Effects of the Adenosine A1 Receptor Antagonist Rolofylline on Renal Function in Patients With Acute Heart Failure and Renal Dysfunction: Results From PROTECT (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)

Adriaan A. Voors, Howard C. Dittrich, Barry M. Massie, Paul DeLucca, George A. Mansoor, Marco Metra, Gad Cotter, Beth D. Weatherley, Piotr Ponikowski, John R. Teerlink, John G.F. Cleland, Christopher M. O'Connor, and Michael M. Givertz

This information is current as of January 8, 2012

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://content.onlinejacc.org/cgi/content/full/57/19/1899

JACC

JOURNAL *of the* AMERICAN COLLEGE *of* CARDIOLOGY

Effects of the Adenosine A$_1$ Receptor Antagonist Rolofylline on Renal Function in Patients With Acute Heart Failure and Renal Dysfunction

Results From PROTECT (Placebo-Controlled Randomized Study of the Selective A$_1$ Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function)

Adriaan A. Voors, MD,* Howard C. Dittrich, MD,† Barry M. Massie, MD,‡ Paul DeLucca, PHD,§
George A. Mansoor, MD,‖ Marco Metra, MD,¶ Gad Cotter, MD,# Beth D. Weatherley, PHD,#
Piotr Ponikowski, MD,†† John R. Teerlink, MD,‡ John G. F. Cleland, MD,‡‡
Christopher M. O'Connor, MD,** Michael M. Givertz, MD§§

*Groningen, the Netherlands; San Diego and San Francisco, California; North Wales, Pennsylvania;
Rahway, New Jersey; Brescia, Italy; Durham, North Carolina; Wroclaw, Poland;
Kingston Upon Hull, United Kingdom; and Boston, Massachusetts*

Objectives   This study sought to assess the effects of rolofylline on renal function in patients with acute heart failure (AHF) and renal dysfunction randomized in PROTECT (Placebo-Controlled Randomized Study of the Selective A$_1$ Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function).

Background   Small studies have indicated that adenosine A$_1$ receptor antagonists enhance diuresis and may improve renal function in patients with chronic heart failure or AHF.

Methods   A total of 2,033 patients with AHF, volume overload, estimated creatinine clearance between 20 and 80 ml/min, and elevated natriuretic peptide levels were randomized (2:1) within 24 h of hospital presentation to rolofylline 30 mg/day or intravenous placebo for up to 3 days. Creatinine was measured daily until discharge or day 7 and on day 14. Persistent worsening renal function was defined as an increase in serum creatinine ≥0.3 mg/dl at both days 7 and 14, or initiation of hemofiltration or dialysis or death by day 7.

Results   At baseline, mean ± SD estimated creatinine clearance was 51.0 ± 20.5 ml/min in the placebo group and 50.4 ± 20.0 ml/min in the rolofylline group. Changes in creatinine and estimated creatinine clearance were similar between placebo- and rolofylline-treated patients during hospitalization and at day 14. After 4 days, mean body weight was reduced by 2.6 and 3.0 kg in placebo and rolofylline patients, respectively ($p = 0.005$). Persistent worsening renal function occurred in 13.7% of the placebo group and 15.0% of the rolofylline group (odds ratio vs. placebo: 1.11 [95% confidence interval: 0.85 to 1.46]; $p = 0.44$).

Conclusions   In this large, phase III clinical trial, the adenosine A$_1$ receptor antagonist rolofylline did not prevent persistent worsening renal function in AHF patients with volume overload and renal dysfunction. (A Study of the Selective A1 Adenosine Receptor Antagonist KW-3902 for Patients Hospitalized With Acute HF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function [PROTECT-1], NCT00328692; and [PROTECT-2], NCT00354458)   (J Am Coll Cardiol 2011;57:1899–907) © 2011 by the American College of Cardiology Foundation

Renal dysfunction is common in patients who are admitted for acute heart failure (AHF) and is associated with increased mortality and rehospitalization during follow-up (1). In addition, worsening renal function (WRF), often defined as an increase in serum creatinine of ≥0.3 mg/dl during hospitalization, occurs in approximately 30% of patients and is independently related to an even poorer prognosis (2–6).

Impaired renal function at admission, and deterioration of renal function during hospitalization, may simply reflect sicker patients with more severe heart failure (HF) and, therefore, may be related to worse outcomes. However, renal dysfunction itself may contribute to deterioration of HF (7). Multiple mechanisms may be involved in renal dysfunction, including increased sodium and fluid retention, neurohormonal activation (8), and resistance to loop diuretics (9). However, a causal relation between renal dysfunction and adverse outcomes in HF can only be established with therapies that improve renal function and clinical outcomes in AHF, without exerting systemic hemodynamic or cardiotoxic or renal toxic effects.

Adenosine is increased in HF patients, because of impaired renal perfusion, venous congestion, and hypoxia (10–13). In addition, adenosine production is stimulated by the use of diuretics. Through stimulation of the adenosine A_1 receptor on the glomerular afferent arteriole, adenosine reduces renal blood flow and glomerular filtration rate (GFR), and through stimulation of the adenosine A_1 receptor on the proximal tubules, it increases sodium and water reabsorption (12). The adenosine A_1 receptor antagonist rolofylline enhanced diuresis in patients with AHF and significantly increased GFR and renal plasma flow in ambulatory patients with chronic HF (14,15). In a dose-ranging study of 301 patients with AHF and an estimated creatinine clearance (eCrCl) between 20 and 80 ml/min (the PROTECT Pilot [Effects of Rolofylline, a New Adenosine A_1 Receptor Antagonist on Symptoms, Renal Function, and Outcomes in Patients With Acute Heart Failure] trial), rolofylline 30 mg/day was associated with a more than 50% reduction in the risk of persistent WRF (16). In the present study, we describe the effects of rolofylline on renal function in 2,033 AHF patients that were included in PROTECT (Placebo-Controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) (17), a large, phase III randomized clinical trial. Our intent was to supplement the results of the primary publication by providing additional details about the renal effects of this therapy.

Methods

Patients. We enrolled 2,033 patients who were ≥18 years of age, hospitalized for AHF with dyspnea at rest or with minimal exertion and signs of fluid overload (manifest by jugular venous pressure >8 cm, pulmonary rales ≥ one-third up the lung fields, or ≥2+ peripheral or presacral edema), and had an anticipated need for intravenous furosemide ≥40 mg/day (or equivalent) for at least 24 h after the start of study drug. Other inclusion criteria were the presence of impaired renal function (eCrCl between 20 and 80 ml/min by the Cockcroft-Gault equation [corrected for height in edematous or obese subjects ≥100 kg]); elevated natriuretic peptide levels (B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide ≥500 or 2,000 pg/ml, respectively); and eligibility for randomization within 24 h of presentation. Key exclusion criteria have been described elsewhere and include a systolic blood pressure <90 or ≥160 mm Hg, acute coronary syndrome, and ongoing or planned treatment with ultrafiltration or dialysis (18).

Study procedures. The trial was approved by the ethics committees at each participating center, and patients provided written informed consent. Intravenous rolofylline 30 mg or placebo was administered as a 4-h infusion daily for 3 days in a double-blind manner according to a computer-generated randomization scheme (allocated 2:1 active to placebo). Patient follow-up continued until the last enrolled patient reached the 180-day point. Telephone contact was made at 60 days to assess vital status and identify hospital readmissions and at 180 days to assess vital status.

Laboratory measurements. At baseline (day 1), days 2 to 6 or discharge if earlier, and days 7 and 14, blood samples were obtained for assessment of serum blood urea nitrogen (BUN) and creatinine, with measurements performed in a central laboratory (ICON Laboratories, Farmingdale, New York). Creatinine was measured using a substrate-triggered rate-blanked method. When pH is alkaline, creatinine

forms a yellow-orange–colored complex with picric acid. The rate of color formation is proportional to the concentration of creatinine present and can be measured photometrically. This type of measurement minimizes interference, and a correction is applied for proteins that nonspecifically react. When performed on human serum, the test has a within-run coefficient of variance of 0.7% and between-run coefficient of variance of 2.3%.

Study outcomes and definitions. The primary endpoint for this study was a 3-category, ordered outcome of *treatment success*, *no change*, or *treatment failure*. Success was defined as patient-reported moderate or marked improvement in dyspnea using a 7-point Likert scale at both 24 and 48 h after study drug administration in the absence of any criterion for failure. Failure criteria included: death or readmission for HF any time through day 7; or worsening symptoms and/or signs of HF occurring >24 h after the start of study drug to day 7 or discharge; or persistent renal impairment as defined by a serum creatinine increase of ≥0.3 mg/dl from randomization to day 7, confirmed at day 14, or the initiation of hemofiltration or dialysis or death through day 7. *Unchanged* was defined as not meeting the criteria for either success or failure.

Two secondary outcomes were pre-specified: 1) time to death from any cause or rehospitalization for cardiovascular or renal causes through day 60; and 2) the proportion of subjects with persistent WRF. In addition, the time to death up to 180 days was assessed (not reported here). Anemia was defined as a hemoglobin <13 g/dl in men and <12 g/dl in women.

Rules for defining persistent WRF. For the analyses of the primary and key secondary endpoints, the following data handling rules were implemented to classify subjects with respect to persistent WRF for those with incomplete serum creatinine data:

- Subjects who died or initiated hemofiltration or dialysis by day 7 were classified as having persistent WRF.
- Subjects who died or initiated hemofiltration or dialysis between days 8 and 14 were considered to have a ≥0.3 mg/dl increase in creatinine at day 14. Therefore, if the day 7 value was increased ≥0.3 mg/dl the subject was considered to have persistent WRF.
- The last available creatinine value between days 2 and 6 was substituted for a missing day 7 creatinine value, and the classification of persistent WRF was based on the change from day 1 to this value and the day 14 value.
- Subjects with an increase in creatinine ≥0.3 mg/dl for the last observation in the time frame up to and including day 7 but with a missing day 14 creatinine value were classified as either unchanged or failure depending on the day that the last available creatinine value was obtained. If the value was obtained before day 6, the subject was classified as unchanged. If the value was obtained on days 6 or 7, the subject was classified as failure.

- Other subjects who did not meet any of the other failure criteria and who were missing creatinine values such that a classification of persistent WRF could not be made were classified as unchanged for the primary endpoint and missing for the key secondary endpoint.

For the analysis of change from baseline in creatinine, the last observation carried forward approach was used. For subjects who died or initiated hemofiltration or dialysis, the last observation before death or initiation of hemofiltration or dialysis was used in the analysis.

Statistical methods. The treatment groups were compared on changes from baseline in serum creatinine, BUN, and weight using analysis of covariance models with treatment, study, region, and the respective baseline values as explanatory variables. The proportion of patients with persistent WRF was analyzed using a Cochran-Mantel-Haenszel test stratified by study and region. Subgroup analyses by baseline eCrCl category (<30 ml/min, 30 to 60 ml/min, 60 to 80 ml/min, and ≥80 ml/min) of the primary trichotomous endpoint and the secondary endpoint of time to death from any cause or rehospitalization for cardiovascular or renal causes through day 60 were performed using: 1) an ordered logistic regression model with treatment, baseline eCrCl category, the interaction of treatment and baseline eCrCl category, study, and region as explanatory variables; and 2) a Cox model with treatment, baseline eCrCl category, the interaction of treatment, and baseline eCrCl category as explanatory variables and study-by-region as strata, respectively.

Univariable and multivariable analyses to predict persistent WRF were performed using logistic regression models. For the multivariable modeling, all explanatory variables were entered into the model at the same time. Statistical significance was set at the unadjusted p value level of 0.05 for the univariable and multivariable models, with no adjustment for multiplicity. Persistent WRF as defined for the secondary endpoint was used in the modeling.

Results

Patients. Of the 2,033 patients, 1,356 were randomized to rolofylline 30 mg and 677 were randomized to placebo. Mean age of the patients was 70 years, 33% were women, and 95% were Caucasian. Most patients (70%) had ischemic heart disease and comorbid conditions, including hypertension (79%), atrial fibrillation (55%), and diabetes (45%), were common. Other baseline characteristics of the study group are presented in Table 1. There were no significant differences in baseline characteristics between placebo and rolofylline-treated patients. In addition, in-hospital treatment in both groups was similar. The median and interquartile range of intravenous (IV) furosemide doses administered from randomization through day 7 or discharge if earlier were 280 mg (120 to 545 mg) and 280 mg (140 to

Table 1	Baseline Characteristics and Therapies		
	Placebo (n = 677)	Rolofylline (n = 1,356)	p Value*
Demographics			
Age, yrs	70 ± 12	70 ± 12	0.94
Male	66.8	67.3	0.82
Caucasian	95.5	95.2	0.73
Measurements			
Body mass index	28.8 ± 6.2	28.9 ± 6.1	0.65
Systolic BP, mm Hg	124 ± 18	124 ± 18	0.85
Diastolic BP, mm Hg	74 ± 12	74 ± 12	0.47
Heart rate, beats/min	81 ± 16	80 ± 15	0.22
eCrCl, ml/min	51.0 ± 20.5	50.4 ± 20.0	0.55
LVEF within 6 months, %	33 ± 14	32 ± 13	0.76
Medical history			
Ischemic heart disease	68.5	70.5	0.36
Hypertension	77.8	80.2	0.21
Atrial fibrillation	57.0	53.5	0.14
Diabetes	45.8	45.2	0.79
COPD or asthma	19.4	20.0	0.75
Medical therapy			
ACE inhibitor or ARB	74.4	76.3	0.36
Beta-blocker	75.7	76.5	0.71
Aldosterone blocker	42.4	44.5	0.36
Nitrates (oral or topical)	23.9	27.0	0.13
Digoxin	29.6	27.3	0.27
Intravenous loop diuretics†			
Furosemide	94.1	93.7	0.91
Bumetanide	4.0	4.1	0.97
Ethacrynic acid	0.1	0.1	0.61
Torsemide	1.0	0.9	0.74

Values are mean ± SD or %. *The p values for comparison of means are from 2-sample *t* test, and percentages are from chi-square test. †Received through day 7 or discharge if earlier.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eCrCl = estimated creatinine clearance; LVEF = left ventricular ejection fraction.

620 mg) in the rolofylline and placebo groups, respectively (p = 0.072). Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use increased from 70.0% at baseline to 81.5% at day 7 or discharge if earlier in the placebo group and from 70.0% to 82.6%, respectively, in the rolofylline group. The use of aldosterone blockers also increased similarly in both groups during the hospitalization from approximately 46% to 60%.

Change in creatinine, BUN, and weight. At baseline, serum creatinine was 1.50 ± 0.59 mg/dl in the placebo group and 1.52 ± 0.56 mg/dl in the rolofylline group. Overall, there was a slight and gradual increase in serum creatinine during the first few days of hospitalization (Fig. 1A), but there were no statistically significant differences in the change from baseline in serum creatinine between the placebo and rolofylline groups. There were no statistically significant differences in the change from baseline in serum creatinine between the placebo and rolofylline group at any time during the observation period.

At baseline, mean BUN was 33.7 ± 17.5 mg/dl in the placebo group and 34.3 ± 17.6 mg/dl in the rolofylline

group. As seen with serum creatinine, there was a slight and gradual increase in serum BUN over the first week of hospitalization (Fig. 1B); with the exception of the change from baseline at day 2 (p < 0.001), there were no statistically significant differences in the change from baseline in BUN between the placebo and rolofylline groups.

Patient weight was recorded during the first 4 days of hospital admission, during which time, there was slightly greater weight loss in the rolofylline-treated patients. Mean body weight decreased from 81.8 ± 19.8 kg at baseline to 79.3 ± 19.0 kg at day 4 (p < 0.001) in the placebo group, and from 82.0 ± 19.4 kg at baseline to 78.7 ± 18.4 kg at day 4 (p < 0.001) in the rolofylline group (between-treatment difference: −0.43 [95% confidence interval (CI): −0.73 to −0.13], p = 0.005).

Persistent WRF. *Persistent WRF*, defined as an increase in serum creatinine of ≥0.3 mg/dl from randomization to day 7, confirmed at day 14, or the initiation of hemofiltration or dialysis or death through day 7, occurred in 13.7% of the placebo group and 15.0% of the rolofylline group (odds ratio
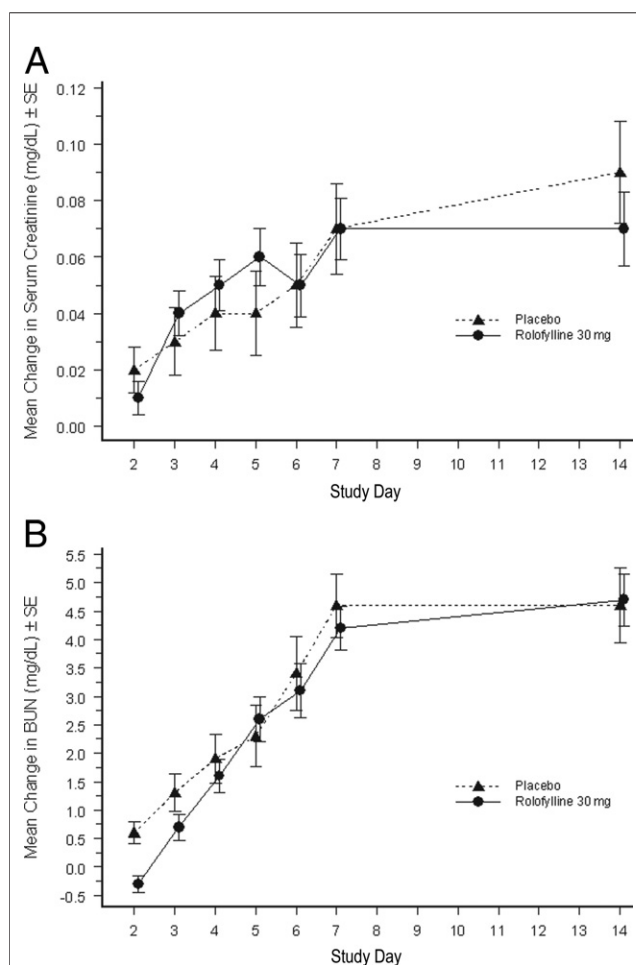

Figure 1	Changes in Renal Function

Mean change in serum creatinine **(A)** and blood urea nitrogen (BUN) **(B)** in patients randomized to placebo **(triangles)** or rolofylline 30 mg **(circles)**.

Table 2	Individual Components of Secondary Efficacy Endpoint of Persistent WRF		
		Placebo	Rolofylline
Subjects in ITT population		677	1,356
Subjects with available data for secondary endpoint		644	1,297
Subjects with persistent WRF*		88 (13.7)	195 (15.0)
SCr increase ≥0.3 mg/dl (days 7 and 14)		72 (81.8)	167 (85.6)
Initiation of hemofiltration or dialysis to day 7		6 (6.8)	6 (3.1)
Death by day 7		14 (15.9)	23 (11.8)

Values are n or n (%). *Numbers of the individual components may add to more than the total n because it is possible for a patient to be counted in more than 1 component (e.g., SCr increase at days 7 and 14 and initiation of dialysis by day 7).

ITT = intention to treat; SCr = serum creatinine; WRF = worsening renal function.

[OR] vs. placebo: 1.11 [95% CI: 0.85 to 1.46]; p = 0.44) (Table 2). Compared with patients with stable or improved renal function, patients who developed persistent WRF were older; more likely to have ischemic heart disease, anemia, and chronic lung disease; and less likely to be treated with neurohormonal antagonists and digoxin (Table 3). Patients with persistent WRF also had a lower eCrCl at baseline (46 ml/min vs. 51 ml/min) and a higher ejection fraction measured within 6 months. A multivariable analysis was performed to establish predictors of persistent WRF (Table 4). In this analysis, the presence of anemia was the only significant predictor of persistent WRF (OR: 1.61 [95% CI: 1.21 to 2.14]; p = 0.001), whereas older age (OR: 1.14 [95% CI: 0.99 to 1.31] per 10 years; p = 0.070), lower baseline eCrCl (OR: 0.92 [95% CI: 0.58 to 1.01] per 10 ml/min; p = 0.061), and diabetes (OR: 0.77 [95% CI: 0.58 to 1.01]; p = 0.058) remained of borderline significance.

Effects of rolofylline on endpoints in relation to baseline renal function. Pre-specified subgroup analyses were performed on the primary and secondary endpoints in patients according to baseline eCrCl: <30 ml/min (n = 281), 30 to 60 ml/min (n = 1,094), 60 to 80 ml/min (n = 412), and >80 ml/min (n = 156). The primary trichotomous endpoint of treatment success, unchanged, or failure was similar between rolofylline- and placebo-treated patients across these subgroups, although the OR for rolofylline (<1.0 indicating better outcome and >1.0 indicating poorer outcome) was 0.88 (95% CI: 0.56 to 1.26) in patients with eCrCl <30 ml/min and 1.37 (95% CI: 0.72 to 2.81) in patients with eCrCl >80 ml/min (Fig. 2). The secondary morbidity/mortality endpoint, the risk of death or cardiovascular or renal rehospitalization through day 60, was lower in the rolofylline group compared with the placebo group only in patients with a baseline eCrCl <30 ml/min (hazard ratio: 0.64; 95% CI: 0.43 to 0.95), but not in the other subgroups (Fig. 3).

Discussion

In this large, randomized phase III clinical trial in 2,033 patients admitted with AHF and renal dysfunction, treatment with the adenosine A_1 receptor antagonist rolofylline had a similar effect as placebo on changes in serum creatinine and BUN over 14 days and did not prevent the development of persistent WRF. However, weight loss was slightly, but significantly greater, and loop diuretic use tended to be less in rolofylline-treated patients, indicating a modest diuretic effect.

Patients admitted with AHF and volume overload have a high prevalence of baseline renal dysfunction and frequently experience WRF during hospitalization. In previous studies, the occurrence of WRF ranged from 12% (both an absolute increase in serum creatinine >0.3 mg/dl *and* a percent increase >25%) to 53% (any increase in serum creatinine), depending on the definition used (2–4,6,19–21). To exclude patients with a transient increase in creatinine, we pre-defined *persistent* WRF as an increase in serum creatinine ≥0.3 mg/dl at both days 7 and 14, or initiation of hemofiltration or dialysis or death by day 7. This explains its lower occurrence of 15%. Persistent WRF was significantly associated with the presence of anemia, with trends toward associations with poorer baseline renal function and diabetes. These findings were very similar to those observed in other studies (2–4,6,19,20).

There are several potential mechanisms that underlie WRF and could serve as targets for therapy. Two important causes of WRF in HF are a decrease in renal blood flow and an increase in central venous pressure (22–26). The most frequently prescribed drugs in the acute setting are loop diuretics. Loop diuretics increase sodium and water excretion, and exert venodilator effects, thereby reducing central venous pressure. However, acute elevations in sodium concentration in the distal tubule result in local production of adenosine, which in turn feeds back on the macula densa and proximal tubule to cause tubuloglomerular feedback and increased sodium reabsorption, respectively. Stimulation of renal adenosine A_1 receptors located in the afferent arteriole results in vasoconstriction (27,28). This will lead to a further decrease in renal blood flow, a decrease in intraglomerular pressure, and further deterioration of GFR. Therefore, selective adenosine A_1 receptor antagonists have been developed to treat and/or prevent renal dysfunction associated with heart failure.

In 63 patients with stable chronic HF and signs of edema despite loop diuretics, the adenosine A_1 antagonist BG9717 given as an IV loading dose and infusion increased both urine output and GFR (11). In contrast, the orally active adenosine A_1 antagonist BG9928 did not increase urine output or improve creatinine clearance in 50 ambulatory HF patients, although it did increase natriuresis (29). Studies with IV rolofylline in both acute and chronic HF consistently showed an increase in urine output and estimated GFR/creatinine clearance (14–16). In a phase IIb dose-ranging study in 301 patients with AHF and an eCrCl between 20 and 80 ml/min (PROTECT Pilot), rolofylline 30 mg/day was associated with improvements in weight, dyspnea, and creatinine clearance, as well as a >50% reduction in the risk of persistent WRF (16). Based on the

Table 3	Baseline Characteristics According to the Presence or Absence of Persistent WRF		
	Persistent WRF (n = 283)	No Persistent WRF (n = 1,658)	Difference (95% CI)*
Demographics			
Age, yrs	72.7 ± 10.2	69.7 ± 11.8	3.0 (1.5 to 4.4)
Male	65.0	67.2	−2.2 (−8.2 to 3.8)
Caucasian	95.0	95.6	−0.6 (−3.3 to 2.2)
Measurements			
Weight, kg	83.2 ± 19.4	81.8 ± 19.5	1.4 (−1.1 to 3.8)
Height, cm	168.7 ± 9.0	168.5 ± 9.2	0.3 (−0.9 to 1.4)
Systolic BP, mm Hg	125.5 ± 17.9	124.2 ± 17.5	1.4 (−0.9 to 3.6)
Diastolic BP, mm Hg	73.6 ± 11.8	73.9 ± 11.8	−0.3 (−1.8 to 1.1)
Heart rate, beats/min	79.9 ± 15.2	80.3 ± 15.5	−0.4 (−2.3 to 1.6)
Respiratory rate, breaths/min	20.9 ± 4.5	21.3 ± 4.5	−0.4 (−1.0 to 0.2)
BNP, pg/ml	n = 80, 1,280 (883–2,125)	n = 429, 1,260 (825–2,259)	11 (−163 to 185)
NT-proBNP, pg/ml	n = 204, 3,000 (3,000–4,696)	n = 1,252, 3,000 (3,000–3,730)	NA
eCrCl, ml/min	46.0 ± 17.1	51.4 ± 20.5	−5.4 (−7.9 to −2.8)
LVEF within 6 months, %	n = 142, 34.2 ± 13.9	n = 788, 31.9 ± 12.8	2.3 (−0.0 to 4.6)
Hgb, g/dl	12.2 ± 1.9	12.8 ± 2.0	−0.6 (−0.9 to −0.4)
Hgb, g/dl <13 men, <12 women	60.6	47.3	13.3 (6.8 to 19.8)
Total diuretic dose (IV + oral) on day 1, mg	100 (60–180)	100 (60–165)	0 (0 to 13)
Total diuretic dose (IV + oral) on day 1, mg			
≤40	55 (19.4)	302 (18.2)	
>40 to ≤80	72 (25.4)	460 (27.7)	
>80 to ≤120	45 (15.9)	321 (19.4)	
>120 to ≤160	31 (11.0)	157 (9.5)	
>160	80 (28.3)	418 (25.2)	
JVP >10 cm	42.1	40.7	1.4 (−5.2 to 7.9)
Medical history			
Heart failure 1 month before admission	94.3	95.0	−0.6 (−3.5 to 2.2)
Ischemic heart disease	74.8	68.7	6.2 (0.6 to 11.7)
Myocardial infarction	51.6	49.3	2.3 (−4.0 to 8.6)
Hypertension	83.0	78.8	4.2 (−0.6 to 9.0)
Atrial fibrillation	52.7	54.9	−2.2 (−8.5 to 4.1)
Implantable cardioverter-defibrillator	13.8	16.1	−2.3 (−6.7 to 2.1)
Biventricular pacemaker	9.5	9.9	−0.4 (−4.1 to 3.4)
Diabetes	43.1	45.8	−2.7 (−8.9 to 3.6)
COPD or asthma	24.8	19.2	5.7 (0.3 to 11.1)
Medical therapy before admission			
ACE inhibitor or ARB	71.0	76.5	−5.5 (−11.1 to 0.2)
Beta-blocker	72.1	77.3	−5.2 (−10.8 to 0.4)
Aldosterone blocker	41.3	44.8	−3.5 (−9.7 to 2.7)
Nitrates (oral or topical)	30.0	25.0	5.0 (−0.7 to 10.7)
Digoxin	19.4	30.1	−10.7 (−15.8 to −5.6)

Values are mean ± SD, %, median (interquartile range), or n (%) unless otherwise indicated. *Difference in means for continuous variables, except for BNP, NT-proBNP, and total diuretic dose, all of which display Hodges-Lehmann nonparametric estimate of between-group difference. Difference in percentages for binary variables.

BNP = B-type natriuretic peptide; CI = confidence interval; Hgb = hemoglobin; IV = intravenous; JVP = jugular venous pressure; NA = not applicable; NT-proBNP = N-terminal pro–B-type natriuretic peptide; other abbreviations as in Tables 1 and 2.

results of the PROTECT Pilot study, the 30-mg dose of rolofylline was chosen for the pivotal phase III PROTECT study, the design of which was nearly identical to that of the PROTECT Pilot study (18). Given the consistent findings in previous studies of adenosine A_1 receptor antagonists, including the PROTECT Pilot, the current findings were therefore unexpected. Although more weight loss occurred with rolofylline than with placebo, suggesting that rolofylline had an additional diuretic effect, no improvement in renal function or prevention of persistent WRF was observed.

Several potential explanations can be offered for the difference between the previous smaller studies and the present large study, of which many can be rejected. First, a difference in patient characteristics is unlikely to explain these findings as the patient population of the PROTECT Pilot study was almost identical to the current PROTECT trial (17). This was expected, because similar enrollment criteria were used. However, subgroup analysis showed a trend toward a more pronounced effect on clinical outcomes in patients with more severe renal impairment at baseline,

Table 4	Univariable and Multivariable Predictors of Persistent WRF		
Variable	**OR per Unit for Continuous Variables**	**Univariable OR (95% CI), p Value***	**Multivariable OR (95% CI), p Value***
Age, yrs	10 yrs	1.27 (1.13–1.42), p < 0.001	1.14 (0.99–1.31), p = 0.070
Male		0.91 (0.70–1.18), p = 0.473	0.95 (0.72–1.26), p = 0.715
Hypertension		1.32 (0.94–1.83), p = 0.106	1.22 (0.86–1.74), p = 0.272
Baseline CrCl, ml/min	10 ml/min	0.86 (0.81–0.93), p < 0.001	0.92 (0.85–1.00), p = 0.061
Diabetes		0.90 (0.70–1.16), p = 0.400	0.77 (0.58–1.01), p = 0.058
Hemoglobin (<13 men, <12 women)		1.72 (1.31–2.25), p < 0.001	1.60 (1.20–2.14), p = 0.001
Total diuretic dose (IV + oral) on day 1, mg		1.04 (0.95–1.13), p = 0.427	1.03 (0.94–1.13), p = 0.553
JVP (>10 cm)		1.06 (0.81–1.39), p = 0.679	1.09 (0.83–1.45), p = 0.533
Ischemic heart disease		1.36 (1.02–1.81), p = 0.038	1.27 (0.94–1.73), p = 0.120
Rolofylline Rx		1.12 (0.85–1.47), p = 0.421	1.10 (0.83–1.45), p = 0.514

*Odds ratios [ORs], 95% CIs, and p values from logistic regression models.
CrCl = creatinine clearance; Rx = treatment; other abbreviations as in Tables 2 and 3.

which suggests that the effects of rolofylline might be more pronounced in patients with greater renal dysfunction. These findings should, however, be interpreted with caution because they represent 1 of many subgroup analyses performed without adjustment for multiplicity for an endpoint in which the overall treatment effect was not statistically significant.

In contrast to the study by Givertz et al. (15), which suggested a diuretic-sparing effect of rolofylline, the cumulative dose of IV loop diuretics was similar in both the
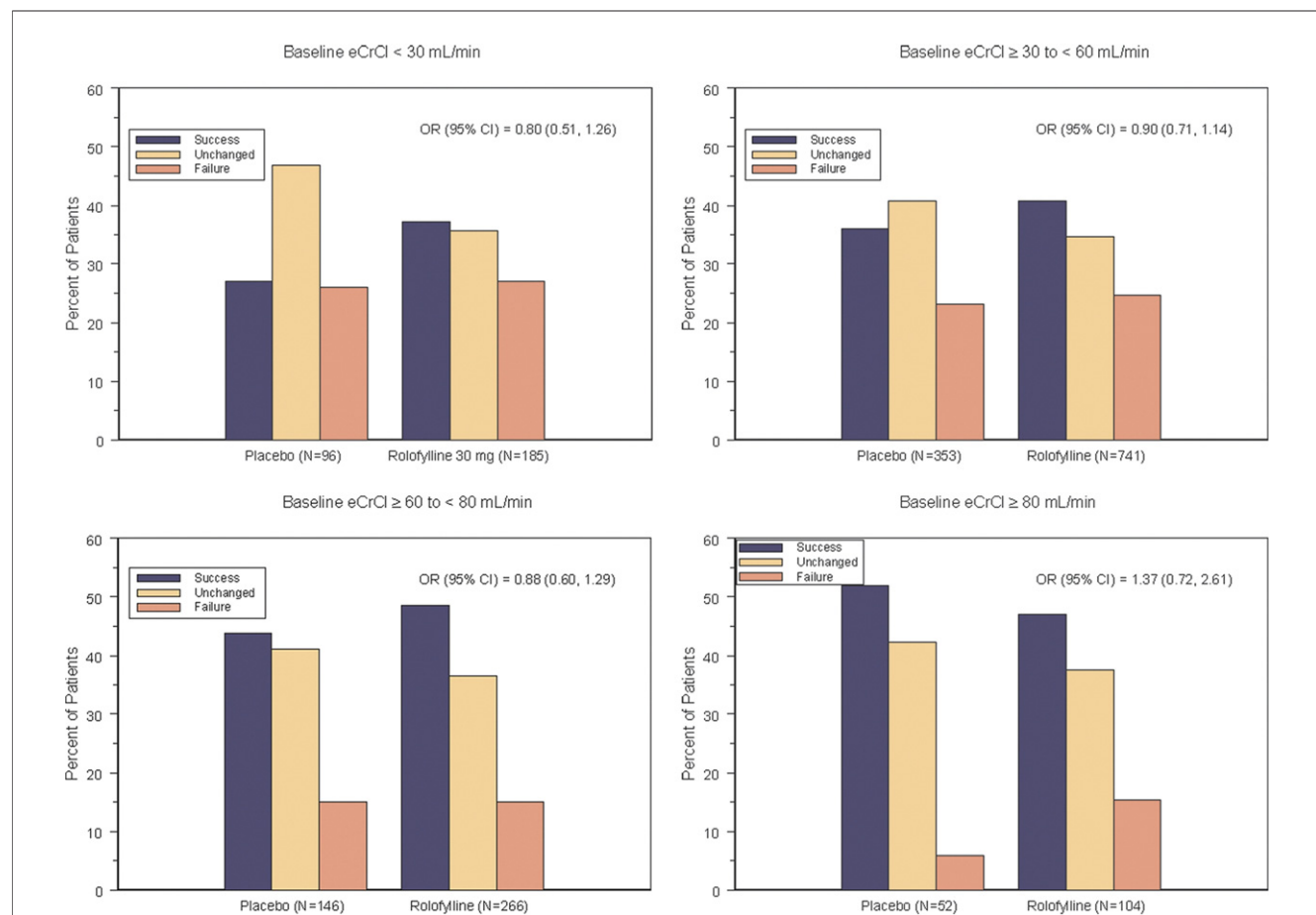

Figure 2	Primary Endpoint in Relation to Baseline Renal Function

Primary endpoint of treatment success, unchanged, or failure in placebo and rolofylline treated patients according to baseline estimated creatinine clearance (eCrCl).
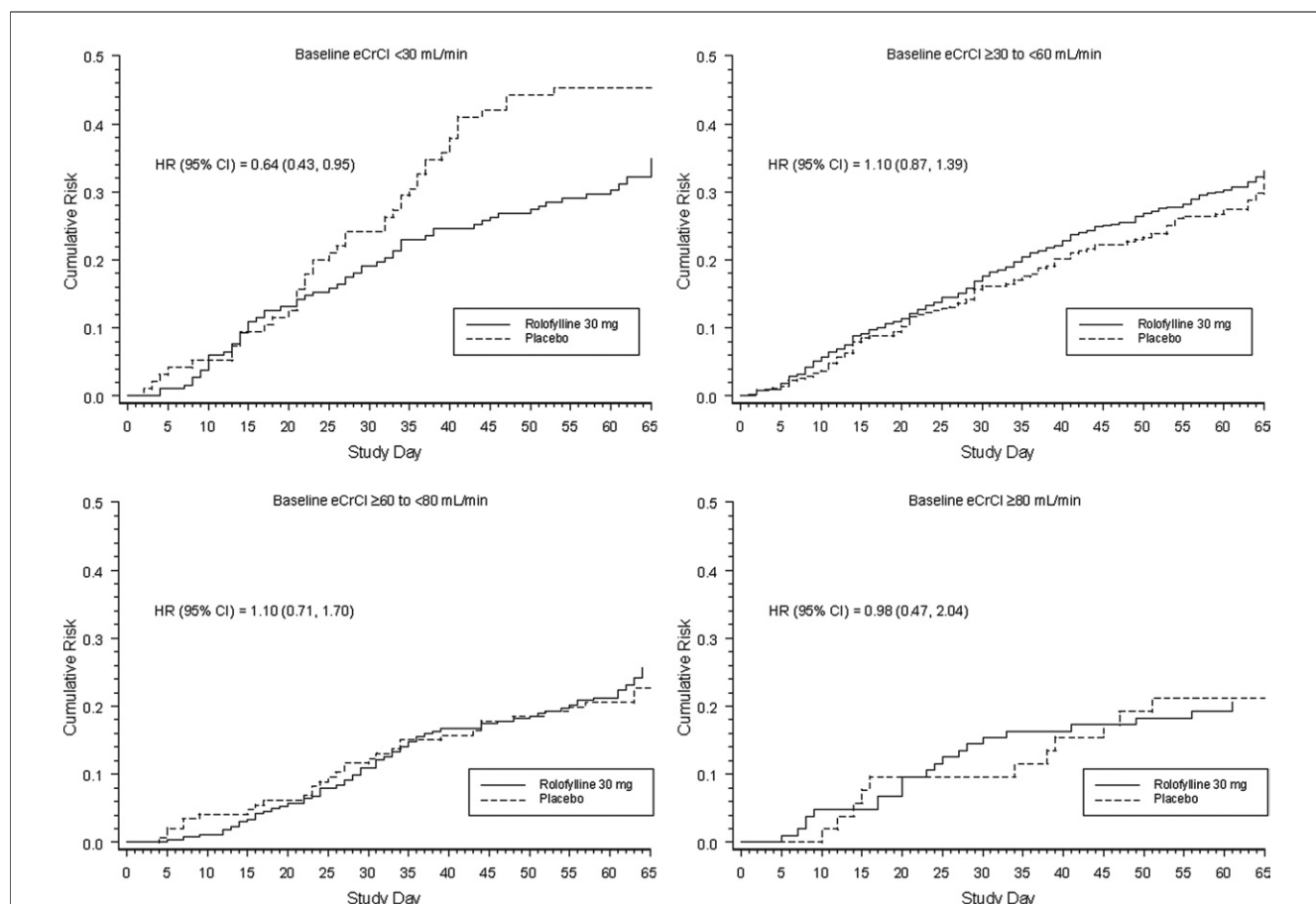CI = confidence interval; OR = odds ratio.

placebo and rolofylline groups. The finding that weight loss was more pronounced in the rolofylline group despite similar doses of diuretics indicates greater diuresis with the combination of rolofylline and loop diuretics than with loop diuretics alone. This enhanced diuretic effect might have offset the effects of rolofylline on preservation of renal function, which might be an explanation for the observed absence of renoprotective effects of adenosine A_1 blockade in the present study. In prior studies by Gottlieb et al. (11) and Dittrich et al. (14) in chronic HF outpatients treated with identical doses of furosemide, addition of an adenosine A_1 antagonist improved both diuresis *and* renal function compared with use of placebo. However, these patients were clinically stable and were not required to be volume-overloaded. Because PROTECT is the largest study to date of the effects of an adenosine A_1 antagonist on renal function, the beneficial effects seen in prior studies might be related to chance findings due to small sample size. The proof-of-concept studies by Givertz et al. (15) were not powered to assess the effects of rolofylline on renal function in AHF, and in patients with chronic HF

studied by Greenberg et al. (29), no effects of BG9928 were observed on either urine volume or renal function. Preliminary data from the TRIDENT-1 (Phase 2b Study to Assess the Safety and Tolerability of IV Tonapofylline in Subjects With Acute Decompensated Heart Failure and Renal Insufficiency) study also shows no benefit of IV BG9928 (tonopofylline) on renal function in AHF (30).

The definition of *persistent* WRF used in PROTECT is distinct from most studies of WRF in which an increase in serum creatinine of ≥0.3 mg/dl at any time during the hospitalization was considered clinically significant. The current, more conservative definition was similar to that used in the PROTECT Pilot study and was specifically designed to exclude patients with *transient* WRF. The relatively low incidence of persistent WRF that we observed is noteworthy and may be due to changes in AHF management that have occurred since the recognition of WRF as an emerging problem with prognostic implications. Use of lower doses of loop diuretics or renin-angiotensin system inhibitors, more careful attention to blood pressure or daily changes in renal function,

or changes in hospital length of stay could explain this observation.

Conclusions

In this large phase III study, rolofylline exerted modest diuretic effects, but had no protective effect on renal function in AHF patients with mild to moderate renal dysfunction.

REFERENCES

1. Heywood JT, Fonarow GC, Costanzo MR, et al., for the ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422–30.
2. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol 2000;85:1110–3.
3. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B, for the POSH Investigators. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). Eur Heart J 2006;27:1216–22.
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients. J Card Fail 2006;12:257–62.
5. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007;13:599–608.
6. Damman K, Jaarsma T, Voors AA, et al., for the COACH Investigators. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). Eur J Heart Fail 2009;11:847–54.
7. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527–39.
8. Fonarow GC, Heywood JT. The confounding issue of comorbid renal insufficiency. Am J Med 2006;119 Suppl 1:S17–25.
9. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med 2008;36 Suppl 1:S75–88.
10. Dohadwala MM, Givertz MM. Role of adenosine antagonism in the cardiorenal syndrome. Cardiovasc Ther 2008;26:276–86.
11. Gottlieb SS, Brater DC, Thomas I, et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation 2002;105:1348–53.
12. Funaya H, Kitakaze M, Node K, Minamino T, Komamura K, Hori M. Plasma adenosine levels increase in patients with chronic heart failure. Circulation 1997;95:1363–5.
13. Franceschi F, Deharo JC, Giorgi R, et al. Peripheral plasma adenosine release in patients with chronic heart failure. Heart 2009;95:651–5.
14. Dittrich HC, Gupta DK, Hack TC, Dowling T, Callahan J, Thomson S. The effect of KW-3902, an adenosine A1 receptor antagonist, on renal function and renal plasma flow in ambulatory patients with heart failure and renal impairment. J Card Fail 2007;13:609–17.
15. Givertz MM, Massie BM, Fields TK, Pearson LL, Dittrich HC, for the CKI-201 and CKI-202 Investigators. The effects of KW-3902, an adenosine A1-receptor antagonist, on diuresis and renal function in patients with acute decompensated heart failure and renal impairment or diuretic resistance. J Am Coll Cardiol 2007;50:1551–60.
16. Cotter G, Dittrich HC, Weatherley BD, et al., for the PROTECT Steering Committee, Investigators, and Coordinators. The PROTECT pilot study: a randomized, placebo-controlled, dose-finding study of the adenosine A1 receptor antagonist rolofylline in patients with acute heart failure and renal impairment. J Card Fail 2008;14:631–40.
17. Massie BM, O'Connor C, Metra M, et al., for the PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419–28.
18. Weatherley BD, Cotter G, Dittrich HC, et al., for the PROTECT Steering Committee, Investigators, and Coordinators. Design and rationale of the PROTECT study: a placebo-controlled randomized study of the selective A1 receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function. J Cardiac Fail 2010;16:25–35.
19. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail 2003;9:13–25.
20. Akhter MW, Aronson D, Bitar F, et al. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. Am J Cardiol 2004;94:957–60.
21. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol 2008;51:1268–74.
22. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. Drugs 1990;39 Suppl 4:10–21.
23. Damman K, Navis G, Smilde TD, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail 2007;9:872–8.
24. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009;53:582–8.
25. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol 2008;51:300–6.
26. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589–96.
27. Elkayam U, Mehra A, Cohen G, et al. Renal circulatory effects of adenosine in patients with chronic heart failure. J Am Coll Cardiol 1998;32:211–5.
28. Edlund A, Ohlsén H, Sollevi A. Renal effects of local infusion of adenosine in man. Clin Sci (Lond) 1994;87:143–9.
29. Greenberg B, Thomas I, Banish D, et al. Effects of multiple oral doses of an A1 adenosine antagonist, BG9928, in patients with heart failure: results of a placebo-controlled, dose-escalation study. J Am Coll Cardiol 2007;50:600–6.
30. Abraham WT. Results of the TRIDENT-1 trial: a phase 2b study to assess the safety and tolerability of IV tonapofylline in subjects with acute decompensated heart failure and renal insufficiency. Paper presented at: the European Society of Cardiology Heart Failure Congress, Late Breaking Clinical Trials; May 30, 2010; Berlin, Germany.

Key Words: adenosine receptor antagonist ■ diuretics ■ heart failure ■ renal function ■ rolofylline.

Effects of the Adenosine A1 Receptor Antagonist Rolofylline on Renal Function in Patients With Acute Heart Failure and Renal Dysfunction: Results From PROTECT (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)

Adriaan A. Voors, Howard C. Dittrich, Barry M. Massie, Paul DeLucca, George A. Mansoor, Marco Metra, Gad Cotter, Beth D. Weatherley, Piotr Ponikowski, John R. Teerlink, John G.F. Cleland, Christopher M. O'Connor, and Michael M. Givertz

This information is current as of January 8, 2012

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/57/19/1899
Supplementary Material	Supplementary material can be found at: http://content.onlinejacc.org/cgi/content/full/57/19/1899/DC1
References	This article cites 29 articles, 14 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/57/19/1899#BIBL
Citations	This article has been cited by 3 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/57/19/1899#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl