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Haemodynamic and clinical effects of ularitide in decompensated heart failure

Veselin Mitrovic[1], Petar M. Seferovic[2], Dejan Simeunovic[2], Arsen D. Ristic[2], Milutin Miric[3], Valentin S. Moiseyev[4], Zhanna Kobalava[4], Klaus Nitsche[5], Wolf-Georg Forssmann[6], Hartmut Lüss[7], and Markus Meyer[7]*

[1] Kerckhoff-Klinik, Bad Nauheim, Germany; [2] Department of Cardiology, Institute for Cardiovascular Diseases, University Medical Center of Serbia, Belgrade, Serbia; [3] 'Zvezdara' University Clinical and Medical Center, Belgrade, Serbia; [4] Russian Peoples Friendship University, Moscow, Russian Federation; [5] Hospital St. Vincenz, Limburg, Germany; [6] Division of Experimental and Clinical Peptide Research, Center of Pharmacology and Toxicology, Hannover Medical School, Hannover, Germany; and [7] CardioPep Pharma GmbH, Karl-Wiechert-Allee 76, D-30625 Hannover, Germany

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Randomized clinical trial

Aims Ularitide is a synthetic form of urodilatin, a natriuretic peptide produced in the kidney with vasodilating, natriuretic, and diuretic effects, that offers promise for the management of decompensated heart failure (DHF). We assessed the efficacy and safety of ularitide in treating patients with DHF.
Methods and results In this Phase II randomized, double-blind, placebo-controlled trial, 221 DHF patients received either placebo ($n = 53$) or ularitide at 7.5 ng/kg/min ($n = 60$), 15 ng/kg/min ($n = 53$), or 30 ng/kg/min ($n = 55$) as a 24-h continuous infusion. At 6 h, ularitide demonstrated a significant decrease in pulmonary capillary wedge pressure ($P = 0.052$, $P = 0.000004$, $P = 0.000002$, respectively) and improved dyspnoea score in the 7.5, 15, and 30 ng/kg/min ularitide group ($P = 0.0026$, $P = 0.0026$, $P = 0.0013$, respectively). Ularitide reduced systemic vascular resistance and increased cardiac index for the 15 and 30 ng/kg/min groups ($P = 0.017$, $P = 0.00002$, respectively). Systolic blood pressure (BP) decreased dose dependency. Heart rate and serum creatinine were unchanged through day 3. Most frequently reported drug-related adverse events through day 3 in all ularitide groups were dose-dependent BP decrease and hypotension.
Conclusion Ularitide lowered cardiac filling pressures and improved dyspnoea without apparent early deleterious effects on renal function in DHF patients. These results suggest that ularitide may play a role in the management of DHF.

Introduction

Heart failure (HF) is a major, expanding public health problem with a poor prognosis and also the most common cause for hospitalization of elderly patients and accounts for ~60% of treatment costs.[1]

Ularitide is a synthetic form of urodilatin, a natriuretic peptide hormone secreted by the kidney.[2] The natriuretic peptide family comprises peptides characterized by a 17-amino-acid ring structure differing in six positions and varying markedly in amino- and carboxy-terminal amino acid sequences.[3] Whereas C-type natriuretic peptide (CNP) is secreted by the endothelium, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are secreted by the heart. In healthy volunteers, these molecules regulate vascular and renal homeostasis[4–6] increase vasodilation and urinary sodium, chloride, and volume excretion[7–10] and decrease neurohumoral vasoconstrictor activation.[9,11,12] In contrast to ANP, BNP, and CNP, endogenous urodilatin is synthesized in renal distal tubular cells. Following luminal secretion, urodilatin binds downstream natriuretic peptide type A receptors in the inner medullary collecting duct, regulating renal sodium and water excretion.

The immediate clinical goal in managing decompensated heart failure (DHF) is to provide symptom relief and to stabilize the patients' haemodynamics. Therapeutic options include diuretics, vasodilators, and positive inotropic agents; however, each of these options is associated with clinical limitations.[13–16] Data from meta-analyses have raised concerns of an increased risk of renal deterioration and mortality in DHF patients administered nesiritide.[13–14] Thus, the search for agents that improve DHF signs and symptoms and preserve renal function without increasing mortality risk has been an area of ongoing research.

In pilot studies, ularitide demonstrated beneficial effects in congestive heart failure (CHF)[17] and acute DHF (ADHF).[18] Bolus injections in ADHF patients stimulated diuresis and natriuresis and significantly reduced pulmonary capillary

* Corresponding author. Tel: +49 511 53045 18; fax: +49 511 53045 10.
E-mail address: mmeyer@cardiopep.de

wedge pressure (PCWP) and systemic vascular resistance (SVR).[18] Further, in the SIRIUS I study, 24-h ularitide infusions reduced PCWP.[19] This Phase II study, SIRIUS II, evaluated the haemodynamic and clinical effects of intravenous (iv) ularitide added to standard therapy in hospitalized DHF patients with dyspnoea at rest or minimal physical activity.

Methods

Study design

This randomized, double-blind, placebo-controlled study in patients with DHF was performed in 13 German, two Serbian, and four Russian centres. Patients were randomized to receive ularitide (7.5, 15, or 30 ng/kg/min) or placebo as a constant 24-h infusion. At initiation of the trial, separate randomization lists were generated for each study centre. Randomization was performed in blocks with each block comprising eight patient numbers; the statistics department of the clinical research organization was responsible for study management and evaluation. Double-blind study medication was prepared according to the assignment scheme. Eligible patients were assigned consecutive random numbers in the order of their inclusion into the trial.

All patients received standard care, including cardiovascular medication. During a 5-h period (beginning 3 h before initiating study drug infusion), iv diuretics, angiotensin-converting enzyme (ACE) inhibitors, vasoactive drugs, phosphodiesterase (PDE) inhibitors, and new iv administration of dopamine/dobutamine were excluded. Ongoing dopamine/dobutamine infusions were continued at a constant dose during this 5-h period. At their discretion, investigators administered diuretics based on patients' haemodynamic and clinical state.

Haemodynamic parameters such as PCWP, right atrial pressure (RAP), and cardiac output (CO) were measured before, during, and 2 h after end of the infusion. Before, at 6 h, and at 24 h after the start of infusion, dyspnoea was assessed independently by the patient and the investigator and samples of pulmonary artery blood were taken for assessment of oxygen saturation. Blood pressure (BP), heart rate (HR), and electrocardiographic (ECG) status were closely monitored throughout the infusion. Adverse events (AEs) were recorded, and serum creatinine (SCr) levels were measured at −60 min, 24, 48, and 72 h after start of dosing and in case of an AE/serious adverse event (SAE). SAEs and mortality were monitored through day 30.

Before and at the end of infusion, safety laboratory assessments (clinical chemistry, haematology, and urinalysis) were performed. At the end of the 30-day follow-up, the investigator contacted each patient or the patient's family doctor to assess rehospitalization and mortality.

Administration of study drug

Ularitide (CardioPep Pharma GmbH, Hannover, Germany), supplied as 1 mg of lyophilized powder containing 10-mg mannitol as an excipient in glass vials, was reconstituted and further diluted with an aqueous solution of 0.9% NaCl.[19] The same procedure was performed for placebo vials containing mannitol only. Medication vials and prepared infusion solution were not distinguishable by study personnel.

Patient population

The study enrolled 221 white patients admitted to the hospital for DHF [cardiac index (CI) $\leq$2.5 L/min/m^2; mean PCWP] $\geq$18 mmHg) and dyspnoea (at rest or with minimal physical activity). Immediately before dosing, four patients did not have a PCWP $\geq$18 mmHg (1, 2, and 1 in the placebo, 7.5-, and 30-ng ularitide group, respectively); however, these patients fulfilled the inclusion criteria at −30 min and were included into the analysis due to the intent-to-treat (ITT) principle. All patients suffered from decompensation of chronic HF due to hypertensive heart disease, coronary heart disease, or dilative cardiomyopathy evaluated by angiography, ECHO, ECG findings, and medical history. All patients gave written informed consent before entry into the study. Baseline haemodynamic measures were CI, mean of 1.9 L/min/m^2; PCWP, mean of 25 mmHg; and ejection fraction, $<$40% (95% of patients). Among the different groups, median interval from time of hospitalization to start of study-drug infusion ranged from 2 to 3 days. All patients had right-sided heart catheterization. Exclusion criteria included *de novo* DHF, systolic blood pressure (SBP) $\leq$90 mmHg, myocardial infarction within the 4 weeks before study entry, severe stenotic valvular diseases, SCr $>$2.5 mg/dL, and cardiogenic shock.

Data of all 221 patients who were randomized to treatment represented the safety population and were also analysed with group assignment according to the ITT principle.

Efficacy endpoint assessments

The co-primary endpoints at 6 h were (i) change in PCWP compared with placebo and (ii) changes in the patient's self-assessed dyspnoea score, conducted without direct interaction with the investigator, compared with placebo.

Haemodynamics

Haemodynamic parameters PCWP, RAP, and CO were determined by right-sided heart catheterization using a 7F Swan-Ganz thermodilution catheter. CO measurements at −30 min and immediately before dosing were not allowed to vary by 15% or more. If variation was $>$15% (i.e. in haemodynamically unstable patients and in those with atrial fibrillation), additional measurements were performed, whereby care was taken to minimize effects of excessive fluid intake. When CO variability was $<$15%, infusion was started later. Haemodynamic parameters were then measured at +30 min; at 1, 2, 4, 6, 8, and 24 h of dosing; and 2 h after the end of dosing (26 h). CI and SVR were calculated by standard formulas. Myocardial oxygen consumption (MVO_2) was calculated using the formula of Rooke and Feigl.[20]

Patient-assessed dyspnoea

At baseline, dyspnoea was assessed as being very severely, severely, moderately, slightly, or not impaired. At 6 h, patients self-assessed the relative change of dyspnoea compared with baseline that was recorded by 7-point Likert scale (minimally, moderately, markedly worse; unchanged; minimally, moderately, markedly better) as described earlier.[21] Patient-assessed dyspnoea was blinded to haemodynamic measurement. We attempted to reduce potential bias by performing dyspnoea self-assessment before haemodynamic measurements, each assisted by different staff members, and by prohibiting investigators from discussing these measurements or assisting patients with completing the symptom evaluation. Nonetheless, multiple haemodynamic measurements were obtained before these dyspnoea assessments, which may have biased the results.

Global clinical status

Changes in global clinical status (GCS) relative to baseline, assessed by the investigator, were recorded by 7-point Likert scale.[21] Here, specific symptoms of CHF (i.e. dyspnoea, fatigue) were assessed. We attempted to reduce potential bias by assessing GCS before haemodynamic measurements.

Renal parameters

Creatinine clearance (CL_{CR}) was estimated from SCr using the Cockroft–Gault equation.[22] This formula has been validated in

several studies of CHF and renal dysfunction but is used only if SCr is measured by the Jaffé method.[23]

N-terminal-proBNP

Plasma concentrations of N-terminal-proBNP (NT-proBNP) were measured in venous blood using the Elecsys 2010 proBNP sandwich-immunoassay system (Roche Diagnostics, Mannheim, Germany) with an analytical range of 20 to 35 000 pg/mL.

Safety endpoint assessments

Enrolled patients were hospitalized and monitored for BP, HR, ECG, and AEs, the last of which was recorded through 72 h. If SBP decreased to $\leq$80 mmHg, confirmed by a control measurement within 5 min, the infusion was interrupted and this event was recorded as an AE. Fluid intake and urine output were documented. Fluid balance was calculated and adjusted according to cardiac filling pressures. A follow-up phone call was made on day 30 for assessment of SAEs and vital status.

Statistical analysis

All efficacy and safety parameters were described and summarized by treatment group and time point [*n*, arithmetic mean, standard deviation (SD), median, minimum, maximum].

The absolute change from baseline in PCWP was evaluated by repeated measures mixed effects analysis of covariance, including baseline as covariate, treatment, and time of assessment as factors as well as treatment-by-assessment interaction. Patients within the treatment group were considered random factors. All differences between treatments were estimated together with a 95% confidence interval. To assess the influence of the baseline adjustment, the test was repeated without the baseline covariate but using the same statistical model.

The statistical interpretation of these data with respect to the primary endpoint (the change in PCWP at 6 h) followed a hierarchical test principle: if the overall *F*-test gave an indication of a global difference between treatment means ($P < 0.05$), the active doses were compared with placebo, starting with the highest dose and ending if one comparison was assessed with a *P*-value larger than 0.05. All active doses showing a significant difference compared with placebo were then compared against each other. Because of the hierarchical test principle, all tests were performed at the local 5% level and no alpha-adjustment was necessary.

P-values for comparisons between treatments were also derived for other parameters, and time points of interest for quantitative parameters using the same methods as described earlier, but without inspection or interpretation of *P*-values for the main effects. These *P*-values can be interpreted as a descriptive measure of the strength of evidence, independent of the scale of measurement, but should not be interpreted as statistical proof of any actual or assumed differences.

The dyspnoea score and global status were described by frequency tables in terms of counts and percentages. Data were analyzed by assessor and time point with the Uleman test, a version of the Mann–Whitney *U*-test for parameters with a low number of outcomes. This test is most suited for frequency tables with ordered categories, whereas the commonly applied Mantel–Haenszel test does not utilize ordering information. Some categories were represented with very low frequencies only; so the results were summarized by showing only the percentages of patients with scores moderately or markedly better, whereas the Uleman test took into account all categories.[24] The same procedure was applied to the scores for GCS.

AEs were coded using the MedDRA dictionary. The incidence of each AE (coded by preferred term) and the number and percentage of subjects experiencing each were determined within each treatment group.

A mean baseline value of 25 mmHg for PCWP was expected in the specified patient population. Assuming that treatment with 0, 7.5, 15, or 30 ng/kg/min ularitide would lead to changes of 0, 2.5, 3.75, or 5 mmHg and that such changes would exhibit an SD of 7.0 mmHg, the estimation of sample size for an analysis of variance procedure with alpha = 0.05, and power = 90%, led to the decision to enroll about 50 patients per group. The assumed SD is consistent with the results of Colucci *et al*.[25]

Results

Patient enrolment

Between February 2003 and October 2004, 221 patients were randomized (53 patients in the placebo group, 60 in the 7.5 ng/kg/min ularitide group, 53 in the 15 ng/kg/min ularitide group, and 55 in the 30 ng/kg/min ularitide group), of which 220 were treated with study drug or placebo over 24 h (*Figure 1*).

Baseline characteristics

Of the 221 randomized patients, 173 (78.3%) were men and 48 (21.7%) were women. The mean study population age was 61 years. Demographic characteristics were comparable among the four treatment groups. There were no relevant differences in age, height, or weight. All subjects were white (*Table 1*).

Mean haemodynamics at baseline were comparable among the different groups with respect to CI, PCWP, and

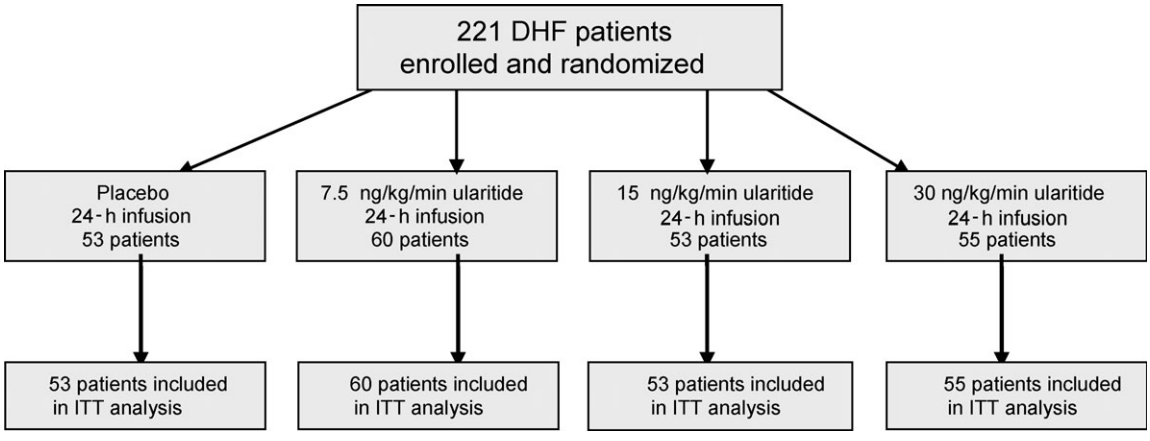

Figure 1 Study flow diagram and patient disposition.

Table 1 Baseline demographics, haemodynamics at enrolment, and medical history

	Placebo ($n = 53$)	Ularitide (ng/kg/min)		
		7.5 ($n = 60$)	15 ($n = 53$)	30 ($n = 55$)
Demographics (mean ± SD)				
Age (years)	60.6 ± 12.3	59.9 ± 13.9	59.8 ± 10.8	61.5 ± 13.8
Height (cm)	174.1 ± 8.9	174.0 ± 8.7	173.7 ± 10.3	174.1 ± 9.4
Weight (kg)	81.0 ± 15.6	85.1 ± 16.8	83.9 ± 18.0	82.7 ± 16.3
Male, *n* (%)	44 (83.0)	50 (83.3)	37 (69.8)	42 (76.4)
Haemodynamics mean ± SD				
HR (b.p.m.)	76.4 ± 2.5	77.8 ± 13.9	75.7 ± 11.8	78.5 ± 13.7
SBP (mmHg)	127.4 ± 19.9	126.1 ± 24.6	124.9 ± 17.6	123.9 ± 21.5
DBP (mmHg)	74.5 ± 12.7	78.5 ± 13.9	77.3 ± 10.6	76.5 ± 13.3
CI (L/min/m^2)	1.9 ± 0.4	1.9 ± 0.4	1.9 ± 0.3	1.9 ± 0.4
PCWP (mmHg)	24.9 ± 6.0	24.4 ± 6.4	25.7 ± 5.8	25.4 ± 5.0
Ejection fraction (≤40%) *n* (%)	50 (94.3)	57 (95)	52 (98.1)	48 (87.3)
NT-proBNP (pg/mL) (median)	3064	3524	2641	2937
Renal function (mean ± SD)				
CL_{CR} (mL/min)	78.3 ± 34.1	85.4 ± 36.6	79 ± 36.0	75.3 ± 30.3
Cause of HF *n* (%)				
ICM	28 (52.8)	28 (46.7)	30 (56.6)	28 (50.9)
DCM	17 (32.1)	25 (41.7)	19 (35.8)	19 (34.5)
HHD	8 (15.1)	7 (11.7)	4 (7.5)	6 (10.9)
Diabetes *n* (%)	16 (30.2)	19 (31.7)	15 (28.3)	29 (52.7)

EF, ejection fraction; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease.

Table 2 Previous and concomitant cardiac medication

Drug *n* (%)	Previous medication *n* (%)				Concomitant medication during study drug infusion *n* (%)			
	Placebo ($n = 53$)	Ularitide (ng/kg/min)			Placebo ($n = 53$)	Ularitide (ng/kg/min)		
		7.5 ($n = 60$)	15 ($n = 53$)	30 ($n = 55$)		7.5 ($n = 60$)	15 ($n = 53$)	30 ($n = 55$)
Diuretics	49 (92.5)	56 (93.3)	50 (94.3)	53 (96.4)	43 (81.1)	51 (85.0)	41 (77.4)	46 (83.6)
Loop diuretics	48 (90.6)	56 (93.3)	46 (88.5)	51 (92.7)	42 (79.2)	51 (85.0)	35 (67.3)	42 (76.4)
iv diuretics	35.8	31.7	30.8	41.8	3.8	5.0	5.8	5.4
Nitrates	25 (47.2)	26 (43.3)	31 (58.5)	21 (38.2)	16 (30.2)	20 (33.3)	19 (35.8)	15 (27.3)
Dobutamine	2 (3.8)	1 (1.7)	4 (7.7)	1 (1.8)	1 (1.9)	0	0	1 (1.8)
Continued at Baseline	NA	NA	NA	NA	1 (1.9)			1 (1.8)
New administration	NA	NA	NA	NA				
Dopamine	1 (1.9)	4 (6.7)	5 (9.4)	3 (5.5)	1 (1.9)	1 (1.7)	1 (1.9)	3 (5.5)
Continued at Baseline	NA	NA	NA	NA	1 (1.9)	1 (1.7)		3 (5.5)
New administration	NA	NA	NA	NA			1 (1.9)	
Digoxin	22 (41.5)	38 (63.3)	36 (67.9)	37 (67.3)	17 (32.1)	32 (53.3)	30 (56.6)	34 (61.8)
ACE inhibitors	47 (88.7)	50 (83.3)	41 (77.4)	43 (78.2)	46 (86.8)	48 (80.0)	40 (75.5)	40 (72.7)
AT-II-receptor blockers	2 (3.8)	4 (6.7)	3 (5.7)	4 (7.3)	1 (1.9)	5 (8.3)	3 (5.7)	4 (7.3)
β-blockers	39 (73.6)	49 (81.7)	36 (67.9)	37 (67.3)	35 (66.0)	47 (78.3)	37 (69.8)	33 (60.0)
Spironolactone	27 (50.9)	41 (68.3)	36 (67.9)	36 (65.5)	28 (52.8)	40 (66.7)	37 (69.8)	35 (63.6)
Aspirin	33 (62.3)	35 (58.3)	36 (67.9)	29 (52.7)	32 (60.4)	34 (56.7)	33 (62.3)	27 (49.1)
Warfarin	11 (20.8)	12 (20.0)	10 (18.9)	20 (36.4)	9 (17.0)	10 (16.7)	7 (13.2)	14 (25.5)

AT-II-receptor blockers, angiotensin II receptor blockers; NA, not applicable.

EF. Median NT-proBNP levels ranged from 2641 to 3524 pg/mL between treatment groups. Cardiovascular medical history was comparable for all four treatment groups. Fifty-two percent of the patients had ischaemic cardiomyopathy (ICM) as the primary aetiology of their CHF (47–57%) (*Table 1*). Main baseline medication consisted of diuretics, ACE-inhibitors, beta-blockers, digoxin, and nitrates (*Table 2*).

Primary endpoints

Pulmonary capillary wedge pressure

At 6 h, the primary endpoint, PCWP (*Figure 2A*), was significantly decreased in the two highest ularitide groups compared with placebo. In both the 15 and 30 ng/kg/min groups, PCWP was significantly reduced at 6 h compared with the 7.5 ng/kg/min group ($P = 0.005$, $P = 0.003$, respectively). There was no difference between the two highest dose groups ($P = 0.943$). Changes from baseline for the 15 and 30 ng/kg/min groups vs. placebo showed significant differences ($P = 0.031$, $P = 0.015$, respectively) 1 h after onset of infusion, lasting until 24 h; for 7.5 ng/kg/min group, these differences ($P = 0.008$) were first evident at 4 h, lasting until 24 h ($P = 0.014$) (*Figure 2A*). In this analysis, the baseline covariate, treatment and time of assessment were found to be highly significant ($P < 0.0001$), whereas there was no treatment-by-assessment interaction ($P = 0.3229$).

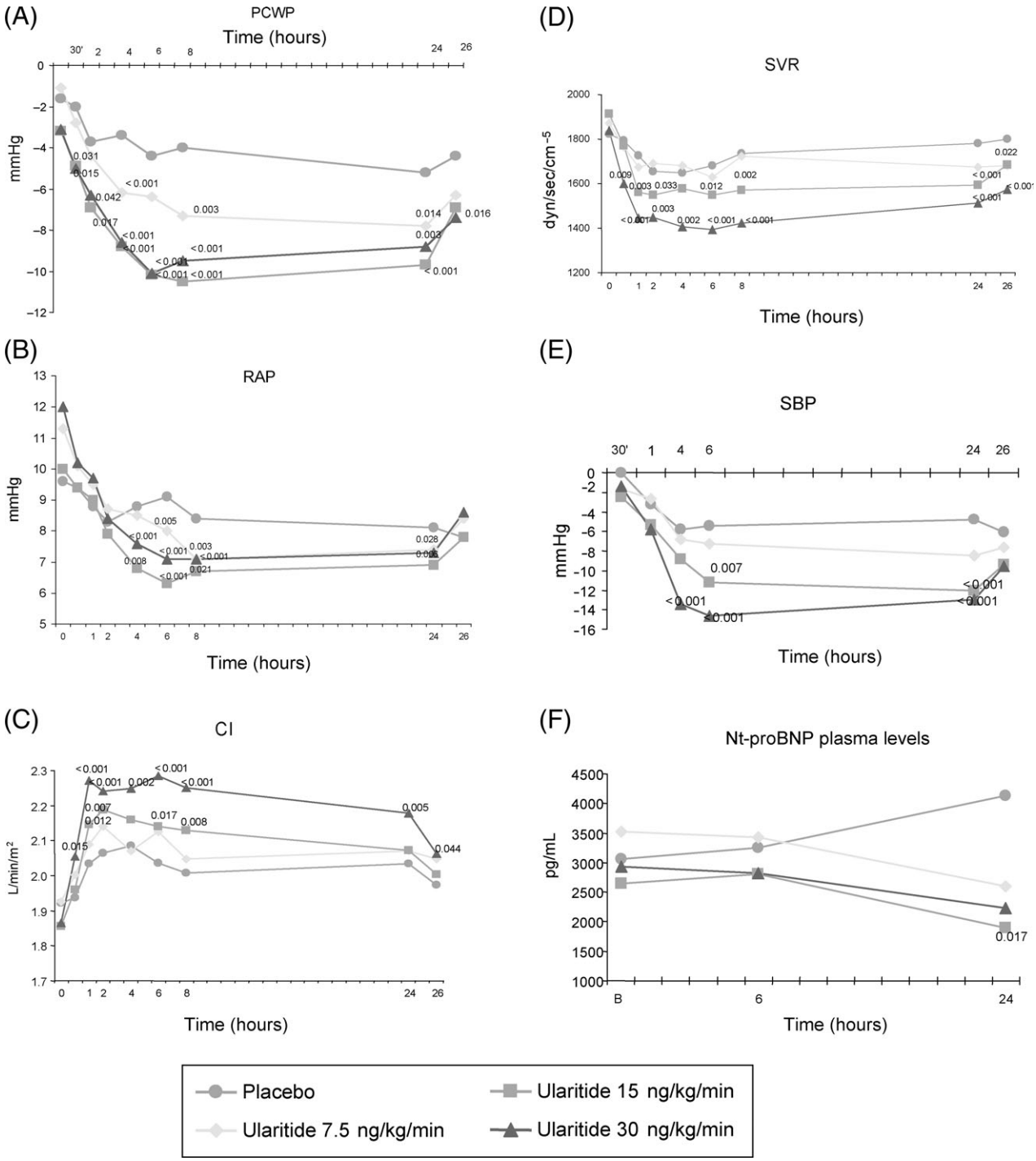

Figure 2 Haemodynamic parameters for placebo (•) and ularitide 7.5 ng/kg/min (◇), 15 ng/kg/min (■), 30 ng/kg/min (▲) dose groups. (*A*) Changes from baseline in PCWP. (*B*) Changes in RAP. (*C*) CI. (*D*) SVR. (*E*) SBP. (*F*) Nt-pro-BNP. *$P < 0.05$ vs. placebo. **$P < 0.01$ vs. placebo.

Patients' dyspnoea assessment

After 6 and 24 h of infusion, patients assessed dyspnoea and investigators assessed GCS relative to baseline each. For dyspnoea, at 6 h, all three ularitide groups differed significantly from the placebo group ($P = 0.0026$, $P = 0.0026$, and $P = 0.0013$ for the 7.5, 15, and 30 ng/kg/min ularitide groups, respectively). More patients in the ularitide groups assessed their changes in dyspnoea as moderately or markedly better, whereas the placebo group most frequently reported no change in dyspnoea. Deterioration in dyspnoea was reported by only one patient receiving placebo. Furthermore, at 24 h, more patients receiving ularitide in the three different dosages reported an improvement of dyspnoea compared with patients treated with placebo (*Figure 3*).

Haemodynamic effects

At baseline, RAP was markedly elevated in all groups. At 4 h, the 15 and 30 ng/kg/min ularitide treatment groups displayed decreased RAP compared with placebo ($P = 0.008$, $P = 0.001$, respectively), lasting until 24 h for the 7.5 and 30 ng/kg/min ularitide groups ($P = 0.028$, $P = 0.006$, respectively) (*Figure 2B*). The mean decrease observed among the 15 ng/kg/min patients at that time was twice that of the placebo group but not statistically larger.

In the 15 and 30 ng/kg/min ularitide groups, an increase in CI was already evident 1 h following start of infusion ($P = 0.013$, $P = 0.00003$, respectively). Throughout the infusion period and 2 h after end of dosing, CI remained elevated in the 30-ng/kg/min group. Ularitide at 15 ng/kg/min increased CI similarly ($P = 0.017$, $P = 0.008$, respectively) at 6 and 8 h (*Figure 2C*).

The time course of SVR mirrored that of CI. SVR decreased 1 h after start of dosing in the 15 and 30-ng/kg/min groups compared with placebo ($P = 0.003$, $P = 0.00009$, respectively), lasting through 24 h, except at 4 h for the 15-ng/kg/min group ($P = 0.123$) (*Figure 2D*).

SBP at baseline was 127.4 ± 19.9 mmHg (placebo), 126.1 ± 24.6 mmHg (7.5 ng/kg/min), 124.9 ± 17.6 mmHg (15 ng/kg/min), and 123.9 ± 21.5 mmHg (30 ng/kg/min). A dose-related decrease in SBP occurred during infusion (*Figure 2E*). After the end of infusion, SBP increased again in the 15 and 30 ng/kg/min ularitide groups. HR at baseline ranged from 75.5 ± 11.8 b.p.m. to 78.6 ± 14.0 b.p.m. among the groups. HR did not change and was not different among the groups (at +30 min, 1, 2, 4, 6, 8, 16, 24, and 26 h) with min. and max. mean changes from baseline of −1.0 to 2.0 b.p.m. (placebo), −2.8 to 1.5 b.p.m. (7.5 ng/kg/min), −1.4 to 2.6 b.p.m. (15 ng/kg/min), −2.2 to 1.8 b.p.m. (30 ng/kg/min) at those time points.

MVO_2 was decreased in a dose-dependent manner (mean changes from baseline in $\Delta \pm$ SD in % at 6/24 h): placebo, $-1 \pm 12.8 / -1.5 \pm 11.5$; ularitide 7.5 ng/kg/min, $-3.4 \pm 11.9 / -4.5 \pm 13.0$; ularitide 15 ng/kg/min, $-4.6 \pm 11.3 /$ to 5.7 ± 13.1; ularitide 30 ng/kg/min, $-7.6 \pm 11.4 / -5.4 \pm 19$.

GCS assessment

For patients' GCS, at 6 h, the two highest ularitide groups differed significantly from the placebo group ($P = 0.0039$, $P = 0.0013$ for the 15 and 30 ng/kg/min group, respectively) (*Figure 3*).

Previous and concomitant medications

Patients' baseline previous and concomitant medication is given in *Table 2*. Average doses of loop diuretics (furosemide equivalents) administered during dosing were 99 mg in placebo and 91 mg, 79 mg, and 115 mg in the 7.5, 15, and 30 ng/kg/min ularitide groups, respectively.

NT-proBNP

At baseline, median plasma NT-proBNP levels were pathologically elevated. No change was seen at 6 h in the ularitide groups vs. placebo (*Figure 2F*), but plasma NT-proBNP significantly decreased in the 15 ng/kg/min group and tended to decrease also in the 30 ng/kg/min group compared with placebo at 24 h ($P = 0.017$).

Renal effects and use of loop diuretics

Mean urine output did not differ significantly among all treatment groups and ranged from 1925 to 2309 mL/24 h (*Figure 4A*); mean fluid intake was comparable in all treatment groups (ranging from 1611 to 1855 mL/24 h). During dosing, loop diuretics tended to be given less frequently in the 15 ng/kg/min group (67.3%) compared with the placebo group (79.2%). At the end of dosing (24 h), SCr changes from baseline were not significant in all treatment groups except the 15 ng/kg/min ularitide group, which tended to display

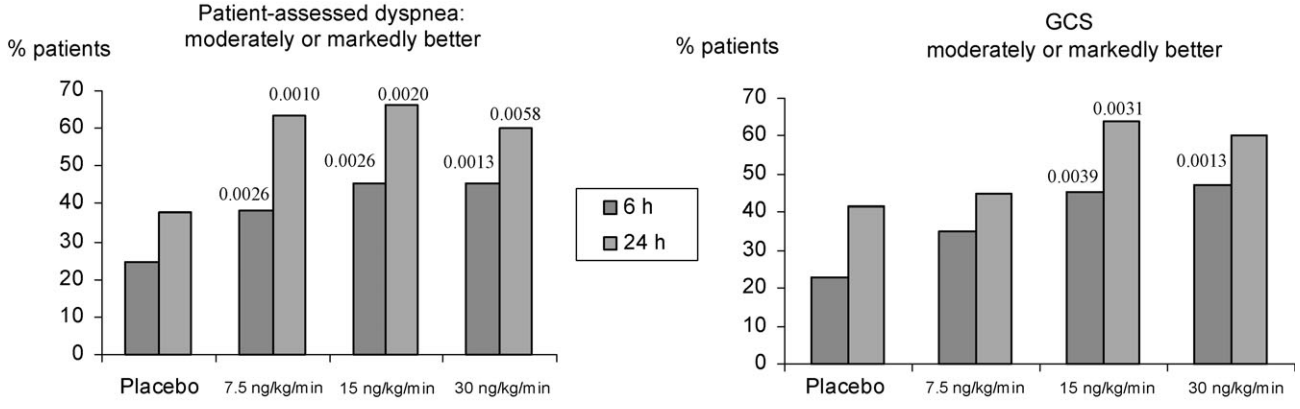

Figure 3 Dyspnoea improvement and global clinical status (GCS) assessment at 6 and 24 h. Summarized patients' dyspnoea and investigators's GCS assessments of 'moderately better' or 'markedly better.' *P*-values of tests vs. placebo, considering all scores.

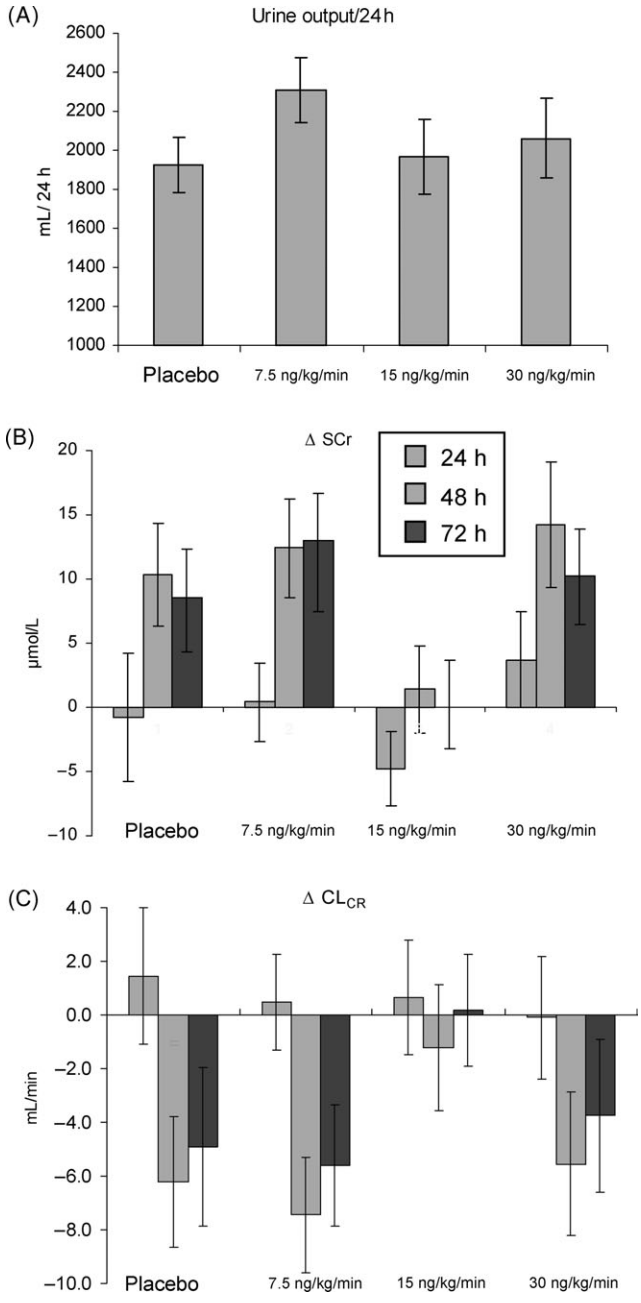

Figure 4 Renal parameters at 24, 48, and 72 h. (*A*) Urine output over 24 h. (*B*) Changes in SCr. (*C*) Changes in CL_{CR}; mean ± SEM.

decreased SCr. At 24 h, CL_{CR} tended to be increased in the placebo group relative to the ularitide groups while at 48 and 72 h CL_{CR} was decreased with both 7.5 and 30 ng/kg/min which, however, was also seen for placebo (*Figure 4B* and *C*).

Safety

An overview of safety results is given in *Table 3*. Most AEs were of mild to moderate intensity. Most frequently reported drug-related AEs in all ularitide groups were BP decrease (5.4%), hypotension (5.4%), sweating (4.2%), and dizziness (3.0%). BP decreases occurred usually 4–12 h after dosing start; about half were asymptomatic. For two patients after 7.5, four patients after 15, and seven patients after 30 ng/kg/min ularitide, infusion was temporarily interrupted because of decreased SBP to below 80 mmHg. For the same reason, only one patient in each ularitide group required permanent discontinuation of study drug. Time to complete resolution of hypotensions was approximately 0.5–1 h in most cases and lasted up to 4 h in four cases and 8 h in two cases. All patients recovered completely either by discontinuation of ularitide infusion or by elevation of legs and saline infusion.

Transiently decreased HR or bradycardia was reported for three patients in the 7.5-ng/kg/min group (5%), for one patient (1.8%) in the 30-ng/kg/min group, but for none in the 15-ng/kg/min and placebo groups. Although not reported in the placebo and 7.5-ng/kg/min group, increased HR or ventricular tachycardia occurred in two patients of the 15-ng/kg/min group (3.8%). Tachyarrhythmia was reported in one patient in the 30-ng/kg/min group (1.8%).

A total of 12 patients died during the study through day 30 (*Table 3*): seven patients (13.2%) in the placebo group, two patients (3.4%) in the 7.5-ng/kg/min group, two patients (3.8%) in the 15-ng/kg/min group, and one patient (1.8%) in the 30-ng/kg/min group. Of the seven placebo patients, five patients died between day 1 and 8, two patients between day 19 and 26. All placebo patients died of HF. Of five patients in the ularitide group, one patient died at day 1, and four patients died between day 11 and 13; three patients of HF and two patients of perforated duodenal ulcer and gastric bleeding. More patients had SAEs in the placebo group compared with the ularitide groups in both the day 1–3 and day 4–30 time periods (*Table 3*).

Median hospitalization time was shorter for the 15 and 30-ng/kg/min groups (122 and 158 h, respectively) compared with 201 and 192 h for placebo and 7.5 ng/kg/min groups, respectively; this difference was not statistically significant and requires further evaluation with larger numbers of patients.

Discussion

In the SIRIUS II trial, the synthetic natriuretic peptide ularitide significantly reduced PCWP and improved dyspnoea in patients with DHF when added to standard therapy. Ularitide exerted expected dose-dependent decreases in BP, as seen also for other vasodilators.[21,25–27] These results suggest that ularitide administered to DHF patients is clinically and haemodynamically active, without apparent deleterious effects on short-term renal function.

The favourable haemodynamic effects of ularitide were sustained through the end of the 24-h infusion period. These data show that ularitide infusion promptly and consistently lowers cardiac filling pressures and also leads to a decrease in MVO_2, a favourable effect in ICM.

An additional aim of the trial was to investigate changes in dyspnoea, a cardinal symptom in patients with DHF. Compared with placebo, patients receiving ularitide in all three dose groups reported more moderate and marked dyspnoea improvements after 6 and 24 h of infusion. These data support the findings of the pilot SIRIUS I study in which a similar trend was seen in a smaller number of patients.[19] Although the dyspnoea scoring assessment used in SIRIUS II is not validated, it has been commonly used in previous studies.[21] Patient's self-assessment may be affected by confounding variables (e.g. if the patient has a right-sided heart

Table 3 Adverse Events

	Placebo ($n = 53$)	Ularitide (ng/kg/min)		
		7.5 ($n = 60$)	15 ($n = 53$)	30 ($n = 55$)
Subjects with any AE day 1–3 *n* (%)	11 (20.8)	17 (28.3)	13 (24.5)	24 (43.6)
Subjects with any drug-related AE day 1–3 *n* (%)	4 (7.5)	10 (16.7)	7 (13.2)	11 (20.0)
Subjects with BP decrease/hypotension day 1–3 *n* (%)	2 (3.8)	5 (8.3)	7 (13.2)	9 (16.4)
Subjects with BP decrease/hypotension during infusion *n* (%)	1 (1.9)	5 (8.3)	6 (11.3)	9 (16.4)
Symptomatic	1 (1.9)	4 (6.7)	3 (5.7)	4 (7.3)
Asymptomatic	0 (0)	1 (1.7)	3 (5.7)	5 (9.1)
Subjects with infusions discontinued/interrupted due to SBP $<$80 mmHg *n* (%)				
Temporarily interrupted	0 (0)	2 (3.3)	4 (7.5)	7 (10.9)
Permanently discontinued	0 (0)	1 (1.7)	1 (1.9)	1 (1.8)
Subjects with any SAE *n* (%)				
Day 1–3	2 (3.8)	1 (1.7)	2 (3.8)	1 (1.8)
Day 4–30	7 (13.2)	4 (6.7)	3 (5.7)	5 (9.1)
Deaths *n*(%)				
Day 1–3	2 (3.8)	0 (0)	0(0)	1 (1.8)
Day 4–30	5 (9.4)	2 (3.3)	2 (3.8)	0 (0)

catheter in place or if haemodynamic parameters are known). In this trial, we attempted to reduce potential bias by performing dyspnoea self-assessment before haemodynamic measurements and by prohibiting investigators from discussing these measurements or assisting patients with completing the symptom evaluation. Also, in the placebo group treated with standard care, reduction of PCWP and an increase in CI were seen; however, it cannot be excluded that knowledge of the degree of PCWP reduction by the nursing and medical staff still might have indirectly affected a patient's self-assessment.

As a secondary endpoint, investigator-assessed patient GCS revealed an improvement in the two highest dose groups at 6 h, which lasted until 24 h in the 15-ng/kg/min group, thus supporting ularitide's beneficial effect on clinical outcome. However, compared with dyspnoea less patients reported an improvement in GCS, which was also reported elsewhere.[21] Even though assessment was performed before haemodynamic measurements, it cannot be excluded that the investigators' assessment could have been somewhat influenced by known haemodynamic parameters.

Reduced cardiac filling pressures that lower ventricular wall stress during ularitide infusions are also reflected in decreased plasma NT-proBNP concentrations. In contrast to placebo, where an increase in plasma NT-proBNP was detected, the two higher ularitide doses decreased NT-proBNP at 24 h, but the decrease was significant for only the 15 ng/kg/min ularitide group. Notably, the response of NT-proBNP was not seen at 6 h but was clearly evident at 24 h. Reductions in right and left ventricular filling pressures may result in a reduction of NT-proBNP with a time lag phase,[28] as shown in a smaller number of patients in the SIRIUS I study.[19] NT-proBNP secretion is controlled at the transcriptional level, usually requiring a longer-term stimulus.[29] Therefore, abrupt reductions in right and left ventricular filling pressures might not directly result in a reduction of NT-proBNP as an intermediate biomarker. The half-life of NT-proBNP is about 120 min, suggesting that haemodynamic changes could be reflected by this test approximately every 12 h.[29]

Renal function frequently deteriorates during treatment of patients hospitalized for HF, and minor increases in SCr are independently predictive of worsened outcome.[30] Therefore, agents that improve haemodynamics, leading to beneficial clinical effects but not deteriorating renal function, are needed for DHF treatment. Ularitide is known to induce renal effects such as diuresis and natriuresis in healthy volunteers.[9] Among the four treatment groups, there was no relevant difference in urine output over 24 h with comparable fluid intake, possibly because of downregulation of the natriuretic peptide A receptor (NPR-A) in CHF[31] or upregulation of neutral endopeptidase (NEP 24.11), an enzyme known to cleave natriuretic peptides. The latter mechanism was reported to be restricted to the kidneys of HF models,[32] which would explain the prominent haemodynamic and the lack of renal responsiveness to ularitide infusion. In addition, mild diuretic effects of ularitide may have been overshadowed by the stronger effects of loop diuretics given during dosing in a range of 91 to 115 mg in the different groups. Compared with placebo, 7.5, and 30-ng/kg/min groups, SCr levels tended to be decreased and CL_{CR} tended to be less decreased in the 15-ng/kg/min group through 72 h. Taken together, the current data demonstrate no evidence of deleterious renal effects induced by ularitide during the infusion and the 2-day follow-up period. Recent data from a meta-analysis raised concern about increased risk of renal deterioration in DHF patients administered nesiritide,[13] whereas in the VMAC trial no such increases were reported through 30 days.[21] Also a recent study reported beneficial effects of nesiritide on postoperative renal function, however, in patients undergoing cardiothoracic surgery.[33] In SIRIUS II short-term renal

effects of ularitide were investigated and therefore prospective trials with longer follow-up periods to investigate the long-term effects of ularitide on renal function are needed.

The most common drug-related AEs were hypotension and BP decrease. Patient baseline BPs in this study were comparable with those of DHF patients in other studies and registries.[21,34] If a patient was symptomatic, symptoms developed over several hours and were usually mild. Hypotension occurred at similar incidence rates with other vasodilators, including ANP,[26] nesiritide, or nitroglycerin administered in HF patients.[21,25,27] In the present study, cardiac arrhythmias, including bradycardia or tachycardia, occurred at low incidence rates, were transient, and resolved completely. In an earlier study, ularitide caused bradycardia and severe hypotension in one patient with CHF.[35] There was no major adverse safety signal with regard to mortality rate in the ularitide groups compared with placebo.

This study has potential limitations. In particular, bias may be introduced by the use of patient-assessed dyspnoea scores if the PCWP is possibly known by either the patient or the observer. In addition, in future studies, AEs and renal function data should be collected after hospitalization to investigate longer term adverse outcomes.

The SIRIUS II trial demonstrated that a 24 h infusion of ularitide at all three doses in patients with DHF resulted in prompt, consistent lowering of PCWP and LV pump function improvement associated with improvements in dyspnoea. Further, ularitide did not impair renal function during the evaluation period. We conclude that ularitide has potential for the treatment of patients with DHF, and future studies with this promising agent are warranted.

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Appendix

Safety Committee

M. Böhm (Department of Internal Medicine III, University Clinical Center of Saarland, Homburg, Germany).

S. Harder (Institute for Clinical Pharmacology, University Hospital Frankfurt, Germany).

J. Hartung (Statistician, Königswinter, Germany).

R. Hust (Focus Clinical Drug Development GmbH, Neuss, Germany).

Clinical Sites and Investigators

Germany

Division of Cardiology, Kerckhoff-Klinik, Bad Nauheim (V. Mitrovic), Hospital St. Vincenz, Limburg (K. Nitsche); Department of Internal Medicine B, Ernst-Moritz-Arndt-University, Greifswald (S.B. Felix, A. Staudt); University of Leipzig Heart Center, Leipzig (F.W. Mohr, D.V. Schmitt); Department of Internal Medicine III, University of Cologne (R. Schwinger, K. Frank); Evangelistic Hospital, Herne (W. Sehnert); Department of Cardiology, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen (D. Horstkotte, B. Lamp); Clinical Center Offenbach, Offenbach (H. Klepzig, G. Winten), Department of Medicine II, Clinical Center Kassel, Kassel (J. Neuzner, M. Möller); Department of Internal Medicine III Martin-Luther University Hospital Halle-Wittenberg, Halle/Saale (M. Buerke); Theresien Hospital and St. Hedwig Clinic, Mannheim (M. Haass, J. Rogalli); Department of Cardiology, Angiology and Pulmonology, Charité Campus, Humboldt University Berlin, Berlin (F. Knebel, S. Schattke); Department of Medicine, Schwalmstadt Clinic, Schwalm-Eder-Kliniken GmbH, Schwalmstadt (R. Zotz, P. Wild).

Serbia and Montenegro

Institute for Cardiovascular Diseases, University Medical Center of Serbia, Belgrade, (P.M. Seferovic, D. Simeunovic, A.D. Ristic, D. Trifunovic-Zamaklar, G. Radovanovic), 'Zvezdara' University Clinical and Medical Center, Belgrade, (M. Miric).

Russian Federation

Russian Peoples Friendship University, Moscow, (V.S. Moiseyev, Z. Kobalava), City Hospital No. 51, Moscow (D. Zateishikov).

Russian Research Center of Surgery, Russian Academy of Medical Science, Moscow (A. Koroteev, A. Eremenko).

Internal Diseases Department of Russian State Medical University, Hospital No. 4, Moscow (G. Aroutiounov, A. Rozanow).

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