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, PhID,# 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

From the *University of Groningen, Groningen, the Netherlands; †NovaCardia, Inc., San Diego, California; the ‡University of California, San Francisco and San Francisco VA Medical Center, San Francisco, California; §Merck Research Laboratories, North Wales, Pennsylvania; ¶Merck Research Laboratories, Rahway, New Jersey; University of Brescia, Brescia, Italy; #Momentum Research, Inc., Durham, North Carolina; **Duke University Medical Center, Durham, North Carolina; ††Medical University, Clinical Military Hospital, Wroclaw, Poland; ‡‡University of Hull, Kingston Upon Hull, United Kingdom; and the §§Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts. This study was funded by NovaCardia, Inc. As of September 2007, NovaCardia is a wholly owned subsidiary of Merck & Co., Inc., Whitehouse Station, New Jersey. Echocardiography was performed using equipment provided by VOLUSON E8 (GE Healthcare) in NovaCardia hospitals and by an echocardiologist from the Clinical Physiology Unit at the Medical University in Wroclaw. A MyoCath (Cordis, Miami, Florida) catheter was used in the Clinical Military Hospital, Wroclaw, Poland.
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 $\geq 0.3$ 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$_2$ 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 $\geq$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 $\geq$ one-third up the lung fields, or $\geq 2+$/ peripheral or presacral edema), and had an anticipated need for intravenous furosemide $\geq$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 $\geq$100 kg]); elevated natriuretic peptide levels (B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide $\geq$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 $\geq 160$ 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

---

**Abbreviations and Acronyms**

- **AHF** = acute heart failure
- **BUN** = blood urea nitrogen
- **CI** = confidence interval
- **eCrCl** = estimated creatinine clearance
- **GFR** = glomerular filtration rate
- **HF** = heart failure
- **IV** = intravenous
- **OR** = odds ratio
- **WRF** = worsening renal function

---

of Merck & Co, Inc. Dr. Voors has received speakers’ fees from and served as a consultant to Merck. Dr. Dittrich has ownership in NovaCardia, and has served as a consultant to and is a minor shareholder in Merck. Dr. Massie has received speaking honorarium from CME providers for satellite symposia supported by Merck-NovaCardia, and has received compensation from Averion for his role as Co-Principal Investigator of the PROTECT trial. Drs. DeLuca and Mensour are employees of Merck. Dr. Metra has received honoraria and travel reimbursement from NovaCardia, Merck, Corthera, Novartis, Cardiolinkie, and Servier. Dr. Ponikowski has received honoraria from Merck, NovaCardia, and Corthera. Drs. Cotter and Weatherley are employees of Momentum Research. Drs. Teerlink, Cleland, and Givertz have received research grants from NovaCardia and served as consultants to Merck. Gregg Fonarow, MD, served as Guest Editor for this paper. Please note: 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 and Co., Inc. determined that the lack of efficacy did not support further development of this compound for the treatment of patients with acute decompensated HF.

Manuscript received August 13, 2010; revised manuscript received November 18, 2010, accepted November 18, 2010.
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 who died or initiated hemofiltration or dialysis or 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, study, and region as explanatory variables.

**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
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

---

**Table 1** Baseline Characteristics and Therapies

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo (n = 677)</th>
<th>Rolofylline (n = 1,356)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>70 ± 12</td>
<td>70 ± 12</td>
<td>0.94</td>
</tr>
<tr>
<td>Male</td>
<td>66.8</td>
<td>67.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Caucasian</td>
<td>95.5</td>
<td>95.2</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rolofylline</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>28.8 ± 6.2</td>
<td>28.9 ± 6.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124 ± 18</td>
<td>124 ± 18</td>
<td>0.85</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 ± 12</td>
<td>74 ± 12</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>81 ± 16</td>
<td>80 ± 15</td>
<td>0.22</td>
</tr>
<tr>
<td>eGFR, ml/min</td>
<td>51.0 ± 20.5</td>
<td>50.4 ± 20.0</td>
<td>0.55</td>
</tr>
<tr>
<td>LVEF within 6 months, %</td>
<td>33 ± 14</td>
<td>32 ± 13</td>
<td>0.76</td>
</tr>
</tbody>
</table>

**Medical history**

<table>
<thead>
<tr>
<th>Ischemic heart disease</th>
<th>Placebo 68.5</th>
<th>Rolofylline 70.5</th>
<th>0.36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>77.8</td>
<td>80.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>57.0</td>
<td>53.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.8</td>
<td>45.2</td>
<td>0.79</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>19.4</td>
<td>20.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Medical therapy**

| ACE inhibitor or ARB | Placebo 74.4 | Rolofylline 76.3 | 0.36 |
| Beta-blocker         | 75.7        | 76.5            | 0.71 |
| Aldosterone blocker  | 42.4        | 44.5            | 0.36 |
| Nitrates             | 23.9        | 27.0            | 0.13 |
| Digoxin              | 29.6        | 27.3            | 0.27 |

**Intravenous loop diuretics†**

| Furosemide           | Placebo 94.1 | Rolofylline 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; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction.
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 $\geq 0.3$ 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 diabetess. 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 decreased renal blood flow, a decrease in intraglomerular pressure, and further deterioration of GFR. Therefore, selective adenosine A1 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 A1 antagonist BG9717 given as an IV loading dose and infusion increased both urine output and GFR (11). In contrast, the orally active adenosine A1 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
The 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 A1 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.
which suggests that the effects of rololoyline 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 rololoyline, the cumulative dose of IV loop diuretics was similar in both the

![Figure 2: Primary Endpoint in Relation to Baseline Renal Function](image-url)

Primary endpoint of treatment success, unchanged, or failure in placebo and rololoyline treated patients according to baseline estimated creatinine clearance (eCrCl). CI = confidence interval; OR = odds ratio.
placebo and rololofylline groups. The finding that weight loss was more pronounced in the rololofylline group despite similar doses of diuretics indicates greater diuresis with the combination of rololofylline and loop diuretics than with loop diuretics alone. This enhanced diuretic effect might have offset the effects of rololofylline on preservation of renal function, which might be an explanation for the observed absence of renoprotective effects of adenosine A₁ 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 A₁ 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 A₁ 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 rololofylline 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 (tonapofylline) 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.

Acknowledgment

The authors wish to thank Dr. Alan Meehan (Merck) for assistance with incorporating edits per the authors’ comments/directives, copyediting, and formatting the manuscript for submission.

Reprint requests and correspondence: Dr. Michael M. Givertz, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: mgivertz@partners.org.

REFERENCES


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

Voors et al. 1907

Renal Effects of Rolofylline in Acute HF