ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 142–151
doi:10.1002/ejhf.3077

RESEARCH ARTICLE

Impact of vasodilators on diuretic response in patients with congestive heart failure: A mechanistic trial of cimlanod (BMS-986231)

Pierpaolo Pellicori[1], John G.F. Cleland[1]*, Maria Borentain[2], Jorg Taubel[3], Fraser J. Graham[1], Javed Khan[1], Dario Bruzzese[4], Paul Kessler[2], John J.V. McMurray[1], Adriaan A. Voors[5], Christopher M. O'Connor[6], John R. Teerlink[7], and G. Michael Felker[8]

[1]British Heart Foundation Cardiovascular Research Centre, School of Cardiovascular & Metabolic Health, University of Glasgow, Glasgow, UK; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]Richmond Pharmacology Ltd, St. George's University of London, London, UK; [4]Department of Public Health, University of Naples 'Federico II', Naples, Italy; [5]University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; [6]Inova Heart and Vascular Institute, Falls Church, VA, USA; [7]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, CA, USA; and [8]Duke University School of Medicine and the Duke Clinical Research Institute, Durham, NC, USA

Received 7 August 2023; revised 4 October 2023; accepted 24 October 2023; online publish-ahead-of-print 28 December 2023

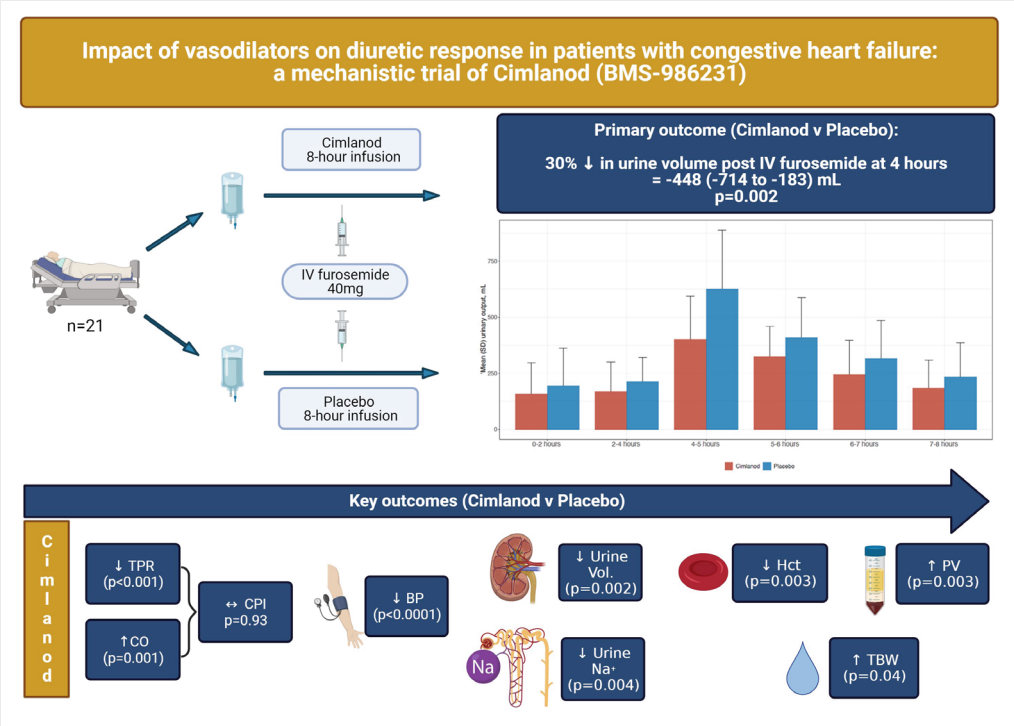
Aim To investigate the effects of Cimlanod, a nitroxyl donor with vasodilator properties, on water and salt excretion after an administration of an intravenos bolus of furosemide.

Methods and results In this randomized, double-blind, mechanistic, crossover trial, 21 patients with left ventricular ejection fraction <45%, increased plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and receiving loop diuretics were given, on separate study days, either an 8 h intravenous (IV) infusion of cimlanod (12 μg/kg/min) or placebo. Furosemide was given as a 40 mg IV bolus four hours after the start of infusion. The primary endpoint was urine volume in the 4 h after the bolus of furosemide during infusion of cimlanod compared with placebo. Median NT-proBNP at baseline was 1487 (interquartile range: 847–2665) ng/L. Infusion of cimlanod increased cardiac output and reduced blood pressure without affecting cardiac power index consistent with its vasodilator effects. Urine volume in the 4 h post-furosemide was lower with cimlanod (1032 ± 393 ml) versus placebo (1481 ± 560 ml) ($p = 0.002$), as were total sodium excretion ($p = 0.004$), fractional sodium excretion ($p = 0.016$), systolic blood pressure ($p < 0.001$), estimated glomerular filtration rate ($p = 0.012$), and haemoglobin ($p = 0.010$), an index of plasma volume expansion.

Conclusions For patients with heart failure and congestion, vasodilatation with agents such as cimlanod reduces the response to diuretic agents, which may offset any benefit from acute reductions in cardiac preload and afterload.

*Corresponding author. British Heart Foundation Cardiovascular Research Centre, School of Cardiovascular & Metabolic Health, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK. Email: john.cleland@glasgow.ac.uk

Graphical Abstract



Trial design and summary results. BP, blood pressure; CO, cardiac output; CPI, cardiac power index; Hct, haematocrit; IV, intravenous; Na^+, sodium; PV, plasma volume; TBW, total body water; TPR, total peripheral resistance; Vol., volume.

Keywords Heart failure • Congestion • Diuretics • Vasodilators • Renal perfusion • Bioimpedance • Natriuresis

Introduction

For 40 years or more, the potential therapeutic benefits of unloading the acutely failing heart by arteriolar dilatation to reduce afterload, or by venous dilatation to reduce preload, have been investigated.[1,2] For patients who are severely breathless at rest because of pulmonary congestion, reducing left atrial pressure is a biologically plausible mechanism by which both loop diuretic and vasodilator agents might relieve symptoms acutely. Despite a lack of randomized trials, loop diuretic agents are used to treat most patients admitted with worsening heart failure, appear to be clinically effective and are strongly recommended by guidelines.[3,4]. Indeed, administration of intravenous loop diuretics is often used as part of the definition of acute heart failure in clinical trials.[5] Vasodilator agents have been studied far more extensively, but evidence of their therapeutic benefit remains elusive,[6] with equivocal support from guidelines.[3,4] In Western Europe and North America only about 5% of patients admitted with worsening heart failure receive intravenous vasodilators.[7]

Many patients hospitalized with heart failure have water and salt retention, leading to symptoms and signs of pulmonary and systemic congestion. Although cardiac dysfunction may be the trigger for congestion, the renal response, in terms of water and salt retention, makes a major contribution to the development of the clinical syndrome.[8] Loop diuretics are the mainstay of treatment for water and salt retention and are usually highly effective at inducing diuresis. Failure to mount a good diuretic response, often associated with worsening renal function, is associated with a poor prognosis.[9,10]

The reasons why cardiac dysfunction causes water and salt retention are not fully understood, but a fall in arterial pressure, activation of neuroendocrine systems, increased renal venous pressure, and changes in intra-renal haemodynamics are all likely to contribute.[11,12] Although vasodilator agents can reduce cardiac preload and afterload, they may exacerbate renal water and salt retention by one or more of the above mechanisms.[13] If true, any benefit from vasodilator agents might be short-lived and, after they are withdrawn, leave an adverse legacy of water and salt retention. The success of some vasodilator agents,

such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor–neprilysin inhibitors (ARNi), may reflect their concomitant effects on neuroendocrine systems that avoid water and salt retention[14] or increase it.[15]

Cimlanod (BMS-986231) is a novel nitroxyl (HNO) donor that causes arteriolar and venous dilatation[16–18], similar to nitrates, but is thought not to induce tachyphylaxis[19]. In common with many other vasodilators, its effects on water and salt excretion have not been explored. The aim of this mechanistic trial was to evaluate the effects of cimlanod compared with placebo on water and salt excretion in the 4 h after a 40 mg intravenous (IV) bolus of furosemide in patients with congestion, chronic heart failure and impaired left ventricular systolic function (ClinicalTrials.gov Identifier: NCT03730961).

Methods

This was a mechanistic, randomized, double-blind, placebo-controlled trial with a crossover design that investigated the effects of cimlanod compared with placebo on urine volume and sodium excretion before and after an IV bolus of furosemide (online supplementary *Figure S1*.). Patients were enrolled at two secondary care centres in the United Kingdom (Queen Elizabeth University Hospital, Glasgow and Richmond Pharmacology, St George's, London). The trial was approved by the Tyne & Wear South Research Ethics Committee (reference: 18/NE/0257). The trial was initiated in January 2019 and was completed in January 2020.

Patients

The main inclusion criteria were a left ventricular ejection fraction (LVEF) <45%, stable treatment for heart failure including at least 40 mg/day of furosemide or 1 mg/day of bumetanide, an estimated glomerular filtration rate (eGFR) of 30–80 ml/min/1.73 m^2, and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) >200 ng/L (or >400 ng/L for those with atrial fibrillation) prior to withholding loop diuretics. Patients were excluded if they were considered at risk of clinical deterioration within 48 h if diuretics were stopped, or if they had a systolic blood pressure (SBP) <115 mmHg or >180 mmHg, hyponatraemia (<130 mmol/L), or a history of urinary retention or bladder dysfunction. A full list of exclusion criteria is provided in the protocol (online supplementary *Appendix S1*). All patients provided written informed consent.

Procedures

On separate days, at least 7 days apart, patients were randomly assigned to receive an 8 h infusion of cimlanod or placebo. Prior to each trial day, patients were asked to follow a similar diet for 3 days and omit oral diuretics for up to 48 h to reduce variability in pre-infusion water and salt balance and to induce a degree of congestion, as previously described.[20] This also avoided administering cimlanod to patients who were dehydrated. In order to minimize the effects of concomitant medications on blood pressure, pre- and afterload and filling pressures, medications were withheld in the morning of each trial treatment day but, at the investigator's discretion, administered at the end of the 8 h infusion. Drinks containing caffeine were omitted on the morning of each trial day, as they might have effects on haemodynamics or diuresis. Prior to the infusion, patients were asked to void urine, had a scan to ensure their bladder was empty, and had baseline investigations done, which included body weight, heart rate, blood pressure, bioimpedance measures of haemodynamics and body water (NI Medical, Tel Aviv, Israel), and an echocardiogram. Echocardiography included measurement of left ventricular end-diastolic and end-systolic volumes and LVEF, left atrial volume, mitral inflow velocities (E and e' wave velocities and their ratio), inferior vena cava and internal jugular vein diameters, and lung B-lines (28-zone scan), ultrasound measures of intravascular and pulmonary congestion.[21]

Table 1 Patient characteristics at baseline

Patient characteristics	
Patients, *n*	21
Age, years, mean ± SD	69 ± 8
Female sex, *n* (%)	2 (10)
BMI, kg/m^2, mean ± SD	28.3 ± 4.0
CAD, *n* (%)	14 (67)
Diabetes, *n* (%)	10 (48)
LVEF, %, mean ± SD	33 ± 12
eGFR <60 mL/min/1.73 m^2, *n* (%)	11 (52)
NT-proBNP (sinus rhythm), ng/L, median (IQR)	966 (599–1723)
NT-proBNP (AF), ng/L, median (IQR)	2356 (1706–3860)
Beta-blocker, *n* (%)	20 (95)
ACEi/ARB/ARNi, *n* (%)	20 (95)
MRA, *n* (%)	16 (76)
SGLT2i, *n* (%)	2 (10)
Digoxin, *n* (%)	7 (33)
Statin, *n* (%)	16 (76)
Loop diuretic, *n* (%)	21 (100)
Daily dose (furosemide equivalent)	
40 mg/day	16 (76)
41–80 mg/day	4 (19)
Missing	1 (5)

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor.
For continuous variables, data are baseline values on the placebo day. Furosemide equivalent doses: 1 mg/bumetanide = 40 mg/furosemide; torsemide not used.
See *Table 2* for additional baseline variables.

Randomization and masking

Infusions of cimlanod or placebo were assigned by a computer-generated randomization scheme provided by PAREXEL using an Interactive Voice Response System. A pharmacist, who was not blinded, prepared the solutions to be infused but was not involved in any other aspect of the trial.

Intervention

Infusions lasted 8 h, with the patient lying semi-recumbent and allowed out of bed only to void urine and to be weighed. Cimlanod was infused at 12 μg/kg/min but could be reduced or stopped if SBP fell below

Table 2 **Longitudinal changes in urinary, haemodynamic, volume distribution, and ultrasound data from baseline to time before (0–4 h) and after (4–8 h) administration of furosemide during infusion of cimlanod or placebo**

	Baseline		Furosemide Bolus Administered at 4 h							
			0–4 h				4–8 h			
	Placebo	Cimlanod	Placebo	Cimlanod	Mean difference (95% CI)	*p*-value	Placebo	Cimlanod	Mean difference (95% CI)	*p*-value
Urine and renal function										
#Urine volume, ml	N/A	N/A	368 ± 231	276 ± 238	−98 (−226 to 30)	0.125	1481 ± 560	1032 ± 393	−448 (−714 to −183)	0.002
Serum sodium, mmol/L	140 ± 2	140 ± 2	139 ± 2	139 ± 3	0 (−1 to 0)	0.419	139 ± 2	139 ± 3	0 (−1 to 1)	0.610
Urine sodium, mmol	N/A	N/A	13 ± 12	11 ± 18	−2 (−7 to 2)	0.331	143 ± 64	88 ± 43	−55 (−90 to −19)	0.004
#FeNa, %	N/A	N/A	0.7 ± 0.8	0.6 ± 0.7	−0.3 (−0.5 to −0.1)	0.019	16.2 ± 7.5	12.0 ± 7.5	−4.3 (−7.6 to −0.9)	0.016
Serum potassium, mmol/L	4.5 ± 0.4	4.5 ± 0.4	4.4 ± 0.4	4.4 ± 0.3	0.0 (−0.1 to 0.2)	0.601	4.3 ± 0.3	4.3 ± 0.4	0 (−0.2 to 0.1)	0.724
Urine potassium, mmol	N/A	N/A	9 ± 5	11 ± 7	2 (−1 to 5)	0.171	27 ± 13	28 ± 12	2 (−3 to 7)	0.491
#FeK, %	N/A	N/A	0.4 ± 0.2	0.5 ± 0.2	0.1 (0.0 to 0.2)	0.160	3.2 ± 1.5	3.7 ± 1.8	0.4 (−0.2 to 1.1)	0.162
#Urine furosemide, mg	N/A	N/A	N/A	N/A	N/A	N/A	14.9 ± 4.7	15.3 ± 5.4	0.5 (−1.8 to 2.7)	0.674
eGFR, ml/min/1.73 m^2	60 ± 13	59 ± 12	62 ± 10	60 ± 13	−2 (−5 to 2)	0.318	62 ± 10	56 ± 11	−5 (−8 to −1)	0.012
Cystatin C, mg/L	1.36 (0.25)	1.37 (0.23)	1.26 (0.21)	1.32 (0.22)	0.05 (0.00 to 0.09)	0.036	1.37 (0.22)	1.45 (0.22)	0.08 (0.02 to 0.13)	0.006
Serum creatinine, mg/dl	1.22 (0.25)	1.23 (0.25)	1.17 (0.21)	1.22 (0.24)	0.04 (−0.02 to 0.09)	0.193	1.17 (0.21)	1.29 (0.23)	0.08 (0.01 to 0.15)	0.022
Creatinine clearance (ml/min)	69.8 (24.1)	68.7 (19.5)	69.2 (16.5)	68.8 (18)	−1.6 (−4.5 to 1.4)	0.279	68.3 (16.5)	65.2 (18.5)	−4.1 (−7.3 to −0.8)	0.016
Haemodynamics										
Respiratory rate, breaths/min	15 ± 3	16 ± 2	16 ± 3	16 ± 2	−0.1 (−1.6 to 1.5)	0.899	17 ± 3	17 ± 3	−0.1 (−1.5 to 1.2)	0.831
Heart rate, bpm	66 ± 11	67 ± 12	64 ± 11	68 ± 10	4 (0 to 8)	0.039	65 ± 12	68 ± 12	3 (−1 to 6)	0.099
Systolic BP, mmHg	134 ± 21	134 ± 21	128 ± 26	108 ± 13	−20 (−29 to −12)	<0.001	131 ± 26	106 ± 16	−25 (−34 to −16)	<0.001
Diastolic BP, mmHg	75 ± 11	74 ± 11	69 ± 13	59 ± 9	−10 (−15 to −5)	<0.001	73 ± 13	59 ± 8	−15 (−20 to −9)	<0.001
Mean BP, mmHg	94 ± 13	93 ± 12	89 ± 16	75 ± 9	−14 (−19 to −8)	<0.001	92 ± 16	74 ± 8	−18 (−24 to −12)	<0.001
Cardiac index, L/min/m^2	1.8 ± 0.4	1.9 ± 0.6	1.9 ± 0.4	2.3 ± 0.5	0.4 (0.2 to 0.6)	0.001	1.8 ± 0.5	2.3 ± 0.6	0.4 (0.2 to 0.7)	0.001
Cardiac output, L/min	3.6 ± 0.8	3.6 ± 1.1	3.7 ± 0.8	4.5 ± 1.1	0.8 (0.4 to 1.3)	0.001	3.6 ± 0.9	4.4 ± 1.2	0.9 (0.4 to 1.3)	0.001
TPR index, dyn*s/cm^3	4367 ± 1370	4506 ± 1783	3970 ± 1117	2827 ± 1057	−1143 (−1637 to −649)	<0.001	4342 ± 1408	2890 ± 1210	−1452 (−2088 to −816)	<0.001
Power index, W/m^2	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.0 (0.0 to 0.1)	0.583	0.4 ± 0.1	0.4 ± 0.1	0.0 (−0.1 to 0.1)	0.929
BNP, ng/L	147 (90–473)	182 (119–435)	156 (110–396)	160 (119–346)	−59 (−184 to 67)	0.339	172 (104–379)	142 (96–267)	−97 (−223 to 30)	0.127
NT-proBNP, ng/L	1487 (847–2665)	1526 (968–3150)	1369 (798–2282)	1551 (1070– 2731)	−65 (−983 to 854)	0.884	1583 (955–2620)	1539 (1132–2829)	−252 (−1158 to 654)	0.568
Volume distribution										
Body weight, kg	84.4 ± 15.9	84.4 ± 15.8	84.3 ± 16.1	84.1 ± 15.8	−0.2 (−0.7 to 0.2)	0.333	84.2 ± 16.1	84.1 ± 15.8	−0.1 (−0.6 to 0.3)	0.557
Body water, L	40.6 ± 6.2	41.1 ± 7.0	39.9 ± 6.1	42.2 ± 10.4	2.3 (−0.3 to 4.9)	0.079	39.3 ± 6.0	41.5 ± 9.5	2.2 (0.1 to 4.3)	0.044
Haemoglobin, g/dl	12.9 ± 1.7	12.9 ± 1.9	12.4 ± 1.8	11.9 ± 1.6	−0.5 (−0.9 to −0.1)	0.015	12.8 ± 1.9	12.0 ± 1.7	−0.7 (−1.2 to −0.2)	0.010
Haematocrit, %	39.1 ± 5.4	39.3 ± 5.5	37.7 ± 5.3	36.3 ± 4.6	−1.5 (−2.7 to −0.3)	0.016	38.4 ± 5.6	36.3 ± 5.1	−2.3 (−3.7 to −0.9)	0.003
Plasma volume, ml	2961 ± 353	3012 ± 425	3030 ± 352	3155 ± 435	77 (13 to 142)	0.022	2990 ± 353	3157 ± 451	119 (47 to 191)	0.003
Ultrasound										
LVEDV, ml	204 ± 63	202 ± 67	202 ± 70	200 ± 75	−2 (−14 to 10)	0.740	203 ± 70	194 ± 72	−9 (−25 to 7)	0.272
LVESV, ml	140 ± 61	137 ± 65	135 ± 64	133 ± 70	−2 (−11 to 7)	0.642	135 ± 60	126 ± 63	−9 (−21 to 3)	0.132
LVEF, %	33 ± 12	35 ± 11	35 ± 11	36 ± 10	1 (−1 to 3)	0.279	35 ± 11	37 ± 10	2 (0 to 5)	0.050
E wave, cm/s	74 ± 28	77 ± 25	77 ± 26	70 ± 26	−7 (−15 to 1)	0.072	72 ± 27	62 ± 22	−10 (−14 to −5)	<0.001
E/e′	12.6 ± 4.5	13.6 ± 4.0	13.3 ± 4.6	12.1 ± 3.8	−1.1 (−2.6 to 0.3)	0.114	12.7 ± 4.6	11.6 ± 4.8	−1.1 (−2.6 to 0.5)	0.162
LA volume, ml	99 ± 28	105 ± 37	96 ± 25	98 ± 41	2 (−13 to 18)	0.753	90 ± 24	98 ± 36	8 (−5 to 21)	0.193
TAPSE, mm	17.9 ± 3.9	17.6 ± 3.8	18.5 ± 4.0	18.0 ± 3.9	−0.6 (−2.0 to 0.9)	0.422	18.9 ± 3.2	17.5 ± 3.7	−1.1 (−2.1 to −0.1)	0.028
Total B-lines	17.2 ± 14.2	17.2 ± 17.9	16.4 ± 13.6	18.3 ± 18.0	1.9 (−7.1 to 10.9)	0.664	14.1 ± 12.8	15.2 ± 15.0	1.0 (−3.9 to 6.0)	0.664
IVC, mm	21 ± 5	21 ± 5	20 ± 5	21 ± 5	1 (−2 to 3)	0.605	20 ± 5	19 ± 4	0 (−2 to 1)	0.695
JVD ratio	4.3 ± 3.0	4.2 ± 2.2	3.9 ± 2.8	3.8 ± 2.1	−0.1 (−0.8 to 0.6)	0.770	4.3 ± 2.7	4.2 ± 2.4	−0.2 (−0.8 to 0.4)	0.446

BNP, B-type natriuretic peptide; BP, blood pressure; CI, confidence interval; E, early mitral inflow velocity; E/e', early mitral inflow velocity to mitral annular early diastolic velocity ratio; eGFR, estimated glomerular filtration rate; FeK, fractional excretion of potassium; FeNa, fractional excretion of sodium; IQR, interquartile range; IVC, inferior vena cava; JVD, jugular vein diameter; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; N/A, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TPR, total peripheral resistance.

#indicates during the entire period; other data refer to the end of each period. Descriptive data are expressed as mean ± SD or median (IQR). Mean differences with 95% confidence intervals and *p*-values for each period are based on paired *t*-test (cimlanod minus placebo).

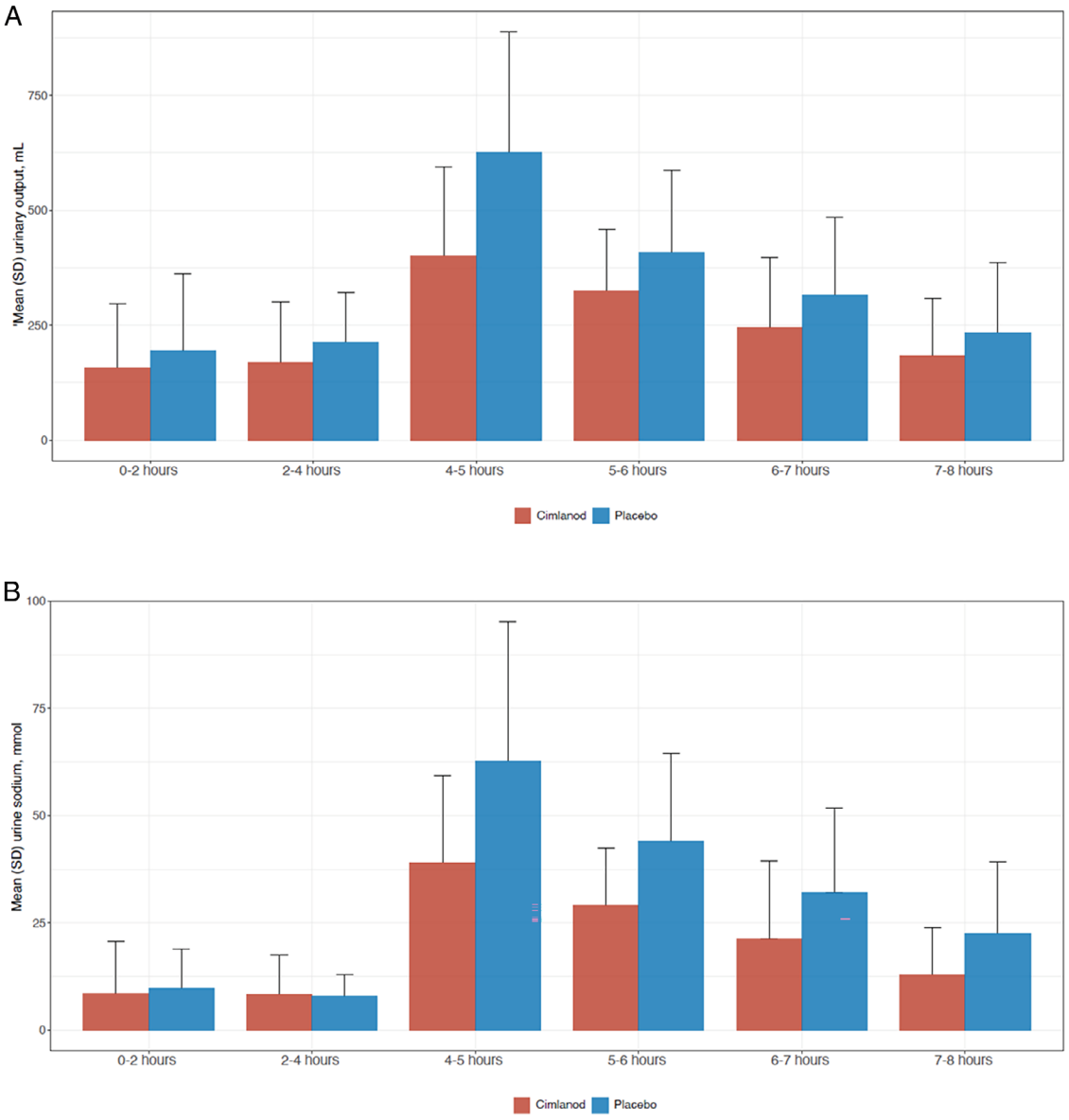


Figure 1 (*A*) Urine output before (0–4 h) and after (4–8 h) an intravenous bolus of furosemide. (*B*) Urine sodium excretion before (0–4 h) and after (4–8 h) an intravenous bolus of furosemide. Urine volume (the primary endpoint) was greater in the 4 h after the furosemide bolus when receiving placebo (mean ± SD: 1481 ± 560 ml) compared with cimlanod (mean ± SD: 1032 ± 393 ml; mean difference 448 [95% CI: −714 to −183], $p = 0.002$). Urine sodium excretion increased substantially after administration of furosemide. However, during the 4 h after the furosemide bolus, urine sodium excretion was greater when receiving placebo (143 ± 64 mmol) compared with cimlanod (88 ± 43 mmol; mean difference − 55 [95% CI: −90 to −19], $p = 0.004$). CI, confidence interval; SD, standard variation.

90 mmHg or if the patient developed symptomatic hypotension. Urine was collected at 2 and 4 h, and then a 40 mg IV bolus of furosemide was given, with hourly urine collections made for the following 4 h; urine volume, electrolytes, and furosemide were measured in each sample. Heart rate and blood pressure were measured at baseline, at 30 and 60 min and then hourly during the infusion. Blood was taken at baseline and at 4, 5, 6, 7, and 8 h for serum electrolytes and creatinine. Haemoglobin, B-type natriuretic peptide (BNP), NT-proBNP, and cystatin C were measured at baseline and at 4 and 8 h. Echocardiography was performed at baseline and repeated at 4 and 8 h. Plasma volume was estimated based on haematocrit,[22] eGFR was calculated using the Modification of Diet in Renal Disease equation, creatinine clearance using Cockcroft–Gault equation. Total peripheral resistance index and cardiac power index were calculated from mean arterial pressure measured by sphygmomanometer and cardiac index measured by whole-body bioimpedance. Previous studies suggest good correlation (r ~0.8–0.9) between cardiac index measured non-invasively using bioimpedance and thermodilution in different clinical settings,[23,24] and that bioimpedance can track changes in cardiac index during infusion of vasodilators.[23] At the end of the infusion, patients were allowed to

get out of bed and were weighed and observed in the unit for a further 3.5 h (or overnight if the patient preferred) to ensure safety.

Outcomes

The primary endpoint was urine volume in the 4 h after the bolus of furosemide during infusion of cimlanod compared with placebo. Secondary endpoints included excretion of sodium, potassium, and furosemide. The principal safety endpoint was clinically relevant hypotension (defined as SBP <90 mmHg or symptomatic hypotension) during infusions. Patients were contacted by telephone the day after each infusion and approximately 30 days later to enquire about possible adverse events and their severity.

Statistical power

The primary hypothesis was that infusion of cimlanod would increase post-furosemide urine volume excretion with respect to placebo. Assuming a urine volume of 250–300 mL/h in the 4 h after an IV bolus of furosemide and a within-patient standard deviation of <35 mL/h, complete data on 20 patients were calculated to provide 90% power to demonstrate a 20% difference in urine volume compared with placebo.

Statistical analyses

Numerical variables were described using mean and standard deviation (SD) or, in case of substantial asymmetry, using median and quartiles. Due to the crossover design, differences between placebo and cimlanod were analysed using a paired *t*-test, and the 95% confidence intervals (95% CIs) on the mean differences are provided. Safety analyses were reported for all randomized patients. Other analyses were done using the treated (per protocol) population. No adjustments were made for multiple comparisons. All analyses other than for the primary endpoint should be considered only nominally significant. Statistical significance was two-sided and defined by a *p*-value of <0.05. All data analyses were performed using SAS version 9.3 or higher (SAS Institute Inc., Cary, NC, USA) and R version 4.1.3.[25]

A difference in the primary outcome was also assessed using a linear mixed model with period and treatment as fixed effects and participant as a random effect. The presence of a carry-over effect was sought by including a period-by-treatment interaction in the model. As the results were almost identical, we only present the main analysis.

Results

Of 23 patients randomized, 21 had complete data for the primary endpoint (online supplementary *Figure S2*.). One patient was withdrawn on the placebo day of the trial because of a chest infection; another patient was not administered furosemide due to hypotension during infusion of cimlanod.

The mean (± SD) age of the 21 patients included in this analysis was 69 ± 8 years, and all but 2 were men (*Table 1*). Mean LVEF was 33 ± 12% and mean SBP was 134 ± 21 mmHg. Median (interquartile range) NT-proBNP was markedly elevated (1487 [847–2665] ng/L). All patients were receiving long-term treatment with oral loop diuretics, and most were treated with either an ACE inhibitor, angiotensin receptor blocker, or ARNi, beta-blockers, and mineralocorticoid receptor antagonists; only two were treated with sodium–glucose cotransporter 2 inhibitors.

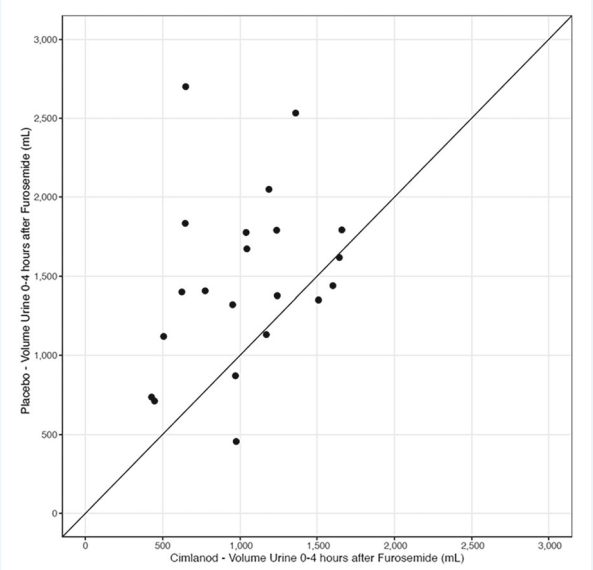


Figure 2 Urine volumes in the cimlanod and placebo groups in the 4 h after infusion of furosemide. Compared with placebo, post-furosemide urine volumes were lower during infusion of cimlanod for 15 of 21 participants (shown on the left side of the line of identity).

Urine volume and sodium excretion were lower during infusion of cimlanod compared with placebo even prior to giving furosemide (*Table 2*). Urine output and electrolyte excretion increased markedly in the 4 h after administration of furosemide but urine volume (the primary endpoint) was 30% lower during infusion of cimlanod compared with placebo (*Figure 1A* and *Table 2*; mean −448 ml [95% CI −714 to −183], $p = 0.002$) and was accompanied by a similar reduction (38%) in sodium excretion (*Figure 1B* and *Table 2*). Fractional excretion of sodium (the proportion of sodium filtered in the glomerulus that is excreted in the urine) after the bolus of furosemide was also 26% lower during infusion of cimlanod. In contrast, excretion of potassium was similar during infusion of placebo and cimlanod. Compared with placebo, post-furosemide urine volumes were lower during infusion of cimlanod for 15 of 21 patients (*Figure 2*).

During the infusion of cimlanod, both before and after the administration of furosemide, cardiac index was higher and total peripheral resistance and blood pressures were lower (*Figure 3*). Cardiac power index did not change, suggesting that cimlanod lacks an inotropic effect (*Table 2*). Transmitral E-wave velocity was lower during infusion of cimlanod, consistent with a fall in left ventricular filling pressure. This was accompanied by non-significant trends to lower plasma BNP and NT-proBNP and an increase in LVEF. Left ventricular end-diastolic volume, left atrial volume, inferior vena cava diameter and lung B-lines were similar during infusion of placebo and cimlanod. However, tricuspid annular plane systolic excursion, a measure or right ventricular function, declined during infusion of cimlanod. During the infusion of cimlanod, haematocrit fell, and estimated total body water and plasma volume increased.

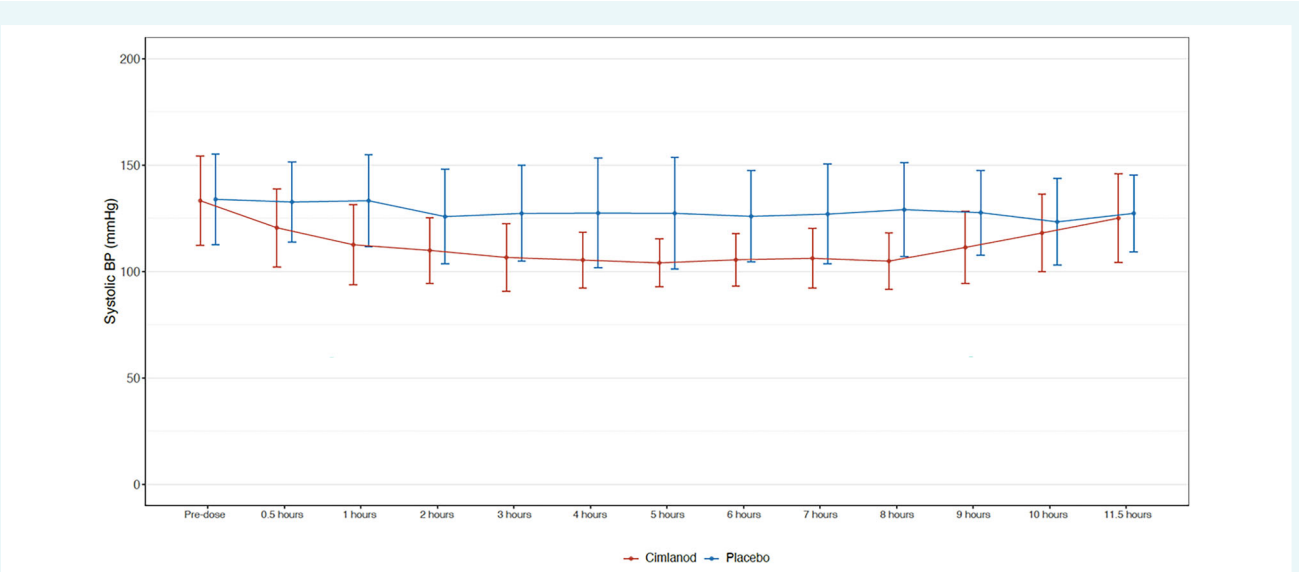


Figure 3 Changes in systolic blood pressure (BP) during treatment with cimlanod or placebo. Compared with when patients received placebo, systolic BP was lower during infusion of cimlanod (0–8 h), prior to returning to baseline around 2 h later.

In summary, cimlanod reduced both left ventricular preload and afterload but caused plasma volume expansion.

Serious adverse events were reported in one patient during the infusion of cimlanod and in two patients during infusion of placebo. Three patients assigned to cimlanod developed clinically relevant hypotension that prompted temporary discontinuation of infusion in two patients, and avoidance of the IV bolus of furosemide in one patient. Only the latter patient was excluded from this analysis.

Discussion

We found that, in patients with HF, congestion and a reduced LVEF, the infusion of cimlanod reduced urine volume and sodium excretion both before and after the administration of furosemide, accompanied by plasma volume expansion and an increase in total body water (*Graphical Abstract*). This may reflect the renal response to a reduction in perfusion pressure and glomerular efferent arteriolar dilatation. These effects are probably shared with many other vasodilator agents.

This trial confirms that cimlanod has vasodilator properties, with a fall in total peripheral resistance, increase in cardiac output, and reductions in left atrial pressure.[26] However, cardiac power index did not increase, suggesting that the rise in cardiac output reflects the response to a reduction in afterload rather than cimlanod having an inotropic effect, as has been previously proposed.[26] Reductions in left atrial and pulmonary venous pressure might be useful for the relief of acute pulmonary oedema in patients who have severe breathlessness at rest when sitting upright. However, contemporary studies suggest that for many admissions, the problem is worsening peripheral oedema with orthopnoea and breathlessness only during exertion, albeit slight.[27] For patients who have few symptoms at rest sitting upright, vasodilator agents may be of little benefit if they reduce diuretic efficacy because any haemodynamic benefit will cease when the agent is stopped, leaving a legacy of water and salt retention that may increase the risk of an early relapse.

Water retention is a well-known side effect of the vasodilator minoxidil.[28] Nitrates also cause a fall in haematocrit, but this has generally been attributed to repatriation of water from the extravascular space into the circulation rather than renal water retention.[13,29,30] However, haematocrit alone might not be a reliable guide to the effect of agents on water excretion. Infusing natriuretic peptides into patients with heart failure causes vasodilatation but increases haematocrit with little effect on renal water excretion, suggesting increased capillary permeability and a shift of water from the circulation into the extravascular space.[31] Trials of nesiritide (recombinant human BNP) failed to show enhanced furosemide-induced diuresis[32,33] or conclusive evidence of clinical benefit in patients with acute heart failure.[34–36] Trials of serelaxin, the recombinant form of the human pregnancy hormone relaxin-2, also had disappointing results.[37,38] Retrospective analyses suggested that serelaxin had little effect on diuretic response, but no formal interaction trial was done.[39,40] Another recent trial of vasodilators for acute heart failure also failed to improve clinical outcome.[6]

Chronic heart failure is a cardiorenal syndrome caused by water and salt retention due to cardiac dysfunction.[8] Decompensated heart failure is often due to retention of water but may also be caused or exacerbated by translocation of blood from the splanchnic venous circulation into the systemic circulation.[41] Research on renal function in heart failure has generally focused on measuring GFR and blood flow rather than on water and salt excretion, which may be more relevant for the clinical management of heart failure. Despite reductions in eGFR and in diuretic-induced water and sodium excretion with cimlanod, urinary furosemide excretion was unchanged. This suggest that renal delivery of

furosemide was maintained but the kidney was less responsive to its effects.

Our trial has limitations. Although small, it was carefully controlled and adequately powered for its primary purpose. Our patients did not have decompensated heart failure, but they did have congestion, as evidenced by increased left atrial volume and high plasma concentrations of natriuretic peptides. A higher dose of furosemide might have counteracted the effects of cimlanod on water and salt excretion, but we did not test this hypothesis. Patients who are severely breathless at rest might benefit from an acute reduction in atrial and venous pressures, but pre-capillary arteriolar vasodilatation could also lead to an increase in pulmonary and systemic capillary volumes and pressure, leading to an increase in hydrostatic pressure and extravasation of fluid and electrolytes into the extravascular space.[42] Moreover, unselective pulmonary vasodilatation may increase blood flow to regions of the lung that are not ventilated, increasing ventilation/perfusion mismatch and worsening oxygenation.[43,44] Similarly, non-selective systemic vasodilatation might shunt blood through tissues without useful exchange of oxygen or waste products and divert flow away from vital organs, such as the kidney and the heart, towards those that already have adequate resting flow, such as skeletal muscle.[45] Finally, changes in renal function may have been underestimated by changes in serum creatinine due to slow equilibrium kinetics.

Conclusions

Infusion of cimlanod attenuates a furosemide-induced diuresis in patients with heart failure and an LVEF <45%, which might have adverse consequences for those who are already congested. Development of interventions for acute heart failure should include research focused on assessing effects on water balance and potential interactions with diuretic agents. Such trials do not need to be large and do not require complex or expensive investigations.

Supplementary Information

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

Acknowledgements

Editorial support was provided by Mary Saurin, MD, of the Healthcare Consultancy Group (Manila, Philippines), with funding from Bristol Myers Squibb.

Funding

The trial sponsor (Bristol Myers Squibb) was involved in the trial design, data collection, data analysis, data interpretation, and writing of this manuscript.

Conflict of interest: P.P. has received research grants from the British Heart Foundation, Heart Research UK and Bristol Myers Squibb, payment or honoraria from Pharmacosmos, AstraZeneca and Vifor Pharma, and support for attending meetings and/or travel from Pharmacosmos, Bristol Myers Squibb and Vifor Pharma. J.G.F.C. has received research grants/honoraria to his institution from Amgen, Bayer, Bristol Myers Squibb, British Heart Foundation, Johnson & Johnson, Medtronic, Myokardia, Pharmacosmos, Pharma Nord, and CSL Vifor. He has received payment/honoraria to his institution for advisory board attendance, steering committee membership, an educational lecture and manuscript writing from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Innolife, NI Medical, Novartis and Servier, and honoraria to self for advisory board attendance and steering committee membership from Torrent. He has received financial support from Boehringer Ingelheim and Pharmacosmos for attending meetings. He has received honoraria for independent data monitoring committee membership from Idorsia and Medtronic. He holds stock in Heartfelt Limited. M.B. is a former employee of Bristol Myers Squibb. J.T. is an honorary senior research fellow at St George's University of London and an employee of Richmond Pharmacology Ltd., in which he also holds stocks. Richmond received payments for the conduct of the clinical conduct of the study. F.G. has received support from Pharmacosmos for attending a meeting. P.K. is an employee of Bristol Myers Squibb and holds stock in the company. J.J.V.M. has received honoraria to his institution for advisory board attendance and steering committee membership from Amgen, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, DalCor, GSK, and Novartis. He has received consultancy fee payments to his institution from AstraZeneca, Boehringer Ingelheim, Ionis Pharmaceuticals, and KBP Biosciences. He has received fee payments as a trial investigator from AstraZeneca, Novartis, and Theracos. He has received lecture fees to self from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus. He has received financial support to his institution from Amgen, AstraZeneca, Cytokinetics, GSK, Ionis Pharmaceuticals, KBP Biosciences, Novartis, and Theracos for attending meetings. A.A.V. has received consulting fee payments to his institution from AstraZeneca, Bayer AG, Boehringer Ingelheim, AnaCardio, Cytokinetics, Eli Lilly, Merck, Moderna, Novartis, Novo Nordisk and Pfizer. C.M.O'C. has received consulting fee payments to self from Abiomed, Bristol Myers Squibb, Merck, Pegasus, Renovacor Inc., Windtree Therapeutics, and Zealcare. J.R.T. has received grants from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Cytokinetics, EBR Systems, Medtronic, Novartis, ViCardia, and Windtree Therapeutics. He has received consulting fee payments from 3ive Labs, Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Medtronic, Merck, Novartis, Verily, ViCardia, and Windtree Therapeutics. He has received payment for data safety monitoring board membership from Cardurion. He is president of the Heart Failure Society of America. G.M.F. has received research grants to his institution from Amgen, Bayer, CSL, and Cytokinetics. He has received consulting fee payments to self from Abbott, American Regent, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cardionomic, Cytokinetics, Medtronic, Myovant, Novartis, Reprieve, Sequana, Windtree Therapeutics, and Whiteswell. He has received payment for data safety monitoring board membership from Amgen, EBR Systems, LivaNova, Medtronic, Merck, Rocket Pharma, Siemens, and V-Wave. All other authors have nothing to disclose.

References

1. Nelson GI, Silke B, Ahuja RC, Hussain M, Taylor SH. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart-failure following myocardial infarction. *Lancet* 1983;**1**:730–733. https://doi.org/10.1016/s0140-6736(83)92025-1
2. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, *et al.* Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998;**351**:389–393. https://doi.org/10.1016/S0140-6736(97)08417-1

3. 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
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.*; ESC Scientific Document Group. 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
5. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, *et al.* 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018;**137**:961–972. https://doi.org/10.1161/CIRCULATIONAHA.117.033502
6. Kozhuharov N, Goudev A, Flores D, Maeder MT, Walter J, Shrestha S, *et al.*; GALACTIC Investigators. Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure rehospitalization among patients with acute heart failure: The GALACTIC randomized clinical trial. *JAMA* 2019;**322**:2292–2302. https://doi.org/10.1001/jama.2019.18598
7. Filippatos G, Angermann CE, Cleland JGF, Lam CSP, Dahlström U, Dickstein K, *et al.* Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure. *JAMA Cardiol* 2020;**5**:401–410. https://doi.org/10.1001/jamacardio.2019.5108
8. Cleland JGF, Pfeffer MA, Clark AL, Januzzi JL, McMurray JJV, Mueller C, *et al.* The struggle towards a universal definition of heart failure – How to proceed? *Eur Heart J* 2021;**42**:2331–2343. https://doi.org/10.1093/eurheartj/ehab082
9. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, *et al.* Diuretic response in acute heart failure: Clinical characteristics and prognostic significance. *Eur Heart J* 2014;**35**:1284–1293. https://doi.org/10.1093/eurheartj/ehu065
10. Pellicori P, Cleland JGF, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P, *et al.* Cardiac dysfunction, congestion and loop diuretics: Their relationship to prognosis in heart failure. *Cardiovasc Drugs Ther* 2016;**30**:599–609. https://doi.org/10.1007/s10557-016-6697-7
11. Cleland JG, Carubelli V, Castiello T, Yassin A, Pellicori P, Antony R. Renal dysfunction in acute and chronic heart failure: Prevalence, incidence and prognosis. *Heart Fail Rev* 2012;**17**:133–149. https://doi.org/10.1007/s10741-012-9306-2
12. Pellicori P, Platz E, Dauw J, ter Maaten JM, Martens P, Pivetta E, *et al.* Ultrasound imaging of congestion in heart failure: Examinations beyond the heart. *Eur J Heart Fail* 2021;**23**:703–712. https://doi.org/10.1002/ejhf.2032
13. Dupuis J, Lalonde G, Lemieux R, Rouleau JL. Tolerance to intravenous nitroglycerin in patients with congestive heart failure: Role of increased intravascular volume, neurohumoral activation and lack of prevention with N-acetylcysteine. *J Am Coll Cardiol* 1990;**16**:923–931. https://doi.org/10.1016/s0735-1097(10)80342-0
14. Good JM, Brady AJ, Noormohamed FH, Oakley CM, Cleland JG. Effect of intense angiotensin II suppression on the diuretic response to furosemide during chronic ACE inhibition. *Circulation* 1994;**90**:220–224. https://doi.org/10.1161/01.cir.90.1.220
15. Vardeny O, Claggett B, Kachadourian J, Desai AS, Packer M, Rouleau J, *et al.* Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: The PARADIGM-HF trial. *Eur J Heart Fail* 2019;**21**:337–341. https://doi.org/10.1002/ejhf.1402
16. Felker GM, Borentain M, Cleland JG, DeSouza MM, Kessler PD, O'Connor CM, *et al.* Rationale and design for the development of a novel nitroxyl donor in patients with acute heart failure. *Eur J Heart Fail* 2019;**21**:1022–1031. https://doi.org/10.1002/ejhf.1504
17. Felker GM, McMurray JJV, Cleland JG, O'Connor CM, Teerlink JR, Voors AA, *et al.* Effects of a novel nitroxyl donor in acute heart failure: The STAND-UP AHF study. *JACC Heart Fail* 2021;**9**:146–157. https://doi.org/10.1016/j.jchf.2020.10.012
18. Cowart D, Venuti RP, Lynch K, Guptill JT, Noveck RJ, Foo SY. A phase 1 randomized study of single intravenous infusions of the novel nitroxyl donor BMS-986231 in healthy volunteers. *J Clin Pharmacol* 2019;**59**:717–730. https://doi.org/10.1002/jcph.1364
19. Irvine JC, Kemp-Harper BK, Widdop RE. Chronic administration of the HNO donor Angeli's salt does not lead to tolerance, cross-tolerance, or endothelial dysfunction: Comparison with GTN and DEA/NO. *Antioxid Redox Signal* 2011;**14**:1615–1624. https://doi.org/10.1089/ars.2010.3269
20. Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland JGF. The effects of short-term omission of daily medication on the pathophysiology of heart failure. *Eur J Heart Fail* 2017;**19**:643–649. https://doi.org/10.1002/ejhf.1346
21. Pellicori P, Shah P, Cuthbert J, Urbinati A, Zhang J, Kallvikbacka-Bennett A, *et al.* Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. *Eur J Heart Fail* 2019;**21**:904–916. https://doi.org/10.1002/ejhf.1383
22. Ling HZ, Flint J, Damgaard M, Bonfils PK, Cheng AS, Aggarwal S, *et al.* Calculated plasma volume status and prognosis in chronic heart failure. *Eur J Heart Fail* 2015;**17**:35–43. https://doi.org/10.1002/ejhf.193
23. Cotter G, Moshkovitz Y, Kaluski E, Cohen AJ, Miller H, Goor D, *et al.* Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance. *Chest* 2004;**125**:1431–1440. https://doi.org/10.1378/chest.125.4.1431
24. Bhavya G, Nagaraja PS, Singh NG, Ragavendran S, Sathish N, Manjunath N, *et al.* Comparison of continuous cardiac output monitoring derived from regional impedance cardiography with continuous thermodilution technique in cardiac surgical patients. *Ann Card Anaesth* 2020;**23**:189–192. https://doi.org/10.4103/aca.ACA_1_19
25. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria. https://www.R-project.org/: R Foundation for Statistical Computing; 2022.
26. Lang NN, Ahmad FA, Cleland JG, O'Connor CM, Teerlink JR, Voors AA, *et al.* Haemodynamic effects of the nitroxyl donor cimlanod (BMS-986231) in chronic heart failure: A randomized trial. *Eur J Heart Fail* 2021;**23**:1147–1155. https://doi.org/10.1002/ejhf.2138
27. Shoaib A, Waleed M, Khan S, Raza A, Zuhair M, Kassianides X, *et al.* Breathlessness at rest is not the dominant presentation of patients admitted with heart failure. *Eur J Heart Fail* 2014;**16**:1283–1291. https://doi.org/10.1002/ejhf.153
28. McKay CR, Chatterjee K, Ports TA, Holly AN, Parmley WW. Minoxidil therapy in chronic congestive heart failure: Acute plus long-term hemodynamic and clinical study. *Am Heart J* 1982;**104**:575–580. https://doi.org/10.1016/0002-8703(82)90229-0
29. Arend SM, Bax JJ, Hermans J, van der Wall EE, Sedney MI. The short-term effect of intravenous nitroglycerin on haematocrit; an additional benefit in patients with myocardial ischaemia? *Eur Heart J* 1994;**15**:114–119. https://doi.org/10.1093/oxfordjournals.eurheartj.a060362
30. Parker JD, Farrell B, Fenton T, Cohanim M, Parker JO. Counter-regulatory responses to continuous and intermittent therapy with nitroglycerin. *Circulation* 1991;**84**:2336–2345. https://doi.org/10.1161/01.cir.84.6.2336
31. Münzel T, Drexler H, Holtz J, Kurtz S, Just H. Mechanisms involved in the response to prolonged infusion of atrial natriuretic factor in patients with chronic heart failure. *Circulation* 1991;**83**:191–201. https://doi.org/10.1161/01.cir.83.1.191
32. Owan TE, Chen HH, Frantz RP, Karon BL, Miller WL, Rodeheffer RJ, *et al.* The effects of nesiritide on renal function and diuretic responsiveness in acutely decompensated heart failure patients with renal dysfunction. *J Card Fail* 2008;**14**:267–275. https://doi.org/10.1016/j.cardfail.2007.12.002
33. Sica D, Oren RM, Gottwald MD, Mills RM; Scios 351 Investigators. Natriuretic and neurohormonal responses to nesiritide, furosemide, and combined nesiritide and furosemide in patients with stable systolic dysfunction. *Clin Cardiol* 2010;**33**:330–336. https://doi.org/10.1002/clc.20787
34. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, *et al.* Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;**365**:32–43. https://doi.org/10.1056/NEJMoa1100171
35. ter Maaten JM, Dunning AM, Valente MAE, Damman K, Ezekowitz JA, Califf RM, *et al.* Diuretic response in acute heart failure – An analysis from ASCEND-HF. *Am Heart J* 2015;**170**:313–321. https://doi.org/10.1016/j.ahj.2015.05.003
36. Wan SH, Stevens SR, Borlaug BA, Anstrom KJ, Deswal A, Felker GM, *et al.* Differential response to low-dose dopamine or low-dose nesiritide in acute heart failure with reduced or preserved ejection fraction: Results from the ROSE AHF trial (Renal Optimization Strategies Evaluation in Acute Heart Failure). *Circ Heart Fail* 2016;**9**:e002593. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002593
37. Metra M, Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, *et al.*; RELAX-AHF-2 Committees Investigators. Effects of serelaxin in patients with acute heart failure. *N Engl J Med* 2019;**381**:716–726. https://doi.org/10.1056/NEJMoa1801291
38. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, *et al.*; RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): A randomised, placebo-controlled trial. *Lancet* 2013;**381**:29–39. https://doi.org/10.1016/S0140-6736(12)61855-8
39. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, *et al.*; RELAX-AHF Investigators. Diuretic response in patients with acute decompensated heart failure: Characteristics and clinical outcome – An analysis from RELAX-AHF. *Eur J Heart Fail* 2014;**16**:1230–1240. https://doi.org/10.1002/ejhf.170

40. Gimpelewicz C, Metra M, Cleland JGF, Szecsödy P, Chang Wun CC, Boer-Martins L, *et al.* Effects of serelaxin on the outcome of patients with or without substantial peripheral edema: A subgroup analysis from the RELAX-AHF trial. *Am Heart J* 2017;**190**:113–122. https://doi.org/10.1016/j.ahj.2017.05.012
41. Njoroge JN, Teerlink JR. Pathophysiology and therapeutic approaches to acute decompensated heart failure. *Circ Res* 2021;**128**:1468–1486. https://doi.org/10.1161/CIRCRESAHA.121.318186
42. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. *Nat Rev Cardiol* 2013;**10**:156–170. https://doi.org/10.1038/nrcardio.2012.191
43. Damy T, Hobkirk J, Walters M, Ciobanu A, Rigby AS, Kallvikbacka-Bennett A, *et al.* Development of a human model for the study of effects of hypoxia, exercise, and sildenafil on cardiac and vascular function in chronic heart failure. *J Cardiovasc Pharmacol* 2015;**66**:229–238. https://doi.org/10.1097/FJC.0000000000000262
44. Kohan DE, Cleland JG, Rubin LJ, Theodorescu D, Barton M. Clinical trials with endothelin receptor antagonists: What went wrong and where can we improve? *Life Sci* 2012;**91**:528–539. https://doi.org/10.1016/j.lfs.2012.07.034
45. Cleland JG, Oakley CM. Vascular tone in heart failure: The neuroendocrine-therapeutic interface. *Br Heart J* 1991;**66**:264–267. https://doi.org/10.1136/hrt.66.4.264