ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3294

SHORT REPORT

Balcinrenone plus dapagliflozin in patients with heart failure and chronic kidney disease: Results from the phase 2b MIRACLE trial

Carolyn S.P. Lam[1]*, Lars Køber[2], Koichiro Kuwahara[3], Lars H. Lund[4], Patrick B. Mark[5], Linda G. Mellbin[4], Morten Schou[6], Patricia Ely Pizzato[7], Anders Gabrielsen[8], Samvel B. Gasparyan[9], Alessandro Ghiretti[9], Judith Hartleib-Geschwindner[10], Greggory J. Housler[7], Paolo Fanti[11], Maria Leonsson-Zachrisson[10], John J.V. McMurray[5], and Scott D. Solomon[12], for the MIRACLE Study Investigators

[1]National Heart Centre, Singapore & Duke-National University of Singapore, Singapore, Singapore; [2]Rigshospitalet, Heart Centre, Copenhagen, Denmark; [3]Shinshu University School of Medicine, Department of Cardiovascular Medicine, Matsumoto, Japan; [4]Karolinska University Hospital, Stockholm, Sweden; and Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [5]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [6]Department of Cardiology, Herlev Hospital, Herlev, Denmark; [7]Early Clinical Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; [8]Early Clinical Development, Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D AstraZeneca, Gothenburg, Sweden; [9]Biometrics, Late Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D AstraZeneca, Gothenburg, Sweden; [10]Late-stage Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D AstraZeneca, Gothenburg, Sweden; [11]Clinical Development, Late Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; and [12]Harvard Medical School, Boston, MA, USA; Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA

Received 19 April 2024; revised 5 May 2024; accepted 6 May 2024

Aims Many patients with heart failure (HF) have chronic kidney disease (CKD) and may not tolerate mineralocorticoid receptor antagonists. We investigated the efficacy and safety of the novel mineralocorticoid receptor modulator balcinrenone in combination with dapagliflozin in a phase 2b study.

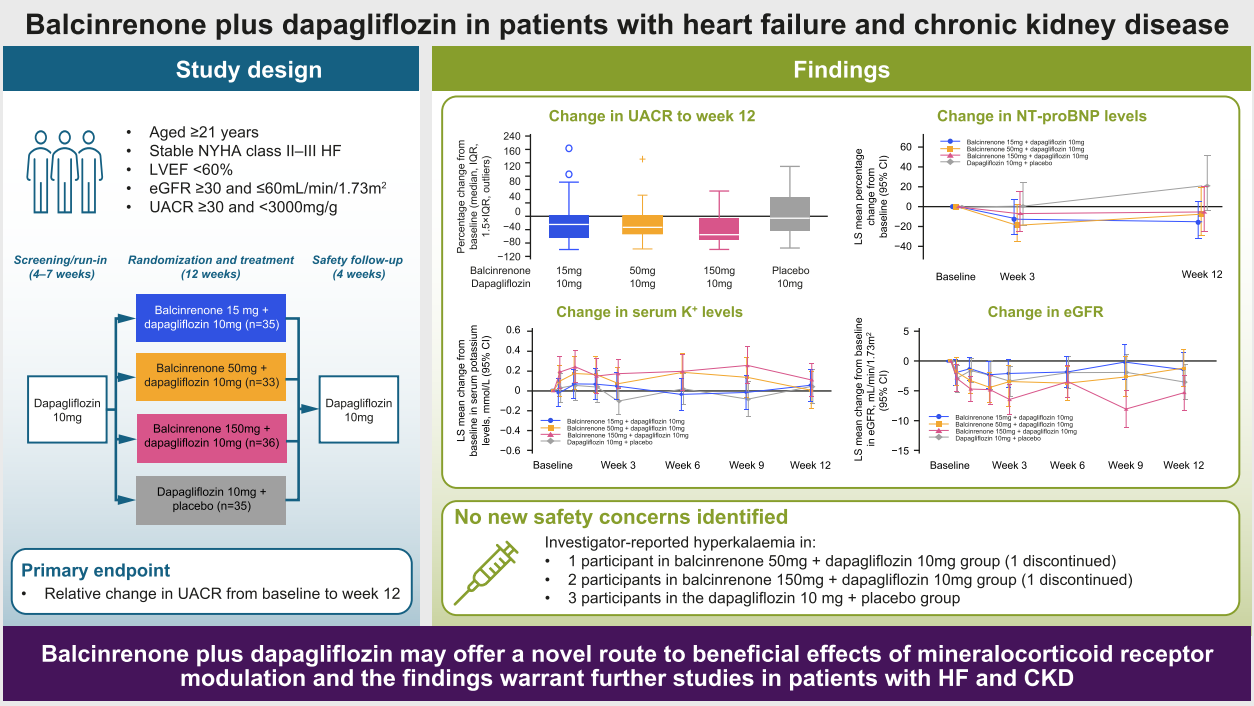
Methods and results From January 2021 to October 2023, we randomized 133 adults with symptomatic HF, ejection fraction <60%, estimated glomerular filtration rate (eGFR) ≥30 to ≤60 ml/min/1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) ≥30 to <3000 mg/g, to receive balcinrenone 15, 50 or 150 mg/day plus dapagliflozin 10 mg/day, or dapagliflozin 10 mg/day plus placebo, for 12 weeks. Enrolment was stopped early because of slow recruitment. Relative reductions in UACR from baseline to week 12 (primary endpoint) were not significantly different between the balcinrenone plus dapagliflozin groups versus dapagliflozin plus placebo. There was no clear balcinrenone dose–response relationship. There were possible dose-dependent increases in serum potassium levels, reduced eGFR in the highest dose group, and non-significant trends towards reduced N-terminal pro-B-type natriuretic peptide levels. Hyperkalaemia adverse events led to discontinuation in two participants receiving balcinrenone plus dapagliflozin and none in those receiving dapagliflozin plus placebo.

Conclusion While the smaller than planned sample size limits interpretation, we did not see significant reduction in UACR in patients treated with balcinrenone plus dapagliflozin compared with dapagliflozin plus placebo.

*Corresponding author. National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609, Singapore. Tel: +65 67048965. Fax: +65 68449069, Email: carolyn.lam@duke-nus.edu.sg

Greggory J. Housler and Anders Gabrielsen: 'Affiliation at the time this research was carried out'

Graphical Abstract



Mineralocorticoid receptor antagonists are a mainstay of treatment in patients with heart failure (HF) with reduced ejection fraction, but are underused in those who also have chronic kidney disease (CKD). Balcinrenone is a novel mineralocorticoid receptor modulator that may reduce the risk of hyperkalaemia. MIRACLE was an international, randomized, double-blind phase 2b trial that aimed to investigate the efficacy and safety of three different doses of balcinrenone plus dapagliflozin compared with dapagliflozin plus placebo in patients with HF (left ventricular ejection fraction [LVEF] <60%) and CKD. Enrolment was terminated early because of slow recruitment and the planned statistical power was not achieved. For the primary endpoint, reductions in relative change in urinary albumin-to-creatinine ratio (UACR) from baseline to week 12 were not significantly different between the balcinrenone plus dapagliflozin groups versus dapagliflozin plus placebo. There was no clear balcinrenone dose–response relationship. There were possible dose-dependent increases in serum potassium levels, reduced estimated glomerular filtration rate (eGFR) in the highest dose group, and non-significant trends towards reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Investigator-reported hyperkalaemia adverse events occurred in 3/98 participants (3.1%) receiving balcinrenone plus dapagliflozin (two participants discontinued) and in 3/33 (9.1%) receiving dapagliflozin plus placebo. These findings support further clinical investigation of mineralocorticoid receptor modulation in patients with HF and CKD. CI, confidence interval; IQR, interquartile range; LS, least-squares; NYHA, New York Heart Association.

Keywords Heart failure • Chronic kidney disease • Mineralocorticoid receptor • Balcinrenone • Dapagliflozin • Urinary albumin-to-creatinine ratio

Introduction

In patients with heart failure (HF), concomitant renal dysfunction is common and negatively affects prognosis and complicates HF treatment.[1] Although mineralocorticoid receptor (MR) antagonists are a foundational therapy for HF with reduced ejection fraction, they are substantially underused in patients with chronic kidney disease (CKD)[2] and are not recommended in those with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2.[3,4] Balcinrenone (previously AZD9977) is a selective MR modulator with partial antagonist activity due to its distinct interaction with the receptor, and potential to separate organ-protective effects from urinary electrolyte excretion.[5] Balcinrenone may offer advantages in patients with HF and CKD who are already receiving standard-of-care treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors (e.g. dapagliflozin). We present the results of MIRACLE (MIneRAlocorticoid reCeptor moduLator and sodium–glucosE cotransporter 2 inhibitor in HF and CKD), an international, randomized, double-blind, phase 2b trial of the efficacy and safety of balcinrenone and dapagliflozin in patients with HF and CKD.

The 12-week MIRACLE study aimed to assess the effect of balcinrenone plus dapagliflozin on urinary albumin-to-creatinine ratio (UACR) compared with dapagliflozin plus placebo (primary

objective); to assess the dose–response relationship of three doses of balcinrenone (15, 50 or 150 mg/day) plus dapagliflozin 10 mg/day with UACR effects (secondary objective); and to assess safety and tolerability of balcinrenone plus dapagliflozin (safety objective). See online supplementary *Table S1* for complete objectives.

Methods

The study was conducted at 160 sites in Asia, Europe and North America from January 2021 to October 2023, in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and local regulations with independent ethical review board approval at each site. The study was sponsored by AstraZeneca (ClinicalTrials.gov NCT04595370). A protocol amendment removed study arms not involving dapagliflozin in response to HF guideline updates.[3,4]

Patients

Eligible patients were aged ≥21 years with New York Heart Association (NYHA) class II–III HF, left ventricular ejection fraction (LVEF) <60%, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels ≥300 pg/ml (≥600 pg/ml in those with atrial fibrillation/flutter), CKD (eGFR ≥30 to ≤60 ml/min/1.73 m^2),[6] serum potassium levels ≥3.5 and <5.0 mmol/L and centrally assessed UACR ≥30 to <3000 mg/g (online supplementary *Table S2*). All patients provided written informed consent.

Procedures

Following a 1-week screening period, eligible patients underwent a 4–7-week dapagliflozin run-in, with those already receiving SGLT2 inhibitors switching to dapagliflozin. Participants were then randomized 1:1:1:1 to oral dapagliflozin 10 mg/day plus oral balcinrenone 15, 50 or 150 mg/day, or matching placebo. Randomization was stratified by type 2 diabetes (yes or no) and eGFR (≥30 to <45, or ≥45 ml/min/1.73 m^2). Participants, investigators, study staff and the sponsor were blinded to study treatment. Participants attended clinic visits at screening; run-in; before and at randomization (baseline); on day 3 and the end of weeks 1, 2, 3, 6, 9 and 12 (end of treatment); and end of follow-up (online supplementary *Figure S1*).

Endpoints

The primary endpoint was relative change in UACR from baseline to week 12, with dose–response assessment as a secondary objective (see online supplementary *Methods* for detail). Safety endpoints included adverse events (AEs), safety laboratory assessments (including change in serum potassium and eGFR), safety topics of interest (hyperkalaemia, hypotension and deteriorating kidney function), vital signs and electrocardiography. Serum potassium levels were analysed centrally and locally according to pre-specified confirmatory methods and thresholds at all study visits. Exploratory endpoints included NT-proBNP levels and aldosterone levels (target engagement).

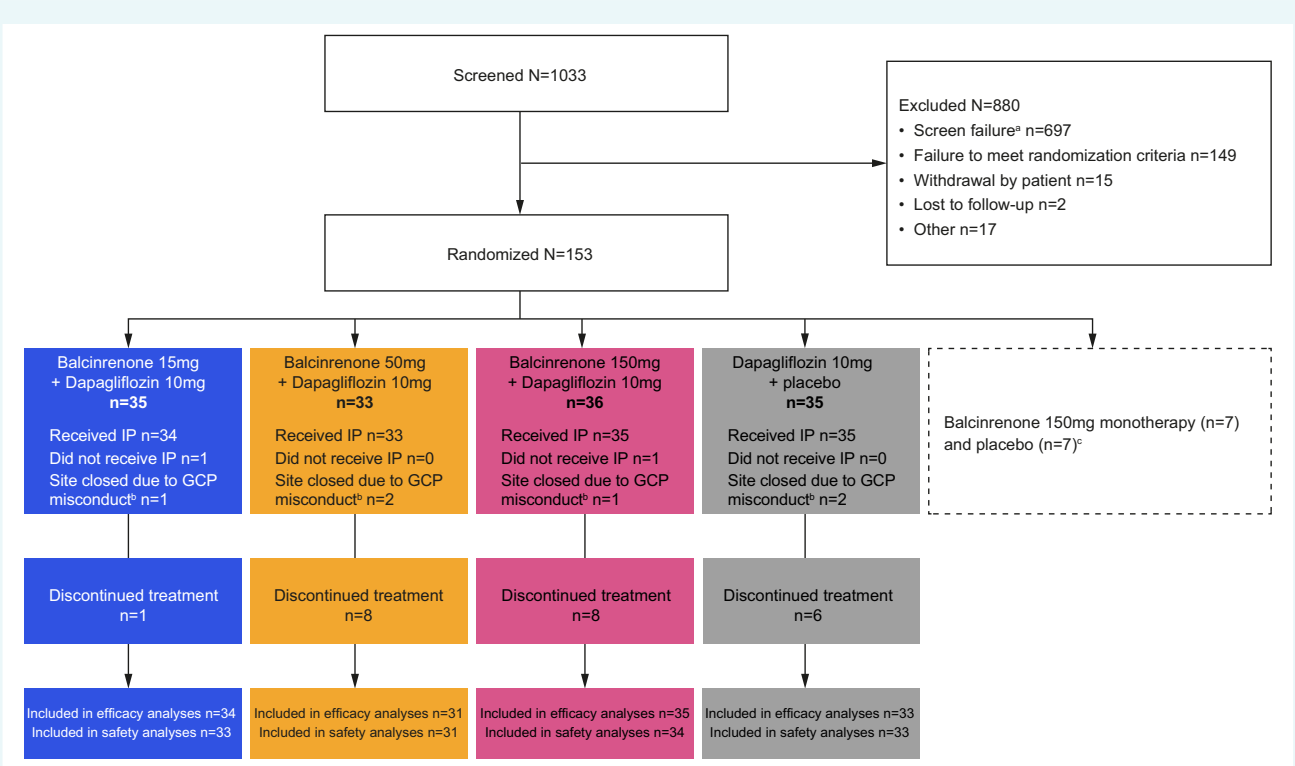


Figure 1 Participant disposition and analysis sets. GCP, Good Clinical Practice; IP, investigational product. [a]The most frequent reasons for participants not meeting the screening or randomization criteria were estimated glomerular filtration rate, urinary albumin-to-creatinine ratio or N-terminal pro-B-type natriuretic peptide levels outside the required ranges. [b]Decision to exclude patients at sites closed owing to GCP misconduct from analyses made during study and before unblinding. [c]Balcinrenone 150 mg monotherapy and placebo groups dropped by protocol amendment; patients in these groups were not included in the presented efficacy or safety analyses.

European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

Statistical methods

The planned sample size of ~500 (125/arm) provided 80% power to detect at least 30% relative reduction in UACR compared with dapagliflozin plus placebo ($\alpha = 0.05$), assuming 5% drop-out. Efficacy analyses were to include all randomized participants, according to intended treatment. Safety and pharmacodynamic analyses were to include all participants who received study drug, according to treatment received. In the pre-specified primary efficacy analysis, a mixed model for repeated measures was applied to the change from baseline in log-transformed UACR with treatment and visit as fixed effects, baseline log-transformed UACR, cohort variable and stratification factors as covariates, and treatment-by-visit as an interaction term (online supplementary *Methods*). Exploratory endpoints and *post hoc* analyses were considered hypothesis-generating.

Results

Participants

Study enrolment was terminated early owing to slow recruitment. Of 1033 patients screened, 153 were randomized into the initial six study arms. After excluding 14 patients in the two removed study arms without dapagliflozin and another 6 patients from two sites with GCP misconduct, 133 were included in efficacy analyses and 131 in safety analyses related to the four remaining treatment arms (*Figure 1*). Mean LVEF was 46%, median eGFR was 39.7 ml/min/1.73 m^2, and median UACR was 103.4 mg/g. Demographics and baseline characteristics were generally balanced among groups (*Table 1*).

Efficacy

Primary and secondary endpoints

Descriptive unadjusted geometric mean percentage changes in UACR from baseline to week 12 were −54.9% in the balcinrenone 15 mg plus dapagliflozin group, −52.5% in the balcinrenone 50 mg plus dapagliflozin group, −47.6% in the balcinrenone 150 mg plus dapagliflozin group, and −29.9% in the dapagliflozin plus placebo group. For the primary endpoint, reductions in UACR from baseline to week 12 were not significantly different in the balcinrenone 15, 50 and 150 mg plus dapagliflozin groups versus the dapagliflozin plus placebo group. Dapagliflozin-plus-placebo-adjusted geometric mean percentage changes in UACR from baseline to week 12 were −33.6% (95% confidence interval [CI] −62.5,+17.6) in the balcinrenone 15 mg group, −11.8% (−52.2,+62.6) in the 50 mg group, and −36.1% (−64.9,+16.1) in the 150 mg group (*Figure 2A*). Median changes in UACR from baseline to week 12 for the three

Table 1 Baseline demographics and characteristics

	Balcinrenone 15 mg + dapagliflozin 10 mg (*n* = 34)	Balcinrenone 50 mg + 10 mg dapagliflozin (*n* = 31)	Balcinrenone 150 mg + dapagliflozin 10 mg (*n* = 35)	Dapagliflozin 10 mg + placebo (*n* = 33)
Age, years, mean (SD)	70.9 (7.1)	72.4 (8.4)	73.7 (8.1)	72.2 (9.4)
Female sex, *n* (%)	11 (32.4)	5 (16.1)	8 (22.9)	10 (30.3)
Race, *n* (%)				
Asian	4 (11.8)	3 (9.7)	7 (20.0)	3 (9.1)
Black/African American	0	1 (3.2)	1 (2.9)	2 (6.1)
White	30 (88.2)	27 (87.1)	27 (77.1)	28 (84.8)
Type 2 diabetes, *n* (%)	22 (64.7)	21 (67.7)	22 (62.9)	22 (66.7)
NYHA functional class, *n* (%)				
I	0	0	1 (2.9)	0
II	25 (73.5)	19 (61.3)	27 (77.1)	26 (78.8)
III	9 (26.5)	12 (38.7)	7 (20.0)	7 (21.2)
Systolic blood pressure, mmHg, mean (SD)	128.7 (15.8)	132.3 (14.1)	135.0 (15.8)	130.9 (15.6)
Atrial fibrillation, *n* (%)	17 (50.0)	16 (51.6)	27 (77.1)	20 (60.6)
eGFR, ml/min/1.73 m^2, mean (SD)	41.9 (13.1)	38.6 (10.2)	43.6 (15.9)	42.2 (12.7)
UACR, mg/g, median (range)	64 (2.4–2216)	138 (14–2355)	64 (18–773)	109 (7.2–1696)
Serum potassium, mmol/L, mean (SD)	4.60 (0.38)	4.44 (0.61)	4.43 (0.45)	4.51 (0.46)
LVEF, %, mean (SD)	44 (9)	46 (10)	48 (8)	46 (9)
Serum NT-proBNP, pg/ml, median (range)	1594 (71–17 136)	1109 (72–12 610)	1329 (212–10 900)	984 (213–11 460)
Previous/concomitant medication, *n* (%)				
ACE inhibitor	13 (38.2)	10 (32.3)	11 (31.4)	14 (42.4)
ARB	7 (20.6)	11 (35.5)	15 (42.9)	12 (36.4)
ARNI	6 (17.6)	7 (22.6)	7 (20.0)	4 (12.1)
β-blocker	24 (70.6)	21 (67.7)	28 (80.0)	19 (57.6)
Loop diuretic	32 (94.1)	29 (93.5)	35 (100.0)	32 (97.0)
SGLT2 inhibitor[a]	10 (29.4)	11 (35.5)	10 (28.6)	13 (39.4)

Data are from all randomized participants analysed according to intended treatment ($n = 133$), excluding those randomized to discontinued treatment arms (see online supplementary *Figure S1*). Participants from sites where there were breaches of Good Clinical Practice were also excluded (see online supplementary *Figure S1*).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2; UACR, urinary albumin-to-creatinine ratio.
[a]Previous only.

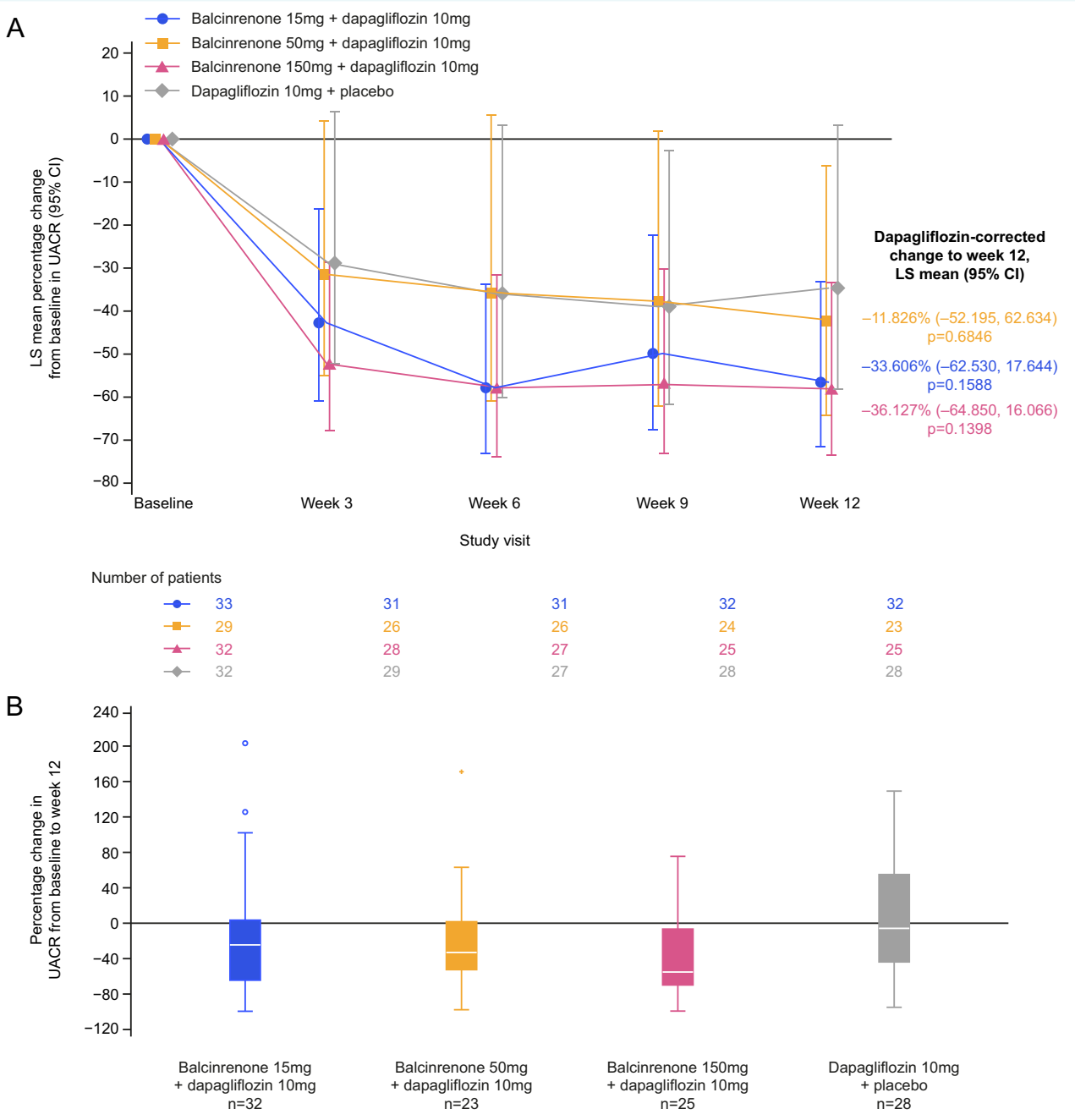


Figure 2 Change from baseline in urinary albumin-to-creatinine ratio (UACR): (*A*) pre-specified primary endpoint analysis and (*B*) observed values. Data in (*A*) are from a mixed model repeated measures of the change from baseline in log-transformed UACR with fixed factors of treatment, visit, type 2 diabetes (yes/no), estimated glomerular filtration rate (≥30 to <45, or ≥45 ml/min/1.73 m^2) and treatment-by-visit interaction, plus covariates of log-transformed baseline value and protocol amendment cohort (before or after removal of non-dapagliflozin groups). Data in (*B*) are observed values for percentage change from baseline in UACR from baseline to week 12. Lines represent median, boxes represent interquartile range (IQR), whiskers represent 1.5 × IQR (excluding outliers) and symbols indicate outliers. Balcinrenone 15 mg: median −24.5 (IQR: −64.4,+3.5; 1.5 × IQR: −99.4,+102.1). Balcinrenone 50 mg: median −33.1 (IQR: −52.5,+1.7; 1.5 × IQR: −97.7,+63.1). Balcinrenone 150 mg: median − 55.1 (IQR: −69.8,−6.6; 1.5 × IQR: −99.2,+75.5. Dapagliflozin alone: median −5.8 (IQR −43.8,+55.0; 1.5 × IQR: −95.0,+149.2). In (*A*) and (*B*), geometric changes are expressed as percentage changes by back-transformation from the log scale. Baseline was defined as the geometric mean of three values from first morning void urine samples collected on 3 consecutive days (ideally day of visit and preceding 2 days). CI, confidence interval; LS, least-squares.

European Journal of Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.

Table 2 Adverse events

	Balcinrenone 15 mg + dapagliflozin 10 mg (*n* = 33)	Balcinrenone 50 mg + dapagliflozin 10 mg (*n* = 31)	Balcinrenone 150 mg + dapagliflozin 10 mg (*n* = 34)	Dapagliflozin 10 mg + placebo (*n* = 33)
Any adverse event, *n* (%)	9 (27.3)	12 (38.7)	18 (52.9)	14 (42.4)
Possibly related to study drug	1 (3.0)	2 (6.5)	5 (14.7)	4 (12.1)
Leading to study drug discontinuation	0	4 (12.9)	3 (8.8)	1 (3.0)
Leading to study withdrawal	0	5 (16.1)	2 (5.9)	1 (3.0)
Serious adverse event, *n* (%)	1 (3.0)[a]	3 (9.7)[b]	2 (5.9)[c]	4 (12.1)[d]
Death	0	2 (6.5)	0	1 (3.0)
Adverse events in ≥2 participants overall, *n* (%)				
Hyperkalaemia	0	1 (3.2)	2 (5.9)	3 (9.1)
CKD	1 (3.0)	1 (3.2)	2 (5.9)	1 (3.0)
Urinary tract infection	0	1 (3.2)	1 (2.9)	3 (9.1)
Glomerular filtration rate decreased	1 (3.0)	1 (3.2)	1 (2.9)	1 (3.0)
Nasopharyngitis	0	0	3 (8.8)	1 (3.0)
Urinary tract infection bacterial	0	2 (6.5)	1 (2.9)	0
Anaemia	0	1 (3.2)	1 (2.9)	1 (3.0)
Atrial fibrillation	1 (3.0)	0	1 (2.9)	1 (3.0)
Fall	0	0	1 (2.9)	2 (6.1)
Cardiac failure	0	1 (3.2)	1 (2.9)	0
Diarrhoea	0	0	2 (5.9)	0
Hypertensive crisis	0	0	2 (5.9)	0
Muscle spasms	1 (3.0)	0	1 (2.9)	0
Nausea	0	0	2 (5.9)	0
Contusion	0	1 (3.2)	0	1 (3.0)
Gout	0	1 (3.2)	0	1 (3.0)
Adverse events in safety topics of interest, *n* (%)				
Deteriorating renal function	1 (3.0)[e]	3 (9.7)[f]	3 (8.8)[g]	2 (6.1)[h]
Hyperkalaemia	0	1 (3.2)[i]	2 (5.9)[i]	3 (9.1)[i]
Hypotension	0	0	2 (5.9)[j]	0

Adverse events with onset or worsening on the day of or after first dose of study drug and within 28 days after last dose of study drug. Data are from all participants who received study drug (*n* = 131), excluding those randomized to discontinued treatment arms (see online supplementary *Figure S1*). Serious adverse events occurred in two participants in the discontinued treatment arms, both receiving placebo alone (one with angina pectoris and cardiac failure, one with COVID-19). Adverse events were coded using MedDRA version 26.0 preferred terms.

CKD, chronic kidney disease; MedDRA, Medical Dictionary for Regulatory Activities.

[a]Hepatic enzyme increased (reported as unrelated to study drugs).

[b]COVID-19 (leading to death 6 days after latest study drug), cardiac failure (leading to death 34 days after latest study drug), both left ventricular failure and osteoarthritis in one participant (all reported as unrelated to study drugs).

[c]Transient ischaemic attack (possibly related to balcinrenone), cardiac failure (reported as unrelated to study drugs).

[d]Sudden cardiac death (2 days after latest study drug), cardiac failure congestive, lower gastrointestinal haemorrhage, peripheral swelling (all reported as unrelated to study drugs).

[e]CKD and glomerular filtration rate decreased, both in one participant.

[f]Acute kidney injury in one participant, CKD in one participant and glomerular filtration rate decreased in one participant.

[g]CKD in two participants and glomerular filtration rate decreased in one participant.

[h]CKD (leading to discontinuation) in one participant and glomerular filtration rate decreased in one participant.

[i]Hyperkalaemia (leading to discontinuation in two participants, one in each of the balcinrenone 50 and 150 mg plus dapagliflozin groups); one participant met the protocol-mandated hyperkalaemia discontinuation criteria.

[j]Hypotension in one participant and syncope in one participant.

balcinrenone plus dapagliflozin groups were −24.5% (interquartile range −64.4,+3.5) in the 15 mg group, −33.1% (−52.5,+1.7) in the 50 mg group and −55.1% (−69.8,−6.6) in the 150 mg group, compared with −5.8% (−43.8,+55.0) in the dapagliflozin plus placebo group (*Figure 2B*). There was no clear dose−response relationship. Trends towards return of UACR to baseline levels at safety follow-up were observed (online supplementary *Table S3*).

Safety

Adverse events

AEs occurred in 9/33 (27.3%), 12/31 (38.7%) and 18/34 (52.9%) participants in the balcinrenone 15, 50 and 150 mg plus dapagliflozin groups, respectively, and in 14/33 (42.4%) in the dapagliflozin plus placebo group; serious AEs were infrequent (*Table 2*). AEs led to discontinuation of study drugs or withdrawal from the study in small numbers of participants. Three deaths were reported. AEs in safety topics of interest led to discontinuation of study drugs in three participants (hyperkalaemia in two and deteriorating renal function in one) (*Table 2*).

Potassium, estimated glomerular filtration rate and other safety outcomes

Serum potassium levels appeared dose-dependently elevated in the balcinrenone 50 and 150 mg plus dapagliflozin groups (*Figure 3A*).

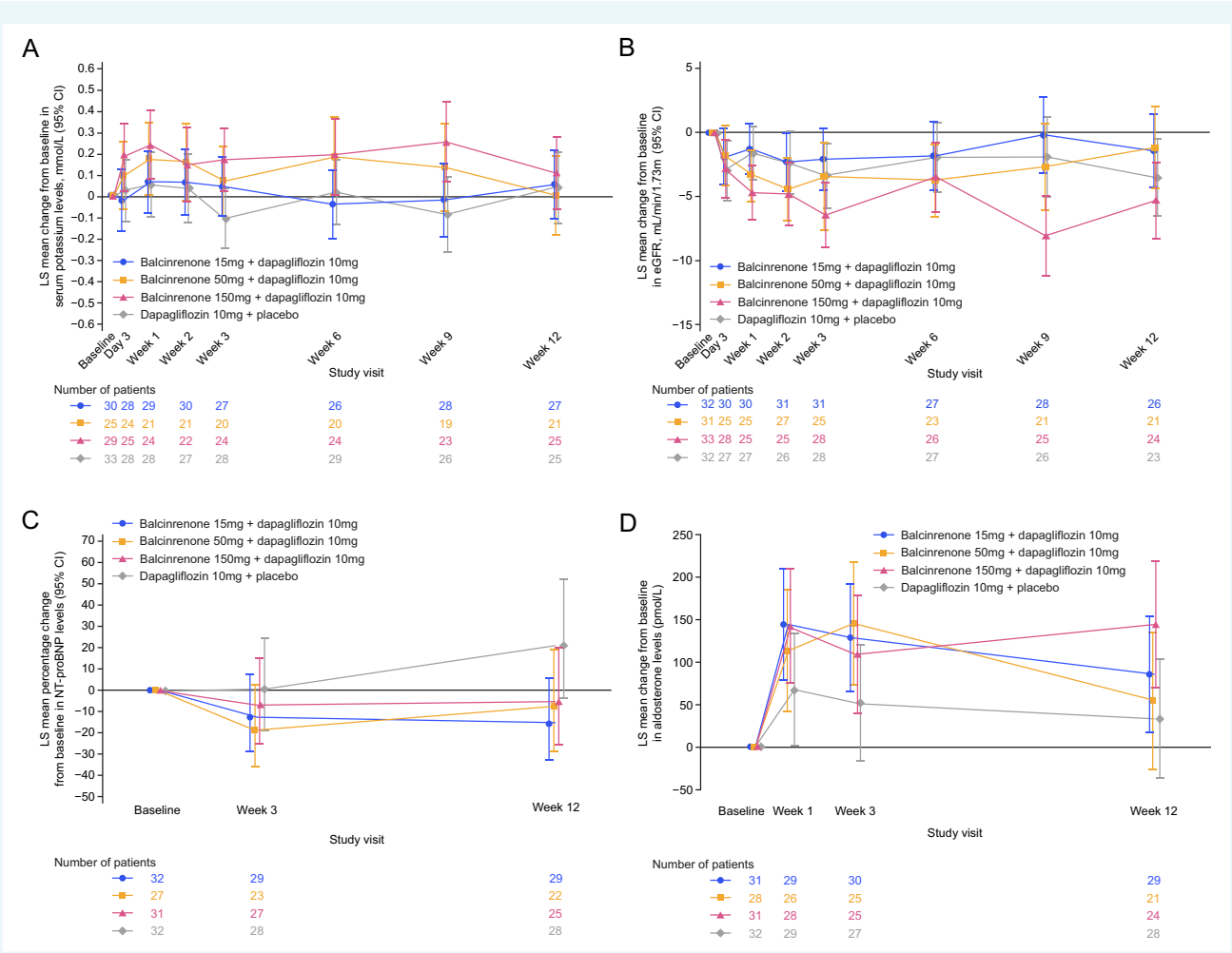


Figure 3 Change from baseline in (*A*) serum potassium levels, (*B*) estimated glomerular filtration rate (eGFR), (*C*) N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and (*D*) aldosterone levels. Data are from mixed model repeated measures of the change from baseline with fixed factors of treatment, visit, type 2 diabetes (yes/no), eGFR (≥30 to <45, or ≥45 ml/min/1.73 m^2) and treatment-by-visit interaction, plus covariates of log-transformed baseline value and protocol amendment cohort (before or after removal of non-dapagliflozin groups). Data are from exploratory or *post hoc* analyses. CI, confidence interval; LS, least-squares.

Confirmed serum potassium levels >5.5 mmol/L were reported in 0, 1 and 1 participant in the balcinrenone 15 and 50 mg plus dapagliflozin groups and the dapagliflozin plus placebo group, respectively, and in 3–4 participants in the balcinrenone 150 mg plus dapagliflozin group, depending on the confirmation method (online supplementary *Table S4*). Trends towards reductions in eGFR were observed in all groups, and appeared greatest in the highest balcinrenone dose group (*Figure 3B*, online supplementary *Table S5*).

One participant met the pre-specified discontinuation criteria for hyperkalaemia (confirmed potassium level >6 mmol/L) and one for deteriorating renal function, both in the balcinrenone 150 mg plus dapagliflozin group (online supplementary *Tables S4* and *S5*). There were no findings of concern in other safety parameters, including clinical chemistry, haematology and electrocardiographic findings.

Exploratory and pharmacodynamic endpoints

Reductions in NT-proBNP levels in the balcinrenone plus dapagliflozin groups were not significantly different versus the dapagliflozin plus placebo group. Mean changes from baseline to week 12 in the balcinrenone plus dapagliflozin groups were −12.7% (95% CI −29.9,+8.8) in the 15 mg group, −7.35% (−28.2,+19.6) in the 50 mg group and −4.4% (−24.6,+21.1) in the 150 mg group, and +20.8% (−3.9,+51.8) in the dapagliflozin plus placebo group (*Figure 3C*, online supplementary *Table S6*). In a *post hoc* analysis, aldosterone levels increased from baseline to week 12 in the balcinrenone plus dapagliflozin groups, and were stable or increased in the dapagliflozin plus placebo group (mean changes of +85.4 pmol/L [95% CI +17.7,+153.1] in the 15 mg group, +54.1 pmol/L [−26.7,+134.9] in the 50 mg group, +143.8 pmol/L [+69.4,+218.3]

in the 150 mg group and +33.1 pmol/L [−36.6,+102.8] in the dapagliflozin plus placebo group) (*Figure 3D*, online supplementary *Table S6*). Systolic blood pressure decreased in the balcinrenone plus dapagliflozin groups during weeks 1−4 and was maintained during weeks 3−12, but was stable in the dapagliflozin plus placebo group (online supplementary *Figure S2*, *Table S6*).

Discussion

UACR was chosen as the primary endpoint because it is an established biomarker of cardiovascular risk in multiple populations, and is known to be modifiable by MR antagonists.[7−12] MIRACLE aimed to test the hypothesis that balcinrenone plus dapagliflozin 10 mg for 12 weeks leads to a greater reduction in albuminuria than dapagliflozin monotherapy in patients with HF and CKD. In the primary endpoint analysis, reductions in UACR from baseline to week 12 with balcinrenone plus dapagliflozin were not significantly different to reductions observed with dapagliflozin plus placebo. Accompanying trends towards reduced NT-proBNP levels in the balcinrenone plus dapagliflozin groups, and evidence of target engagement by balcinrenone (increased aldosterone), were also observed. Within the limitations of the small sample size and short treatment period, balcinrenone tolerability appeared acceptable.

Patients with HF and CKD represent a high-risk population with continued unmet needs. Concomitant renal dysfunction in patients with HF severely limits the use of HF medications, with hyperkalaemia as the main AE of concern. In the present study, hyperkalaemia was infrequent, especially at the lower balcinrenone doses. Premature termination of enrolment in MIRACLE reduced sample size and statistical power. Whether balcinrenone would have reduced UACR or NT-proBNP if this study had recruited the originally planned number of patients and whether balcinrenone would result in improvements in clinical outcomes in this population warrants further study.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

The authors thank the investigators (see list of principal investigators in online supplementary material), study site staff and the participants.

Funding

The study was supported by AstraZeneca.

Conflict of interest: C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Novo Nordisk and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly and Company, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, ProSciento Inc., Quidel Corporation, Radcliffe Group Ltd, Recardio Inc., Recor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai. L.K. reports speaker's honoraria from AstraZeneca, Boehringer, Novartis and Novo Nordisk. K.K. has received lecture fees from Astellas Pharma Inc., AstraZeneca K.K., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Kowa Co., Ltd., Sanofi K.K., Sumitomo Dainippon Pharma Co., Ltd. (Sumitomo Pharma Co., Ltd.), Mitsubishi Tanabe Pharma Corp., Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Novo Nordisk Pharma Ltd., Bayer Yakuhin, Ltd., Pfizer Japan Inc., and Janssen Pharmaceutical K.K.; funded research or joint research expenses from Kowa Co., Ltd., AstraZeneca K.K., Daiichi Sankyo Co., Ltd., and Astellas Pharma Inc., and his affiliated institution (Shinshu University School of Medicine) has received grants from Otsuka Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corp., Nippon Boehringer Ingelheim Co., Ltd., and Kyowa Kirin Co., Ltd. L.H.L. is supported by Karolinska Institutet, the Swedish Research Council (grant 523−2014-2336), the Swedish Heart Lung Foundation (grants 20 190 310, 20 220 540), and the Stockholm County Council (grants 20 170 112, 20 190 525); and reports grants, consulting, honoraria from Alleviant, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Edwards, Merck/MSD, Novartis, Novo Nordisk, Owkin Pharmacosmos; and stock ownership for AnaCardio. P.B.M. reports lecture or advisory board honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, Pharmacomsos, Astellas, GSK and Vifor. L.G.M. has received consulting and speaker fees for participation in advisory boards, lectures and clinical trials supported and funded by Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Novartis, Novo Nordisk, and Sanofi; and received research grants from Amgen and Bayer AG. M.S. reports lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis and Novo Nordisk. J.J.V.M. reports payments through Glasgow University from work on clinical trials, consulting and other activities from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, KBP Biosciences, and Novartis; personal consultancy fees from Alnylam Pharma., Bayer, BMS, George Clinical PTY Ltd., Ionis Pharma., Novartis, Regeneron Pharma., River 2 Renal Corporation; personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions Ltd., Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharma. Ltd., Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica health, Intas Pharma, J.B. Chemicals & Pharma. Ltd., Lupin Pharma, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharma., The Corpus, Translation Research Group, Translational Medicine Academy; and is a director of Global Clinical Trial Partners Ltd. S.D.S. has received research grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos/Bridgebio, Gossamer, GSK, Ionis, Lilly, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Tenaya, Theracos US2.AI; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Lilly, Novartis, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Valo. P.E.P., S.B.G., A.Gh., J.H.G., P.F., M.L.Z. are employees and stockholders of AstraZeneca. A.Ga. and G.J.H. are former employees of AstraZeneca.

References

1. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, *et al.* Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014;**64**:2281−2293. https://doi.org/10.1016/j.jacc.2014.08.036

2. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al.* Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
5. Bamberg K, Johansson U, Edman K, William-Olsson L, Myhre S, Gunnarsson A, *et al.* Preclinical pharmacology of AZD9977: A novel mineralocorticoid receptor modulator separating organ protection from effects on electrolyte excretion. *PLoS One* 2018;**13**:e0193380. https://doi.org/10.1371/journal.pone.0193380
6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–612. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
7. Agarwal R, Tu W, Farjat AE, Farag YMK, Toto R, Kaul S, *et al.* Impact of finerenone-induced albuminuria reduction on chronic kidney disease outcomes in type 2 diabetes: A mediation analysis. *Ann Intern Med* 2023;**176**:1606–1616. https://doi.org/10.7326/M23-1023
8. Chung EY, Ruospo M, Natale P, Bolignano D, Navaneethan SD, Palmer SC, *et al.* Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2020;CD007004;**10**. https://doi.org/10.1002/14651858.CD007004.pub4
9. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, *et al.* Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: The DEFINE-HF trial. *Circulation* 2019;**140**:1463–1476. https://doi.org/10.1161/CIRCULATIONAHA.119.042929
10. Pollock C, Stefansson B, Reyner D, Rossing P, Sjostrom CD, Wheeler DC, *et al.* Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): A randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019;**7**:429–441. https://doi.org/10.1016/S2213-8587(19)30086-5
11. Selvaraj S, Claggett B, Shah SJ, Anand I, Rouleau JL, O'Meara E, *et al.* Prognostic value of albuminuria and influence of spironolactone in heart failure with preserved ejection fraction. *Circ Heart Fail* 2018;**11**:e005288. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005288
12. Writing Group for the CKD Prognosis Consortium;Grams ME, Coresh J, Matsushita K, Ballew SH, Sang Y, Surapaneni A, *et al.* Estimated glomerular filtration rate, albuminuria, and adverse outcomes: An individual-participant data meta-analysis. *JAMA* 2023;**330**:1266–1277. https://doi.org/10.1001/jama.2023.17002