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Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study

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Aims Dyspnoea and pulmonary and/or peripheral congestion are the most frequent manifestations of acute heart failure (AHF) and are important targets for therapy. We have assessed changes in dyspnoea, their relationship with mortality, and the effects of the adenosine A1 receptor antagonist rolofylline on these endpoints in patients enrolled in the PROTECT trial.

Methods and results PROTECT was a prospective, double-blind, placebo-controlled study assessing the effect of rolofylline in patients hospitalized for AHF with dyspnoea, fluid overload, increased plasma natriuretic peptides, and mild-to-moderate renal dysfunction. Early dyspnoea relief, prospectively defined as moderately or markedly better dyspnoea at both 24 and 48 h after the start of study drug administration, occurred in 49.8% of the patients. Early dyspnoea relief was associated with greater weight loss and with reduced mortality at Days 14 and 30 [hazard ratio (HR) 0.28, 95% confidence interval (CI): 0.15, 0.50; and 0.35, 95% CI: 0.22, 0.55, respectively]. Rolofylline administration was associated with an increase in the proportion of patients showing early dyspnoea relief (HR 1.30; 95% CI: 1.08, 1.57) and with a numerically lower mortality at 14 and 30 days, largely driven by the mortality due to HF [at 30 days, HR (95% CI, *P*-value): 0.65 (0.38–1.10, $P = 0.107$)]. Rolofylline did not reduce episodes of in-hospital worsening HF or post-discharge re-admissions, nor did it improve survival at 60 or 180 days.

Conclusion The present analysis from PROTECT demonstrated that more weight loss was associated with early dyspnoea relief and reduced short-term mortality.

Keywords Acute heart failure • Dyspnoea • Diuretics

Introduction

Dyspnoea and pulmonary and/or peripheral congestion are the main clinical manifestations of acute heart failure (AHF) and are important targets for therapy. Acute heart failure is associated with a poor prognosis with deaths or rehospitalizations occurring in ~50% of the patients in the 3–6 months after discharge.[1–3] An improvement in dyspnoea did not predict a reduction in deaths and rehospitalizations in most previous drug intervention trials,[4–10] leading to concerns about the validity of dyspnoea as an endpoint, especially when considered alone.[11] This lack of association between the effects of treatment on dyspnoea and on outcomes, observed in previous studies, may have multiple causes. First, the severity of dyspnoea as a symptom leading to hospitalization may

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vary and patients with milder symptoms and, thus, little room for improvement may have been included in previous trials. Secondly, drugs tested in recent AHF trials, such as nesiritide and levosimendan,[6,7] although providing some symptomatic relief, may have concomitant untoward effects (worsening renal function, hypotension, and arrhythmias), which can modify outcomes independently from their actions on dyspnoea.[2,5,12] Thus, treatment may reduce symptoms but not the factors determining prognosis.

Many patients admitted with AHF have renal dysfunction, and renal function worsens in 20–40% during hospitalization.[13–15] Since kidney dysfunction has been shown in epidemiological and retrospective analyses of clinical trials to be associated with poorer prognosis, it has been considered a potential cause of the poor outcome of the patients with AHF.[15–19] Adenosine A1 receptor antagonists have been studied in patients with AHF because of their diuretic effects with concomitant renal protection through glomerular afferent arteriole dilatation.[20] Despite the pathophysiological basis and the favourable results of initial studies with these agents,[21–25] a large randomized, placebo-controlled trial, the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT), failed to show any effect of the adenosine A1 receptor antagonist rolofylline on the primary and secondary endpoints. However, there were suggestions that although rolofylline administration had no beneficial effect on renal function, it might have favourable effects on dyspnoea relief.[26]

The aim of this study is to analyse the clinical and prognostic significance of changes in symptoms, namely dyspnoea, in the patients enrolled in the PROTECT trial. With this purpose, we performed a *post hoc* analysis of two of the three components of the primary endpoint of the study, namely dyspnoea relief and worsening heart failure (WHF) at Day 7, as well as additional analyses of the effects of rolofylline on changes in dyspnoea up to Day 7 and on short-term (in-hospital, 14, and 30 days) outcomes.

Methods

Inclusion criteria and study design

PROTECT was a multicentre, randomized, double-blind, placebo-controlled trial in patients hospitalized for AHF conducted in North America, Europe, Israel, and Argentina. A detailed description of the study design has been published previously.[26,27] For entry, patients were required to have dyspnoea at rest or with minimal activity, signs, and symptoms of volume overload requiring intravenous (i.v.) loop diuretic therapy, impaired renal function (estimated creatinine clearance of 20–80 mL/min by the Cockcroft–Gault equation corrected for weight in oedematous or obese subjects $\geq$100 kg), and elevated natriuretic peptide levels [brain natriuretic peptide (BNP) $\geq$500 pg/mL or N-terminal-pro-BNP (NT-proBNP) $\geq$2000 pg/mL]. Exclusion criteria are outlined in the design paper.[27] Our study fulfilled the requirements stated in the Declaration of Helsinki and it was approved by the Ethics Committees at each participating centre. Patients provided written informed consent.

Patients were randomized to receive rolofylline 30 mg administered as a daily 4 h infusion for 3 days or placebo in a double-blind manner according to a computer-generated randomization scheme; with a 2:1 rolofylline to placebo allocation. Heart failure signs (jugular venous pressure, rales, and oedema) and symptoms (dyspnoea and orthopnoea) were evaluated by a physician just prior to the initial study drug administration, daily through discharge on Day 6, and on Days 7 and 14. Patients' self-reported symptoms (dyspnoea and general well-being, each assessed utilizing a seven-point Likert scale of change compared with baseline) were recorded daily from Days 2 to 6 or to discharge, if earlier, and at Days 7 and 14. Assessments at Days 2 and 3 corresponded to measurements taken at 24 and 48 h from study drug initiation. Blood samples for measurements of serum creatinine, blood urea nitrogen, and uric acid were obtained daily. Electrolytes, glucose, and complete blood count were measured at baseline and Days 2, 7, and 14.

Follow-up evaluations at Days 7 and 14 included a physician assessment, interim history, laboratory tests as noted above, and adverse event evaluation. Adverse events were captured through Day 7; serious adverse events were recorded through Day 14. Patients were contacted by telephone to identify deaths and re-admissions up to Day 60 and to assess vital status at Day 180.

Endpoints in PROTECT

The primary and secondary endpoints of the PROTECT study are described in the design paper and have been recently reported.[26,27] Briefly, the primary endpoint was an ordered composite endpoint according to which patients were classified as success, unchanged, or failure. Success was defined as patient-reported moderately or markedly better dyspnoea using a seven-point Likert scale at both 24 and 48 h after the initiation of study drug administration in the absence of any criterion for treatment failure. Failure included any of the following: death through Day 7, WHF or rehospitalization for HF through Day 7, or persistent renal impairment. Worsening heart failure was reported based on worsening signs and symptoms of HF with resulting intensification of i.v. therapy for HF or mechanical circulatory or ventilator support. Persistent renal impairment was defined as a serum creatinine increase of $\geq$0.3 mg/dL (26.5 μmol/L) from randomization to Day 7, confirmed at Day 14, or the initiation of haemofiltration or dialysis through Day 7.

Endpoints of the present analysis

The endpoints of the present analysis were changes in symptoms (i.e. dyspnoea relief and occurrence of WHF rate through Day 7 from randomization) and short-term (through Days 14 and 30) mortality rates.

Dyspnoea relief was defined according to the definition used for the primary endpoint of PROTECT, i.e. moderately or markedly better dyspnoea at both 24 and 48 h randomization. The criteria for WHF to Day 7 are defined above (see components of the primary endpoint). Cause-specific mortality was analysed according to the adjudications of the blinded Clinical Events Committee.

Statistical methods

Continuous variables are summarized as mean $\pm$ standard deviation (SD), or as median and inter-quartile range (IQR). Statistical analyses were performed using SAS version 9.2. All analyses were performed by the intention-to-treat method. We used two-sided *t*-tests for statistical comparisons. A *P*-value of $<$0.05 was considered as threshold for statistical significance. The Kaplan–Meier estimates of mortality rates are given. In-hospital mortality for patients who were still hospitalized at Day 30 was censored at 30 days. Hazard ratios (HRs) were estimated from the Cox regression models, odds ratios (OR) were estimated from logistic regression models, and mean differences

Table 1 Baseline characteristics of the patients subdivided on the basis of relief of dyspnoea

Variable	Dyspnoea relief			
	No (n = 1003)	Yes (n = 995)	Difference (95% CI)[a]	P-value
Age (years)	70 ± 11	70 ± 12	−0.2 (−1.2, 0.8)	0.710
Gender, males (%)	69	66	−2.6 (−6.8, 1.5)	0.204
Race, white/Caucasian (%)	95	96	0.6 (−1.3, 2.4)	0.559
Weight (kg)				
n	1002	995	−0.4 (−2.2, 1.3)	0.600
Mean ± SD	82.3 ± 19.4	81.9 ± 19.8		
Baseline creatinine clearance (mL/min)				
n	966	959	3.3 (1.5, 5.1)	<0.001
Mean ± SD	49.0 ± 19.7	52.3 ± 20.5		
Baseline BNP (pg/mL)				
n	258	272	−14 (−231, 203)	0.901
Median (IQR)	1270.0 (818.0, 2235.0)	1229.0 (819.0, 2161.5)		
Baseline NT-proBNP (pg/mL)[b]				
n	749	742	−276 (−1446, 894)	0.642
Median (IQR)	3000.0 (3000.0, 3732.0)	3000.0 (3000.0, 3879.0)		
Systolic blood pressure (mmHg)				
n	1003	994	1.8 (0.2, 3.3)	0.024
Mean ± SD	123.5 ± 17.6	125.3 ± 17.6		
Diastolic blood pressure (mmHg)				
n	1003	994	1.2 (0.3, 1.8)	0.137
Mean ± SD	73.0 ± 11.8	74.2 ± 11.9		
Heart rate (b.p.m.)				
n	1003	993	1.4 (0.5, 2.2)	0.222
Mean ± SD	79.0 ± 15.3	80.5 ± 15.5		
Respiratory rate (b.p.m.)				
n	945	963	0.1 (−.7, 1.0)	0.094
Mean ± SD	21.0 ± 4.7	21.1 ± 4.2		
NYHA class prior to hospitalization				
n	942	952	−4.0 (−7.5, −0.6) in % NYHA class = III or IV	0.012
Class I	0.9	1.1		
Class II	15	19		
Class III	50	52		
Class IV	34	28		
History of hypertension (%)	78	81	3.1 (−0.6, 6.5)	0.104
History of atrial fibrillation/flutter (%)	55	54	−1.4 (−5.7, 3.0)	0.550
History of automatic internal cardiac defibrillators (%)	18	14	−3.7 (−6.9, −0.5)	0.025
History of congestive heart failure (%)	94	96	1.6 (−0.4, 3.5)	0.113
History of diabetes mellitus (%)	48	43	−4.8 (−9.2, −0.4)	0.032
History of asthma, bronchitis, or chronic obstructive pulmonary disease (%)	21	18	−3.5 (−6.9, 0.0)	0.053
History of ischemic heart disease (%)	72	68	−4.4 (−8.5, −0.4)	0.032
History of myocardial infarction (%)	50	49	−0.1 (−4.4, 4.3)	0.981
History of biventricular pacing (%)	12	8.7	−2.8 (−5.5, −0.2)	0.036
Left ventricular ejection fraction (% units)				
n	488	470	−1.1 (−2.7, 0.5)	0.190
Mean ± SD	32.7 ± 13.7	31.6 ± 12.3		

Continued

Table 1 *Continued*

Variable	Dyspnoea relief			
	No (n = 1003)	Yes (n = 995)	Difference (95% CI)[a]	P-value
Prior ACE-inhibitors or ARB (%)	74	77	2.9 (−0.9, 6.7)	0.130
Prior β-blockers (%)	77	76	−0.2 (−3.9, 3.5)	0.921
Prior aldosterone antagonists (%)	46	42	−3.6 (−7.8, 0.9)	0.120
Prior digoxin (%)	29	28	−0.8 (−4.7, 3.2)	0.701
Prior nitrates (%)	27	25	−2.0 (−5.8, 1.9)	0.314
ACE-inhibitors or ARB at discharge (%)	79	85	6.3 (2.9, 9.6)	<0.001
β-Blockers at discharge (%)	83	87	4.3 (1.2, 7.5)	0.007
Aldosterone antagonists at discharge (%)	59	61	1.4 (−3.0, 5.7)	0.550
Digoxin at discharge (%)	35	31	−4.4 (−8.6, −0.3)	0.036
Nitrates at discharge (%)	23	17	−6.0 (−9.6, −2.5)	0.001
Days treated with study drug (%)				
n	1003	995	2.2 (−0.1, 4.4)	0.049
0	0.6	0.6	in % treated days = 3	
1	3.3	1.4		
2	4.5	4.2		
3	91.6	93.8		
Total dose of i.v. loop diuretics from Days 1 to 7 (mg)				
n	1003	995	−261 (−335, −186)	<0.001
Median (IQR)	350.0 (160.0, 780.0)	227 (120.0, 420)		
Treated with i.v. inotropes/vasopressors prior to Day 7 (%)	11.4	3.2	−8.2 (−10.4, −5.9)	<0.001
Treated with vasodilators prior to Day 7 (%)	12.6	10.3	−2.2 (−5.0, 0.6)	0.121

n indicates number of patients.
[a]Differences (95% CIs) are for patients with dyspnoea relief vs. those with no dyspnoea relief.
[b]Most of the equipments did not give values when NT-proBNP values were >3000 pg/mL.

were from linear regression models, adjusted for study (PROTECT-1 vs. -2) and region (USA, Canada, Western Europe, and Israel vs. Central Europe and Argentina). Multivariable Cox regression analysis was used to assess whether the relation between dyspnoea relief and 14 and 30 days mortality was independent from other variables known to affect outcomes in AHF [namely age, New York Heart Association (NYHA) class, serum creatinine, serum sodium, BNP levels, and blood pressure]. *P*-values were calculated by the Wald χ^2 analysis. No adjustment was made to this analysis for its *post hoc* nature, and all *P*-values and confidence intervals (CIs) were reported at their nominal levels. All analyses were stratified by region and study.

Results

Patient characteristics and short-term follow-up

Complete evaluations of early dyspnoea changes were obtained in 1998 of 2033 patients enrolled in PROTECT. Thirty-five patients were excluded since they did not have full data on dyspnoea relief. Early dyspnoea relief, using the rigorous definition described above, occurred in only 49.8% of the patients. Worsening heart failure through Day 7 occurred in 10.7% of the patients; 3.6 and 4.8% of the patients died by Days 14 and 30, respectively.

Baseline characteristics of patients with and without dyspnoea relief are presented in *Table 1*. Patients with dyspnoea relief had lower NYHA class prior to admission, lower creatinine, and slightly higher blood pressure. They were treated with less i.v. furosemide, inotropes, or vasodilators and were more likely to receive angiotensin-converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARBs) and β-blockers at discharge or up to Day 7.

Patients who experienced dyspnoea relief had a greater average decline in body weight over Days 2–4 after enrolment [mean difference (95% CI), −0.48 (−0.27, −0.70) kg], and this difference was evident across all subgroups tested (*Table 2*). Baseline characteristics of patients who survived to Days 14 and 30 are depicted in *Table 3*.

Prognostic significance of early changes in symptoms

Patients with early dyspnoea relief had numerically lower mortality at both 14 and 30 days and the estimated magnitude of the

Table 2 Average change in body weight (kg) on Days 2, 3, and 4 by dyspnoea relief

Variable	Dyspnoea relief		Group difference (95% CIs)
	No	Yes	
All patients			
n	978	989	−0.5 (−0.3, −0.7)
Mean ± SD	−1.9 ± 2.5	−2.4 ± 2.4	
Median (IQR)	−1.7 (−0.7, −2.8)	−2.0 (−1.0, −3.7)	
NYHA class I–III			
n	600	681	−0.3 (−0.6, − 0.1)
Mean ± SD	−1.9 ± 2.6	−2.2 ± 2.3	
Median (IQR)	−1.7 (−2.8, −0.7)	−1.9 (−3.3, −1.0)	
NYHA class IV			
n	321	266	−0.8 (−1.2, −0.4)
Mean ± SD	−2.0 ± 2.3	−2.8 ± 2.2	
Median (IQR)	−1.7 (−2.9, −0.7)	−2.3 (−4.2, −1.2)	
Baseline serum creatinine <1.5 mg/dL (median)			
n	423	495	−0.5 (−0.9, −0.2)
Mean ± SD	−1.9 ± 2.5	−2.4 ± 2.4	
Median (IQR)	−1.7 (−2.8, −0.7)	−2.0 (−3.5, −1.0)	
Baseline serum creatinine ≥1.5 mg/dL (median)			
n	528	463	−0.5 (−0.8, −0.2)
Mean ± SD	−2.0 ± 2.5	−2.4 ± 2.5	
Median (IQR)	−1.7 (−3.0, −0.7)	−2.0, (−3.7, −1.0)	
Baseline creatinine clearance <48 mL/min (median)			
n	496	446	−0.4 (−0.7, −0.1)
Mean ± SD	−1.9 ± 2.6	−2.3 ± 2.3	
Median (IQR)	−1.6 (−2.8, −0.6)	−1.9 (−3.4, −1.0)	
Baseline creatinine clearance ≥48 mL/min (median)			
n	453	511	−0.6 (−0.9, −0.2)
Mean ± SD	−2.0 ± 2.4	−2.5 ± 2.5	
Median (IQR)	−1.8 (−2.9, −0.7)	−2.2 (−3.7, −1.0)	

association was similar within subgroups defined by baseline variables, including variables related with the severity of HF before hospitalization (NYHA class, serum creatinine or creatinine clearance, systolic blood pressure, blood levels of natriuretic peptides; *Table 4*). Of note, patients with dyspnoea relief had lower NYHA class prior to admission, lower creatinine, and slightly higher blood pressure. In addition, they were more likely to receive ACE-inhibitors or ARBs and β-blockers at discharge or up to Day 7. These suggest that patients with dyspnoea relief had lower severity of HF. However, the association between dyspnoea relief and better survival, irrespective of the study group, remained significant also after adjustment for age, NYHA class, baseline BNP level, serum creatinine, serum sodium, and blood pressure at multivariable analysis (*Table 5*).

In-hospital WHF was associated with a marked increase in the risk of subsequent death at 14 days [HR (95% CI): 6.84 (4.12, 11.35)] and 30 days [HR (95% CI): 4.78 (3.10, 7.37)], compared with the absence of this event, and this association was also consistent across all subgroups examined (*Table 6*).

Effects of rolofylline administration

Compared with placebo, rolofylline administration was associated with greater weight loss. At 72 h, the mean (95% CI) body weight decrease in patients assigned to placebo was −2.55 (−2.79, −2.3) kg compared with −2.98 (−3.15, −2.81) kg with rolofylline [mean (95% CI) treatment difference: −0.43 (−0.73, −0.13) kg]. This occurred despite the initial administration of similar doses of loop diuretics to the patients receiving rolofylline and placebo and a numerically lower dose administered post-randomization in rolofylline-treated patients (the mean ± SD dose of furosemide was of 526 ± 869 mg in the rolofylline group vs. 553 ± 850 mg in the placebo group; *P* = NS).

Rolofylline administration was associated with higher proportion of patients showing moderately to markedly better dyspnoea than

Table 3 Baseline characteristics of the patients subdivided on the basis of mortality at Days 14 and 30

Variable	All-cause deaths at Day 14			*P*-value	All-cause deaths at Day 30			*P*-value
	No (*n* = 1960)	Yes (*n* = 73)	Difference (95% CI)[a]		No (*n* = 1927)	Yes (*n* = 106)	Difference (95% CI)[a]	
Age (years)								
n	1960	73	4.5 (2.3, 6.6)	0.001	1927	106	3.5 (1.4, 5.6)	0.002
Mean ± SD	70.0 ± 11.7	74.5 ± 8.9			70.0 ± 11.6	73.5 ± 10.4		
Gender, males (%)	67.2	64.4	−2.8 (−14.0, 8.4)	0.616	67	68	0.8 (−8.3, 10.0)	0.852
Race, white/Caucasian (%)	95.2	98.6	3.4 (0.6, 6.3)	0.255	95	98	2.9 (0.1, 5.7)	0.233
Weight (kg)								
n	1959	73	−1.3 (−5.6, 3.1)	0.589	1926	106	−1.2 (−5.0, 2.6)	0.548
Mean ± SD	82.1 ± 19.6	80.8 ± 18.2			82.1 ± 19.6	80.9 ± 19.1		
Baseline creatinine clearance (mL/min)								
n	1873	70	−6.6 (−10.5, −2.8)	0.007	1843	100	−5.8 (−9.4, −2.3)	0.005
Mean ± SD	50.8 ± 20.3	44.2 ± 15.9			50.9 ± 20.2	45.0 ± 17.2		
Baseline BNP (pg/mL)								
n	522	15	1330 (−693, 3353)	0.003	514	23	593 (−751, 1935)	0.110
Median (IQR)	1255.0 (813.0, 2204.0)	2516.2 (1120.0, 3113.0)			1270 (820, 2275)	1207 (818, 2952)		
Baseline NT-proBNP (pg/mL)[b]								
n	1460	58	1079 (−1138, 3296)	0.481	1434	84	1768 (−811, 2579)	0.491
Median (IQR)	3000.0 (3000.0, 3777.6)	3000.0 (3000.0, 6471.0)			3000 (3000, 3732)	3000 (3000, 6721)		
Systolic blood pressure (mmHg)								
n	1959	73	−3.0 (−6.9, 0.8)	0.148	1926	106	−6.9 (−10.2, −3.5)	<0.001
Mean ± SD	124.4 ± 17.7	121.4 ± 16.3			125 ± 17.6	118 ± 17.1		
Diastolic blood pressure (mmHg)								
n	1959	73	−0.7 (−3.6, 2.1)	0.599	1926	106	−2.4 (−4.7, −0.2)	0.036
Mean ± SD	73.7 ± 11.84	73.0 ± 12.0			74.0 ± 11.9	71.4 ± 11.4		
Heart rate (b.p.m.)								
n	1958	73	2.8 (−1.1, 6.6)	0.130	1925	106	2.1 (−1.2, 5.1)	0.175
Mean ± SD	80.0 ± 15.4	82.8 ± 16.3			80.0 ± 15.4	82.1 ± 16.7		
Respiration rate (b.p.m.)								
n	1868	70	0.3 (−1.2, 1.8)	0.545	1838	100	−0.1 (−1.3, 1.0)	0.784
Mean ± SD	21.2 ± 4.4	21.5 ± 6.2			21.2 ± 4.3	21.1 ± 5.7		

NYHA class prior to hospitalization (%)								
n	1856	69	5.0 (−3.1, 13.1)	0.656	1826	99	3.9 (−3.2, 11.0) ln %	0.764
Class I	0.9	1.5	% NYHA class III or IV		1	1	NYHA class = III or IV	
Class II	17	12			17	13		
Class III	51	54			51	55		
Class IV	31	33			31	31		
History of hypertension (%)	79	82	2.8 (−6.1, 11.8)	0.553	79	79	−0.2 (−8.1, 7.7)	0.960
History of atrial fibrillation/ flutter (%)	55	57	2.4 (−9.3, 14.1)	0.688	54	59	4.6 (−5.0, 14.3)	0.350
History of congestive heart failure (%)	95	95	−0.3 (−5.6, 5.0)	0.790	95	93	−1.5 (−6.3, 3.4)	0.509
History of diabetes mellitus (%)	45	44	−1.6 (−13.2, 10.0)	0.788	45	43	−2.1 (−11.8, 7.6)	0.674
History of asthma, bronchitis, or chronic obstructive pulmonary disease (%)	20	23	3.6 (−6.3, 13.5)	0.448	20	21	1.0 (−6.9, 8.9)	0.803
History of ischemic heart disease (%)	69	83	14.1 (5.2, 22.9)	0.011	69	82	12.8 (5.1, 20.4)	0.006
History of myocardial infarction (%)	49	51	1.4 (−10.4, 13.2)	0.817	49	55	5.7 (−4.1, 15.6)	0.254
Previous ICD implantation (%)	16	6.9	−9.5 (−15.5, −3.5)	0.030	16	11	−5.0 (−11.2, 1.3)	0.178
History of CRT (%)	10	5.5	−4.9 (−10.3, 0.5)	0.172	10	7	−3.8 (−8.8, 1.1)	0.205
Left ventricular ejection fraction (% units)								
n	939	36	1.2 (−3.7, 6.1)	0.603	920	55	0.8 (−3.0, 4.6)	0.666
Mean ± SD	32.3 ± 13.1	33.5 ± 14.3			32.3 ± 13.1	33.1 ± 13.9		
Prior ACE-inhibitors or ARB (%)	76	73	−3.2 (−13.6, 7.3)	0.538	76	72	−4.2 (−13.0, 4.6)	0.331
Prior β-blockers (%)	77	64	−12.3 (−23.4, −1.2)	0.015	77	65	−11.8 (−21.0, −2.5)	0.006
Prior aldosterone antagonists (%)	44	52	8.5 (−3.1, 20.2)	0.148	43	52	8.6 (−1.2, 18.3)	0.085
Prior digoxin (%)	28	21	−7.8 (−17.3, 1.7)	0.145	29	19	−8.8 (−16.6, −0.9)	0.052
Prior nitrates (%)	26	32	5.7 (−5.1, 16.6)	0.271	26	29	3.5 (−5.4, 12.3)	0.428
ACE-inhibitors or ARB at discharge (%)	83	50	−33.0 (−47.5, −18.4)	<0.001	84	51	−32.8 (−44.0, −21.7)	<0.001
β-Blockers at discharge (%)	85	51	−34.4 (−48.8, −19.4)	<0.001	86	55	−30.6 (−41.7, −19.4)	<0.001
Aldosterone antagonists at discharge (%)	60	42	−18.2 (−32.7, −3.6)	0.014	61	46	−14.4 (−25.6, −3.1)	0.011
Digoxin at discharge (%)	33	22	−11.3 (−23.4, 0.9)	0.108	33	24	−9.0 (−18.7, 0.6)	0.093
Nitrates at discharge (%)	20	17	−3.0 (−14.1, 8.1)	0.612	21	15	−5.4 (−13.5, 2.7)	0.244

Continued

Table 3 *Continued*

Variable	All-cause deaths at Day 14			*P*-value	All-cause deaths at Day 30			*P*-value
	No (*n* = 1960)	Yes (*n* = 73)	Difference (95% CI)[a]		No (*n* = 1927)	Yes (*n* = 106)	Difference (95% CI)[a]	
Days treated with study drug (%)								
n	1960	73	−5.7 (−34.2, 12.8) % of days treated = 3	<0.001	1927	106	−16.6 (−24.8, −8.3) in % treated days = 3	<0.001
0	1.5	1.4			2	1		
1	2.4	19.2			2	15		
2	4.1	11.0			4	9		
3	92.0	68.5			92	75		
Total dose of i.v. loop diuretics from Days 1 to 7 (mg)								
n	1960	73	649 (346, 952)	<0.001	1927	108	614 (332, 895)	<0.001
Median (IQR)	275.6 (120.0, 531.3)	795.0 (440.0, 1140.0)			260 (120, 560)	710 (320, 1120)		
Treated with i.v. inotropes/ vasopressors prior to Day 7 (%)	5.8	53	47.9 (36.2, 59.2)	<0.001	6	43	37.9 (28.4, 47.4)	<0.001
Treated with vasodilators prior to Day 7 (%)	11	23	12.3 (2.6, 22)	<0.001	11	18	6.7 (−0.5, 14)	<0.001

ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.
[a]Differences are for patients who died, compared with those who were alive, at either Day 14 or Day 30.
[b]Most of the equipments did not give values when NT-proBNP values were >3000 pg/mL.

Table 4 Associations between dyspnoea relief and all-cause mortality

	Dyspnoea relief		Hazard ratio (95% CIs)
	Yes, event/total (%)[a]	No, event/total (%)[a]	
All patients			
14 days	14/995 (1.4)	49/1003 (4.9)	0.28 (0.15, 0.50)
30 days	25/995 (2.5)	70/1003 (7.0)	0.35 (0.22, 0.55)
Age <72 years			
14 days	6/497 (1.2)	15/482 (3.1)	0.36 (0.14, 0.94)
30 days	10/497 (2.0)	24/482 (5.0)	0.38 (0.18, 0.79)
Age ≥72 years			
14 days	8/498 (1.6)	34/521 (6.5)	0.24 (0.11, 0.52)
30 days	15/498 (3.0)	46/521 (8.8)	0.33 (0.18, 0.59)
NYHA class I–III			
14 days	10/685 (1.5)	30/618 (4.9)	0.29 (0.14, 0.59)
30 days	19/685 (2.8)	42/618 (6.8)	0.39 (0.22, 0.67)
NYHA class IV			
14 days	4/267 (1.5)	16/324 (5.0)	0.26 (0.09, 0.78)
30 days	5/267 (1.9)	23/324 (7.1)	0.24 (0.09, 0.62)
Systolic blood pressure at screening <124 mmHg			
14 days	6/458 (1.3)	28/526 (5.3)	0.24 (0.10, 0.57)
30 days	15/458 (3.3)	46/526 (8.8)	0.35 (0.20, 0.64)
Systolic blood pressure at screening ≥124 mmHg			
14 days	8/536 (1.5)	21/477 (4.4)	0.34 (0.15, 0.76)
30 days	10/536 (1.9)	24/477 (5.1)	0.37 (0.18, 0.78)
BNP ≤ 750 pg/mL/NT-proBNP ≤ 3000 pg/mL			
14 days	5/573 (0.9)	29/592 (4.9)	0.18 (0.07, 0.45)
30 days	11/573 (1.9)	41/592 (6.9)	0.27 (0.14, 0.53)
BNP > 750 pg/mL/NT-proBNP > 3000 pg/mL			
14 days	9/421 (2.1)	19/408 (4.7)	0.41 (0.18, 0.91)
30 days	14/421 (3.3)	28/408 (6.9)	0.45 (0.24, 0.86)
Baseline creatinine <1.5 mg/dL			
14 days	6/496 (1.2)	18/430 (4.2)	0.28 (0.11, 0.72)
30 days	11/496 (2.2)	26/430 (6.1)	0.36 (0.18, 0.72)
Baseline creatinine ≥1.5 mg/dL			
14 days	8/467 (1.7)	29/545 (5.3)	0.31 (0.14, 0.67)
30 days	14/467 (3.0)	41/545 (7.5)	0.38 (0.21, 0.70)
Baseline creatinine clearance <48 mL/min			
14 days	8/447 (1.8)	27/509 (5.3)	0.33 (0.15, 0.72)
30 days	14/447 (3.1)	36/509 (7.1)	0.43 (0.23, 0.80)
Baseline creatinine clearance ≥48 mL/min			
14 days	6/512 (1.2)	20/457 (4.4)	0.26 (0.10, 0.65)
30 days	11/512 (2.2)	30/457 (6.6)	0.32 (0.16, 0.64)

Cut-off values for age, systolic blood pressure, serum creatinine, and creatinine clearance were the median values.
[a]The Kaplan–Meier estimates.

placebo, at 24 and 48 h from randomization. Early relief of dyspnoea occurred in 301 of 663 patients (45.40%) on placebo vs. 694 of 1335 patients (51.99%) on rolofylline [OR (95% CI): 1.30 (1.08, 1.57)] with a number needed to treat with rolofylline to achieve one early dyspnoea relief of 15 (95% CI: 9, 52; *Table 7*). This difference persisted, although reduced in magnitude, to Day 14 (*Figure 1*). Similar results were found with respect to the assessment of NYHA class with a lower proportion of patients in NYHA class IV in the rolofylline group commencing with Day 2 up to Day 14 (*Figure 2*). Overall, the proportion of patients meeting criteria for WHF was similar with rolofylline (10.5%) and placebo [11.2%, OR (95% CI): 0.93 (0.69, 1.25)]. No differences in pre-

Table 5 Multivariable analysis of the association between dyspnoea relief and mortality at Days 14 and 30

Variable	HR	95% CI	*P*-value
14-day mortality			
Dyspnoea relief at Days 2 and 3	0.34	0.18, 0.62	<0.0001
Age, per 1 year increase	1.04	1.01, 1.07	0.021
NYHA class before admission IV vs. I/II/II	0.92	0.52, 1.63	0.780
Systolic blood pressure at screening, per 1 mmHg increase	0.99	0.98, 1.01	0.426
Screening BNP > 750 or NT-proBNP > 3000 pg/mL	1.32	0.77, 2.26	0.306
Day 1 serum sodium, per 1 mEq/L increase	0.90	0.85, 0.95	<0.001
Baseline creatinine clearance, per 1 mL/min increase	0.99	0.97, 1.01	0.295
30-day mortality			
Dyspnoea relief at Days 2 and 3	0.42	0.26, 0.67	<0.0001
Age, per 1 year increase	1.03	1.00, 1.05	0.025
NYHA class before admission IV vs. I/II/II	0.79	0.49, 1.28	0.332
Systolic blood pressure at screening, per 1 mmHg increase	0.98	0.97, 0.99	0.004
Screening BNP > 750 or NT-proBNP > 3000 pg/mL	1.17	0.75, 1.82	0.492
Day 1 serum sodium, per 1 mEq/L increase	0.90	0.86, 0.94	<0.001
Baseline creatinine clearance, per 1 mL/min increase	0.99	0.98, 1.01	0.252

Table 6 Associations between worsening heart failure and all-cause mortality

	WHF through Day 7		Hazard ratio (95% CI)
	Yes, event/total (%)[a]	No, event/total (%)[a]	
All patients			
14 days	25/189 (13.2)	38/1811 (2.1)	6.84 (4. 12, 11.35)
30 days	30/189 (15.9)	66/1811 (3.7)	4.78 (3.10, 7.37)
NYHA class I–III			
14 days	14/128 (10.9)	26/1177 (2.2)	5.18 (2.70, 9.93)
30 days	18/128 (14.1)	44/1177 (3.8)	4.04 (2.33, 6.99)
NYHA class IV			
14 days	10/48 (20.8)	10/543 (1.9)	14.40 (5.96, 34.79)
30 days	11/48 (22.9)	17/543 (3.1)	9.22 (4.28, 19.88)
Baseline creatinine <1.5 mg/dL (median)			
14 days	8/65 (12.3)	8/65 (12.3)	7.02 (2.99, 16.46)
30 days	10/65 (15.4)	27/861 (3.1)	5.42 (2.61, 11.23)
Baseline creatinine ≥1.5 mg/dL (median)			
14 days	17/123 (13.8)	20/889 (2.3)	6.68 (3.49, 12.77)
30 days	20/123 (16.3)	35/889 (4.0)	4.51 (2.60, 7.83)
Baseline creatinine clearance <48 mL/min (median)			
14 days	15/109 (13.8)	20/847 (2.4)	6.17 (3.16, 12.06)
30 days	17/109 (15.6)	33/847 (3.9)	4.30 (2.39, 7.73)
Baseline creatinine clearance ≥48 mL/min (median)			
14 days	10/77 (13.0)	16/892 (1.8)	8.40 (3.80, 18.58)
30 days	13/77 (16.9)	28/892 (3.1)	6.32 (3.26, 12.24)

[a]The Kaplan–Meier estimates.

Table 7 Effects of rolofylline on dyspnoea relief and worsening heart failure: subgroup analysis

Variable	Placebo	Rolofylline	Treatment difference (95% CIs)[a]	*P*-value for interaction between treatment and covariate
Dyspnoea relief, no. of patients/total (%)				
NYHA class I–III	211/441 (47.9)	474/862 (55.0)	1.34 (1.06, 1.68)	
NYHA class IV	77/190 (40.5)	190/401 (47.4)	1.33 (0.94, 1.90)	0.971
Baseline creatinine <1.5 mg/dL (132.6 μmol/L) (median)	158/326 (48.5)	338/600 (56.3)	1.37 (1.04, 1.80)	
Baseline creatinine ≥1.5 mg/dL (132.6 μmol/L) (median)	132/317 (41.6)	335/695 (48.2)	1.30 (1.00, 1.71)	0.795
Baseline creatinine clearance <48 mL/min (median)	127/301 (42.2)	320/655 (48.9)	1.31 (1.00, 1.73)	
Baseline creatinine clearance ≥48 mL/min (median)	162/340 (47.7)	350/629 (55.6)	1.38 (1.06, 1.80)	0.790
Worsening heart failure, no. of patients/total (%)				
NYHA class I–III	50/444 (11.3)	93/867 (10.7)	0.95 (0.66, 1.36)	
NYHA class IV	21/192 (10.9)	37/402 (9.2)	0.83 (0.47, 1.45)	0.689
Baseline creatinine <1.5 mg/dL(132.6 μmol/L) (median)	28/327 (8.6)	51/602 (8.5)	0.98 (0.61, 1.59)	
Baseline creatinine ≥1.5 mg/dL (132.6 μmol/L) (median)	46/319 (14.4)	88/699 (12.6)	0.85 (0.58, 1.25)	0.644
Baseline creatinine clearance <48 mL/min (median)	40/304 (13.2)	82/658 (12.5)	0.95 (0.63, 1.42)	
Baseline creatinine clearance ≥48 mL/min (median)	33/340 (9.7)	56/632 (8.9)	0.91 (0.58, 1.44)	0.903
Length of hospitalization (days)				
NYHA class I–III				
Mean ± SD	14.3 ± 23.4	13.0 ± 19.8	−1.33 (−3.74, 1.08)	
Median (IQR)	7.0 (5.0, 12.0)	7 (5.0, 12.0)		
NYHA class IV				
Mean ± SD	19.3 ± 24.9	16.8 ± 20.7	−2.40 (−6.17, 1.36)	0.622
Median (IQR)	13 (7.0, 17.5)	12.0 (7.0, 18.0)		
Baseline creatinine <1.5 mg/dL (132.6 μmol/L) (median)				
Mean ± SD	13.9 ± 19.7	14.3 ± 20.2	0.23 (−2.45, 2.91)	
Median (IQR)	8.0 (6.0, 14.0)	8.0 (6.0, 15.0)		
Baseline creatinine ≥1.5 mg/dL (132.6 μmol/L) (median)				
Mean ± SD	17.9 ± 26.9	14.9 ± 21.4	−3.06 (−6.14, 0.01)	0.103
Median (IQR)	8.0 (6.0, 15.0)	8.0 (6.0, 14.0)		
Baseline creatinine clearance <48 mL/min (median)				
Mean ± SD	17.0 ± 25.4	15.4 ± 22.9	−1.38 (−4.6, 1.85)	
Median	8.0 (6.0, 15.0)	8.0 (6.0, 14.0)		
Baseline creatinine clearance ≥48 mL/min (median)				
Mean ± SD	14.8 ± 21.6	13.8 ± 18.5	−1.14 (−3.72, 1.44)	0.815
Median (IQR)	8.0 (6.0, 15.0)	8.0 (6.0, 15.0)		

[a]Treatment difference was measured as OR (rolofylline/placebo) for dyspnoea relief and worsening heart failure, and difference in means (rolofylline−placebo) for length of hospital stay.

defined subgroups based on NYHA class before hospitalization, serum creatinine, or creatinine clearance at baseline were found (*Table 7*).

The duration of hospital stay was numerically shorter with rolofylline, compared with placebo [mean ± SD, 14.5 ± 20.8 vs. 16.0 ± 23.8 days; treatment difference (95% CI) −1.54 (−3.56, 0.48) days] (*Table 7*). Days 14 and 30 and in-hospital mortality are presented in *Figure 3*. Hazard ratios (95% CI) for all-cause mortality for rolofylline vs. placebo at Days 14 and 30 were 0.80 (0.50, 1.29) and 0.86 (0.56, 1.27), respectively. These results were largely driven by mortality due to HF [30-day HF mortality, HR (95% CI): 0.65 (0.38, 1.1); *Figure 3*]. Overall mortality to Day 180 was not different between placebo and rolofylline (17.6 vs. 18%, respectively), but HF mortality was numerically lower also at Day 180 (8.3 vs. 10.8%).

Discussion

In the PROTECT study, about half of the patients did not achieve marked or moderate relief of dyspnoea within 24 h, and 10.7%

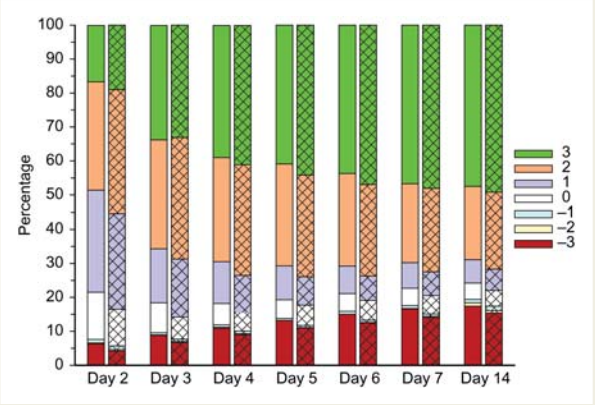

Figure 1 Change in dyspnoea by day and treatment group (solid bars, placebo; hatched bars, rolofylline). Changes in dyspnoea were ranked based on the Likert scale: −3, markedly worse; −2, moderately worse; −1, minimally worse; 0, no change; 1, minimally better; 2, moderately better; 3, markedly better.

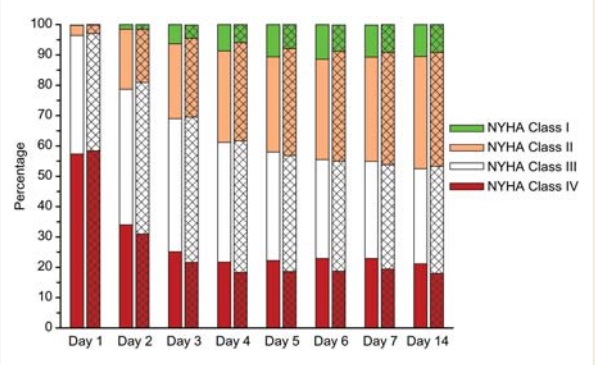

Figure 2 New York Heart Association class by day and treatment group (solid bars: placebo; hatched bars, rolofylline).

developed WHF during the first week of hospitalization. Lack of dyspnoea relief and WHF were each associated with increased mortality at 14 and 30 days and this relation persisted after adjustment for other variables known to affect outcomes in patients with AHF. Rolofylline administration was associated with a greater decline in body weight, more patients obtaining early dyspnoea relief and a non-significant, although numerically lower, mortality in the first month, which was mostly due to fewer deaths caused by HF.

The results of the present study are consistent with those of the previously published PROTECT Pilot trial. Favourable effects of rolofylline on dyspnoea and a relation between dyspnoea relief and short-term outcomes were shown also in that study.[25,28] However, the lack of effects of rolofylline on serum creatinine levels and its untoward central nervous system effects became evident only in the much larger main PROTECT trial.[26] These discrepancies emphasize the need to perform large multicentre trials in order to confirm favourable findings from smaller pilot studies and evaluate drug safety.[11]

Clinical significance of dyspnoea relief

Dyspnoea relief was a main component of the primary endpoint in PROTECT. This variable has been criticized as an endpoint because it is subjective, difficult to measure, and can be expected to improve in the control group because of concomitant treatments.[2,11,29] However, it is the main cause of hospitalization for the patients with AHF, has been used as primary endpoint in virtually all AHF trials,[6–9,25,29] and has shown differences between active treatment and placebo in most of them.[6–8]

In the PROTECT study, the proportion of patients who achieved moderate or marked dyspnoea relief at 24 and 48 h was low (49.8%). This value was, however, similar to that found in the pilot study of PROTECT (54%)[25] and to that shown by an observational study regarding early changes in dyspnoea after an admission for AHF.[30,31] Our proportion of patients improving was, however, lower compared with previous studies where ~65% of the patients assigned to placebo showed an early improvement of dyspnoea.[6,7] This may relate to the definition of dyspnoea relief (i.e. a moderate to marked better dyspnoea at both Days 2 and 3) as well as the inclusion criteria of the study, including signs of fluid overload, need of i.v. diuretic therapy, underlying renal dysfunction, and, most importantly, elevated natriuretic peptides plasma levels, probably excluding patients with non-cardiac causes of dyspnoea and with mild HF.[32] Our results suggest that current AHF therapy is suboptimal not only with respect to outcomes but also with respect to symptom relief.[30,31]

In the present study, dyspnoea relief was associated with lower all-cause mortality at both 14 and 30 days. However, only a few baseline variables (NYHA class before admission, renal impairment) were different between patients with and without dyspnoea relief, underlining our limited understanding of the pathophysiology of AHF and of, specifically, pulmonary congestion.[12,33] Measurement of left ventricular ejection fraction could have increased the predictive value of the model. This variable was not assessed and reported systematically in PROTECT as the drug was perceived to act trough effects on fluid retention and renal protection.

Effects of rolofylline

In the PROTECT study, early dyspnoea relief was associated with a greater decline in body weight and rolofylline induced more weight loss and dyspnoea relief, compared with placebo. These effects are consistent with rolofylline's mild diuretic action and confirm data from previous studies with adenosine A1 receptor antagonists.[23,24] These agents inhibit sodium reuptake in the proximal tubule and may therefore enhance the effects of loop diuretics.

Although the effects of rolofylline on dyspnoea may be deemed as small [OR (95% CI): 1.30 (1.08, 1.57) for achievement of dyspnoea relief with rolofylline vs. placebo], they are of larger magnitude than those reported with other drugs currently approved for the treatment of AHF in many countries[6–8] as well as with those achieved by a 2.5-fold increase in furosemide dose in the Diuretic Optimization Strategies Evaluation (DOSE) Study.[34] In that trial, the administration of higher doses of furosemide was associated with a slight improvement in dyspnoea relief and weight loss and with a

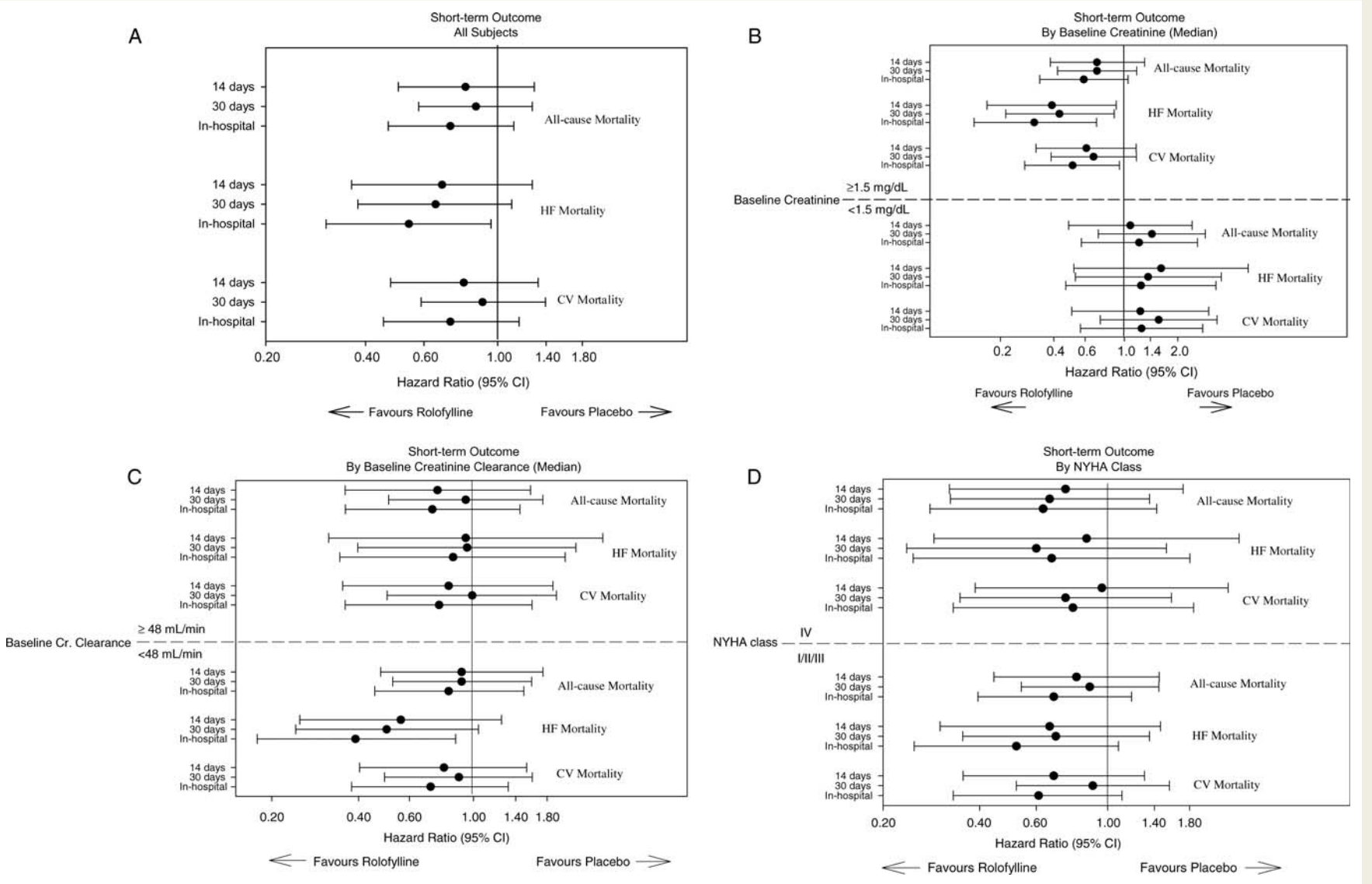

Figure 3 All-cause mortality, heart failure (HF) mortality, and cardiovascular (CV) mortality to Days 14 and 30 by treatment for all subjects (*A*) and subjects subdivided by baseline serum creatinine (*B*), baseline creatinine clearance (*C*), and New York Heart Association class before hospitalization (*D*).

transient increase in creatinine (seemingly larger than that reported in PROTECT). Although a head-to-head comparison of rolofylline and high-dose furosemide was not performed, these data show that enhanced diuresis (either by more i.v. furosemide or rolofylline), in patients with fluid overload and high natriuretic peptide levels, can have some beneficial effects on symptoms, even in the absence of any favourable effect on kidney function or while leading to some mostly transient creatinine increases.

In contrast to the results from studies with the treatment of chronic HF[1,3] as well as with coronary revascularization in patients with acute myocardial infarction, the non-significant numerically smaller number of early deaths in the rolofylline- vs. placebo-treated patients did not persist after 30 days, suggesting that there it may be a chance finding. However, the fact that these effects were mostly driven by disease-specific (i.e. HF) mortality, while non-disease-specific mortality was not affected, increases the likelihood that they represent a real effect. Secondly, patients admitted for AHF are older and have substantial background morbidity. Such non-cardiovascular or non-HF co-morbidities have a strong impact on prognosis,[1,16,35] but HF-specific therapies may have limited effectiveness on them. Indeed, numerically lower HF mortality was observed at 180 days from enrolment, but the effect on all-cause mortality was diluted by death from other causes. Thirdly, episodes of AHF may represent the manifestation of advanced to end-stage HF, a condition in which medical treatment is less likely to improve effectively long-term prognosis.[36] Finally, it is likely that an intervention with favourable effects needs to be repeated rather than administered only once in the context of a randomized trial, to be effective. These observations suggest that a short-term treatment associated with early symptoms improvement is more likely to have an impact on short-term outcomes, whereas long-term outcomes are more dependent on co-morbidities and mechanisms causing disease progression. Most importantly, the present analyses suggest that short-term outcomes may be strongly related with early dyspnoea relief and that different from previous trials,[5,7] symptoms' improvement may be associated with a neutral, if not better, short-term outcome.

Limitations

Although the dyspnoea relief endpoints examined in the present manuscript were pre-defined as components of the primary endpoint, their separate analysis was not pre-defined in the PROTECT programme. PROTECT was not powered to detect a modest effect of rolofylline on mortality and its effects on short-term mortality constituted a *post hoc* analysis. Hence, these results cannot be regarded as definitive. With respect of subgroup analysis, baseline serum creatinine, estimated creatinine clearance, and NYHA class were identified as of interest a priori and included in the subgroup analysis for the primary and secondary endpoints of PROTECT.[26] They were included also in the present study, although their relation with short-term outcomes is a *post hoc* analysis. As no differences between rolofylline and placebo were present with respect to baseline characteristics, no adjustment for baseline characteristics by multivariable analysis was performed in the present analysis. An assessment of the clinical significance of symptoms relief and short-term outcomes would need adjustment for baseline data.

Severity of symptoms at baseline may influence their changes after treatment.[30,31] Although it is possible that some patients did not report improvement because their symptoms were not particularly severe at baseline, the selection criteria for the study favoured inclusion of more severe patients. Patients who did not have dyspnoea relief had more high-risk features and had three to four times higher mortality, suggesting that the lack of dyspnoea relief occurred for the most part in sicker patients who did not improve with current available therapies. Unfortunately, no data regarding the severity of symptoms at baseline were collected in PROTECT except for NYHA class as dyspnoea was measured using the Likert scale to compare the severity of breathlessness with baseline values.

Conclusions

Using objective inclusion criteria based on plasma natriuretic peptides, marked or moderate dyspnoea relief at 24 and 48 h occurred in slightly $<50\%$ of patients in the PROTECT study. Early dyspnoea relief was associated with lower short-term (30 days) mortality.

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Disclaimer: Based upon the results of the Phase III PROTECT trial assessing the effects of rolofylline on short- and long-term outcomes presented at the European Society of Cardiology in 2009, Merck & Co., Inc. determined that the lack of efficacy did not support further development of this compound for the treatment of patients with acute decompensated heart failure.

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CARDIOVASCULAR FLASHLIGHT

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Percutaneous implantation of an Edwards SAPIEN valve in a failing pulmonary bioprosthesis in palliated Tetralogy of Fallot

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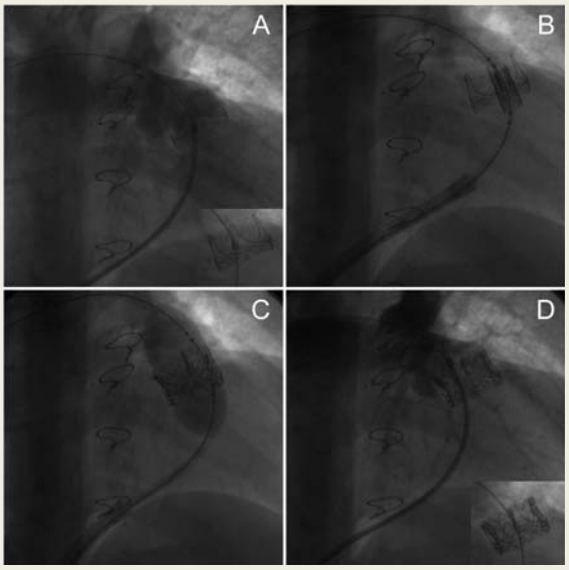
A 15-year-old boy with Tetralogy of Fallot, palliated neonatally by transannular patch repair, had a surgical 25 mm Perimount pericardial pulmonary bioprosthesis following the development of severe pulmonary regurgitation (PR) with severe right ventricular (RV) dilatation aged 10. Now with moderate exercise capacity reduction and further RV dilation and PR following bioprosthesis degeneration, it was elected to implant another pulmonary valve percutaneously.



Angiography showed severe PR with a dilated pulmonary root and outflow tract (*Panel A*, bioprosthesis inset). The bioprosthetic valve annulus provided support in the outflow tract. After initial positioning (*Panel B*), a balloon expandable Edwards SAPIEN 26 mm valve was deployed via the right femoral vein using the Edwards Retroflex 2 Transfemoral Delivery System (*Panel C*). Angiography confirmed good valve position and PR resolution (*Panel D*, valve-in-valve inset).

This is the first percutaneous 'valve in valve' Edwards SAPIEN valve implanted in a patient with a bioprosthetic pulmonary valve without a conduit/prestenting. This is an 'off-label' use of the device but percutaneous pulmonary valve implantation is accepted as a less invasive and safe way to improve haemodynamics following RV outflow tract repair and re-emergence of outflow-tract stenosis and/or PR with RV dysfunction. Outflow tract size is critical in considering whether a conventional Melody valve (used in RV–PA conduits measuring less than 22 mm) or Edwards SAPIEN valve (available in 23 or 26 mm sizes) can be used. A valve in valve approach here allowed treatment of the RV outflow tract without the risk associated with further sternotomy, a reduced hospital stay, and may be an option in those with previous bioprosthetic valves.