proBNP, and baseline Kansas City Cardiomyopathy Questionnaire

clinical summary score. These variables are known predictors of risk in patients with HF.[102, 156]

Total (including recurrent) hospitalizations for HF were analyzed using the Lin, Wei, Yang, and Ying model, including treatment effect, and reported as crude and adjusted rate ratios.[157] The Lin, Wei, Yang, and Ying model is a generalization of the Cox proportional-hazards model which considers each repeat event as a separate term. It is based on a gap-time approach considering the time since a previous event to account for the dependency of within-subject events. The model employs a robust standard error to account for the interdependency of events within an individual. The change in KCCQ-TSS from baseline to 8 months was analyzed using a repeated measures mixed model adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient with an unstructured covariance structure. When analyzing changes by HF duration, this term and its interaction with time were entered into the model. For adjusted models, we adjusted for the same variables as noted above for the Cox models. The effect of dapagliflozin compared to placebo on the proportion of patients with clinically significant (≥5 point) improvement or deterioration in KCCQ-TSS at 8 months from baseline (responder analysis) was analyzed using previously described methods and reported as odds ratios.[158] For treatment effect, the primary variable of interest was the interaction P value for randomized treatment group and HF duration. For the analysis of adverse events and study drug discontinuation, we used logistic regression and the likelihood ratio test to report interaction between randomized treatment and HF duration. We also performed a threshold analysis where the treatment effect of dapagliflozin, compared to placebo, on the primary composite outcome was calculated for each threshold value for the minimum HF duration (>0, >0.25, >0.5, >1, >2, and >5 years), using a Cox model adjusted for prognostic variables mentioned above. For each threshold value, the model was applied to data for patients with HF duration of at least the threshold value.

A 2-tailed P value of <0.05 was considered significant. Statistical analyses were conducted using STATA version 16.0 (Stata Corp. College Station, TX) and SAS version

9.4 (SAS Institute). All analysis were performed by myself using STATA software, with the exception of the KCCQ-TSS analysis which was analyzed by the 3rd author, Jhund PS using SAS software.

5.4 Results

Among the 4744 patients in DAPA-HF, the number in each HF-duration category analyzed was ≥2 to ≤12 months 1098 (23.1%), >1 to 2 years 686 (14.5%), >2 to 5 years 1105 (23.3%), and >5 years 1855 (39.1%).

5.4.1 Baseline Characteristics

Most baseline characteristics including demographics, comorbidities, symptoms, and functional status differed in relation to time since diagnosis of HF (Table 5-1). Patients with longer-duration HF were older (mean 68.1 years in the HF >5 years group versus 64.4 years in the ≥2 to ≤12 months group) and more comorbid; a greater proportion had a history of hypertension (76.5% versus 70.4%), myocardial infarction (48.4% versus 36.7%), stroke (11.6% versus 7.8%), obesity (36.1% versus 32.8%), atrial fibrillation (43.9% versus 31.2%), and chronic kidney disease (45.8% versus 32.1%).

NT-proBNP levels did not differ by duration of HF, even after accounting for differences in frequency of atrial fibrillation. LVEF differed only slightly by HF duration (30.5% versus 31.9%). Severity of symptoms and functional limitation as reported by patients using the KCCQ-TSS and Kansas City Cardiomyopathy Questionnaire clinical summary score was greater in patients with longer-standing HF although functional limitation assessed by physicians (New York Heart Association Class) did not differ by duration of HF.

5.4.2 Treatments at Baseline

Pharmacological treatments for HF were similar across all durations of HF, except for mineralocorticoid receptor antagonist use which was greatest in those with the most recent diagnosed HF (≥2 to ≤12 months). Conversely, there was a 3- to 5-fold difference in rates of device therapy in relation to duration of HF. Patients with HF

>5 years were most likely to have a defibrillating device (36.9% in the HF >5 years group versus 10.7% in the ≥2 to ≤12 months group) and a cardiac resynchronization device (11.1% versus 2.2%, respectively).

Patients with diabetes who had longer-duration HF were significantly more likely to be treated with insulin therapy.

Table 5-1 Baseline Characteristics according to duration of heart failure

Characteristic	HF ≥2 months- 1 year (N=1098)	HF >1-2 years (N=686)	HF >2-5 years (N=1105)	HF >5 years (N=1855)	*P*-value for trend
Age – years	64.4±11.7	64.9±11.4	66.4±10.5	68.1±10.1	<0.001
Age >75 years – no. (%)	195 (17.8)	132 (19.2)	206 (18.6)	470 (25.3)	<0.001
Female sex – no. (%)	251 (22.9)	156 (22.7)	260 (23.5)	442 (23.8)	0.487
Race or ethnic group – no. (%)					<0.001
- White	740 (67.4)	471 (68.7)	785 (71.0)	1337 (72.1)	
- Black	30 (2.7)	28 (4.1)	64 (5.8)	104 (5.6)	
- Asian	304 (27.7)	176 (25.7)	244 (22.1)	392 (21.1)	
- Other	24 (2.2)	11 (1.6)	12 (1.1)	22 (1.2)	
Region – no. (%)					<0.001
- North America	121 (11.0)	78 (11.4)	164 (14.8)	314 (16.9)	
- Latin America	176 (16.0)	124 (18.1)	203 (18.4)	314 (16.9)	
- Europe	498 (45.4)	312 (45.5)	502 (45.4)	842 (45.4)	
- Asia Pacific	303 (27.6)	172 (25.1)	236 (21.4)	385 (20.8)	
Systolic BP- mmHg	123.6±16.7	122.2±16.4	121.8±15.9	120.6±16.2	<0.001
Heart rate – bpm	72.9±11.9	71.9±12.4	72.1±11.3	70.2±11.4	<0.001
BMI - kg/m^2	27.7±5.9	28.0±5.9	28.3±5.9	28.4±6.0	<0.001
- BMI classification					0.003
• Obesity (BMI≥30)	360 (32.8)	244 (35.6)	399 (36.1)	669 (36.1)	
• Overweight (BMI 25-29.9)	374 (34.1)	246 (35.9)	402 (36.4)	700 (37.8)	
• Normal weight (BMI 18.5-24.9)	342 (31.1)	180 (26.2)	284 (25.7)	455 (24.6)	

• **Underweight (BMI<18.5)**	22 (2.0)	16 (2.3)	20 (1.8)	29 (1.6)	
Haemoglobin – g/L	136.4±16.6	134.9±16.7	136.0±15.7	134.9±16.0	0.040
Serum Creatinine – µmol/L	98.9±28.7	102.4±30.2	106.4±30.2	107.3±31.1	<0.001
eGFR - mL/min/1.73m^2	70.3±20.0	68.0±20.3	64.5±19.3	63.0±18.2	<0.001
Clinical HF features					
- **Ischemic cardiomyopathy – no. (%)**	575 (52.4)	400 (58.3)	621 (56.2)	1078 (58.1)	0.009
- **LVEF - %**	31.9±6.7	31.2±6.7	31.1±6.6	30.5±6.9	<0.001
- **Median NT-proBNP (IQR) pmol/L**	1374 (807-2536)	1387 (843-2748)	1489 (890-2825)	1477 (879-2597)	0.056
• **Median NT-proBNP (IQR) pmol/L if AF history**	1812 (1107-3074)	1841 (1157-3110)	1818 (1170-3083)	1744 (1084-3019)	0.476
• **Median NT-proBNP (IQR) pmol/L if no AF history**	1238 (737-2268)	1217 (724-2412)	1293 (739-2492)	1269 (759-2298)	0.287
NYHA Class – no. (%)					0.592
- **II**	761 (69.3)	442 (64.4)	756 (68.4)	1244 (67.1)	
- **III**	323 (29.4)	233 (34.0)	343 (31.0)	599 (32.3)	
- **IV**	14 (1.3)	11 (1.6)	6 (0.5)	12 (0.6)	
KCCQ-TSS (baseline). (IQR)	79.2 (60.4-93.8)	79.2 (60.4-91.7)	77.1 (58.3-91.7)	77.1 (58.3-91.7)	0.019
KCCQ-CSS (baseline) (IQR)	76.0 (58.3-89.6)	75.0 (56.9-87.5)	74.3 (56.9-88.9)	73.6 (55.6-87.5)	0.002
Medical History – no. (%)					
- **Hypertension**	773 (70.4)	503 (73.3)	827 (74.8)	1419 (76.5)	<0.001
- **Diabetes (history)**	421 (38.3)	294 (42.9)	474 (42.9)	794 (42.8)	0.031
- **Diabetes (at randomization)**	467 (42.5)	311 (45.3)	510 (46.2)	851 (45.9)	0.090
- **Atrial Fibrillation (History)**	343 (31.2)	226 (32.9)	434 (39.3)	815 (43.9)	<0.001
- **Atrial Fibrillation (ECG)**	234 (21.3)	142 (20.7)	255 (23.1)	440 (23.8)	<0.001

- **Prior HF hospitalization**	569 (51.8)	324 (47.2)	503 (45.5)	855 (46.1)	0.003
- **MI**	403 (36.7)	312 (45.5)	479 (43.3)	898 (48.4)	<0.001
- **Stroke**	86 (7.8)	56 (8.2)	109 (9.9)	215 (11.6)	<0.001
- **COPD**	125 (11.4)	92 (13.4)	138 (12.5)	230 (12.4)	0.587
- **CKD (eGFR<60 mL/min/1.73m^2)**	352 (32.1)	241 (35.1)	484 (43.8)	849 (45.8)	<0.001
- **Anaemia***	295 (27.0)	199 (29.3)	281 (25.6)	527 (28.7)	0.560
HF treatments – no. (%)					
- **ACEi/ARB/ARNI**	1036 (94.4)	641 (93.4)	1025 (92.8)	1740 (93.8)	0.569
- **B-blocker**	1042 (94.9)	660 (96.2)	1068 (96.7)	1788 (96.4)	0.053
- **Diuretic**	1023 (93.2)	649 (94.6)	1043 (94.4)	1718 (92.6)	0.393
- **Digitalis**	164 (14.9)	124 (18.1)	221 (20.0)	378 (20.4)	<0.001
- **MRA**	799 (72.8)	506 (73.8)	797 (72.1)	1268 (68.4)	0.004
- **ICD/CRT-D**	117 (10.7)	144 (21.0)	297 (26.9)	684 (36.9)	<0.001
- **CRT-P/CRT-D**	24 (2.2)	32 (4.7)	93 (8.4)	205 (11.1)	<0.001
Diabetes treatments – no. (%)†					
- **Biguanides**	238 (56.5)	158 (53.7)	243 (51.3)	377 (47.5)	0.002
- **DPP-4 inhibitors**	55 (13.1)	34 (11.6)	76 (16.0)	145 (18.3)	0.004
- **GLP-1 analogues**	2 (0.5)	5 (1.7)	6 (1.3)	8 (1.0)	0.623
- **Sulfonylureas**	104 (24.7)	67 (22.8)	91 (19.2)	176 (22.2)	0.278
- **Insulin**	91 (21.6)	71 (24.2)	140 (29.5)	238 (30.0)	0.001

Abbreviations: ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; B-blocker, beta-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ-TSS and KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire total symptom score and clinical summary score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

* Anaemia: haemoglobin <130 g/L in males and haemoglobin <120 g/L in females.

† Only in patients with a pretrial history of diabetes.

5.4.3 Primary and Secondary Outcomes in Relation to Duration of HF

The rate (per 100 patient-years) of the primary composite outcome of worsening HF or cardiovascular death increased with duration of HF: ≥2 to ≤12 months 10.2 (95% CI, 8.7–12.0), >1 to 2 years 10.6 (8.7–12.9), >2 to 5 years 15.5 (13.6–17.7), and >5 years 15.9 (14.5–17.6). The hazard ratio adjusted for prognostic variables, using the HF ≥2 to ≤12 months group as the reference, was 0.98 (95% CI, 0.75–1.27), 1.53 (1.23–1.90), and 1.60 (1.31–1.96), respectively, for HF >1 to 2, >2 to 5, and >5 years duration (Table 5-2 and Figure 5-1). Similar trends were seen for cardiovascular and all-cause mortality, with lower and similar rates in the first 2 duration categories (≥2 to ≤12 months and >1–2 years) and substantially higher, but again similar, rates in the 2 longer-duration groups (>2–5 and >5 years). Worsening HF (and HF hospitalization by itself) showed a more graded rise in risk with increasing duration of HF, rather than the bimodal distribution of risk for death (and the composites including death) centered around 2 years.

All duration groups showed an average overall improvement (increase) in KCCQ-TSS between baseline and month 8. The improvement in KCCQ-TSS scores was smaller in patients with longer-standing HF. The mean improvement in KCCQ-TSS from baseline to month 8 was 6.48±0.53 (unadjusted) and 6.17±0.53 (adjusted) in the ≥2 to ≤12 months group, decreasing to 3.07±0.41 (unadjusted) and 3.35±0.41 (adjusted) in the >5 years group.

We repeated these analyses using the more granular HF-duration groups of ≥2 to 6 months and >6 months to 12 months, >1 to 2 years, >2 to 5 years, and >5 years and found the same patterns (Table 5-3).

Table 5-2 Event rate (per 100 patient-years) and risk of study endpoints according to duration of heart failure (HF ≥2 months-1 year as reference)

	HF ≥2 months-1 year	HF >1-2 years	HF >2-5 years	HF >5 years	*P*-value for trend
No. of patients	1098	686	1105	1855	
Worsening HF or cardiovascular death – no. (%)	**154 (14.0)**	**101 (14.7)**	**230 (20.8)**	**403 (21.7)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	10.2 (8.7-12.0)	10.6 (8.7-12.9)	15.5 (13.6-17.7)	15.9 (14.5-17.6)	
- **Unadjusted* HR**	1.00 (ref)	1.03 (0.80-1.33)	1.56 (1.27-1.91)	1.58 (1.32-1.91)	
- **Adjusted† HR**	1.00 (ref)	0.98 (0.75-1.27)	1.53 (1.23-1.90)	1.60 (1.31-1.96)	
Hospitalization or urgent visit for HF - no. (%)	**84 (7.7)**	**65 (9.5)**	**138 (12.5)**	**276 (14.9)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.6 (4.5-6.9)	6.8 (5.4-8.7)	9.3 (7.9-11.0)	10.9 (9.7-12.3)	
- **Unadjusted* HR**	1.00 (ref)	1.22 (0.88-1.69)	1.73 (1.32-2.27)	2.01 (1.58-2.57)	
- **Adjusted† HR**	1.00 (ref)	1.24 (0.88-1.74)	1.76 (1.31-2.35)	2.03 (1.55-2.65)	
HF hospitalization - no. (%)	**80 (7.3)**	**65 (9.5)**	**135 (12.2)**	**269 (14.5)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.3 (4.3-6.6)	6.8 (5.4-8.7)	9.1 (7.7-10.8)	10.6 (9.4-12.0)	
- **Unadjusted* HR**	1.00 (ref)	1.29 (0.93-1.78)	1.78 (1.35-2.35)	2.06 (1.60-2.64)	
- **Adjusted† HR**	1.00 (ref)	1.31 (0.93-1.85)	1.81 (1.35-2.43)	2.08 (1.58-2.73)	
Urgent HF visit - no. (%)	**6 (0.5)**	**2 (0.3)**	**9 (0.8)**	**16 (0.9)**	**0.179**
- **Event rates per 100 patient-years (95% CI)**	0.4 (0.2-0.9)	0.2 (0.1-0.8)	0.6 (0.3-1.1)	0.6 (0.4-1.0)	

- **Unadjusted* HR**	1.00 (ref)	0.50 (0.10-2.50)	1.52 (0.54-4.28)	1.57 (0.61-4.01)	
- **Adjusted† HR**	1.00 (ref)	0.56 (0.11-2.91)	1.58 (0.50-4.97)	1.77 (0.61-5.14)	
Cardiovascular death - no. (%)	**90 (8.2)**	**54 (7.9)**	**129 (11.7)**	**227 (12.2)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.7 (4.7-7.0)	5.4 (4.2-7.1)	8.2 (6.9-9.7)	8.4 (7.4-9.6)	
- **Unadjusted* HR**	1.00 (ref)	0.94 (0.67-1.31)	1.44 (1.10-1.89)	1.47 (1.15-1.87)	
- **Adjusted† HR**	1.00 (ref)	0.85 (0.59-1.21)	1.36 (1.02-1.81)	1.46 (1.12-1.90)	
Cardiovascular death or HF hospitalization - no. (%)	**151 (13.8)**	**101 (14.7)**	**229 (20.7)**	**396 (21.3)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	10.0 (8.5-11.7)	10.6 (8.7-12.9)	15.4 (13.6-17.6)	15.6 (14.1-17.2)	
- **Unadjusted* HR**	1.00 (ref)	1.05 (0.82-1.36)	1.58 (1.29-1.94)	1.58 (1.31-1.91)	
- **Adjusted† HR**	1.00 (ref)	1.00 (0.77-1.31)	1.55 (1.25-1.94)	1.60 (1.31-1.97)	
Total no. of HF hospitalizations and Cardiovascular deaths					
- **Total events**	211	148	325	625	
- **Event rates per 100 patient-years (95% CI)**	13.5 (11.3-16.2)	14.9 (11.9-18.9)	20.7 (18.0-23.9)	23.3 (20.9-26.1)	
- **Unadjusted* RR****	1.00 (ref)	1.10 (0.82-1.47)	1.58 (1.26-1.98)	1.75 (1.42-2.16)	
- **Adjusted† RR****	1.00 (ref)	1.07 (0.78-1.46)	1.52 (1.19-1.95)	1.70 (1.35-2.14)	
All-cause mortality (no. of events) - no. (%)	**110 (10.0)**	**63 (9.2)**	**160 (14.5)**	**272 (14.7)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	7.0 (5.8-8.4)	6.3 (4.9-8.1)	10.1 (8.7-11.8)	10.1 (9.0-11.4)	

- **Unadjusted* HR**	1.00 (ref)	0.89 (0.65-1.22)	1.46 (1.14-1.86)	1.43 (1.15-1.79)	
- **Adjusted† HR**	1.00 (ref)	0.81 (0.59-1.12)	1.36 (1.05-1.76)	1.40 (1.10-1.78)	
Change in KCCQ-TSS at 8 mo‡ (±SE)					
- Unadjusted§	6.48±0.53	5.46±0.67	4.70±0.54	3.07±0.41	
- Adjusted‖	6.17±0.53	5.27±0.67	4.76±0.54	3.35±0.41	
Significant worsening in KCCQ-TSS (≥5) at 8 months‡					
- **Unadjusted¶ OR**	1.00 (ref)	0.89 (0.77-1.03)	1.07 (0.94-1.20	1.15 (1.05-1.28)	
- **Adjusted# OR**	1.00 (ref)	0.89 (0.77-1.03)	1.06 (0.94-1.20)	1.14 (1.02-1.27)	
Significant improvement in KCCQ-TSS (≥5) at 8 months‡					
- **Unadjusted¶ OR**	1.00 (ref)	1.04 (0.91-1.18)	0.99 (0.88-1.10)	0.85 (0.78-0.94)	
- **Adjusted# OR**	1.00 (ref)	1.04 (0.91-1.18)	0.99 (0.89-1.11)	0.87 (0.79-0.96)	

Abbreviations: HF indicates heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LWYY, Lin, Wei, Yang, and Ying; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and OR, odds ratio.

* Model adjusted for randomized therapy, previous HF hospitalization, and stratified by diabetes status.

† Model adjusted for model * and for age, sex, race, region, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, atrial fibrillation, and log NT-proBNP.

‡ Scores on the KCCQ range from 0 to 100 (higher scores indicating fewer symptoms and physical limitations associated with HF).

§ Model adjusted for baseline KCCQ-TSS score and randomized treatment.

‖ Model adjusted for model § and for age, sex, race, region, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, atrial fibrillation, and log NT-proBNP.

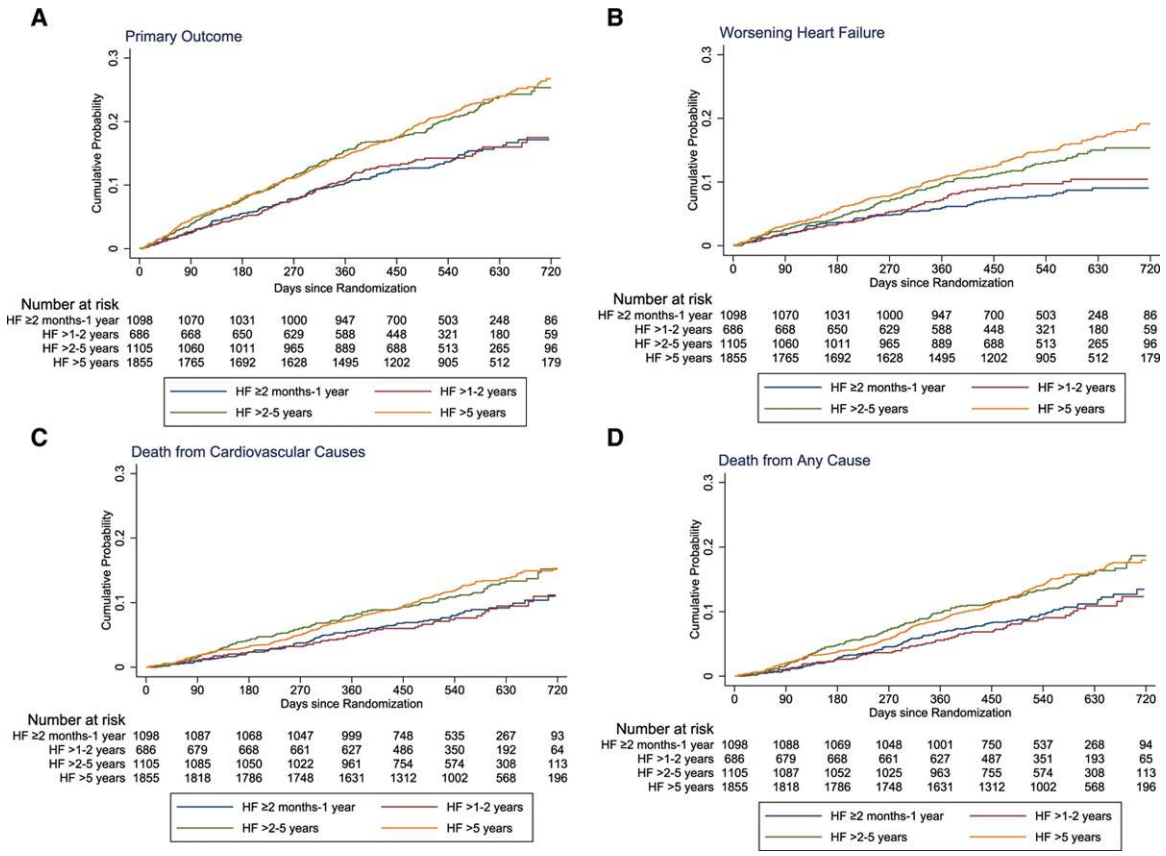
¶ Model adjusted for baseline KCCQ-TSS score rank, diabetes status, and randomized treatment.

Model adjusted for model ¶ and for age, sex, race, region, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, atrial fibrillation, and log NT-proBNP.

** RR denotes rate ratios with 95% CI within parentheses, assessed using the LWYY model.

The KCCQ-TSS responder analysis was analyzed by the 3rd author, Jhund PS.

Figure 5-1 Kaplan-Meier curves for key study outcomes, according to heart failure (HF) duration



The primary outcome was the composite of time to first worsening HF event or death from cardiovascular causes. The panels in this figure show cumulative event curves for (A) Primary composite outcome (worsening HF or death from cardiovascular causes), (B) worsening HF, (C) death from cardiovascular causes, and (D) death from any cause.

Table 5-3 Event rate (per 100 patient-years) and risk of study endpoints according to duration of heart failure (HF ≥2-≤6 months as reference)

	HF ≥2-6 months	HF >6-12 months	HF >1-2 years	HF >2-5 years	HF >5 years	*P*-value for trend
No. of patients	543	555	686	1105	1855	
Worsening HF or cardiovascular death – no. (%)	**78 (14.4)**	**76 (13.7)**	**101 (14.7)**	**230 (20.8)**	**403 (21.7)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	10.4 (8.4-13.0)	10.0 (8.0-12.5)	10.6 (8.7-12.9)	15.5 (13.6-17.7)	15.9 (14.5-17.6)	
- **Unadjusted * HR**	1.00 (ref)	0.96 (0.70-1.31)	1.01 (0.75-1.36)	1.52 (1.18-1.97)	1.55 (1.22-1.97)	
- **Adjusted† HR**	1.00 (ref)	0.84 (0.60-1.18)	0.89 (0.65-1.22)	1.40 (1.06-1.84)	1.46 (1.12-1.90)	
Hospitalization or urgent visit for HF - no. (%)	**44 (8.1)**	**40 (7.2)**	**65 (9.5)**	**138 (12.5)**	**276 (14.9)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.9 (4.4-7.9)	5.3 (3.9-7.2)	6.8 (5.4-8.7)	9.3 (7.9-11.0)	10.9 (9.7-12.3)	
- **Unadjusted * HR**	1.00 (ref)	0.89 (0.58-1.36)	1.15 (0.79-1.69)	1.63 (1.16-2.29)	1.90 (1.38-2.61)	
- **Adjusted† HR**	1.00 (ref)	0.72 (0.45-1.14)	1.05 (0.70-1.57)	1.49 (1.04-2.14)	1.72 (1.22-2.43)	
HF hospitalization - no. (%)	**42 (7.7)**	**38 (6.8)**	**65 (9.5)**	**135 (12.2)**	**269 (14.5)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.6 (4.2-7.6)	5.0 (3.6-6.9)	6.8 (5.4-8.7)	9.1 (7.7-10.8)	10.6 (9.4-12.0)	
- **Unadjusted * HR**	1.00 (ref)	0.88	1.21	1.67	1.94	

		(0.57-1.37)	(0.82-1.78)	(1.18-2.37)	(1.40-2.68)	
- **Adjusted† HR**	1.00 (ref)	0.69 (0.43-1.10)	1.09 (0.72-1.63)	1.50 (1.04-2.16)	1.72 (1.22-2.44)	
Urgent HF visit - no. (%)	**3 (0.6)**	**3 (0.5)**	**2 (0.3)**	**9 (0.8)**	**16 (0.9)**	**0.212**
- **Event rates per 100 patient-years (95% CI)**	0.4 (0.1-1.2)	0.4 (0.1-1.2)	0.2 (0.1-0.8)	0.6 (0.3-1.1)	0.6 (0.4-1.0)	
- **Unadjusted * HR**	1.00 (ref)	1.00 (0.20-4.94)	0.50 (0.08-3.01)	1.52 (0.54-4.28)	1.57 (0.61-4.01)	
- **Adjusted† HR**	1.00 (ref)	1.30 (0.21-7.85)	0.65 (0.09-4.65)	1.83 (0.38-8.83)	2.06 (0.45-9.35)	
Cardiovascular death - no. (%)	**46 (8.5)**	**44 (7.9)**	**54 (7.9)**	**129 (11.7)**	**227 (12.2)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.9 (4.4-7.9)	5.5 (4.1-7.5)	5.4 (4.2-7.1)	8.2 (6.9-9.7)	8.4 (7.4-9.6)	
- **Unadjusted * HR**	1.00 (ref)	0.94 (0.62-1.42)	0.91 (0.61-1.35)	1.40 (1.00-1.96)	1.42 (1.04-1.95)	
- **Adjusted† HR**	1.00 (ref)	0.80 (0.52-1.24)	0.75 (0.50-1.14)	1.21 (0.84-1.74)	1.30 (0.92-1.83)	
Cardiovascular death or HF hospitalization - no. (%)	**76 (14.0)**	**75 (13.5)**	**101 (14.7)**	**229 (20.7)**	**396 (21.3)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	10.2 (8.1-12.7)	9.8 (7.8-12.3)	10.6 (8.7-12.9)	15.4 (13.6-17.6)	15.6 (14.1-17.2)	
- **Unadjusted * HR**	1.00 (ref)	0.97 (0.70-1.33)	1.04 (0.77-1.40)	1.55 (1.20-2.02)	1.56 (1.22-1.99)	
- **Adjusted† HR**	1.00 (ref)	0.83 (0.59-1.17)	0.91 (0.66-1.25)	1.41 (1.07-1.86)	1.45 (1.11-1.90)	

Total no. of HF hospitalizations and Cardiovascular deaths						
- **Total events**	118	93	148	325	625	
- **Event rates per 100 patient-years (95% CI)**	15.2 (12.7-18.2)	11.8 (9.6-14.4)	14.9 (11.9-18.9)	20.7 (18.0-23.9)	23.3 (20.9-26.1)	
- **Unadjusted * RR****	1.00 (ref)	0.77 (0.54-1.09)	0.97 (0.69-1.37)	1.40 (1.04-1.87)	1.55 (1.17-2.05)	
- **Adjusted† RR****	1.00 (ref)	0.64 (0.44-0.93)	0.86 (0.60-1.23)	1.22 (0.89-1.67)	1.36 (1.01-1.84)	
All-cause mortality (no. of events) - no. (%)	**54 (9.9)**	**56 (10.1)**	**63 (9.2)**	**160 (14.5)**	**272 (14.7)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	6.9 (5.3-9.0)	7.1 (5.4-9.2)	6.3 (4.9-8.1)	10.1 (8.7-11.8)	10.1 (9.0-11.4)	
- **Unadjusted * HR**	1.00 (ref)	1.02 (0.70-1.49)	0.90 (0.63-1.30)	1.48 (1.08-2.01)	1.45 (1.08-1.94)	
- **Adjusted† HR**	1.00 (ref)	0.87 (0.58-1.29)	0.75 (0.51-1.10)	1.26 (0.91-1.74)	1.30 (0.95-1.78)	
Change in KCCQ-TSS at 8 mo‡ (±SE)						
- Unadjusted§	6.01±0.76	6.95±0.75	5.46±0.67	4.70±0.54	3.07±0.41	
- Adjusted‖	5.75±0.76	6.59±0.75	5.27±0.67	4.76±0.54	3.35±0.41	
Significant worsening in KCCQ-TSS (≥5) at 8 months‡						
- **Unadjusted ¶ OR**	1.00 (ref)	0.92 (0.78-1.09)	0.91 (0.78-1.06)	1.09 (0.96-1.24)	1.17 (1.05-1.31)	

- **Adjusted[#] OR**	1.00 (ref)	0.92 (0.78-1.10)	0.90 (0.77-1.05)	1.08 (0.94-1.23)	1.15 (1.03-1.30)	
Significant improvement in KCCQ-TSS (≥5) at 8 months[‡]						
- **Unadjusted [¶] OR**	1.00 (ref)	1.08 (0.93-1.26)	1.01 (0.88-1.16)	0.96 (0.85-1.08)	0.83 (0.75-0.92)	
- **Adjusted[#] OR**	1.00 (ref)	1.06 (0.91-1.24)	1.02 (0.88-1.18)	0.97 (0.86-1.10)	0.85 (0.76-0.94)	

* Model adjusted for randomized therapy, previous heart failure hospitalization and stratified by diabetes status.

† Model adjusted for model * and for age, sex, race, region, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, atrial fibrillation, and log NT-proBNP.

‡ Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100

§ Model adjusted for baseline KCCQ-TSS score and randomized treatment.

‖ Model adjusted for model § and for age, sex, race, region, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, atrial fibrillation, and log NT-proBNP.

¶ Model adjusted for baseline KCCQ-TSS score, diabetes and randomized treatment.

Model adjusted for model ¶ and for age, sex, race, region, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, atrial fibrillation, and log NT-proBNP.

** RR denotes rate ratios with 95% CI within parentheses, assessed using LWYY model.

The KCCQ-TSS responder analysis was analyzed by the 3rd author, Jhund PS.

5.4.4 Effects of Dapagliflozin According to Duration of HF

The benefit of dapagliflozin was consistent across the spectrum of HF duration, for all outcomes examined (Tables 5-4 and 5-5). The overall hazard ratio for the primary composite outcome was 0.74 (95% CI, 0.65–0.85), in the ≥2 to ≤12 months group it was 0.86 (0.63–1.18) and in the >5 years group it was 0.64 (0.53–0.78), interaction P=0.26. Because the absolute risk was highest in patients with the longest-duration HF, the absolute benefit was also greatest in those patients, assuming a constant relative treatment effect-size across HF-duration categories. On this basis, for the primary outcome, the number needed to treat over the median duration of the trial (18.2 months) was 18 for patients with HF >5 years, compared with a number needed to treat of 28 for patients with HF of ≥2 to ≤12 months duration.

Dapagliflozin improved KCCQ-TSS between baseline and month 8, compared with placebo, and there was no statistically significant heterogeneity of effect by duration of HF. The KCCQ-TSS responder analysis corroborated these findings.

Table 5-4 Treatment effect according to duration of heart failure (dapagliflozin vs placebo hazard ratio or difference and 95% confidence interval)

	Overall HR (95% CI) or Difference	**HF ≥2 months-1 year HR (95% CI) or Difference**	**HF >1-2 years HR (95% CI) or Difference**	**HF >2-5 years HR (95% CI) or Difference**	**HF >5 years HR (95% CI) or Difference**	***P* for interaction**
Number of patients	4744	1098	686	1105	1855	-
Worsening HF or cardiovascular death	0.74 (0.65-0.85)	0.86 (0.63-1.18)	0.95 (0.64-1.42)	0.74 (0.57-0.96)	0.64 (0.53-0.78)	0.26
Hospitalization or urgent visit for HF	0.70 (0.59-0.83)	0.76 (0.49-1.17)	0.92 (0.56-1.50)	0.64 (0.46-0.90)	0.64 (0.51-0.82)	0.52
HF hospitalization	0.70	0.71	0.92	0.65	0.66	0.61

	(0.59-0.83)	(0.45-1.11)	(0.56-1.50)	(0.46-0.91)	(0.52-0.84)	
Urgent HF visit	0.43 (0.20-0.90)	1.04 (0.21-5.16)	1.16 (0.07-18.75)	0.25 (0.05-1.23)	0.31 (0.10-0.97)	0.49
Cardiovascular death	0.82 (0.69-0.98)	0.96 (0.63-1.45)	0.79 (0.45-1.36)	0.94 (0.67-1.33)	0.72 (0.55-0.93)	0.54
Cardiovascular death or HF hospitalization	0.75 (0.65-0.85)	0.84 (0.61-1.16)	0.96 (0.64-1.42)	0.75 (0.58-0.97)	0.65 (0.53-0.80)	0.33
Total number of HF hospitalizations* and cardiovascular deaths	0.75 (0.65-0.88)	0.79 (0.55-1.13)	0.80 (0.51-1.28)	0.81 (0.61-1.08)	0.68 (0.55-0.85)	0.77
All-cause mortality	0.83 (0.71-0.97)	0.97 (0.66-1.40)	0.80 (0.48-1.33)	0.92 (0.68-1.26)	0.72 (0.57-0.92)	0.52
Significant worsening in KCCQ-TSS† (≥5) at 8 months‡	0.96 (0.91-1.01)	0.91 (0.79-1.04)	0.85 (0.71-1.02)	0.82 (0.72-0.95)	0.79 (0.72-0.88)	0.11
Significant improvement in KCCQ-TSS† (≥5) at 8 months‡	1.01 (0.96-1.06)	1.16 (1.02-1.31)	1.17 (1.00-1.38)	1.09 (0.96-1.25)	1.19 (1.08-1.31)	0.79
Change in KCCQ-TSS§ at 8 months	2.81±0.61	3.28±1.27	1.01±1.59	0.81±1.31	4.47±0.95	0.08

* Effect of dapagliflozin on total HF hospitalizations was assessed using the LWYY model and is shown as rate ratios (RRs).

† Scores on the KCCQ range from 0 to 100

‡ Effect of dapagliflozin on significant improvement or worsening in KCCQ-TSS (≥5) at 8 months is shown as odds ratios (ORs).

§ Treatment difference in mean change in KCCQ scores ± standard error (SE).

The KCCQ-TSS responder analysis was analyzed by the 3rd author, Jhund PS.

Table 5-5 Treatment effect according to duration of heart failure (dapagliflozin vs placebo hazard ratio or difference and 95% confidence interval) – ≥2-6 months, >6-12 months, >1-2 years, >2-5 years, and >5 years

	Overall HR (95% CI) or Difference	**HF ≥2-6 months HR (95% CI) or Difference**	**HF >6-12 months HR (95% CI) or Difference**	**HF >1-2 years HR (95% CI) or Difference**	**HF >2-5 years HR (95% CI) or Difference**	**HF >5 years HR (95% CI) or Difference**	***P* for interaction**
Number of patients	4744	543	555	686	1105	1855	-
Worsening HF or cardiovascular death	0.74 (0.65-0.85)	0.84 (0.54-1.32)	0.88 (0.56-1.38)	0.95 (0.64-1.42)	0.74 (0.57-0.96)	0.64 (0.53-0.78)	0.403
Hospitalization or urgent visit for HF	0.70 (0.59-0.83)	0.70 (0.38-1.28)	0.83 (0.45-1.55)	0.92 (0.56-1.50)	0.64 (0.46-0.90)	0.64 (0.51-0.82)	0.667
HF hospitalization	0.70 (0.59-0.83)	0.62 (0.33-1.16)	0.83 (0.44-1.57)	0.92 (0.56-1.50)	0.65 (0.46-0.91)	0.66 (0.52-0.84)	0.699
Cardiovascular death	0.82 (0.69-0.98)	1.07 (0.60-1.90)	0.86 (0.47-1.55)	0.79 (0.45-1.36)	0.94 (0.67-1.33)	0.72 (0.55-0.93)	0.662
Cardiovascular death or HF hospitalization	0.75 (0.65-0.85)	0.79 (0.50-1.25)	0.89 (0.57-1.41)	0.96 (0.64-1.42)	0.75 (0.58-0.97)	0.65 (0.53-0.80)	0.472

Total number of HF hospitalizations* and cardiovascular deaths	0.75 (0.65-0.88)	0.74 (0.44-1.24)	0.87 (0.54-1.40)	0.80 (0.51-1.28)	0.81 (0.61-1.08)	0.68 (0.55-0.85)	0.841
All-cause mortality	0.83 (0.71-0.97)	1.06 (0.62-1.82)	0.88 (0.52-1.49)	0.80 (0.48-1.33)	0.92 (0.68-1.26)	0.72 (0.57-0.92)	0.654
Significant worsening in KCCQ-TSS† (≥5) at 8 months‡	0.96 (0.91-1.01)	0.92 (0.76-1.13)	0.89 (0.73-1.08)	0.85 (0.71-1.02)	0.82 (0.72-0.95)	0.79 (0.72-0.88)	0.008
Significant improvement in KCCQ-TSS† (≥5) at 8 months‡	1.01 (0.96-1.06)	1.21 (1.00-1.44)	1.12 (0.93-1.33)	1.17 (1.00-1.38)	1.09 (0.96-1.25)	1.19 (1.08-1.31)	<0.001
Change in KCCQ-TSS§ at 8 months	2.81±0.61	3.12±1.87	3.37±1.73	1.01±1.59	0.81±1.31	4.47±0.95	0.146

* Effect of dapagliflozin on total HF hospitalizations was assessed using the LWYY model and is shown as rate ratios (RRs).

† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100 (higher scores indicating fewer symptoms and physical limitations associated with heart failure).

‡ Effect of dapagliflozin on significant improvement or worsening in KCCQ total symptom score (≥5) at 8 months is shown as odds ratios (ORs).

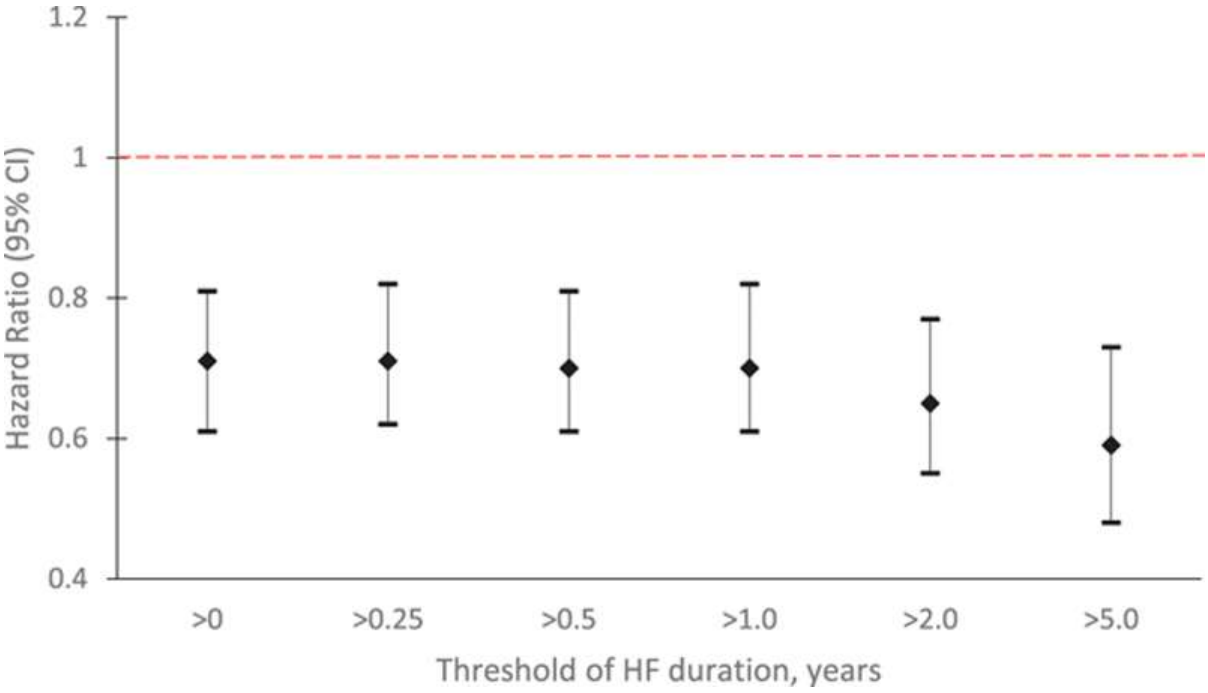
§ Treatment difference in mean change in KCCQ scores ± standard error (SE).

The KCCQ-TSS responder analysis was analyzed by the 3rd author, Jhund PS.

5.4.5 Threshold Analysis

The threshold analysis illustrated the consistent benefit of dapagliflozin, compared with placebo, on the primary end point, regardless of the threshold value for HF duration (Figure 5-2). The adjusted hazard ratio for the primary end point was 0.71 (95% CI, 0.62–0.82) for patients with HF duration >0.25 years, 0.70 (0.61–0.81) if HF duration >0.5 years, 0.70 (0.61–0.82) if HF duration >1 year, 0.65 (0.55–0.77) if HF duration >2 years, and 0.59 (0.48–0.73) if HF duration >5 years.

Figure 5-2 Treatment effect of dapagliflozin on the primary composite outcome (cardiovascular death or worsening heart failure) according to threshold duration of HF



Treatment effect for the primary composite outcome using a Cox model adjusted for prognostic variables as per Table 5-2, according to threshold duration of HF.

5.4.6 Tolerability and Safety

Adverse events were more common with increasing duration of HF, as was discontinuation of randomized therapy. However, neither adverse events nor discontinuation were more common with dapagliflozin, compared with placebo (Table 5-6).

Table 5-6 Prespecified adverse events and study drug discontinuation according to duration of heart failure*

	HF ≥2 months-1 year		HF >1-2 years		HF >2-5 years		HF >5 years		*P* for interaction
	Placebo (n=566)	Dapa (n=530)	Placebo (n=366)	Dapa (n=319)	Placebo (n=527)	Dapa (n=577)	Placebo (n=909)	Dapa (n=942)	
Any discontinuation – no. (%)	57 (10.1)	47 (8.9)	43 (11.8)	32 (10.0)	53 (10.1)	59 (10.2)	105 (11.6)	111 (11.8)	0.87
Discontinuation due to AE – no. (%)	18 (3.2)	13 (2.5)	13 (3.6)	19 (6.0)	31 (5.9)	27 (4.7)	54 (5.9)	52 (5.5)	0.36
Adverse events – no. (%)									
Volume depletion	21 (3.7)	30 (5.7)	14 (3.8)	18 (5.6)	38 (7.2)	55 (9.5)	89 (9.8)	75 (8.0)	0.05
Renal	22 (3.9)	25 (4.7)	17 (4.6)	16 (5.0)	48 (9.1)	43 (7.5)	83 (9.1)	69 (7.3)	0.27
Fracture	10 (1.8)	9 (1.7)	6 (1.6)	4 (1.3)	12 (2.3)	11 (1.9)	22 (2.4)	25 (2.7)	0.94
Amputation	1 (0.2)	2 (0.4)	0 (0)	3 (0.9)	3 (0.6)	1 (0.2)	8 (0.9)	7 (0.7)	-
Major hypoglycaemia	1 (0.2)	1 (0.2)	0 (0)	1 (0.3)	3 (0.6)	0 (0)	0 (0)	2 (0.2)	-

*Only in the safety set except for discontinuation due to any cause

Abbreviations: AE,adverse events; Dapa, dapagliflozin, HF, heart failure.

5.5 Discussion

Three main aspects of these findings merit further discussion. First, our description of baseline characteristics provides insight into how patient demographics, comorbidities, symptoms, and treatments vary in relation to time from diagnosis in patients with chronic HFrEF, findings surprisingly rarely reported.[152, 153] Second, we describe the relationship between chronicity of HF and clinical outcomes. Third, we report whether the benefits of treatment with dapagliflozin were modified by duration of HF.

Most of the few studies that have described variation of patient characteristics and outcomes in relation to duration of HF have focused on individuals hospitalized with acute HF.[159-163] By contrast, little has been written about heterogeneity related to HF duration in the chronic setting, with only an original report from the SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial), in which patients were recruited between 2006 and 2009, and a follow-up report from the PARADIGM-HF trial (Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) in which patients were enrolled between 2009 and 2012.[152, 153] As in SHIFT and PARADIGM-HF, we found that patients with longer-duration HF were older, had a greater prevalence of comorbidities, and were more likely to have an ischemic cause. The latter is, at first sight, counterintuitive, given that prognosis is worse in patients with an ischemic cause. However, recovery of LVEF is less common in patients with an ischemic cause, compared with a nonischemic cause, and among patients with long-standing HFrEF, proportionately more ischemic than nonischemic patients with a persistently low LVEF might be expected. Nevertheless, some survivor bias is still likely and is supported by the observation of a similar median NT-proBNP level in patients in each of the HF-duration categories, a finding also observed in PARADIGM-HF.[153]

The older age and greater prevalence of noncardiovascular and cardiovascular comorbidities in patients with a longer history of HF is also important in that, collectively, these might reduce tolerability of treatment. In turn, this may increase

the likelihood of study drug discontinuation and reduce the overall efficacy of randomized therapy. This question was not tested in SHIFT and could not be fully addressed in PARADIGM-HF because of the long run-in period requiring tolerance of the target-dose of both enalapril and sacubitril/valsartan before randomization. In DAPA-HF, adverse events were more common with increasing duration of HF, as was study drug discontinuation, but neither was more common with dapagliflozin, compared with placebo. The same considerations may explain the lower use of nonrandomized mineralocorticoid receptor antagonist therapy in patients with the longest-standing HF, probably reflecting the worse renal function in these individuals. Conversely, device use was higher in patients with longer-duration HF, presumably because devices are indicated only when LVEF remains low and symptoms persist, despite an adequate period of optimized pharmacological therapy.

In terms of clinical outcomes, we demonstrated worse outcomes with longer-duration HF, including in patient-reported symptoms (KCCQ-TSS). Although the rates of all hospitalization and death outcomes examined were higher with longer-duration HF, the extent to which risk was augmented differed between mortality (whether cardiovascular or all-cause) and worsening HF, including HF hospitalization. There was a clear stepwise increment in risk of HF hospitalization between the HF-duration groups as was seen in SHIFT, whereas the risk of death was similarly elevated in patients with HF for >2 to 5 years and those with HF >5 years which differs from the mortality trends observed in SHIFT. These findings, although interesting, require further validation. Importantly, the incremental risk associated with a longer duration of HF persisted after extensive adjustment for prognostic variables. This suggests that the excess risk related to duration of HF is not wholly explained by conventional prognostic variables including age, demographics, and comorbidity. This raises the interesting future research question as to what does account for the higher risk associated with longer-standing HF. Our findings, along with those from SHIFT, also differ from those in the ASCEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) where event rates were lower among patients with recently diagnosed HF (0–1 month) than in patients with longer-duration HF and event rates were similar among those with HF durations of >1 to 12 months,

>12 months to 60 months, and >60 months. However, these differences are hard to compare because ASCEND-HF enrolled decompensated patients with both HF with preserved ejection fraction and HFrEF and only examined short-term outcomes (mainly 30 days but up to 180 days for all-cause mortality). The intermediate duration group also spanned a duration of 1 to 5 years.

Lastly, we showed a consistent benefit of dapagliflozin, compared to placebo, across the whole spectrum of HF duration for all the outcomes examined, both by categorized HF duration, as well as using a threshold analysis. This is important, clinically because it means that it is not too late to start treatment in patients who may have had HF for some time and maybe considered as stable survivors. As is clear from the foregoing discussion, this is far from the case. Indeed, because these patients have a much higher absolute risk of events, they obtain a larger absolute risk reduction than patients with shorter-duration HF (number needed to treat 18 for patients with HF >5 years, compared with a number needed to treat of 28 for patients with HF of ≥2–≤12 months duration). Not only was the size of this treatment benefit notable, but patients with the longest-duration HF received good pharmacological treatment and, as noted above, had the highest use of device therapy.

5.6 Study Limitations

As with all studies like this, there are limitations. This analysis was post hoc. Although we used a large, contemporary, geographically representative clinical trial dataset, patients enrolled in a clinical trial are selected according to specific inclusion and exclusion criteria. Clearly, patients with longer-duration HF are survivors, and patients with de novo HF were excluded in DAPA-HF. HF duration was documented categorically in the database, hence could not be assessed as a continuous variable. We did not have independent verification of HF duration as it was reported by the investigators.

5.7 Summary and Conclusions

In summary, patients with longer-duration HF were older and more comorbid. Despite this, dapagliflozin was as well tolerated as placebo in patients with longer-duration HF. Patients with longer-duration HF had more severe symptoms and higher rates of worsening HF and death. However, the benefits of dapagliflozin were consistent irrespective of HF duration, with greater absolute benefits obtained in patients with longer-duration HF.

Chapter 6 Relationship between duration of heart failure, patient characteristics, outcomes, and effect of therapy in PARADIGM-HF

6.1 Abstract

6.1.1 Aims

Little is known about patient characteristics, outcomes, and the effect of treatment in relation to duration of heart failure (HF). We have investigated these questions in PARADIGM-HF. The aim of the study was to compare patient characteristics, outcomes, and the effect of sacubitril/valsartan, compared with enalapril, in relation to time from HF diagnosis in PARADIGM-HF.

6.1.2 Methods and results

HF duration was categorized as 0–1, >1–2, >2–5, and >5 years. Outcomes were adjusted for prognostic variables, including N-terminal pro-brain natriuretic peptide (NT-proBNP). The primary endpoint was the composite of HF hospitalization or cardiovascular death. The number of patients in each group was as follows: 0–1 year, 2523 (30%); >1–2 years, 1178 (14%); >2–5 years, 2054 (24.5%); and >5 years, 2644 (31.5%). Patients with longer-duration HF were older, more often male, and had worse New York Heart Association class and quality of life, more co-morbidity, and higher troponin-T but similar NT-proBNP levels. The primary outcome rate (per 100 person-years) increased with HF duration: 0–1 year, 8.4 [95% confidence interval (CI) 7.6–9.2]; >1–2 years, 11.2 (10.0–12.7); >2–5 years, 13.4 (12.4–14.6); and >5 years, 14.2 (13.2–15.2); $P < 0.001$. The hazard ratio was 1.26 (95% CI 1.07–1.48), 1.52 (1.33–1.74), and 1.53 (1.33–1.75), respectively, for >1–2, >2–5, and >5 years, compared with 0–1 year. The benefit of sacubitril/valsartan was consistent across HF duration for all outcomes, with the primary endpoint hazard ratio 0.80 (95% CI 0.67–0.97) for 0–1 year and 0.73 (0.63–0.84) in the >5 year group. For the primary outcome, the number needed to treat for >5 years was 18, compared with 29 for 0–1 year.

6.1.3 Conclusions

Patients with longer-duration HF had more co-morbidity, worse quality of life, and higher rates of HF hospitalization and death. The benefit of a neprilysin inhibitor was consistent, irrespective of HF duration. Switching to sacubitril/valsartan had substantial benefits, even in patients with long-standing HF.

6.2 Introduction

Large-scale clinical trials in chronic ambulatory heart failure (HF) usually enrol patients diagnosed at least 1 month previously but rarely report anything further about duration of HF prior to enrolment. Few have reported any data on duration of HF at the time of inclusion, the relation between HF duration and patient characteristics, or whether outcomes vary according to time from diagnosis of HF.[152, 164] Likewise, little is known about whether duration of HF and chronicity of neurohumoral activation influences the effect of therapy. Potentially, increasing age and co-morbidity might reduce the benefit of treatment in patients with HF of longer duration. We have investigated these questions further in the Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF), the largest trial to date in patients with HF with reduced ejection fraction (HFrEF).

Our aims were to compare patient characteristics and treatment, co-morbidities, and functional status according to HF duration, as well as outcomes in relation to time from diagnosis of HF. In addition, we examined the effect of sacubitril/valsartan, compared with enalapril, according to duration of HF prior to enrolment.

6.3 Methods

The design, baseline characteristics, and results or PARADIGM-HF are published.[24, 165, 166]

6.3.1 Study patients

Patients were eligible if they were ≥18 years, New York Heart Association (NYHA) class II–IV, left ventricular ejection fraction (LVEF) ≤ 35%, elevated natriuretic peptide levels, taking a stable dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker equivalent to enalapril 10 mg daily for at least 4 weeks, taking a stable dose of beta-blocker for at least 4 weeks (unless contraindicated or not tolerated), and a mineralocorticoid receptor antagonist, if indicated.

The key exclusion criteria included symptomatic hypotension or systolic blood pressure (SBP) < 95 mmHg, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, and potassium > 5.4 mmol/L.

6.3.2 Categorization of heart failure duration

Time from diagnosis was collected in the case report form in the following categories: 0–3 months, >3–6 months, >6–12 months, >1–2 years, >2–5 years, and >5 years. To ensure adequate numbers for analysis in each category, the first three groups were combined, that is, 0–12 months, although all predefined categories were used in the threshold analysis (see below).[167]

6.3.3 Trial outcomes

We analysed the primary outcome (a composite of hospitalization for HF or death from cardiovascular causes), the components of the primary outcome, and all-cause mortality. We also reported recurrent hospitalizations for HF and the two major modes of cardiovascular death, that is, sudden death and death from progressive pump failure. We determined the proportion of patients experiencing a 5 or greater point reduction or improvement from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), as this is considered to be a clinically significant difference in health-related quality of life.[168, 169]

Biomarker measurements In addition to N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin-T (hsTnT), growth differentiation factor-15 (GDF-15), soluble suppression of tumorigenicity-2 (sST2), tissue inhibitor of matrix metalloproteinase (TIMP)-1, matrix metalloproteinase (MMP)-2, MMP-9, galectin-3 (Gal-3), and kidney injury molecule-1 (KIM-1) were measured, as previously described.[170-173]

6.3.4 Statistical analysis

Baseline characteristics are reported as means ± standard deviations or medians and inter-quartile ranges (Q1–Q3) for continuous variables, and frequencies with percentages for categorical variables. A Wilcoxon-type test for trend (non-parametric test for trend for categorical variables and a test for trend by means of variance weighted least square regression for continuous variables) was used to compare baseline characteristics between groups.[133]

Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the time-to-event endpoints, and logistic regression analysis was used to determine odds ratios (ORs) for the endpoint of ≥5 points fall or rise in KCCQ-CSS at 8 months. Along with crude HRs, we report adjusted HRs from models including age, sex, race, previous HF hospitalization, heart rate, SBP, body mass index, NYHA class, LVEF, eGFR, history of myocardial infarction (MI), history of atrial fibrillation, diabetes, NT-proBNP, and baseline KCCQ-CSS. These are variables known to be predictors of risk in patients with HF.[102, 156] ORs were adjusted for all variables listed above, except previous HF hospitalization. All models were adjusted for randomized treatment arm and region.
Recurrent hospitalizations for HF were analysed using the Lin, Wei, Yang, and Ying (LWYY) model.[157] We reported both the crude rate ratio (RR) and RRs adjusted for all variables mentioned above.

The change in mean KCCQ-CSS at 8 months from baseline was assessed using a repeated-measures mixed effects model with baseline KCCQ values, region,

treatment arm, study visit, and the interaction between study visit and HF duration study group included in the model. The treatment difference of change in mean KCCQ-CSS at 8 months was assessed using a similar model, but with interaction between study visit and treatment arm used in the model. Interaction between duration of HF and treatment was tested for using the Wald method.

In the analyses of treatment effect, we used Cox proportional hazard models to estimate overall HRs (with 95% CIs), along with HRs according to HF duration for each time-to-event endpoint. We used the LWYY model to estimate treatment effect on recurrent HF hospitalizations, and it is shown as RRs. As before, we used logistic regression analysis for the endpoints of ≥5 points fall or rise in KCCQ-CSS at 8 months, which is reported as ORs. Along with treatment arm and region, this model was adjusted for baseline KCCQ-CSS. The primary variable of interest was the interaction P-value for randomized treatment × HF duration. We also performed a threshold analysis, where the HR for the effect of sacubitril/valsartan, compared with enalapril, on the primary endpoint was calculated for each threshold value for HF duration (0.25 to >5 years), using a Cox model adjusted for prognostic variables mentioned earlier. For each threshold value, the model was applied to data for patients with HF duration of at least the threshold value.

A two-tailed P-value of <0.05 was considered significant. Statistical analyses were conducted using STATA version 16.0 (Stata Corp., College Station, Texas, USA).

6.4 Results

Among the 8399 patients in PARADIGM-HF, the number in each time-from-diagnosis category was as follows: 0–1 year, 2523 (30%); >1–2 years, 1178 (14%); >2–5 years, 2054 (24.5%); and >5 years, 2644 (31.5%).

6.4.1 Baseline characteristics

Most baseline characteristics differed in relation to time since diagnosis of HF (Table 6-1). Some of the largest differences were in age (mean 66.5 years in the HF > 5 year group vs. 61.0 years in the 0–1 year group), aetiology (64.8% ischaemic vs. 52.7%, respectively), and prevalence of co-morbidities, all of which were substantially more common in patients with longer-duration HF, with the exception of anaemia where the reverse was true (Table 6-1). The proportion of patients with multiple co-morbidities also increased with increasing duration of HF (Figure 6-1).

eGFR was considerably lower in patients with longer-duration HF (62.9 vs. 72.6 mL/min/1.73 m^2), and severity of functional limitation was greater (28.2% vs. 17.6% NYHA class III/IV). However, LVEF did not differ notably by duration of HF, and nor did most symptoms or signs, except for dyspnoea (rest or effort) and peripheral oedema (23.6% vs. 17.2%). The difference in the proportion of patients with a history of prior HF hospitalization, in relation to duration of HF, was also modest (64.7% vs. 61.0%). Furthermore, NT-proBNP level did not differ by duration of HF, although levels of hsTnT (median 0.018 vs. 0.014 µg/L), Gal-3 (median 17.48 vs. 16.03 ng/mL), GDF-15 (median 1772 vs. 1473 ng/L), and sST2 (median 33 vs. 30 ng/mL) did.

Table 6-1 Baseline characteristics according to duration of heart failure

Characteristic	HF 0-1 year (N=2523)	HF >1-2 years (N=1178)	HF >2-5 years (N=2054)	HF >5 years (N=2644)	*P*-value for trend (ptrend)
Age - years	61.0±12.1	62.4±11.8	64.5±10.9	66.5±10.1	<0.001
Age ≥70 years - no. (%)	651 (25.8)	344 (29.2)	713 (34.7)	1090 (41.2)	<0.001
Female sex - no. (%)	622 (24.7)	253 (21.5)	422 (20.5)	535 (20.2)	<0.001
Race or ethnic group - no. (%)					<0.001
- White	1353 (53.6)	711 (60.4)	1403 (68.3)	2077 (78.6)	
- Black	127 (5.0)	74 (6.3)	100 (4.9)	127 (4.8)	
- Asian	718 (28.5)	256(21.7)	312 (15.2)	223 (8.4)	
- Other	325 (12.9)	137 (11.6)	239 (11.6)	217 (8.2)	
Region - no. (%)					<0.001
- North America	110 (4.4)	53 (4.5)	119 (5.8)	320 (12.1)	
- Latin America	475 (18.8)	209 (17.7)	366 (17.8)	383 (14.5)	
- Western Europe and other	509 (20.2)	250 (21.2)	474 (23.1)	818 (30.9)	
- Central Europe	715 (28.3)	414 (35.1)	793 (38.6)	904 (34.2)	
- Asia Pacific	714 (28.3)	252 (21.4)	302 (14.7)	219 (8.3)	
Systolic BP- mmHg	121±15	122±16	122±15	120±15	0.014
Heart rate - bpm	73±12	73±12	73±12	71±12	<0.001
BMI - kg/m^2	27.3±5.5	27.7±5.4	28.5±5.6	29.0±5.4	<0.001
- BMI classification					<0.001
Obesity (BMI≥30)	690 (27.4)	343 (29.2)	685 (33.4)	1001 (37.9)	
Overweight (BMI 25-29.9)	929 (36.9)	452 (38.4)	818 (39.8)	1,050 (39.8)	
Normal weight (BMI 18.5-24.9)	814 (32.3)	352 (29.9)	526 (25.6)	576 (21.8)	
Underweight (BMI<18.5)	87 (3.5)	29 (2.5)	24 (1.2)	13 (0.5)	
Haemoglobin - g/L	137.7±16.2	138.8±16.4	140.4±15.8	140.4±15.6	<0.001
Serum Creatinine - mg/dL	1.06±0.3	1.10±0.3	1.14±0.3	1.19±0.3	<0.001
eGFR - mL/min/1.73m^2	72.6±21.8	69.8±20.1	66.7±18.7	62.9±18.2	<0.001
Clinical HF features					
- Ischaemic cardiomyopathy - no. (%)	1329 (52.7)	699 (59.3)	1295 (63.1)	1713 (64.8)	<0.001
- LVEF - %	29.3±6.0	29.7±6.3	29.7±6.3	29.3±6.3	0.438

- **Median BNP (IQR) pg/mL**	242 (139-468)	268 (159-502)	261 (161-483)	247 (157-441)	0.326
- **Median NT-proBNP (IQR) pg/mL**	1550 (845-3183)	1838 (1008-3521)	1648 (889-3368)	1570 (888-3016)	0.948
• **Median NT-proBNP (IQR) pg/mL if AF on ECG**	1992 (1115-3700)	2249 (1220-4038)	1919 (1174-3908)	2015 (1209-3833)	0.754
• **Median NT-proBNP (IQR) pg/mL if no AF on ECG**	1450 (804-3021)	1765 (961-3360)	1512 (831-3137)	1428 (790-2798)	0.255
NYHA Class – no. (%)					<0.001
- **I**	151 (6.0)	56 (4.8)	84 (4.1)	98 (3.7)	
- **II**	1924 (76.3)	819 (69.5)	1376 (67.0)	1800 (68.1)	
- **III**	435 (17.2)	281 (23.9)	576 (28.0)	726 (27.5)	
- **IV**	10 (0.4)	16 (1.4)	15 (0.7)	19 (0.7)	
- **Missing data**	3 (0.1)	6 (0.5)	3 (0.2)	1 (0.0)	
KCCQ-CSS (baseline)	79.3±18.2	75.6±19.4	74.8±19.3	74.0±19.9	<0.001
Symptoms and signs – no. (%)					
- **Effort dyspnoea**	2115 (84.0)	1000 (85.3)	1798 (87.7)	2294 (86.8)	0.001
- **Rest dyspnoea**	65 (2.6)	31 (2.6)	106 (5.2)	107 (4.0)	<0.001
- **Fatigue**	1234 (49.0)	603 (51.5)	1118 (54.5)	1388 (52.5)	0.003
- **Orthopnoea**	182 (7.2)	89 (7.6)	139 (6.8)	198 (7.5)	0.903
- **Paroxysmal Nocturnal Dyspnoea**	100 (4.0)	57 (4.9)	125 (6.1)	117 (4.4)	0.210
- **Rales**	169 (6.8)	96 (8.2)	196 (9.6)	202 (7.6)	0.091
- **Oedema**	432 (17.2)	241 (20.6)	450 (21.9)	625 (23.6)	<0.001
- **Jugular Venous Distention**	238 (9.5)	120 (10.2)	209 (10.2)	251 (9.5)	0.932
- **3rd Heart Sound**	271 (10.8)	121 (10.3)	198 (9.7)	206 (7.8)	<0.001
Median Biomarkers (IQR)					
- **Gal-3 – ng/mL**	16.03 (13.16-20.15)	17.41 (14.64-20.81)	16.69 (13.41-21.21)	17.48 (14.32-21.97)	0.001
- **GDF-15 - ng/L**	1473 (1005-2126)	1828 (1284-2552)	1554 (1100-2184)	1772 (1281-2644)	<0.001

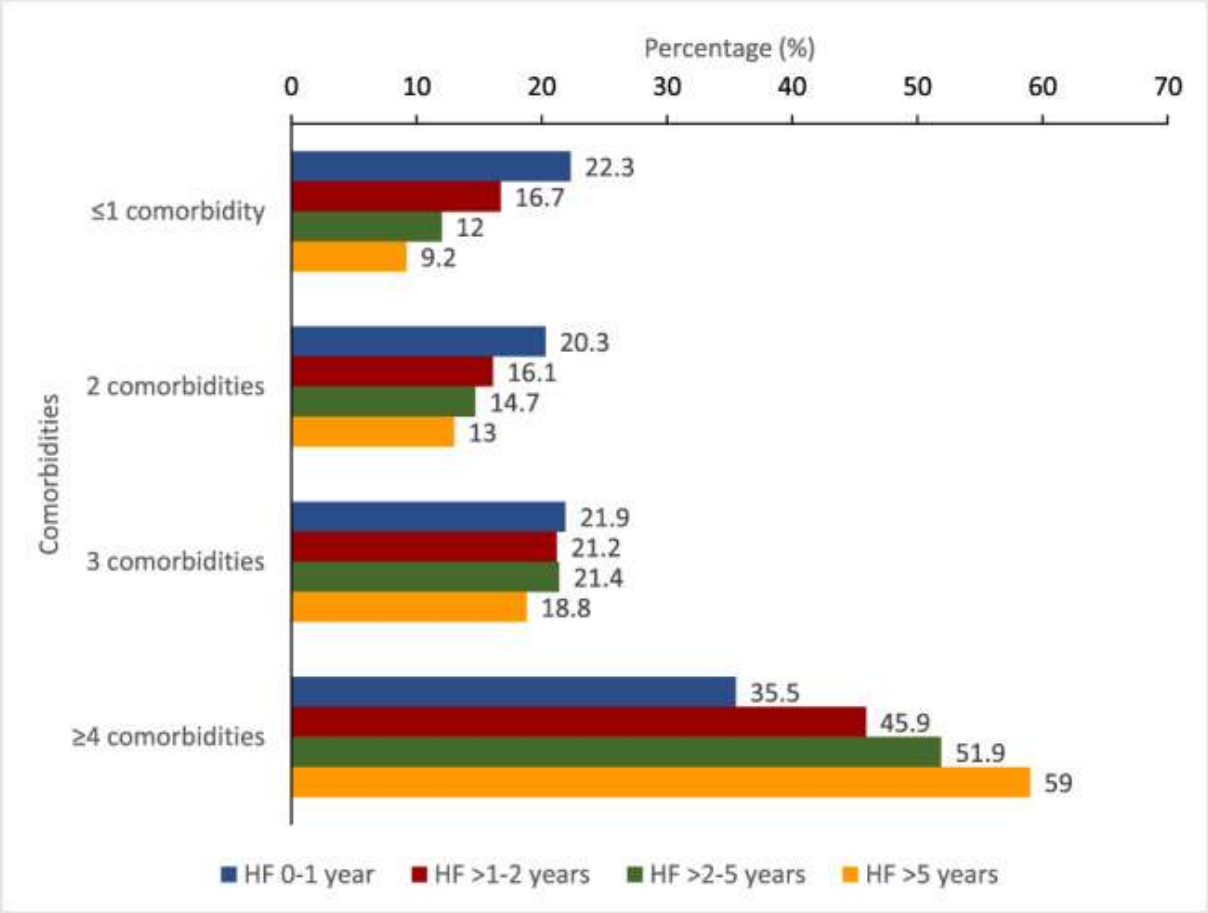
- **KIM-1 - pg/mL**	128 (84-180)	146 (104-221)	125 (82-192)	128 (88-192)	0.629
- **MMP-2 - ng/mL**	132.64 (114.50-155.69)	137.64 (115.52-160.86)	133.03 (114.53-153.67)	136.03 (118.59-156.69)	0.350
- **MMP-9 - ng/mL**	57.57 (38.37-120.61)	62.26 (40.18-124.52)	71.73 (39.16-137.39)	63.67 (38.16-128.26)	0.599
- **sST2 – ng/mL**	30 (25-40)	32 (26-42)	32 (25-41)	33 (27-42)	0.003
- **TIMP1 – ng/mL**	121 (101-146)	127 (107-152)	124 (106-151)	126 (105-154)	0.059
- **hs-TnT - µg/L**	.014 (.009-.022)	.0175 (.012-.028)	.017 (.01-.024)	.018 (.012-.027)	<0.001
Medical History – no. (%)					
- **Hypertension**	1646 (65.2)	825 (70.0)	1527 (74.3)	1942 (73.5)	<0.001
- **Diabetes**	765 (30.3)	388 (32.9)	718 (35.0)	1036 (39.2)	<0.001
- **Atrial Fibrillation (History)**	696 (27.6)	410 (34.8)	804 (39.1)	1181 (44.7)	<0.001
- **Atrial Fibrillation (ECG)**	481 (19.1)	271 (23.0)	559 (27.2)	725 (27.4)	<0.001
- **Prior HF hospitalization**	1539 (61.0)	740 (62.8)	1285 (62.6)	1710 (64.7)	0.009
- **Coronary Heart Disease**	1121 (44.4)	609 (51.7)	1199 (58.4)	1656 (62.6)	<0.001
- **MI**	845 (33.5)	478 (40.6)	940 (45.8)	1371 (51.9)	<0.001
- **Stroke**	149 (5.9)	98 (8.3)	194 (9.4)	284 (10.7)	<0.001
- **PAD**	98 (3.9)	54 (4.6)	125 (6.1)	217 (8.2)	<0.001
- **COPD**	244 (9.7)	155 (13.2)	291 (14.2)	390 (14.8)	<0.001
- **CKD (eGFR<60 mL/min/1.73m^2)**	692 (27.4)	391 (33.2)	766 (37.3)	1212 (45.8)	<0.001
- **Anaemia[a]**	573 (23.3)	262 (22.9)	373 (18.8)	484 (19.1)	<0.001
Treatments at randomisation – no. (%)					
- **Diuretic**	1981 (78.5)	977 (82.9)	1622 (79.0)	2158 (81.6)	0.040
- **Digitalis**	751 (29.8)	356 (30.2)	617 (30.0)	815 (30.8)	0.443
- **B-blocker**	2327 (92.2)	1092 (92.7)	1902 (92.6)	2490 (94.2)	0.010

- **MRA**	1388 (55.0)	673 (57.1)	1144 (55.7)	1466 (55.4)	0.885
- **ICD/CRT-D**	132 (5.2)	112 (9.5)	339 (16.5)	660 (25.0)	<0.001
- **CRT-P/CRT-D**	51 (2.0)	55 (4.7)	138 (6.7)	330 (12.5)	<0.001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy with pacemaker (P) or defibrillator (D); ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; HF, heart failure; hsTnT, high-sensitivity troponin-T; ICD, implantable cardioverter-defibrillator; IQR, inter-quartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; KIM-1, kidney injury molecule-1; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral arterial disease; sST2, soluble suppression of tumorigenicity-2; TIMP-1, tissue inhibitor of matrix metalloproteinase-1.

[a]Anaemia: haemoglobin < 130 g/L in men and haemoglobin < 120 g/L in women.

Figure 6-1 Relationship between duration of heart failure and number of co-morbidities.



6.4.2 Treatments at baseline

There were no major differences in pharmacological treatment for HF according to duration of HF. Conversely, there was a five-fold difference in rates of device therapy in relation to duration of HF. Patients with HF > 5 years were more likely than those in the 0–1 year duration group to have a defibrillating device (25.0% vs. 5.2%) and a cardiac resynchronization device (12.5% vs. 2.0%).

6.4.3 Primary and secondary outcomes in relation to duration of heart failure

Rates of the primary composite outcome of first HF hospitalization or cardiovascular death (per 100 patient-years) increased with increasing duration of HF: 0–1 year, 8.4 (95% CI 7.6–9.2); >1–2 years, 11.2 (10.0–12.7); >2–5 years, 13.4 (12.4–14.6); and >5 years, 14.2 (13.2–15.2); P < 0.001. The HR, using the HF 0–1 year group as the reference, and adjusting for other prognostic variables, was 1.26 (95% CI 1.07–1.48), 1.52 (1.33–1.74), and 1.53 (1.33–1.75), respectively, for >1–2, >2–5, and >5 years' duration (Table 6-2). Similar trends were seen for the other outcomes, including the components of the primary composite, all-cause mortality and recurrent hospitalizations for HF. Inspection of the Kaplan–Meier curves (Figure 6-2) suggested the cumulative incidence of cardiovascular (and all-cause) death was similar in the >2–5 and >5 years' groups for most of the follow-up period. There appeared to be a clearer gradient between the HF duration groups for the outcomes of first HF hospitalization and recurrent HF hospitalizations.

There was no significant difference in rates of sudden death regardless of HF duration: 0–1 year, 2.9 (95% CI 2.5–3.4); >1–2 years, 1.5 (1.1–2.1); >2–5 years, 3.3 (2.8–3.9); and >5 years, 2.8 (2.4–3.3) per 100 person-years, P = 0.826. Conversely, the rate of death from pump failure increased with increasing duration of HF: 0–1 year, 1.0 (0.7–1.3); >1–2 years, 1.5 (1.1–2.1); >2–5 years, 1.7 (1.4–2.1); and >5 years, 2.2 (1.8–2.6) per 100 person-years, P < 0.001 (Table 2).

All groups had a decrease (deterioration) in KCCQ-CSS between baseline and 8 months. The extent of reduction in KCCQ-CSS increased with duration of HF. The reduction in mean score from baseline to month 8 was 1.19 points in the 0–1 year group, 4.31 points in the >1–2 year group, 4.82 points in the >2–5 year group, and 5.10 points in the >5 year group (P < 0.001).

Table 6-2 Event rate (per 100 patient-years) and risk of study endpoints according to duration of heart failure (HF 0-1 year as reference)

	HF 0-1 year	HF >1-2 years	HF >2-5 years	HF >5 years	*P*-Value
No. of patients	2523	1178	2054	2644	
HF hospitalization or cardiovascular death – no. (%)	**442 (17.5)**	**270 (22.9)**	**569 (27.7)**	**750 (28.4)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	8.4 (7.6-9.2)	11.2 (10.0-12.7)	13.4 (12.4-14.6)	14.2 (13.2-15.2)	
- **Unadjusted HR**	1.00 (ref)	1.35 (1.16-1.57)	1.65 (1.46-1.87)	1.76 (1.56-1.98)	
- **Adjusted[a] HR**	1.00 (ref)	1.26 (1.07-1.48)	1.52 (1.33-1.74)	1.53 (1.33-1.75)	
Cardiovascular death - no. (%)	**295 (11.7)**	**160 (13.6)**	**346 (16.8)**	**450 (17.0)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	5.3 (4.8-6.0)	6.2 (5.3-7.2)	7.5 (6.8-8.4)	7.7 (7.0-8.5)	
- **Unadjusted HR**	1.00 (ref)	1.18 (0.97-1.43)	1.49 (1.27-1.74)	1.63 (1.40-1.90)	
- **Adjusted[a] HR**	1.00 (ref)	1.15 (0.93-1.42)	1.40 (1.18-1.66)	1.44 (1.22-1.71)	
HF hospitalization - no. (%)	**225 (8.9)**	**158 (13.4)**	**334 (16.3)**	**478 (18.1)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	4.3 (3.7-4.9)	6.6 (5.6-7.7)	7.9 (7.1-8.8)	9.0 (8.2-9.9)	
- **Unadjusted HR**	1.00 (ref)	1.54 (1.26-1.89)	1.86 (1.57-2.21)	2.05 (1.74-2.42)	
- **Adjusted[a] HR**	1.00 (ref)	1.33 (1.07-1.66)	1.63 (1.36-1.96)	1.66 (1.39-1.98)	
All-cause mortality (no. of events) - no. (%)	**362 (14.3)**	**199 (16.9)**	**432 (21.0)**	**553 (20.9)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	6.6 (5.9-7.3)	7.7 (6.7-8.8)	9.4 (8.5-10.3)	9.5 (8.7-10.3)	
- **Unadjusted HR**	1.00 (ref)	1.18 (1.00-1.41)	1.48 (1.29-1.70)	1.56 (1.36-1.79)	
- **Adjusted[a] HR**	1.00 (ref)	1.15 (0.96-1.39)	1.37 (1.17-1.60)	1.35 (1.16-1.58)	
Sudden death – no. (%)	**162 (6.4)**	**77 (6.5)**	**154 (7.5)**	**168 (6.4)**	**0.826**
- **Event rates per 100 patient-years (95% CI)**	2.9 (2.5-3.4)	2.9 (2.3-3.6)	3.3 (2.8-3.9)	2.8 (2.4-3.3)	
- **Unadjusted HR**	1.00 (ref)	1.05 (0.80-1.37)	1.26 (1.01-1.57)	1.19 (0.95-1.49)	
- **Adjusted[a] HR**	1.00 (ref)	1.09 (0.81-1.46)	1.23 (0.96-1.57)	1.19 (0.93-1.53)	

Pump failure death – no. (%)	**54 (2.1)**	**40 (3.4)**	**78 (3.8)**	**128 (4.8)**	**<0.001**
- **Event rates per 100 patient-years (95% CI)**	1.0 (0.7-1.3)	1.5 (1.1-2.1)	1.7 (1.4-2.1)	2.2 (1.8-2.6)	
- **Unadjusted HR**	1.00 (ref)	1.56 (1.04-2.36)	1.73 (1.22-2.45)	2.32 (1.68-3.22)	
- **Adjusted[a] HR**	1.00 (ref)	1.57 (1.01-2.46)	1.67 (1.14-2.45)	1.95 (1.35-2.83)	
Recurrent HF hospitalizations					**<0.001**
- **Total events**	339	255	536	800	
- **Event rates per 100 patient-years (95% CI)**	6.1 (5.5-6.8)	9.8 (8.7-11.1)	11.6 (10.7-12.7)	13.7 (12.8-14.7)	
- **Unadjusted RR[b]**	1.00 (ref)	1.61 (1.37-1.90)	1.92 (1.68-2.21)	2.20 (1.93-2.51)	
- **Adjusted[a] RR**	1.00 (ref)	1.36 (1.14-1.62)	1.56 (1.34-1.80)	1.66 (1.43-1.91)	
Significant worsening in KCCQ-CSS (≥5) at 8 months[d] - no. (%)	**592 (23.7)**	**346 (29.4)**	**617 (30.3)**	**852 (32.5)**	**<0.001**
- **Unadjusted OR**	1.00 (ref)	1.35 (1.15-1.59)	1.32 (1.16-1.52)	1.46 (1.28-1.65)	
- **Adjusted[c] OR**	1.00 (ref)	1.27 (1.08-1.50)	1.22 (1.06-1.40)	1.25 (1.09-1.44)	
Significant improvement in KCCQ-CSS (≥5) at 8 months[d] - no. (%)	**689 (27.5)**	**316 (26.9)**	**572 (28.1)**	**668 (25.5)**	**0.20**
- **Unadjusted OR**	1.00 (ref)	0.79 (0.66-0.93)	0.76 (0.66-0.88)	0.62 (0.54-0.70)	
- **Adjusted[c] OR**	1.00 (ref)	0.84 (0.70-0.99)	0.82 (0.71-0.95)	0.70 (0.61-0.81)	
Change in KCCQ-CSS at 8 mo[e] (±SE)	**-1.19±0.44**	**-4.31±0.63**	**-4.82±0.46**	**-5.10±0.41**	**<0.001**

[a] Model adjusted for age, sex, treatment arm, race, region, previous heart failure hospitalization, heart rate, systolic blood pressure, body mass index, New York Heart Association classification, left ventricular ejection fraction, baseline KCCQ clinical summary score, estimated glomerular filtration rate, history of myocardial infarction, history of atrial fibrillation, diabetes and NT-proBNP.

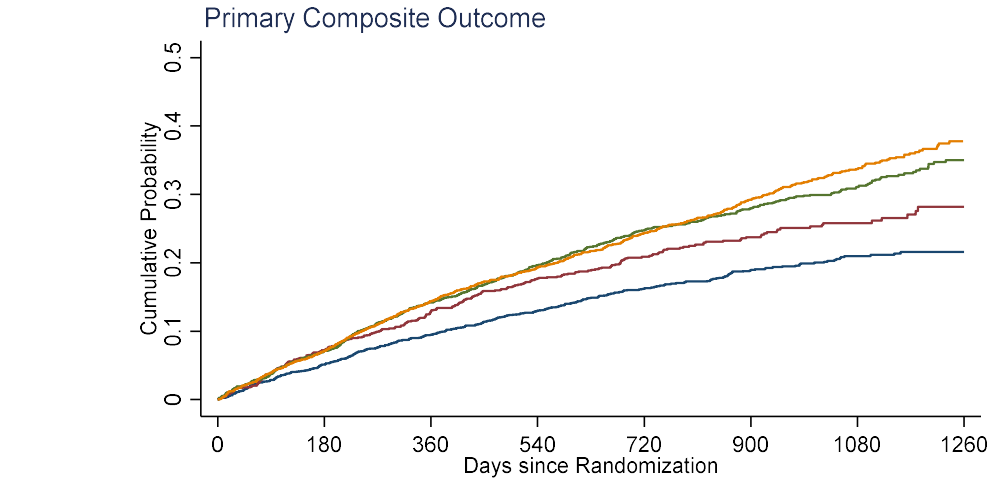
[b] RR denotes rate ratios with 95% confidence intervals (CI) assessed using LWYY.

[c] Model adjusted as for [a] except previous heart failure hospitalization.

[d] Scores on KCCQ range from 0 to 100 (higher scores indicating fewer symptoms).

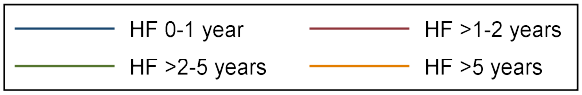
[e] Change in mean KCCQ-CSS at 8 months from baseline was assessed using a repeated measure mixed effects model with baseline KCCQ values, region, treatment arm, study visit, and the interaction between study visit and HF duration study group included in the model.

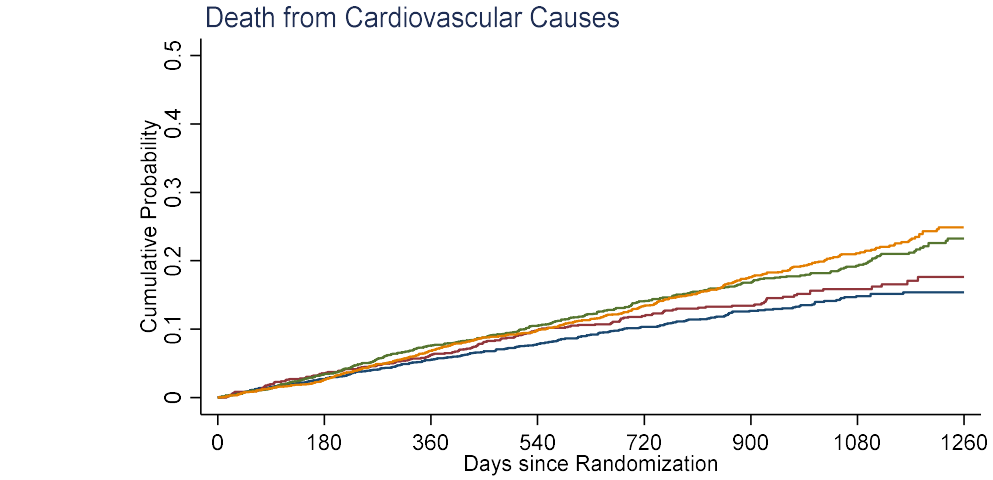
Figure 6-2 Kaplan-Meier curves for key study outcomes, according to heart failure duration



Number at risk

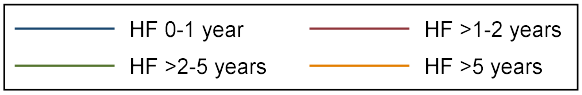
HF 0-1 year	2523	2380	2258	1891	1350	901	505	135
HF >1-2 years	1178	1087	1014	827	619	428	240	44
HF >2-5 years	2054	1898	1737	1424	1087	779	487	160
HF >5 years	2644	2440	2233	1798	1324	924	517	146

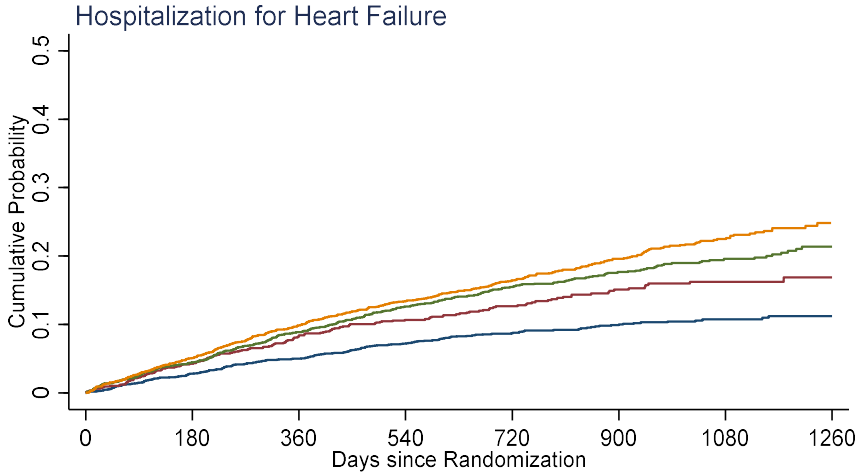




Number at risk

HF 0-1 year	2523	2442	2358	2008	1443	971	542	142
HF >1-2 years	1178	1130	1092	911	695	491	275	53
HF >2-5 years	2054	1974	1870	1580	1229	887	557	184
HF >5 years	2644	2561	2431	2014	1521	1093	625	180





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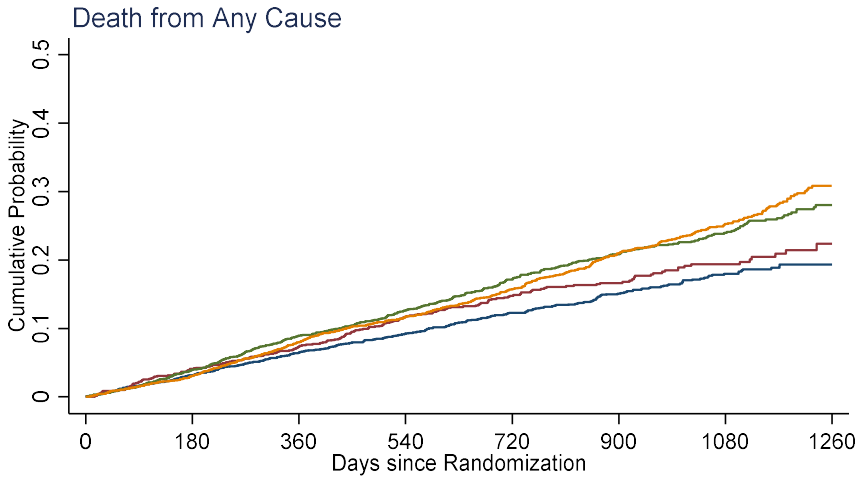

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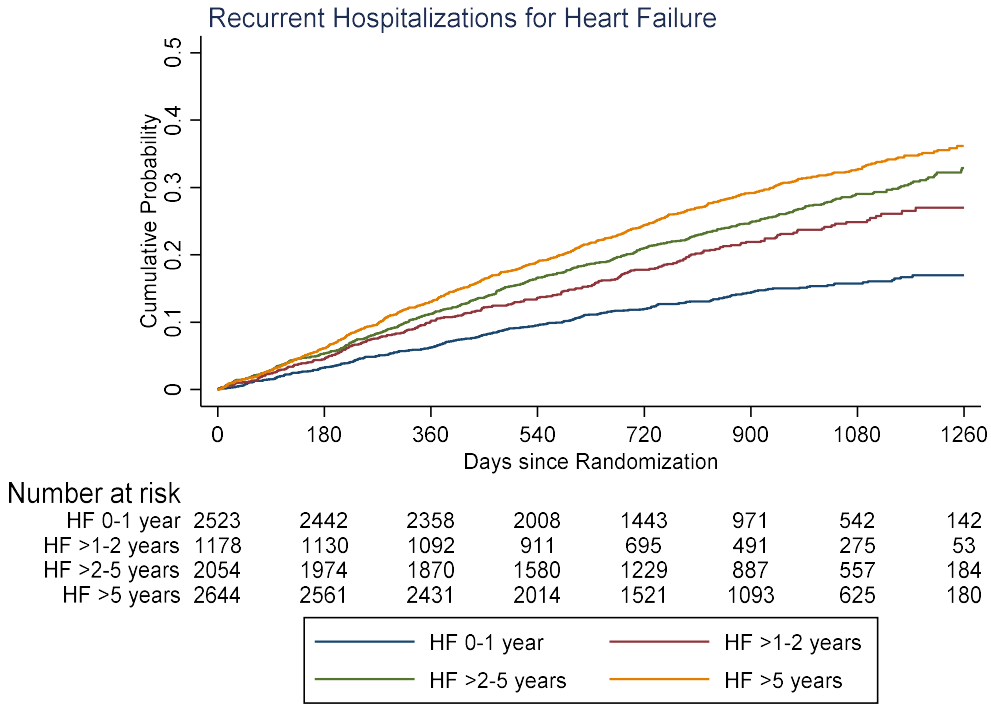


The panels in this figure show cumulative event curves for primary composite outcome (death from cardiovascular causes or first hospitalization for heart failure), death from cardiovascular causes, first hospitalization for heart failure, death from any cause, and recurrent hospitalizations for heart failure.

6.4.4 Effects of sacubitril/valsartan according to duration of heart failure

The benefit of sacubitril/valsartan was consistent in relation to duration of HF for all outcomes examined (Table 6-3). For example, the HR for the primary endpoint in the trial overall was 0.80 (95% CI 0.73–0.87); in the 0–1 year group, it was 0.80 (0.67–0.97); and in the >5 year group, it was 0.73 (0.63–0.84), interaction P = 0.31. As a result, the absolute benefit was greatest in those with the longest duration of HF; for example, applying the overall 20% relative risk reduction to the event rate in the enalapril group gave an absolute risk reduction of 3.50% and a number needed to treat (NNT) of 29 in patients with HF 0–1 year, compared with an absolute risk reduction of 5.7% and NNT of 18 in patients with HF >5 years (over a median follow-up of 27 months).

Table 6-3 Treatment effect according to duration of heart failure (sacubitril/valsartan vs enalapril hazard ratio or difference and 95% confidence interval)

	Overall HR (95% CI) or Difference	HF 0-1 year HR (95% CI) or Difference	HF >1-2 years HR (95% CI) or Difference	HF >2-5 years HR (95% CI) or Difference	HF >5 years HR (95% CI) or Difference	P for interaction
HF hospitalization or cardiovascular death	0.80 (0.73-0.87)	0.80 (0.67-0.97)	0.95 (0.75-1.21)	0.83 (0.70-0.98)	0.73 (0.63-0.84)	0.3089
Cardiovascular death	0.80 (0.71-0.89)	0.74 (0.59-0.94)	0.83 (0.61-1.14)	0.95 (0.77-1.17)	0.73 (0.61-0.88)	0.3066
HF hospitalization	0.79 (0.71-0.89)	0.75 (0.58-0.97)	1.12 (0.82-1.54)	0.83 (0.67-1.04)	0.71 (0.59-0.85)	0.0837
All-cause mortality	0.84 (0.76-0.93)	0.78 (0.63-0.96)	0.88 (0.67-1.17)	1.01 (0.83-1.22)	0.77 (0.65-0.91)	0.1754
Sudden death	0.80 (0.68-0.94)	0.78 (0.57-1.06)	0.70 (0.45-1.11)	0.85 (0.62-1.17)	0.83 (0.61-1.13)	0.9173
Pump failure death	0.85 (0.68-1.07)	0.83 (0.49-1.42)	1.08 (0.58-2.02)	1.05 (0.67-1.64)	0.70 (0.49-0.99)	0.4407
Recurrent HF hospitalizations[a]	0.78 (0.68-0.90)	0.64 (0.47-0.88)	1.15 (0.80-1.65)	0.93 (0.71-1.20)	0.67 (0.54-0.84)	0.0252
Significant worsening in KCCQ-CSS[b] (≥5) at 8 months[c]	0.82 (0.74-0.90)	0.81 (0.67-0.98)	1.03 (0.79-1.34)	0.79 (0.65-0.95)	0.78 (0.66-0.92)	0.2867

Significant improvement in KCCQ-CSS[b] (≥5) at 8 months[c]	1.09 (0.98-1.21)	1.11 (0.91-1.35)	1.03 (0.77-1.37)	1.06 (0.86-1.31)	1.14 (0.94-1.37)	0.9068
Change in KCCQ-CSS at 8 months[d]	1.64 (0.73-2.56)	0.64 (-1.00 - 2.29)	1.01 (-1.52 - 3.54)	1.98 (0.05-3.90)	2.39 (0.84-3.95)	0.2950

[a] Effect of sacubitril/valsartan on recurrent HF hospitalizations was assessed using the LWYY model and is shown as rate ratios (RRs)

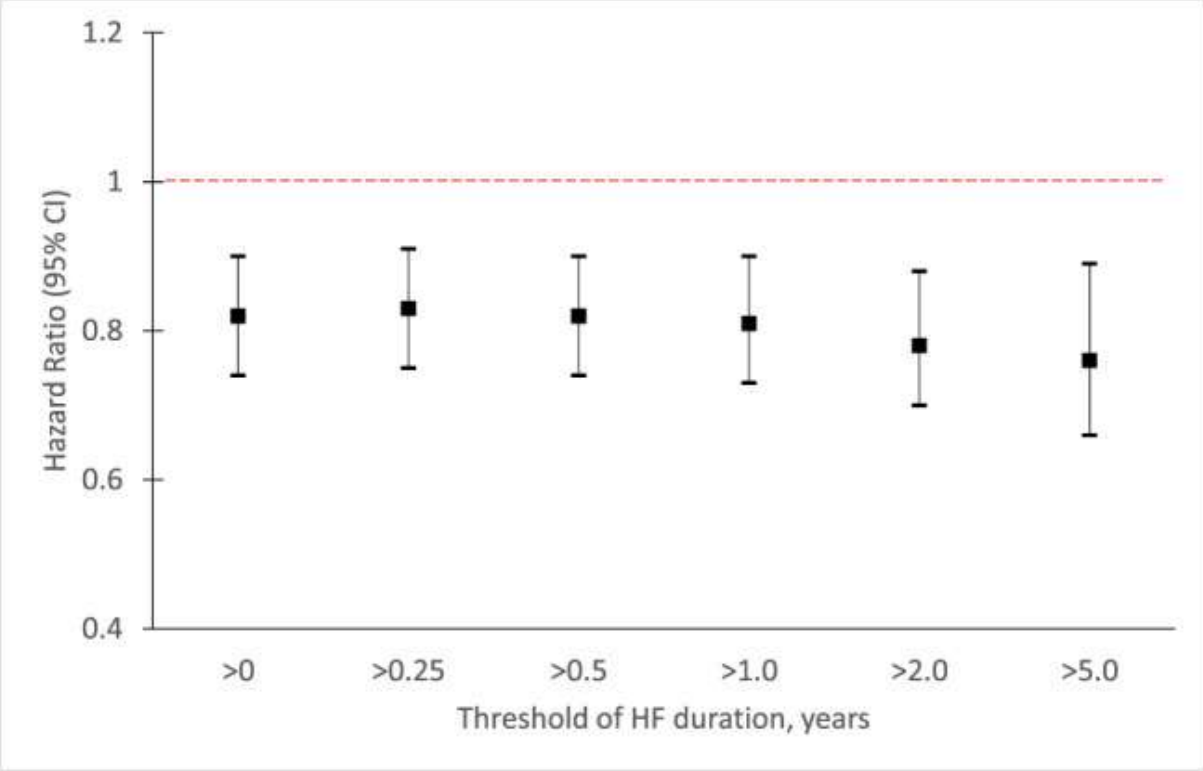
[b] Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100 (higher scores indicating fewer symptoms).

[c] Effect of sacubitril/valsartan on improvement or worsening KCCQ clinical summary score (≥5) at 8 months was estimated by logistic regression and is shown as odds ratios (ORs)

[d] The treatment difference of change in mean KCCQ-CSS at 8 months from baseline was assessed using a repeated measure mixed effects model with baseline KCCQ values, region, treatment arm, study visit, and the interaction between study visit and treatment arm used in the model.

In the threshold analysis, the benefit of sacubitril/valsartan, compared with enalapril, on the primary endpoint was consistent for each threshold value for HF duration (0.25 to >5 years) (Figure 6-3). The HR for the primary endpoint (adjusted for prognostic variables) was 0.83 (95% CI 0.75–0.91) for patients with HF duration > 0.25 years, 0.82 (0.74–0.90) if HF duration > 0.5 years, 0.81 (0.73–0.90) if HF duration > 1 year, 0.78 (0.70–0.88) if HF duration > 2 years, and 0.76 (0.66–0.89) if HF duration > 5 years.

Figure 6-3 Treatment effect of sacubitril/valsartan on the primary composite outcome (cardiovascular death or first hospitalization for heart failure) according to threshold duration of heart failure



Treatment effect for the primary composite outcome using Cox model adjusted for prognostic variables as per Table 6-2 ([a]), according to threshold duration of heart failure. CI, confidence interval.

6.5 Discussion

Two aspects of the current findings are worthy of discussion. First, we provide one of the few descriptions of how patient characteristics and outcomes vary by time from diagnosis in patients with chronic HFrEF. Second, we examined whether the effects of treatment were modified by duration of HF.

There has been much debate about the heterogeneity of patients admitted to hospital with acute HF, with several studies focusing on the importance of duration of HF. In those reports, particular attention was paid to comparison of patients presenting 'de novo' and those with acute worsening of chronic HF.[159-163, 174] By contrast, little has been written about heterogeneity related to duration of HF in the ambulatory setting. Indeed, we could find only one other report, which was from the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT).[152] As in SHIFT, and in the studies of patients hospitalized with HF mentioned above, we found that patients with longer-duration HF were older and more often had coronary heart disease. While the former finding is not surprising, the latter is not so intuitive. As patients with concomitant coronary artery disease have a worse prognosis than patients without, a survivor bias in favour of patients with a non-ischaemic aetiology might be expected. However, recovery of left ventricular systolic function is less common in ischaemic patients, and the preponderance of the latter patients in HFrEF trials probably reflects this alternative bias. Likewise, the smaller proportion of women with longer-duration HF probably reflects the male predominance of coronary heart disease, especially as women with HFrEF have a better survival, overall, than men. Other differences between individuals with a longer-duration and shorter-duration HF are not unexpected in view of the foregoing discussion, for example, worse symptoms (reflecting the progressive nature of HF over time), more chronic obstructive pulmonary disease (a smoking-related disease, like coronary heart disease), worse renal function and more atrial fibrillation (both strongly age-related co-morbidities), and more diabetes and hypertension (both age-related and associated with coronary heart disease). Indeed, the burden of co-morbidity overall was much greater in patients with a longer history of HF, likely contributing to worse prognosis of these patients and possibly reducing the tolerability and effectiveness of therapy. This

potential for this heterogeneity to influence response to therapy has been highlighted in the acute HF literature.

We also identified some new findings related to duration of HF. We measured a panel of biomarkers, which was not done in SHIFT. Surprisingly, patients with longer-duration of HF had a similar median NT-proBNP concentration to patients with shorter-duration HF, despite their worse overall clinical picture and higher prevalence of atrial fibrillation. Whether this just reflects survivor bias is uncertain. It is notable that in contrast to NT-proBNP, individuals with longer-duration HF had higher high-sensitivity troponin-T, sST2, Gal-3, and GDF-15 levels, consistent with more advanced HF, although the differences between groups were small. This raises the question of whether the adaptive natriuretic peptide response in HF is preserved in the long term.[175-177]

Turning to outcomes, we also identified some new findings in relation to duration of HF. First, we examined a patient-reported outcome, the KCCQ, which has not been done before. Overall, KCCQ-CSS decreased (deteriorated) from baseline to 8 months in PARADIGM-HF. The size of decrease increased in a stepwise fashion with duration of HF, exceeding the clinically meaningful threshold of 5 points in those with an HF duration of >5 years (compared with a mean decrease of 1.19 points in patients with a duration of 0–1 year).[169] The proportion of patients with a ≥5-point decrease in KCCQ-CSS was significantly larger (and the proportion with a ≥ 5 point increase smaller) in individuals with longer-duration compared with shorter-duration HF. Second, we found a graded relationship between duration of HF and morbidity/mortality outcomes, which is consistent with most, but not all, prior acute HF trials and with SHIFT. However, the pattern of augmented risk was different for mortality and hospitalization. There was a clear stepwise increment in risk of hospital admission across each of the pre-specified time periods (although the gradient was less steep between >2–5 and >5 years than between 0–to 1 and >1–2 years); this was apparent for recurrent as well as first admissions. However, the risk of death appeared to be similar in the 0–1 and >1–2 year periods and in the >2–5 and >5 year periods. Third and perhaps most importantly, the incremental risk associated with a

longer duration of HF persisted after extensive multivariable adjustment. This suggests that the excess risk related to duration of HF is not wholly explained by age and co-morbidity and likely reflects the progressive neurohumoral, myocardial, renal, and other manifestations of HF and their consequences. Therefore, modifiable risk related to disease activity per se persists remains, even in long-standing HF.

In keeping with this, we found no evidence of diminution of the effect of sacubitril/valsartan with duration of HF. The benefit over enalapril was consistent over the time periods examined for all the outcomes of interest, whether fatal or non-fatal. The benefit in the patients with HF of the longest duration was notable in that these patients had the highest rate of use of device therapy (five-fold higher than in the shortest-duration patients), as well as consistently good pharmacological treatment. Importantly, because the event rate was substantially higher in patients with longer-duration HF, the similar relative risk reduction translated into a larger absolute risk reduction in those with a HF duration > 5 years—their NNT for the primary outcome was only 18, compared with 29 for patients with HF of 0–1 year duration.

6.6 Study limitations

As in any study of this type, there are limitations. The analyses conducted were not pre-specified. The patients studied were selected for a clinical trial and will differ from those in ordinary practice. Our study has strengths as well. It used a large, contemporary, geographically representative clinical trial dataset, with well-characterized patients and an extensive range of adjudicated outcomes.

6.7 Conclusions

In summary, patients with longer-duration HF were older, had more co-morbidity, worse quality of life, and higher rates of hospitalization and death. However, the benefits of sacubitril/valsartan over enalapril were similar irrespective of HF

duration, and if anything, greater in longer-duration HF. While early treatment with a neprilysin inhibitor may be preferable to improve quality of life and outcomes, the current data show that it is not too late to switch to sacubitril/valsartan in individuals with established HF and that substantial benefits may be obtained in these patients.

Chapter 7 Effects of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction patients with chronic obstructive pulmonary disease in EMPHASIS-HF and RALES

7.1 Abstract

7.1.1 Aims

Heart failure with reduced ejection fraction (HFrEF) and chronic obstructive pulmonary disease (COPD) individually cause significant morbidity and mortality. Their coexistence is associated with even worse outcomes, partly due to suboptimal heart failure therapy, especially underutilisation of beta-blockers. Our aim was to investigate outcomes in HFrEF patients with and without COPD, and the effects of mineralocorticoid receptor antagonists (MRAs) on outcomes.

7.1.2 Methods and results

We studied the effect of MRA therapy in a post-hoc pooled analysis of 4397 HFrEF patients in the RALES and EMPHASIS-HF trials. The primary endpoint was the composite of heart failure hospitalisation or cardiovascular death. A total of 625 (14.2%) of the 4397 patients had COPD. Patients with COPD were older, more often male, and smokers, but less frequently treated with a beta-blocker. In patients with COPD, event rates (per 100 person-years) for the primary endpoint and for all-cause mortality were 25.2 (95% confidence interval 22.1–28.7) and 17.2 (14.9–19.9), respectively, compared with 19.9 (18.8–21.1) and 12.8 (12.0–13.7) in participants without COPD. The risks of all-cause hospitalisation and sudden death were also higher in patients with COPD. The benefit of MRA, compared with placebo, was consistent in patients with or without COPD for all outcomes, e.g. hazard ratio for the primary outcome 0.66 (0.50–0.85) for COPD and 0.65 (0.58–0.73) for no COPD (interaction p = 0.93). MRA-induced hyperkalaemia was less frequent in patients with COPD.

7.1.3 Conclusions

In RALES and EMPHASIS-HF, one-in-seven patients with HFrEF had coexisting COPD. HFrEF patients with COPD had worse outcomes than those without. The benefits of MRAs were consistent, regardless of COPD status.

7.2 Introduction

Chronic obstructive pulmonary disease (COPD) is more common in patients with heart failure and reduced ejection fraction (HFrEF) than in the general population because each condition can arise as a complication of smoking.[178-182] Concomitant COPD is associated with even worse symptoms, functional limitation and clinical outcomes than in HFrEF alone.[183-185] Coexisting COPD also creates therapeutic difficulties. Beta-blockers are a key, life-saving treatment for HFrEF, but may not be tolerated in people with COPD, antagonise the effects of beta-2 adrenoceptor agonists, a core therapy for COPD, and can cause exacerbations of COPD.[186] However, many if not most patients with COPD can tolerate a beta-1 selective blocker and this treatment should not be withheld in patients with COPD. Conversely, beta-2 adrenoceptor agonists can cause tachycardia and hypokalaemia, neither of which is desirable in HFrEF. Both hypokalaemia and methylxanthines, another therapy for COPD, can predispose to arrhythmias. Corticosteroids, especially if given orally, cause fluid retention which is undesirable in HFrEF and in COPD, which is itself a sodium- and water-retaining state (although both methylxanthines and systemic corticosteroids are used in a small minority of patients in most countries).

Clearly, it would be ideal to be able to use all other effective therapies for HFrEF in patients with concomitant COPD in view of their heightened risk of adverse outcomes and potential intolerance of beta-blockers. In many ways mineralocorticoid receptor antagonists (MRAs) seem an ideal treatment for patients with both HFrEF and COPD. Each condition is associated with an increase in plasma aldosterone concentration and MRAs should help counter fluid retention, block any adverse effects of exogenous corticosteroids at the mineralocorticoid receptor and mitigate the risk of

hypokalaemia with beta-2 agonists.[86, 181, 187, 188] In addition, MRAs seem to attenuate pathogenic vascular remodelling in the lungs, and right ventricular failure, in experimental models of pulmonary hypertension.[189-193] These problems also occur as secondary complications in some patients with COPD. Surprisingly, however, in a large Danish nationwide cohort, use of spironolactone in such patients was associated with a higher mortality than no use of spironolactone, the opposite of what was found for beta-blockers and renin–angiotensin system antagonists.[194] While this unexpected finding may reflect the specific characteristics of the Danish patients (all of whom had right heart failure) or unmeasured or uncorrected confounding in an observational cohort, it does suggest the subject merits further investigation. MRAs can cause worsening of kidney function and renal dysfunction is common in both HFrEF and COPD. MRAs can also lead to hyperkalaemia which may lead to ventricular arrhythmias and patients with the combination of HFrEF and COPD may be particularly vulnerable to these.[195-197] Despite the Danish observational data and potential for hyperkalaemia to increase the risk of arrhythmias, our hypothesis was that MRAs would be as beneficial in HFrEF patients with COPD, as in those without. Fortunately, there are prospective randomised controlled trial data which allow us to examine both the efficacy and safety of MRAs in HFrEF patients with concomitant COPD. Therefore, in a post hoc analysis, we examined the effect of MRAs in relation to COPD status in patients with HFrEF enrolled in the RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trials.[27, 198]

7.3 Methods

RALES and EMPHASIS-HF were each prospective, double-blind, placebo-controlled, event-driven mortality/morbidity trials. Each trial received ethics committee approval and all participants provided written informed consent. Their design, baseline findings, and primary results are published in full.[27, 198-200] The mean follow-up in RALES was 24 months and median follow-up in EMPHASIS-HF was 21 months.

7.3.1 Trial patients

In RALES, patients with New York Heart Association (NYHA) functional class III or IV heart failure, a left ventricular ejection fraction (LVEF) of ≤35% and receiving current treatment with an angiotensin-converting enzyme (ACE) inhibitor (if tolerated) and a loop diuretic, were randomly assigned to receive either spironolactone or placebo. In EMPHASIS-HF, patients with NYHA functional class II heart failure, LVEF of ≤30% (or ≤35% if QRS duration >130 ms) and receiving optimal ACE inhibitor/angiotensin receptor blocker (ARB) and beta-blocker therapy (unless contraindicated), were randomly assigned to either eplerenone or placebo. Exclusion criteria are detailed in the design and results papers.[27, 200]

There was no exclusion related to COPD in either trial, although investigators were asked to exclude patients with another clinically important condition (e.g. cancer) likely to greatly shorten life expectancy.

7.3.2 Trial treatments

In RALES, patients were assigned to a starting dosage of 25 mg of spironolactone once daily or a matching placebo. After 8 weeks, the dose could be increased to 50 mg once daily 'if the patient showed signs or symptoms of progression of heart failure without evidence of hyperkalaemia'. In EMPHASIS-HF, eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated glomerular filtration rate was 30 to 49 mL/min/1.73 m2), provided the serum potassium level was no more than 5.0 mmol/L.

7.3.3 Identification of chronic obstructive pulmonary disease

Diagnosis of COPD was reported by investigators in the medical history section of the case report forms in each of RALES and EMPHASIS-HF. There was a specific 'yes or

no' question about COPD, but no specific criteria were provided for a diagnosis of COPD.

7.3.4 Study outcomes

The primary outcome in RALES was death from any cause and in EMPHASIS-HF it was time to first occurrence of heart failure hospitalisation or death from a cardiovascular cause. The latter was used as the primary endpoint in the present analysis. We also examined the components of this composite, non-cardiovascular and all-cause death, as well as pump failure and sudden cardiac death.

7.3.5 Statistical analysis

In order to maximise the number of COPD patients and events, as well as cover the full spectrum of heart failure symptom severity (NYHA class II to IV), we merged the RALES and EMPHASIS-HF databases. Certain baseline data were collected in EMPHASIS-HF, but not RALES. Hence, the baseline analysis is presented in two tables: Table 7-1 (baseline characteristics collected in both RALES and EMPHASIS-HF) and Table 7-2 (additional baseline data collected in EMPHASIS-HF only).

Baseline characteristics are reported as means and standard deviations for continuous variables and frequencies with percentages for categorical variables. Time-to-event endpoints were evaluated using Kaplan–Meier estimates and Cox proportional hazard models, stratified according to trial and adjusted for randomised treatment group to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Along with crude HRs, we also report HRs adjusted for age, sex, race, heart rate, systolic blood pressure, NYHA classification, LVEF, estimated glomerular filtration rate, history of myocardial infarction, diabetes and atrial fibrillation. In a sensitivity analysis, we also adjusted for beta-blocker use at baseline, given the anticipated imbalance in the use of these drugs between patients with and without COPD and their powerful effect of clinical outcomes in HFrEF.

The treatment effect for each time-to-event endpoint was estimated using Cox models with an interaction term between baseline COPD status and treatment group. The interaction between COPD status and effect of randomised treatment on adverse events and study drug discontinuation was analysed using a logistic regression model with an interaction term between baseline COPD status and treatment. A P-value of < 0.05 was considered significant. Statistical analyses were conducted using STATA version 16.0 (Stata Corp., College Station, TX, USA).

7.4 Results

Overall, 4397 patients were included in the analysis, of whom 2212 were randomised to placebo and 2185 to an MRA. Of the included patients, 625 (14.2%) had COPD: 321 (14.7%) in the MRA group and 304 (13.7%) in the placebo group.

7.4.1 Baseline characteristics according to chronic obstructive pulmonary disease status

The baseline characteristics of patients in the combined RALES and EMPHASIS-HF dataset are shown in Table 7-1 according to COPD status. Patients with COPD were older and more often men. They were also more likely than patients without COPD to have a history of hypertension, atrial fibrillation and stroke but not of coronary heart disease. NYHA functional class distribution, LVEF and kidney function were similar in each COPD subgroup. Patients with COPD were significantly less likely to be treated with a beta-blocker. Data on beta-blocker selectivity were not available.

Table 7-2 contains additional data collected in EMPHASIS-HF only. In EMPHASIS-HF, patients with COPD were more often current smokers (21.7%) than those without COPD (8.9%).

Table 7-1 Baseline characteristics according to chronic obstructive pulmonary disease status

	All Patients	Without COPD	With COPD	*P*-value
	(N=4397)*	(N=3772)	(N=625)	
Age (years)	67.4 ± 9.6	67.1 ± 9.8	69.1 ± 7.9	<0.001
Women	1056 (24.0)	946 (25.1)	110 (17.6)	<0.001
Race				<0.001
White	3706 (84.3)	3140 (83.2)	566 (90.6)	
Black	187 (4.3)	178 (4.7)	9 (1.4)	
Asian	347 (7.9)	308 (8.2)	39 (6.2)	
Other	157 (3.6)	146 (3.9)	11 (1.8)	
Heart rate (bpm)	75.2 ± 13.9	74.9 ± 13.8	76.8 ± 13.9	0.001
SBP (mmHg)	123.4 ± 18.2	123.4 ± 18.3	123.2 ± 17.4	0.80
DBP (mmHg)	74.6 ± 10.8	74.7 ± 10.7	74.1 ± 11.0	0.16
Hypertension	2208 (50.2)	1857 (49.2)	351 (56.2)	0.001
Diabetes	1228 (27.9)	1054 (27.9)	174 (27.8)	0.96
Myocardial infarction	1852 (42.1)	1571 (41.6)	281 (45.0)	0.12
Atrial Fibrillation/Flutter	1026 (23.3)	861 (22.8)	165 (26.4)	0.051
Ischaemic CVA	248 (5.7)	199 (5.3)	49 (7.9)	0.010
HF aetiology				0.22
• Ischaemic	2792 (63.6)	2383 (63.2)	409 (65.8)	
• Non-Ischaemic	1600 (36.4)	1387 (36.8)	213 (34.2)	
NYHA				0.19
• II	2740 (62.3)	2349 (62.3)	391 (62.6)	
• III	1173 (26.7)	1021 (27.1)	152 (24.3)	
• IV	483 (11.0)	401 (10.6)	82 (13.1)	
LVEF (%)	25.8 ± 5.6	25.9 ± 5.5	25.6 ± 5.8	0.30
eGFR (ml/min/1.73m^2)	68.6 ± 22.4	68.6 ± 22.4	68.3 ± 22.4	0.74

eGFR<60	1702 (38.8)	1460 (38.8)	242 (38.8)	0.97
Creatinine (mg/dL)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.24
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.054
Diuretic	3826 (87.3)	3283 (87.3)	543 (87.6)	0.83
ACEi/ARB	4145 (94.6)	3552 (94.4)	593 (95.6)	0.21
Beta-blocker	2543 (58.0)	2234 (59.4)	309 (49.8)	<0.001
Digoxin	1955 (44.6)	1680 (44.7)	275 (44.4)	0.89

Data are presented as mean ± standard deviation for continuous measures, and n (%) for categorical measures.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

*** For 4397 patients of the 4400 randomised because COPD status was not recorded in 3 patients.**

Table 7-2 Additional baseline characteristics according to COPD status (EMPHASIS-HF only).

	All Patients	Without COPD	With COPD	*P*-value
	(N=2737)*	(N=2343)	(N=391)	
BMI (kg/m^2)	27.5 ± 4.9	27.6 ± 4.8	27.4 ± 5.1	0.47
BMI Classification				0.29
• Underweight (BMI<18.5)	50 (1.8)	40 (1.7)	10 (2.6)	
• Normal weight (BMI 18.5-24.9)	765 (28.1)	644 (27.6)	121 (31.1)	
• Overweight (BMI 25-29.9)	1165 (42.8)	1010 (43.3)	155 (39.8)	
• Obesity (BMI≥30)	739 (27.2)	636 (27.3)	103 (26.5)	
Smoking status				<0.001
• Never	1222 (44.7)	1125 (48.0)	97 (24.8)	
• Former	1219 (44.6)	1010 (43.1)	209 (53.5)	
• Current	293 (10.7)	208 (8.9)	85 (21.7)	
Haemoglobin (g/L)	138.0 ± 15.7	137.8 ± 15.7	139.3 ± 15.9	0.079
Anaemia	616 (23.1)	533 (23.3)	83 (21.7)	0.49
PCI	596 (21.8)	524 (22.4)	72 (18.4)	0.079
CABG	516 (18.9)	434 (18.5)	82 (21.0)	0.25
CRT-P/CRT-D	230 (8.7)	201 (8.8)	29 (7.8)	0.51
ICD/CRT-D	421 (15.8)	358 (15.6)	63 (16.7)	0.59

Data are presented as mean ± SD for continuous measures and n (%) for categorical measures.

Abbreviations: COPD, Chronic obstructive pulmonary disease; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CRT-P or -D, cardiac resynchronisation therapy with pacemaker or defibrillator; ICD, implantable cardioverter-defibrillator.

* 3 patients missing COPD data

7.4.2 Clinical outcomes according to chronic obstructive pulmonary disease status

The incidence rate (per 100 person-years) and unadjusted risk of most outcomes examined were higher in patients with COPD compared to those without (the exception was pump failure death, although numbers of this event in the COPD groups were small). The elevated risks were attenuated by multivariable adjustment (Table 7-3).

Table 7-3 Event rate (per 100 patient-years) and risk of study endpoints according to chronic obstructive pulmonary disease status

	Without COPD (N=3772)	**With COPD (N=625)**	***P*-value**
HF hospitalisation or cardiovascular death			
Events – no. (%)	1195 (31.7)	227 (36.3)	
Event rate per 100 pt. years	19.9 (18.8 – 21.1)	25.2 (22.1 – 28.7)	
Unadjusted HR	1.00 (ref.)	1.25 (1.08 – 1.44)	0.002
Adjusted HR*	1.00 (ref.)	1.16 (1.00 – 1.35)	0.045
Adjusted HR†	1.00 (ref.)	1.12 (0.96 – 1.30)	0.139
HF hospitalisation			
Events – no. (%)	783 (20.8)	150 (24.0)	
Event rate per 100 pt. years	13.1 (12.2 – 14.0)	16.6 (14.2 – 19.5)	
Unadjusted HR	1.00 (ref.)	1.25 (1.05 – 1.49)	0.011
Adjusted HR*	1.00 (ref.)	1.17 (0.98 – 1.40)	0.091
Adjusted HR†	1.00 (ref.)	1.12 (0.93 – 1.34)	0.225
All-cause hospitalisation			
Events – no. (%)	1510 (40.0)	294 (47.0)	
Event rate per 100 pt. years	29.2 (27.8 – 30.7)	39.9 (35.6 – 44.7)	
Unadjusted HR	1.00 (ref.)	1.33 (1.17 – 1.51)	<0.001

Adjusted HR*	1.00 (ref.)	1.25 (1.10 – 1.42)	0.001
Adjusted HR†	1.00 (ref.)	1.23 (1.08 – 1.40)	0.002
Non-Cardiovascular hospitalisation			
Events – no. (%)	394 (10.4)	105 (16.8)	
Event rate per 100 pt. years	6.8 (6.1 – 7.5)	12.2 (10.0 – 14.8)	
Unadjusted HR	1.00 (ref.)	1.79 (1.44 – 2.22)	<0.001
Adjusted HR*	1.00 (ref.)	1.68 (1.34 – 2.10)	<0.001
Adjusted HR†	1.00 (ref.)	1.69 (1.35 – 2.12)	<0.001
Cardiovascular death			
Events – no. (%)	729 (19.3)	142 (22.7)	
Event rate per 100 pt. years	10.8 (10.0 – 11.6)	13.4 (11.4 – 15.8)	
Unadjusted HR	1.00 (ref.)	1.25 (1.04 – 1.49)	0.016
Adjusted HR*	1.00 (ref.)	1.13 (0.93 – 1.36)	0.211
Adjusted HR†	1.00 (ref.)	1.10 (0.91 – 1.32)	0.329
Non-Cardiovascular death			
Events – no. (%)	142 (3.8)	40 (6.4)	
Event rate per 100 pt. years	2.1 (1.8 – 2.5)	3.8 (2.8 – 5.2)	
Unadjusted HR	1.00 (ref.)	1.82 (1.28 – 2.58)	0.001
Adjusted HR*	1.00 (ref.)	1.85 (1.29 – 2.65)	0.001
Adjusted HR†	1.00 (ref.)	1.81 (1.26 – 2.60)	0.001
All-cause death			
Events – no. (%)	871 (23.1)	182 (29.1)	
Event rate per 100 pt. years	12.8 (12.0 – 13.7)	17.2 (14.9 – 19.9)	
Unadjusted HR	1.00 (ref.)	1.34 (1.14 – 1.57)	<0.001
Adjusted HR*	1.00 (ref.)	1.24 (1.05 – 1.46)	0.010
Adjusted HR†	1.00 (ref.)	1.21 (1.03 – 1.43)	0.024
Pump failure death			

Events – no. (%)	358 (9.5)	64 (10.2)	
Event rate per 100 pt. years	5.3 (4.7 – 5.8)	6.1 (4.7 – 7.7)	
Unadjusted HR	1.00 (ref.)	1.14 (0.88 – 1.49)	0.327
Adjusted HR*	1.00 (ref.)	0.96 (0.73 – 1.27)	0.778
Adjusted HR†	1.00 (ref.)	0.94 (0.71 – 1.24)	0.656
Sudden cardiac death			
Events – no. (%)	267 (7.1)	60 (9.6)	
Event rate per 100 pt. years	3.9 (3.5 – 4.4)	5.7 (4.4 – 7.3)	
Unadjusted HR	1.00 (ref.)	1.44 (1.09 – 1.91)	0.011
Adjusted HR*	1.00 (ref.)	1.35 (1.01 – 1.80)	0.042
Adjusted HR†	1.00 (ref.)	1.31 (0.98 – 1.76)	0.064

* Model adjusted for age, sex, race, heart rate, systolic blood pressure, NYHA, LVEF, eGFR, history of myocardial infarction, diabetes and atrial fibrillation.

† Adjusted as for * with additional adjustment for beta blocker prescription at baseline.

7.4.3 Primary outcome (composite of heart failure hospitalisation or cardiovascular death)

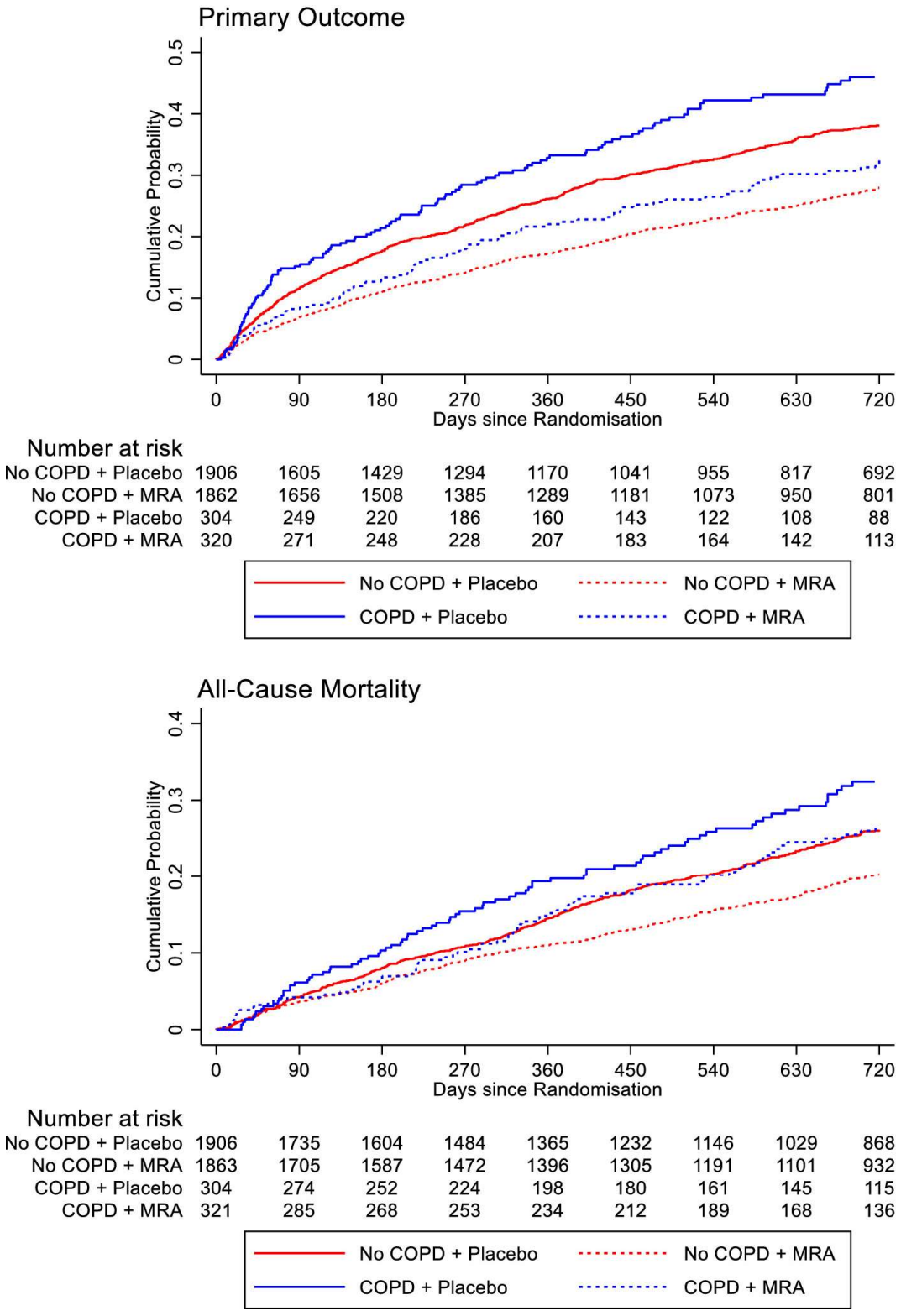
The event rates were 25.2 (95% CI 22.1–28.7) in patients with COPD, vs. 19.9 (95% CI 18.8–21.1) in those without COPD with unadjusted HR 1.25 (95% CI 1.08–1.44), using patients without COPD as the reference group (Figure 7-1). The elevated risk was attenuated to HR 1.16 (95% CI 1.00–1.35) after adjustment for standard prognostic variables. A similar picture was seen for the components of the composite outcome.

7.4.4 Mortality

The higher rate of cardiovascular mortality in patients with COPD was driven by an elevated risk of sudden death compared with pump failure death, compared to patients without COPD: unadjusted HR 1.44 (95% CI 1.09–1.91) for sudden death vs. 1.14 (95% CI 0.88–1.49) for pump failure death.

The rate of non-cardiovascular mortality, and therefore all-cause mortality, was also higher in patients with COPD, with a greater elevation in risk of non-cardiovascular death vs. cardiovascular death, compared to participants without COPD [unadjusted HR 1.82 (95% CI 1.28–2.58) for non-cardiovascular death vs. 1.25 (95% CI 1.04–1.49) for cardiovascular death] (Figure 7-1). Examination of causes of non-cardiovascular deaths showed an excess of deaths due to infection/sepsis in patients with COPD compared to those without COPD (Figure 7-2).

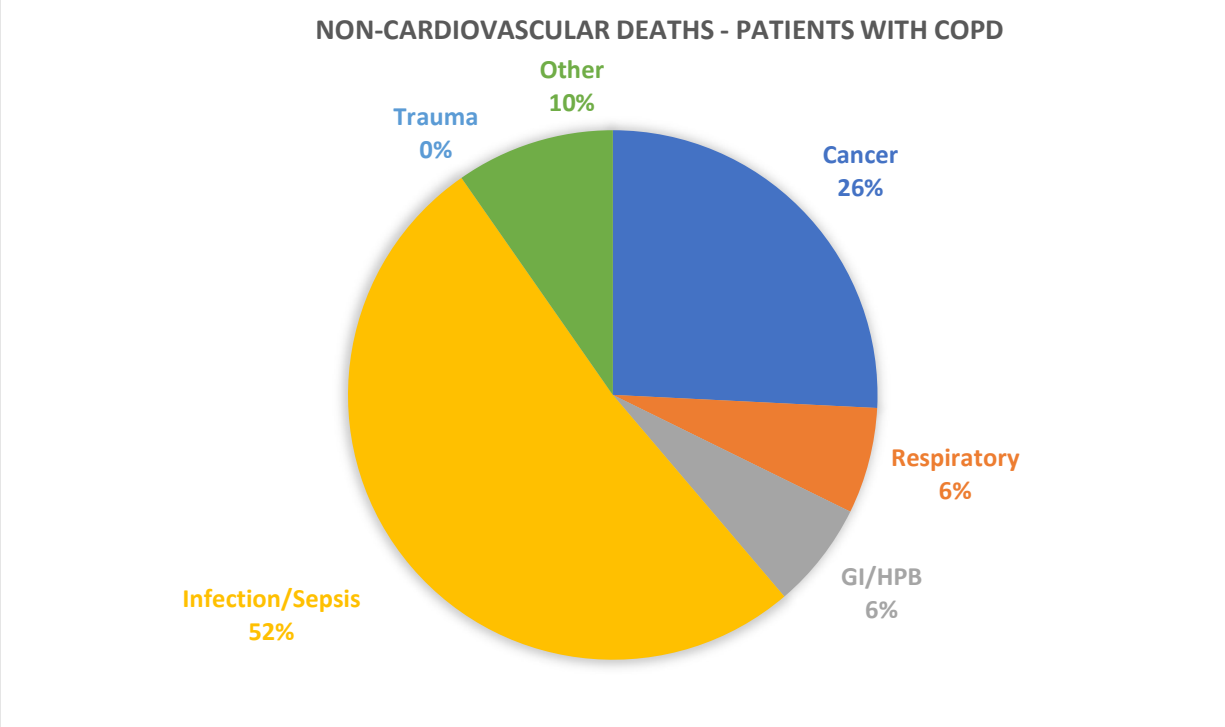
Figure 7-1 Kaplan-Meier curves for key outcomes, according to baseline chronic obstructive pulmonary disease (COPD) status and randomised treatment



The primary outcome was the composite of heart failure hospitalisation and death from cardiovascular causes. MRA, mineralocorticoid receptor antagonist.

Figure 7-2 Causes of non-cardiovascular death in patients with and without COPD (RALES and EMPHASIS-HF combined)

Abbreviations: GI/HPB, gastrointestinal/hepatobiliary



7.4.5 Hospitalisations

Patients with COPD had higher all-cause, heart failure and non-cardiovascular hospitalisations [unadjusted HR 1.33 (95% CI 1.17–1.51), 1.25 (95% CI 1.05–1.49) and 1.79 (95% CI 1.44–2.22), respectively]. In contrast to heart failure hospitalisations, the elevated risk of all-cause and non-cardiovascular hospitalisations persisted with multivariable adjustment.

In the sensitivity analyses, further adjusting for beta-blocker slightly attenuated the excess risk related to COPD, more so for heart failure hospitalisation than the other outcomes.

These findings were consistent when RALES and EMPHASIS-HF were analysed separately (Tables 7-4 and 7-5).

7.4.6 Efficacy of mineralocorticoid receptor antagonists according to chronic obstructive pulmonary disease status

The benefits of MRAs, compared with placebo, were consistent in patients with and without COPD for all mortality and hospitalisation outcomes (Table 7-6 and Figure 7-1). The HR for the primary outcome was 0.66 (95% CI 0.50–0.85) in patients with COPD and 0.65 (95% CI 0.58–0.73) in patients without COPD (P-value for interaction =0.93). The HR for all-cause mortality was 0.77 (95% CI 0.58–1.03) in patients with COPD and 0.72 (95% CI 0.63–0.82) in patients without COPD (P-value for interaction =0.65) (Figure 7-1).

These findings were consistent when RALES and EMPHASIS-HF were analysed separately (Tables 7-7 and 7-8).

Table 7-4 Event rate (per 100 patient-years) and risk of study endpoints according to COPD status (RALES only)

	Without COPD (N= 1429)	With COPD (N=234)	*P*-value
HF hospitalisation or cardiovascular death			
Events – no. (%)	695 (48.6)	123 (52.6)	
Event rate per 100 pt. years	33.1 (30.7 – 35.7)	38.7 (32.4 – 46.2)	
Unadjusted HR	1.00 (ref.)	1.15 (0.95 – 1.39)	0.151
Adjusted HR*	1.00 (ref.)	1.05 (0.86 – 1.28)	0.608
Adjusted HR†	1.00 (ref.)	1.03 (0.85 – 1.26)	0.740
HF hospitalisation			
Events – no. (%)	440 (30.8)	76 (32.5)	
Event rate per 100 pt. years	21.0 (19.1 – 23.1)	23.9 (19.1 – 29.9)	
Unadjusted HR	1.00 (ref.)	1.11 (0.87 – 1.42)	0.387
Adjusted HR*	1.00 (ref.)	1.01 (0.79 – 1.30)	0.929
Adjusted HR†	1.00 (ref.)	0.99 (0.77 – 1.28)	0.955
All-cause hospitalisation			
Events – no. (%)	766 (53.6)	140 (59.8)	
Event rate per 100 pt. years	43.4 (40.5 – 46.6)	54.8 (46.4 – 64.7)	
Unadjusted HR	1.00 (ref.)	1.23 (1.03 – 1.48)	0.022
Adjusted HR*	1.00 (ref.)	1.13 (0.94 – 1.36)	0.195
Adjusted HR†	1.00 (ref.)	1.12 (0.93 – 1.35)	0.219
Non-Cardiovascular hospitalisation			
Events – no. (%)	248 (17.4)	56 (23.9)	
Event rate per 100 pt. years	14.1 (12.4 – 15.9)	21.7 (16.6 – 28.2)	
Unadjusted HR	1.00 (ref.)	1.51 (1.13 – 2.03)	0.005
Adjusted HR*	1.00 (ref.)	1.44 (1.07 – 1.94)	0.017
Adjusted HR†	1.00 (ref.)	1.45 (1.07 – 1.95)	0.015

Cardiovascular death			
Events – no. (%)	455 (31.8)	85 (36.3)	
Event rate per 100 pt. years	17.7 (16.2 – 19.4)	20.8 (16.8 – 25.8)	
Unadjusted HR	1.00 (ref.)	1.18 (0.94 – 1.49)	0.163
Adjusted HR*	1.00 (ref.)	1.05 (0.83 – 1.33)	0.684
Adjusted HR†	1.00 (ref.)	1.04 (0.82 – 1.32)	0.769
Non-Cardiovascular death			
Events – no. (%)	101 (7.1)	29 (12.4)	
Event rate per 100 pt. years	3.9 (3.2 – 4.7)	7.1 (4.9 – 10.2)	
Unadjusted HR	1.00 (ref.)	1.83 (1.21 – 2.77)	0.004
Adjusted HR*	1.00 (ref.)	1.84 (1.20 – 2.82)	0.005
Adjusted HR†	1.00 (ref.)	1.80 (1.17 – 2.76)	0.007
All-cause death			
Events – no. (%)	556 (38.9)	114 (48.7)	
Event rate per 100 pt. years	21.6 (19.9 – 23.5)	27.9 (23.2 – 33.6)	
Unadjusted HR	1.00 (ref.)	1.30 (1.06 – 1.59)	0.012
Adjusted HR*	1.00 (ref.)	1.19 (0.96 – 1.46)	0.105
Adjusted HR†	1.00 (ref.)	1.17 (0.95 – 1.44)	0.140
Pump failure death			
Events – no. (%)	275 (19.2)	41 (17.5)	
Event rate per 100 pt. years	10.7 (9.5 – 12.0)	10.0 (7.4 – 13.6)	
Unadjusted HR	1.00 (ref.)	0.94 (0.68 – 1.31)	0.727
Adjusted HR*	1.00 (ref.)	0.78 (0.56 – 1.09)	0.150
Adjusted HR†	1.00 (ref.)	0.77 (0.55 – 1.08)	0.127
Sudden cardiac death			
Events – no. (%)	155 (10.8)	37 (15.8)	
Event rate per 100 pt. years	6.0 (5.2 – 7.1)	9.1 (6.6 – 12.5)	
Unadjusted HR	1.00 (ref.)	1.51 (1.06 – 2.17)	0.024
Adjusted HR*	1.00 (ref.)	1.44 (1.00 – 2.09)	0.052

Adjusted HR†	1.00 (ref.)	1.42 (0.98 – 2.05)	0.062

* Model adjusted for age, sex, race, heart rate, systolic blood pressure, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, history of myocardial infarction, diabetes and atrial fibrillation.

† Adjusted as for * with additional adjustment for beta blocker prescription at baseline.

Table 7-5 Event rate (per 100 patient-years) and risk of study endpoints according to COPD status (EMPHASIS-HF only)

	Without COPD (N= 2343)	**With COPD (N= 391)**	***P*-value**
HF hospitalisation or cardiovascular death			
Events – no. (%)	500 (21.3)	104 (26.6)	
Event rate per 100 pt. years	12.8 (11.8 – 14.0)	17.8 (14.7 – 21.6)	
Unadjusted HR	1.00 (ref.)	1.39 (1.13 – 1.72)	0.002
Adjusted HR*	1.00 (ref.)	1.32 (1.05 – 1.64)	0.015
Adjusted HR†	1.00 (ref.)	1.26 (1.01 – 1.58)	0.042
HF hospitalisation			
Events – no. (%)	343 (14.6)	74 (18.9)	
Event rate per 100 pt. years	8.8 (7.9 – 9.8)	12.7 (10.1 – 15.9)	
Unadjusted HR	1.00 (ref.)	1.44 (1.12 – 1.86)	0.004
Adjusted HR*	1.00 (ref.)	1.35 (1.03 – 1.75)	0.028
Adjusted HR†	1.00 (ref.)	1.29 (0.98 – 1.69)	0.065
All-cause hospitalisation			
Events – no. (%)	744 (31.8)	154 (39.4)	
Event rate per 100 pt. years	21.8 (20.3 – 23.5)	32.1 (27.4 – 37.5)	
Unadjusted HR	1.00 (ref.)	1.43 (1.20 – 1.70)	<0.001
Adjusted HR*	1.00 (ref.)	1.37 (1.14 – 1.65)	0.001
Adjusted HR†	1.00 (ref.)	1.33 (1.11 – 1.60)	0.002

Non-Cardiovascular hospitalisation			
Events – no. (%)	146 (6.2)	49 (12.5)	
Event rate per 100 pt. years	3.6 (3.0 – 4.2)	8.2 (6.2 – 10.8)	
Unadjusted HR	1.00 (ref.)	2.25 (1.63 – 3.12)	<0.001
Adjusted HR*	1.00 (ref.)	2.09 (1.48 – 2.94)	<0.001
Adjusted HR†	1.00 (ref.)	2.13 (1.51 – 3.03)	<0.001
Cardiovascular death			
Events – no. (%)	274 (11.7)	57 (14.6)	
Event rate per 100 pt. years	6.5 (5.8 – 7.3)	8.8 (6.8 – 11.4)	
Unadjusted HR	1.00 (ref.)	1.36 (1.03 – 1.81)	0.033
Adjusted HR*	1.00 (ref.)	1.30 (0.96 – 1.75)	0.089
Adjusted HR†	1.00 (ref.)	1.26 (0.93 – 1.71)	0.132
Non-Cardiovascular death			
Events – no. (%)	41 (1.7)	11 (2.8)	
Event rate per 100 pt. years	1.0 (0.7 – 1.3)	1.7 (0.9 – 3.1)	
Unadjusted HR	1.00 (ref.)	1.77 (0.91 – 3.45)	0.092
Adjusted HR*	1.00 (ref.)	1.81 (0.92 – 3.57)	0.086
Adjusted HR†	1.00 (ref.)	1.82 (0.92 – 3.61)	0.086
All-cause death			
Events – no. (%)	315 (13.4)	68 (17.4)	
Event rate per 100 pt. years	7.5 (6.7 – 8.4)	10.5 (8.3 – 13.3)	
Unadjusted HR	1.00 (ref.)	1.42 (1.09 – 1.84)	0.009
Adjusted HR*	1.00 (ref.)	1.37 (1.04 – 1.80)	0.025
Adjusted HR†	1.00 (ref.)	1.34 (1.02 – 1.77)	0.038
Pump failure death			
Events – no. (%)	83 (3.5)	23 (5.9)	
Event rate per 100 pt. years	2.0 (1.6 – 2.4)	3.5 (2.4 – 5.3)	
Unadjusted HR	1.00 (ref.)	1.82 (1.15 – 2.89)	0.011
Adjusted HR*	1.00 (ref.)	1.74 (1.05 – 2.87)	0.031

Adjusted HR†	1.00 (ref.)	1.77 (1.06 – 2.94)	0.028
Sudden cardiac death			
Events – no. (%)	112 (4.8)	23 (5.9)	
Event rate per 100 pt. years	2.7 (2.2 – 3.2)	3.5 (2.4 – 5.3)	
Unadjusted HR	1.00 (ref.)	1.34 (0.85 – 2.09)	0.205
Adjusted HR*	1.00 (ref.)	1.24 (0.77 – 1.99)	0.373
Adjusted HR†	1.00 (ref.)	1.20 (0.74 – 1.93)	0.462

* Model adjusted for age, sex, race, heart rate, systolic blood pressure, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, history of myocardial infarction, diabetes and atrial fibrillation.

† Adjusted as for * with additional adjustment for beta blocker prescription at baseline.

Chronic obstructive pulmonary disease (COPD); heart failure (HF); hazard ratio (HR).

Table 7-6 Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval)

	Without COPD		With COPD		
	Placebo (N=1908)	**MRA (N=1864)**	**Placebo (N=304)**	**MRA (N=321)**	***P*-value for interaction**
HF hospitalisation or cardiovascular death					
Events – no. (%)	700 (36.7)	495 (26.6)	128 (42.1)	99 (30.8)	
Event rate per 100 pt. yrs.	24.4 (22.6 – 26.2)	15.8 (14.5 – 17.3)	31.5 (26.5 – 37.5)	20.0 (16.4 – 24.3)	
Unadjusted HR	0.65 (0.58 – 0.73)		0.66 (0.50 – 0.85)		0.93
HF hospitalisation					
Events – no. (%)	465 (24.4)	318 (17.1)	88 (28.9)	62 (19.3)	
Event rate per 100 pt. yrs.	16.2 (14.8 – 17.7)	10.2 (9.1 – 11.4)	21.7 (17.6 – 26.7)	12.5 (9.8 – 16.1)	
Unadjusted HR	0.64 (0.55 – 0.73)		0.59 (0.43 – 0.82)		0.79
All-cause hospitalisation					
Events – no. (%)	814 (42.7)	696 (37.3)	158 (52.0)	136 (42.4)	
Event rate per 100 pt. yrs.	32.8 (30.6 – 35.1)	25.9 (24.1 – 27.9)	48.6 (41.6 – 56.8)	33.0 (27.9 – 39.1)	
Unadjusted HR	0.80 (0.72 – 0.89)		0.71 (0.57 – 0.90)		0.28
Non-Cardiovascular hospitalisation					
Events – no. (%)	185 (9.7)	209 (11.2)	53 (17.4)	52 (16.2)	
Event rate per 100 pt. yrs.	6.5 (5.6 – 7.5)	7.0 (6.1 – 8.1)	13.9 (10.6 – 18.2)	10.8 (8.2 – 14.2)	
Unadjusted HR	1.06 (0.87 – 1.30)		0.78 (0.53 – 1.14)		0.16

Cardiovascular death					
Events – no. (%)	420 (22.0)	309 (16.6)	79 (26.0)	63 (19.6)	
Event rate per 100 pt. yrs.	12.5 (11.4 – 13.8)	9.0 (8.1 – 10.1)	16.1 (12.9 – 20.1)	11.1 (8.7 – 14.3)	
Unadjusted HR	0.72 (0.62 – 0.83)		0.72 (0.52 – 1.00)		1.00
All-cause death					
Events – no. (%)	501 (26.3)	370 (19.8)	98 (32.2)	84 (26.2)	
Event rate per 100 pt. yrs.	15.0 (13.7 – 16.3)	10.8 (9.7 – 11.9)	20.0 (16.4 – 24.3)	14.8 (12.0 – 18.4)	
Unadjusted HR	0.72 (0.63 – 0.82)		0.77 (0.58 – 1.03)		0.65
Pump failure death					
Events – no. (%)	212 (11.1)	146 (7.8)	38 (12.5)	26 (8.1)	
Event rate per 100 pt. yrs.	6.3 (5.5 – 7.2)	4.3 (3.6 – 5.0)	7.7 (5.6 – 10.6)	4.6 (3.1 – 6.7)	
Unadjusted HR	0.67 (0.54 – 0.83)		0.61 (0.37 – 1.01)		0.80
Sudden cardiac death					
Events – no. (%)	154 (8.1)	113 (6.1)	32 (10.5)	28 (8.7)	
Event rate per 100 pt. yrs.	4.6 (3.9 – 5.4)	3.3 (2.7 – 4.0)	6.5 (4.6 – 9.2)	4.9 (3.4 – 7.2)	
Unadjusted HR	0.71 (0.56 – 0.91)		0.80 (0.48 – 1.33)		0.73

Abbreviations: Chronic obstructive pulmonary disease (COPD); mineralocorticoid receptor antagonist (MRA); heart failure (HF); hazard ratio (HR).

Table 7-7 Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval) – RALES only

	Without COPD		With COPD		
	Placebo (N=725)	MRA (N=704)	Placebo (N=116)	MRA (N=118)	*P*-value for interaction
HF hospitalisation or cardiovascular death					
Events – no. (%)	405 (55.9)	290 (41.2)	67 (57.8)	56 (47.5)	
Event rate per 100 pt. yrs.	41.7 (37.9 – 46.0)	25.7 (22.9 – 28.8)	46.2 (36.4 – 58.8)	32.4 (24.9 – 42.1)	
Unadjusted HR	0.64 (0.55 – 0.75)		0.74 (0.52 – 1.05)		0.50
HF hospitalisation					
Events – no. (%)	257 (35.4)	183 (26.0)	43 (37.1)	33 (28.0)	
Event rate per 100 pt. yrs.	26.6 (23.5 – 30.0)	16.3 (14.1 – 18.8)	29.7 (22.0 – 40.0)	19.1 (13.6 – 26.9)	
Unadjusted HR	0.65 (0.53 – 0.78)		0.68 (0.43 – 1.07)		0.84
All-cause hospitalisation					
Events – no. (%)	407 (56.1)	359 (51.0)	75 (64.7)	65 (55.1)	
Event rate per 100 pt. yrs.	49.0 (44.4 – 54.0)	38.5 (34.7 – 42.7)	68.4 (54.6 – 85.8)	44.4 (34.8 – 56.7)	
Unadjusted HR	0.81 (0.70 – 0.93)		0.70 (0.50 – 0.98)		0.34
Non-Cardiovascular hospitalisation					
Events – no. (%)	116 (16.0)	132 (18.8)	31 (26.7)	25 (21.2)	
Event rate per 100 pt. yrs.	14.0 (11.6 – 16.7)	14.2 (11.9 – 16.8)	28.3 (19.9 – 40.2)	16.6 (11.2 – 24.8)	
Unadjusted HR	1.03 (0.80 – 1.33)		0.61 (0.35 – 1.04)		0.08
Cardiovascular death					
Events – no. (%)	267 (36.8)	188 (26.7)	47 (40.5)	38 (32.2)	
Event rate per 100 pt. yrs.	21.3 (18.9 – 24.0)	14.3 (12.4 – 16.5)	23.8 (17.9 – 31.7)	18.0 (13.1 – 24.8)	
Unadjusted HR	0.68 (0.56 – 0.82)		0.77 (0.50 – 1.17)		0.63
All-cause death					
Events – no. (%)	323 (44.6)	233 (33.1)	63 (54.3)	51 (43.2)	
Event rate per 100 pt. yrs.	25.8 (23.1 – 28.7)	17.7 (15.5 – 20.1)	31.9 (25.0 – 40.9)	24.2 (18.4 – 31.8)	
Unadjusted HR	0.69 (0.58 – 0.82)		0.76 (0.53 – 1.11)		0.64
Pump failure death					

Events – no. (%)	164 (22.6)	111 (15.8)	25 (21.6)	16 (13.6)	
Event rate per 100 pt. yrs.	13.0 (11.2 – 15.2)	8.5 (7.0 – 10.2)	12.7 (8.6 – 18.8)	7.6 (4.6 – 12.4)	
Unadjusted HR	0.66 (0.52 – 0.84)		0.60 (0.32 – 1.13)		0.80
Sudden cardiac death					
Events – no. (%)	92 (12.7)	63 (8.9)	18 (15.5)	19 (16.1)	
Event rate per 100 pt. yrs.	7.3 (6.0 – 9.0)	4.8 (3.7 – 6.1)	9.1 (5.8 – 14.5)	9.0 (5.7 – 14.1)	
Unadjusted HR	0.66 (0.48 – 0.91)		1.01 (0.53 – 1.92)		0.26
Abbreviations: COPD, Chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; HF, heart failure; HR, hazard ratio.					

Table 7-8 Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval) – EMPHASIS-HF only

	Without COPD		**With COPD**		
	Placebo (N=1183)	**MRA (N=1160)**	**Placebo (N=188)**	**MRA (N=203)**	***P*-value for interaction**
HF hospitalisation or cardiovascular death					
Events – no. (%)	295 (24.9)	205 (17.7)	61 (32.4)	43 (21.2)	
Event rate per 100 pt. yrs.	15.5 (13.8 – 17.4)	10.3 (9.0 – 11.8)	23.4 (18.2 – 30.0)	13.3 (9.9 – 18.0)	
Unadjusted HR	0.67 (0.56 – 0.80)		0.57 (0.38 – 0.84)		0.54
HF hospitalisation					
Events – no. (%)	208 (17.6)	135 (11.6)	45 (23.9)	29 (14.3)	
Event rate per 100 pt. yrs.	10.9 (9.5 – 12.5)	6.8 (5.7 – 8.0)	17.2 (12.9 – 23.1)	9.0 (6.3 – 12.9)	
Unadjusted HR	0.62 (0.50 – 0.77)		0.51 (0.32 – 0.83)		0.56
All-cause hospitalisation					
Events – no. (%)	407 (34.4)	337 (29.1)	83 (44.1)	71 (35.0)	
Event rate per 100 pt. yrs.	24.6 (22.4 – 27.1)	19.2 (17.3 – 21.4)	38.5 (31.0 – 47.7)	26.8 (21.2 – 33.8)	
Unadjusted HR	0.79 (0.69 – 0.91)		0.73 (0.53 – 1.00)		0.58
Non-Cardiovascular hospitalisation					
Events – no. (%)	69 (5.8)	77 (6.6)	22 (11.7)	27 (13.3)	
Event rate per	3.4 (2.7 –	3.8 (3.0 –	8.1 (5.3 –	8.2 (5.6 –	

100 pt. yrs.	4.3)	4.7)	12.3)	12.0)	
Unadjusted HR	1.11 (0.81 – 1.54)		1.02 (0.58 – 1.80)		0.80
Cardiovascular death					
Events – no. (%)	153 (12.9)	121 (10.4)	32 (17.0)	25 (12.3)	
Event rate per 100 pt. yrs.	7.3 (6.2 – 8.5)	5.7 (4.8 – 6.8)	10.9 (7.7 – 15.4)	7.0 (4.8 – 10.4)	
Unadjusted HR	0.78 (0.62 – 0.99)		0.65 (0.39 – 1.10)		0.52
All-cause death					
Events – no. (%)	178 (15.0)	137 (11.8)	35 (18.6)	33 (16.3)	
Event rate per 100 pt. yrs.	8.5 (7.3 – 9.8)	6.5 (5.5 – 7.7)	11.9 (8.6 – 16.6)	9.3 (6.6 – 13.1)	
Unadjusted HR	0.76 (0.61 – 0.95)		0.79 (0.49 – 1.27)		0.92
Pump failure death					
Events – no. (%)	48 (4.1)	35 (3.0)	13 (6.9)	10 (4.9)	
Event rate per 100 pt. yrs.	2.3 (1.7 – 3.0)	1.7 (1.2 – 2.3)	4.4 (2.6 – 7.6)	2.8 (1.5 – 5.2)	
Unadjusted HR	0.72 (0.46 – 1.11)		0.64 (0.28 – 1.46)		0.81
Sudden cardiac death					
Events – no. (%)	62 (5.2)	50 (4.3)	14 (7.4)	9 (4.4)	
Event rate per 100 pt. yrs.	3.0 (2.3 – 3.8)	2.4 (1.8 – 3.1)	4.8 (2.8 – 8.0)	2.5 (1.3 – 4.9)	
Unadjusted HR	0.80 (0.55 – 1.16)		0.55 (0.24 – 1.28)		0.41

7.4.7 Safety of mineralocorticoid receptor antagonists according to chronic obstructive pulmonary disease status

Mild hyperkalaemia (potassium >5.5 mmol/L) was more common on an MRA than on placebo in patients with or without COPD although moderate-to-severe hyperkalaemia (potassium >6.0 mmol/L) appeared to be increased by MRA therapy only in patients without COPD (Table 7-9).

Table 7-9 Adverse effects of interest and permanent study drug discontinuation according to randomised treatment and COPD status at baseline

Event	Without COPD		With COPD		
	Placebo (N=1908)	MRA (N=1864)	Placebo (N=304)	MRA (N=321)	*P*-value for interaction
Hypotension					
Events (%)	76 (4.0)	86 (4.6)	10 (3.3)	14 (4.4)	
Unadjusted OR	1.17 (0.85 – 1.60)		1.36 (0.59 – 3.12)		0.76
Creatinine ≥2.5mg/dL					
Events (%)	59 (3.1)	83 (4.5)	6 (2.0)	14 (4.4)	
Unadjusted OR	1.47 (1.05 – 2.08)		2.38 (0.89 – 6.33)		0.39
Creatinine ≥3.0mg/dL					
Events (%)	25 (1.3)	32 (1.7)	3 (1.0)	7 (2.2)	
Unadjusted OR	1.32 (0.78 – 2.24)		2.32 (0.59 – 9.12)		0.47
Potassium >5.5mmol/L					
Events (%)	111 (5.8)	244 (13.1)	22 (7.2)	42 (13.1)	
Unadjusted OR	2.44 (1.93 – 3.08)		1.95 (1.13 – 3.36)		0.44
Potassium >6.0mmol/L					
Events (%)	23 (1.2)	60 (3.2)	9 (3.0)	6 (1.9)	
Unadjusted OR	2.73 (1.68 – 4.43)		0.63 (0.22 – 1.79)		**0.01**
Potassium <3.5mmol/L					
Events (%)	263 (13.8)	130 (7.0)	36 (11.8)	24 (7.5)	
Unadjusted OR	0.47 (0.38 – 0.58)		0.60 (0.35 – 1.04)		0.41
Study Drug Discontinuation (all-cause)					
Events (%)	377 (19.8)	365 (19.6)	64 (21.1)	71 (22.1)	
Unadjusted OR	0.99 (0.84 – 1.16)		1.08 (0.73 – 1.58)		0.73

OR-odds ratio with 95% confidence interval.

Abbreviations: COPD, Chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist.

7.5 Discussion

The prevalence of COPD in this combined RALES and EMPHASIS-HF cohort (14.2%) was similar to that reported in other large-scale HFrEF trials including the Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF; prevalence 12.9%), the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF; prevalence 12.3%) and in a 'real-world' study (the European Society of Cardiology long-term registry; prevalence 14.1%).[24, 38, 201]

As expected, patients with COPD in RALES and EMPHASIS-HF were older and more often male than those without COPD, smoked more (in EMPHASIS-HF) and had more hypertension and atrial fibrillation, although not diabetes, coronary artery disease, or chronic kidney disease.[184, 185, 202, 203] There was also no difference in LVEF or NYHA class between the two groups. Therefore, it was notable that despite these rather modest differences in recognised prognostic factors, participants with COPD were at considerably higher risk of hospitalisation and death, as has been documented in other studies. As anticipated, some of the excess mortality in patients with COPD was due to non-cardiovascular causes, primarily due to infection/sepsis. Interestingly, however, we found a higher risk of sudden death in patients with COPD, compared with those without. We are not aware of a prior report of this finding. It suggests the possibility of a proarrhythmic milieu in patients with COPD related, for example, to beta-2 agonist induced hypokalaemia, methylxanthine and digoxin use, and hypoxaemia, as well as loss of the antiarrhythmic protection of beta-blockers. Interestingly, the excess risk of sudden death (and heart failure hospitalisation) was slightly attenuated by adjustment for baseline beta-blocker use. Concomitant right ventricular dysfunction, which is common in patients with COPD, may further elevate the risk of arrhythmias and sudden death.[180, 181, 195-197]

Indeed, because some patients with COPD cannot tolerate beta-blockers, it is even more important that other treatments are available and shown to be effective in HFrEF patients with concomitant COPD. In fact, MRAs may be particularly suited to

HFrEF patients with COPD. The importance in avoiding hyperkalaemia has already been highlighted. COPD is itself a fluid-retaining state associated with hyperaldosteronism.[86, 181, 187, 188] The harmful effects of hyperaldosteronism in HFrEF are well recognised and aldosterone may also have detrimental effects in the pulmonary vasculature, which is especially relevant given the propensity of patients with COPD to develop pulmonary hypertension.[189-193]

We showed that MRAs have substantial benefits in HFrEF patients with COPD. The proportional risk reductions in all key outcomes were similar to those obtained in HFrEF patients without COPD, with around a 35% relative risk reduction in the primary composite endpoint and a 30% reduction in cardiovascular death. The absolute risk reductions were also large. In both patient subgroups, the number needed to treat to prevent one patient experiencing the primary endpoint was only 10–12 over a median follow-up of approximately 2 years. Our findings appear to refute those of the Danish observational study which reported higher mortality in patients with COPD and right heart failure using spironolactone. While this is likely due to unmeasured or uncorrected confounding in the Danish cohort, the patients in the two studies were different. All patients in RALES and EMPHASIS-HF had HFrEF whereas the patients in the Danish observational study were selected because of a diagnosis of COPD and pulmonary hypertension and treatment with diuretics; approximately 60% had a concomitant diagnosis of heart failure (ejection phenotype not defined).[194]

Finally, MRA therapy was as well tolerated in patients with COPD, as in those without. While severe hyperkalaemia was more common in placebo-treated patients with COPD, compared to those without COPD, severe hyperkalaemia was significantly less common in MRA-treated patients with COPD, compared to those without COPD, potentially due to the ‘protective’ effect of chronic respiratory acidosis, metabolic alkalosis, and corticosteroid therapy or beta-agonist treatment, or both.

Use of MRA in patients with HFrEF has been increasing with rates in patients with COPD, compared with no COPD, of 65.6% vs. 71.8% in DAPA-HF (2019), 54.2% vs. 55.8%

in PARADIGM-HF (2014) and 57.0% vs. 52.3% in the ESC Long-Term Registry (data collected 2011–13).

7.5.1 Translational outlook

Although the exact reasons why patients with HFrEF and concomitant COPD are at such high risk are unknown, these data show the risk of sudden death is particularly elevated, compared to patients without COPD. This may be an area of additional research into other preventive strategies.

7.6 Limitations

This study has several limitations. The analyses conducted were not pre-specified. COPD was investigator-reported, COPD severity was not recorded, and we did not know in whom spirometry had been performed. The patients studied were selected for a clinical trial and will differ from those in ordinary every-day practice. Biomarkers and quality of life data were not collected, and smoking status was only documented in EMPHASIS-HF (and not in RALES).

7.7 Conclusion

This analysis highlights the importance of MRA therapy in HFrEF patients with COPD. In the RALES and EMPHASIS-HF trials, one-in-seven patients with HFrEF had coexisting COPD. Patients with HFrEF and concomitant COPD had much worse outcomes but the benefit of MRA therapy was consistent across all morbidity and mortality outcomes examined, regardless of COPD status.

Chapter 8 Summary

The six publications comprising this thesis collectively expand our understanding of the effect of SGLT2 inhibitors, ARNI and MRAs on clinical symptoms, worsening heart failure events and mortality outcomes, and their action on sodium and water imbalance in patients with acute and chronic heart failure. Recent heart failure guidelines emphasise the importance of early initiation and optimisation of evidence-based medical therapies, with various proposed rapid and simultaneous sequencing strategies.[1, 204-207] Our findings in the DAPA-RESIST clinical trial support the use of SGLT2 inhibitors as an additional diuretic agent in combination with intravenous loop diuretics to augment diuresis and decongestion in patients with heart failure who are resistant to loop diuretics. The SGLT2i inhibitor dapagliflozin provides a comparable decongestive effect to the thiazide-like diuretic metolazone, albeit with higher diuretic doses required, as evidenced by weight loss, lung decongestion, overall decongestion (modified ADVOR clinical congestion score) and clinical symptoms, with a more favourable safety profile throughout the 96-hour study period. As of yet, there are no other clinical trials studying SGLT2 inhibitors in patients with diuretic-resistant heart failure extending beyond this study treatment period. However, there have been acute heart failure trials showing the clinical benefit of SGLT2 inhibitors such as the EMPA-RESPONSE-AHF clinical trial which had a study treatment period of 30 days, and the EMPULSE clinical trial which had a study treatment period of 90 days, as well as the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) in patients hospitalised with worsening heart failure for which the median duration of treatment was 7.8 months.[43, 91, 106] The short-term initiation of a second diuretic agent such as metolazone, or acetazolamide as per the ADVOR clinical trial, or hydrochlorothiazide in the CLOROTIC clinical trial, has not been shown to reduce hospital length of stay or confer longer-term improved mortality or rehospitalization outcomes. This supports the argument for earlier initiation of an SGLT2 inhibitor even in diuretic resistant heart failure patients, and subsequent continuation of this treatment throughout the remainder of the HF admission and after hospital discharge, as

opposed to using an alternative second diuretic agent and switching this therapy to an SGLT2 inhibitor thereafter.[43, 71, 208-210]

The effect of SGLT2 inhibitors on renal sodium and water handling is complex and poorly understood on a tubular level in patients with heart failure. We investigated the effects of SGLT2 inhibitors on sodium levels in a post-hoc analysis of the DAPA-HF clinical trial and on sodium levels and urinary sodium excretion in the DAPA-RESIST clinical trial. In DAPA-RESIST, patients randomised to dapagliflozin achieved comparable diuresis with significantly lower natriuresis over the 96-hour study period. Patients randomised to dapagliflozin were significantly less likely to develop decreases in serum sodium levels over the 96-hour study period compared to patients randomised to metolazone. Over the longer term, our post-hoc analysis of hyponatraemia in the DAPA-HF trial has shown a small and transient decline in serum sodium at day-14 of dapagliflozin therapy, which fully reversed thereafter. Notably, focusing on patients with pre-existing hyponatraemia in this analysis, dapagliflozin resulted in a more marked and consistent improvement in serum sodium compared to placebo. Neither DAPA-HF nor DAPA-RESIST are mechanistic studies. However, these findings correspond with new studies on SGLT2 inhibitors and sodium handling on a renal tubular level.[211] Alongside inhibition of the sodium/glucose cotransporter 2, SGLT2 inhibitors result in inhibition of the sodium-hydrogen exchanger 3 (NHE3) in the proximal renal tubules thus inhibiting sodium reabsorption in the acute period. However, there is rapid tubular compensation resulting in increased sodium reabsorption in the loop of Henle and distal nephron, thus preserving the biochemical safety profile of SGLT2 inhibitors.[211] The diuretic benefit of dapagliflozin beyond the 96-hour study treatment period was not directly assessed in DAPA-RESIST. However current early evidence points towards a maintenance of euvolaemia and fluid homeostasis with lower RAAS and sympathetic nervous system activation in patients on SGLT2i. [49, 212-217]

Future areas of research should include the diuretic effect and long-term outcomes of SGLT2 inhibitors over a longer study treatment period in patients with diuretic-

resistant heart failure. Furthermore, during recruitment for the DAPA-RESIST clinical trial, we identified that a significant proportion (18.5%) of patients with diuretic resistance who underwent screening, had to be excluded due to pre-existing SGLT2 inhibitor and/or thiazide diuretic use. Due to the evident benefits of SGLT2 inhibitors in HF clinical trials across the spectrum of left ventricular ejection fraction and the current HF, diabetes and kidney disease guidelines recommendations, we would expect a rising proportion of these patients to be prescribed SGLT2 inhibitors in the near future.[1, 39, 41, 218] This will be reflected in the higher proportion of patients admitted with HF who are already on SGLT2 inhibitors despite their lower risk of worsening HF events including HF hospitalisations, some of whom may develop diuretic resistance despite SGLT2 inhibitor and high-dose loop diuretic therapy. Therefore, this raises the question as to whether research is needed into the safety and efficacy of combining a third diuretic agent such as a thiazide or thiazide-like diuretic, acetazolamide, a vasopressin receptor antagonist or dopamine in patients with diuretic-resistant heart failure with insufficient diuresis despite loop diuretics and an SGLT2 inhibitor. SGLT2 inhibitors inhibit both SGLT2 and NHE3 in the proximal tubule. Loop diuretics act on the sodium-potassium-chloride co-transporter in the thick ascending limb of the loop of Henle. Theoretically, inhibiting a third and more distal site on the nephron may further augment diuresis and natriuresis by blocking downstream counterregulatory sodium and water reabsorption. Acetazolamide would not be a sensible third diuretic therapy, as it inhibits carbonic anhydrase, which then inhibits NHE3 in the proximal tubules similarly to SGLT2 inhibitors. Thiazide or thiazide-like diuretics act on the distal convoluted tubule and collecting duct while vasopressin receptor antagonists act primarily on the collecting ducts and dopamine acts on dopamine receptors throughout the nephron. Hence, these three drug classes could be considered for further research as a third diuretic agent. However, we recognise that this cohort comprises a small and difficult to manage subset of HF patients who are usually multi-morbid, which would complicate study recruitment.

I have discussed the role of neurohormonal activation in sodium and water retention driving the pathophysiology of heart failure, including upregulation of the renin-angiotensin-aldosterone system, sympathetic nervous system, natriuretic peptides

and vasopressin which provide pharmacologic targets for heart failure therapies. Endothelin-1 (ET-1) is another neurohormonal biomarker which is thought to have diuretic, natriuretic and vasoconstrictive effects, and is associated with poorer outcomes, but is less well-understood.[22, 23, 85] In clinical trials, endothelin receptor antagonists (ERA) had deleterious effects in heart failure by causing worsening fluid retention.[141-143] Our analysis of ET-1 in the DAPA-HF trial confirms the prognostic role or ET-1 in HF patients, i.e., an elevated risk of heart failure and mortality outcomes with higher ET-1 levels, and a higher risk of renal dysfunction and decline in renal function in these patients. The relationship between endothelin-1 and kidney function decline could be explained by the vasoconstrictive effect of ET-1 and ET-1 induced renal tubular stress and apoptosis, as well as podocyte dysfunction which causes proteinuria.[145, 219] Proteinuria, renal impairment and worsening renal function are known independent risk factors for mortality in patients with heart failure.[220, 221] In our analysis, we demonstrated the persisting elevated risk of worsening HF events, cardiovascular mortality and all-cause mortality in patients with higher ET-1 levels even after adjustment for prognostic variables including estimated glomerular filtration rate, but urinary albumin was not collected in DAPA-HF, hence it was not included in this risk adjustment. We also demonstrate a small but statistically significant reduction in ET-1 levels with dapagliflozin compared to placebo which could be due to direct inhibition of ET-1 secretion at the proximal renal tubules by the SGLT2 inhibitor, or by indirect improvement in the HF patient and overall congestive state.[130] SGLT2 inhibitors have been shown to slow down the progression of renal dysfunction in patients with chronic kidney disease in the DAPA-CKD trial, patients with HFrEF in DAPA-HF and EMPEROR-Reduced clinical trials, and patients with HFpEF in the DELIVER and EMPEROR-Preserved trials.[16, 36, 40, 42, 222] Hence, it stands to reason the hypothesis that combined ERA and SGLT2 inhibition may have greater, and possibly additive, renal benefits whilst counteracting the sodium and fluid retention caused by ERA therapy. ZENITH-CKD is a recent phase 2b clinical trial of the ERA zibotentan combined with the SGLT2 inhibitor dapagliflozin in patients with CKD. Zibotentan plus dapagliflozin significantly reduced urinary albumin excretion with comparable fluid retention events in the low-dose group compared with placebo plus dapagliflozin.[223] The findings from ZENITH-CKD will be further

evaluated in a phase 3 clinical trial (ZENITH High Proteinuria) to investigate the efficacy and safety of zibotentan plus dapagliflozin in reducing the risk renal dysfunction in patients with CKD and proteinuria. Patients with symptomatic or clinical HF are presently excluded from these combined ERA/SGLT2 inhibitor trials, but this two-pronged cardiorenal approach remains an area of interest for potential future HF therapy.

Although early and rapid optimisation of all four pillars of HF therapy, namely beta-blockers, ARNIs, MRAs and SGLT2 inhibitors are recommended in an ideal clinical scenario, we recognise that this may not be possible in real-world clinical practice for a variety of reasons including health care system factors, local resource-allocation, clinician factors and clinical inertia, together with patient factors including adherence, comorbidities and side effects including worsening renal function and hypotension.[207, 224-227] Our post-hoc analyses of the DAPA-HF and PARADIGM-HF clinical trials show no diminution in benefits of dapagliflozin and sacubitril/valsartan in patients who have had HF for a long time, with therapy being safe and well-tolerated, and even leading to a larger absolute risk reduction in such patients. There is much work to be done in improving the health system infrastructure for timely guideline-directed medical therapy (GDMT) implementation and adherence, including future areas of research into real-world GDMT practices, barriers for success and longitudinal data on patient outcomes across different countries, as well as the role of digital health technology.[228-230] However, in the meantime, our findings provide hope that, it is never too late to start and optimise HF treatments to obtain their substantial therapeutic benefit. Furthermore, our analysis of HFrEF patients with COPD in the EMPHASIS-HF and RALES clinical trials provide insight into the impact of comorbidities, in this case COPD, on clinical outcomes, limitations of GDMT implementation and adherence with low beta blocker prescription rates in these patients, and the benefits obtained by MRA therapy despite these factors. We demonstrated that HFrEF patients with COPD were significantly less likely to be on beta-blocker therapy, and had significantly higher risk of all-cause mortality and hospitalisation even after accounting for beta-blocker therapy. The lower rates of beta-blocker use in COPD patients could be due to

physician and patient factors including perceived and/or true side-effects of bronchospasm and COPD exacerbations.[186, 231] Also, COPD in itself causes sympathetic nervous system, RAAS and natriuretic peptide activation which results in fluid retention, a condition that is further aggravated by corticosteroid therapy which is part of treatment for COPD exacerbations.[86, 187, 188] In our analysis, MRA therapy was well-tolerated in patients with COPD and improved all mortality and hospitalisation outcomes studied, with similar relative risk reduction in HFrEF patients with COPD as without. This emphasises the importance of MRA therapy in HFrEF patients with COPD, especially in patients intolerant to other HFrEF therapies. Future research should be performed on the impact and prognosis of various significant comorbidities using longitudinal data in a contemporary cohort of heart failure patients and the effect of GDMT on clinical outcomes.

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Appendix

1. DAPA-RESIST Eligibility Criteria

Inclusion criteria

- Male or female ≥18 years of age
- Informed consent
- Primary reason for ongoing hospital admission is worsening HF meeting the European Society of Cardiology (ESC) definition.[14]
- Diuretic Resistance as defined as: Lack of weight loss (decrease <1kg) or insufficient negative fluid balance (decrease <1 litre) over prior 24 hours despite treatment with high dose IV loop diuretic (equivalent of ≥160mg IV furosemide in 24 hours)
- Plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL in current hospital admission
- Ongoing clinical evidence of congestion: pitting peripheral oedema and/or ascites and/or elevated jugular venous pressure, and/or radiographic or ultrasonic evidence of pulmonary congestion
- Expected hospital length of stay >3 days

Exclusion criteria

- Inability to give informed consent e.g. due to significant cognitive impairment
- Intravascular volume depletion based on investigator's clinical assessment
- Type 1 Diabetes Mellitus
- eGFR <20 mL/min/1.73 m^2
- Alternative explanation for worsening renal function such as obstructive nephropathy, contrast induced nephropathy, or acute tubular necrosis
- Enrollment in another randomised clinical trial involving medical or device-based interventions (co-enrolment in observational studies is permitted)
- Women of child-bearing potential. For the purposes of this trial, this means any woman aged <60 years unless they have had a hysterectomy or bilateral tubal ligation or are aged >50 years and have undergone the menopause and had amenorrhea for at least 3 years
- History of allergy to SGLT2i or thiazide or thiazide-like diuretics or any of the excipients
- Hypertrophic obstructive cardiomyopathy (HOCM) or significant valvular disease in whom surgical or percutaneous repair or replacement may be considered.
- SGLT2i, thiazide or thiazide-like diuretics administration in the previous 48 hours prior to randomisation
- Active genital tract infections
- Anyone who, in the investigators' opinion, is not suitable to participate in the trial for other reasons

2. Lung Ultrasound

Lung ultrasound (LUS) examinations were performed using a Philips Lumify ultrasound machine with a phased-array transducer in sagittal orientation at an imaging depth of 18 cm with patients in semi-recumbent position. Patients were assessed with an 8-zone imaging protocol (4 zones on each hemithorax), in addition to examination of pleural effusions laterally at the level of the diaphragm. LUS methods and results are reported according to previously published recommendations.[232]

B-line quantification

Six second video clips were recorded for each zone and offline image analysis was performed centrally at a core imaging laboratory by investigators with experience in LUS analysis. The highest number of B-lines visualized in one intercostal space was quantified in a freeze frame after review of the entire clip for each zone and the sum of B-lines across 8 zones was used for all analyses. In patients with missing B-line data in ≤2 out of 8 zones we imputed B-line data from anatomically adjacent zones: Zones 1 and 2, zones 3 and 4, zones 5 and 6, zones 7 and 8s previously described.[89, 233] The imputed B-line data were used for all main analyses. In sensitivity analyses, results for the secondary efficacy endpoint were similar when using imputed (n=56) vs. non-imputed (n=40) B-line data. When excluding patients with conditions that can impact B-line count (e.g. interstitial lung disease, pneumonia) which were reported in 2 patients in the dapagliflozin group and in 6 patients in the metolazone group, results were similar for the secondary efficacy endpoint. Per protocol, all primary analyses were performed in the Full Analysis Set.

Pleural effusion score

The score for pleural effusion size for use in modified ADVOR score was the sum of pleural effusion scores from both hemi-diaphragms. Pleural effusion size was scored using the following: 0 = No pleural effusion visible; 1 = pleural effusion only visible in the costophrenic angle; 2 = pleural effusion extends over the costophrenic angle without a clear separation of the lung base from the diaphragm; 3 = Clear separation between diaphragm and lung base at any point during the respiratory; 4 = pleural effusion occupies more than 50% of the basal

pleural cavity visible in the standardised imaging plane cycle. In patients with missing pleural effusion data, imputation was performed by using multiple imputation with chained equations (MICE). Ten imputed datasets were created, using predictive mean matching. Mean values at baseline, mean changes from baseline, and model-derived estimates of between-group differences were extracted from each imputed dataset and combined using Rubins's rules. Imputed pleural effusion data were used for all main analyses. The pleural effusion score ranged from 0-4 on each hemi-diaphragm, hence the final score (sum) ranged from 0-8.[90]

- Final score 0 = score 0 for pleural effusion on the Modified ADVOR score

- Final score 1-4 = score 2 for pleural effusion (minor pleural effusion) on the Modified ADVOR score

- Final score 5-8 = score 3 for pleural effusion (major pleural effusion) on the Modified ADVOR score