If you come to a fork in the road, take it.
—Yogi Berra, US baseball player, coach, and manager (1925–)

Up to one half of patients with chronic heart failure and two thirds of patients with acute heart failure have concomitant renal dysfunction—a clinicopathophysiologic association that has been termed the cardiorenal syndrome.1 When present, baseline renal impairment contributes to adverse outcomes in both ambulatory and hospital settings, and the attributable risk increases with progression of both cardiac and renal disease. Although independent risk factors have been identified (eg, hypertension and diabetes) and underlying mechanisms described, targeted therapies are lacking. Complicating in-hospital management further, renal function may worsen, leading to diuretic resistance and an inability or unwillingness to administer life-prolonging therapies due to a circulatory-renal limitation. Against this backdrop, a novel class of drugs, the adenosine A1 receptor antagonists, has emerged as potential agents that can oppose an important pathway in the cardiorenal syndrome.2

### Adenosine Receptor Antagonists and Cardiorenal Syndrome

Adenosine, an endogenous purine nucleoside formed from the breakdown of adenosine triphosphate, exerts pleiotropic effects throughout the human body through its interaction with at least 4 receptor subtypes (A1, A2A, A2B, and A3)2,3. In the cardiovascular system, activation of A1 receptors reduces cardiac contractility, inhibits norepinephrine release from sympathetic nerve terminals, and suppresses sinoatrial and atrioventricular conduction. Recent data from transgenic mice also suggest that myocardial A1 receptors may contribute to adverse ventricular remodeling.4 The renal actions of adenosine mediated by A1 receptors are equally complex3 and include vasoconstriction of afferent arterioles, sodium reabsorption in the proximal tubules, and stimulation of tubuloglomerular feedback in the macula densa. The effect of adenosine on tubuloglomerular feedback is particularly relevant in states of volume overload such as heart failure, in which each nephron reaches a fluid and salt load beyond capacity. Local adenosine levels rise to stimulate proximal tubular reabsorption, while simultaneously the macula densa senses the elevated salt load and transmits adenosine—as the mediator of tubuloglomerular feedback—to cause afferent glomerular constriction and renin inhibition. The net effect is further volume retention and reduced glomerular filtration rate. In theory, selective adenosine A1 receptor antagonists should benefit patients with heart failure by attenuating volume dysregulation and preventing further deterioration in renal function that limits therapy and contributes to excess risk.

Although several adenosine A1 receptor antagonists have been developed for bench research, 4 agents have undergone significant clinical development to target cardiorenal syndrome. As shown in the Table, the A1 receptor affinity and plasma half-life of these agents varies significantly. Early clinical studies with adenosine receptor antagonists in patients with cardiorenal syndrome demonstrated consistent benefits on diuresis and natriuresis with preservation or even improvement in renal function2,6. Although data from a 300-patient pilot study with rolofylline demonstrated short- and medium-term clinical benefits in association with renal protection,7 these encouraging results were not confirmed in a pivotal study.8 Experts now wonder whether a fork in the road has been reached.

### The Current Study in Context

In this issue of Circulation: Heart Failure, Mitrovic et al9 report the results of a phase II study with the selective adenosine A1 receptor antagonist SLV320 in heart failure—a study that was carried out in 2005, first reported at a national meeting in 2008,10 and appears now after peer review. To determine the cardiorenal effects of adenosine receptor blockade, investigators randomly assigned 111 patients with chronic systolic heart failure and edema despite loop diuretic therapy to receive a 1-hour infusion of SLV320 (5, 10, or 15 mg), furosemide 40 mg, or placebo. Hemodynamic variables were measured over 12 hours using a pulmonary artery catheter, and renal function was assessed by serial measures of cystatin C, in addition to urine volume and electrolyte excretion over 8 to 12 hours.

The primary outcome of this proof-of-concept study was the change in pulmonary capillary wedge pressure. However, given the absence of published hemodynamic data with other adenosine A1 antagonists and the known presence of myocardial and vascular A1 receptors, several relevant hemodynamic parameters were reported, including systemic vascular resistance. Compared with placebo, treatment with SLV320 caused no significant change in heart rate, blood pressure, systemic vascular resistance, or any other invasive hemodynamic measure, whereas furosemide expectedly lowered both right- and left-sided cardiac filling pressures and increased systemic vascular resistance.11 With regard to renal function,
there were no significant differences in change in cystatin C levels between the placebo and 3 SLV320 groups when corrected for multiple comparisons. As expected, intravenous furosemide caused an acute worsening of renal function as indicated by an increase in cystatin C. Dose-dependent increases in urinary volume and electrolytes were observed with SLV320, although significantly less than with furosemide over the first 6 hours. Importantly when considering drug development, SLV320 was well tolerated with minor adverse events (eg, dizziness, nausea, and transient hypotension) reported in <10% of subjects.

Mitrovic et al are to be congratulated for enrolling 100 patients in a dose-ranging, hemodynamic study of a novel therapeutic agent. These studies are challenging to perform in patients with heart failure receiving multiple background therapies, and these require careful planning and close monitoring for both efficacy and safety. In addition, the investigators have provided novel observations on acute, serial changes in cystatin C in this population. Cystatin C, a nonglycosylated protein that is freely filtered by the glomerulus, has emerged as a more accurate estimator of glomerular filtration rate than creatinine, and it has theoretical advantages in patients with heart failure as it is less dependent on age, protein intake, and body composition. Cystatin C has also been shown to be an independent marker of risk even in patients with normal serum creatinine.

For purposes of clinical research, however, use of clearance methods to determine glomerular filtration rate or renal plasma flow or both, as has been done with other adenosine antagonists, would have provided more direct, validated data on acute changes in renal function. Hopefully, future studies will also assess biomarkers of renal tubular injury, such as KIM-1 or NGAL, which are released directly into the circulation or urine in response to ischemia.

There are several points to consider in interpreting these phase II data and placing them in context of current and future studies. The first point focuses on clinical applicability. So far, intravenous adenosine A1 receptor antagonists have been targeted to patients with acute heart failure and renal dysfunction, whereas oral agents in this class have been studied in chronic heart failure. Mitrovic et al studied intravenous SLV320 in middle-aged men with stable, chronic heart failure (74% New York Heart Association class III), preserved renal function (baseline serum creatinine, 1.05 mg/dL), and low-normal cardiac output (4.50 L/min). Notably, study drug was tested against placebo and furosemide rather than on top of furosemide as in previous studies of adenosine blockade. This latter point may explain the lack of a greater impact on renal function given the underlying biology of adenosine in the kidney. Tubuloglomerular feedback is particularly activated when increased sodium reaches the distal tubule (ie, with higher doses of loop diuretics), and therefore, an adenosine A1 antagonist might be expected to exert its most beneficial renal effects in patients with advanced cardiorenal syndrome receiving high-dose diuretics. Although this seemed to be the case with rololofylline in the PROTECT Pilot study, these favorable findings were not confirmed in a pivotal phase III study. A phase IIb, placebo-controlled study of intravenous SLV320 on top diuretics in patients with acute heart failure with renal dysfunction has been initiated (https://www.clinicaltrials.gov/ct2/show/NCT00744341), but enrollment was suspended in July 2009.

Table. Pharmacokinetics of Adenosine A1 Receptor Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Affinity for A1 Receptor, Ki, nM</th>
<th>Half-Life, hrs</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rolofylline (KW-3902)</td>
<td>0.72 (human) 0.19 (rat)</td>
<td>12 to 14</td>
<td></td>
</tr>
<tr>
<td>BG9719</td>
<td>0.45 (human)</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Tonapofylline (BG9928)</td>
<td>7 (human)</td>
<td>8 to 16</td>
<td></td>
</tr>
<tr>
<td>SLV320</td>
<td>1 (rat)</td>
<td>1.5 to 2</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Slawsky and Givertz, with permission.
Subgroup analyses from the PROTECT pivotal study should assess the effects of adenosine receptor blockade in patients receiving the highest dose of diuretics or with the greatest impairment of renal function.

The second point to consider when interpreting the results of a proof-of-concept, pharmacological study in heart failure is the dose of drug tested. The authors chose the dosages of SLV320 (5 to 15 mg) based on phase I data in healthy volunteers (not in patients with heart failure), which reportedly demonstrated diuretic properties without safety signals. However, the current pharmacokinetics, ex vivo adenosine antagonism, and lack of a clear dose-response curve for most of the cardio-renal end points suggest that a relatively narrow range was tested. On the other hand, the effects of SLV320 seem to plateau with the middle dose (10 mg), and similar observations have been made with BG9928 and rololofylline. This plateau effect may be because of the dual mode of action that adenosine A1 antagonists exert on the kidney as discussed by the authors (see Discussion, Renal Effects) or to nonselective adenosine receptor interaction at higher doses. Getting the dose “right,” however, may depend more on the patients studied than the end points observed, as demonstrated in the PROTECT program in which the dose of rololofylline (30 mg) found to be most beneficial in the pilot study failed to improve renal function in a 2000-patient pivotal study. Although inclusion/exclusion criteria were similar, further analyses are underway to understand differences in baseline characteristics or subsequent course that may have accounted for these divergent results.

Other issues to consider in evaluating the current results relate to sample size, end points, and statistical analysis because these are critical to assessing the validity of the findings. The sample size (22 subjects per group) was considered sufficient to detect a 5 mm Hg difference in change from baseline in pulmonary capillary wedge pressure between SLV320 and furosemide. Although this design is appropriate for a study comparing 2 groups, Mitrovic et al randomized patients to 5 different treatment groups, which raises the possibility that the study was underpowered to detect differences in hemodynamics and/or renal function. In fact, the trend toward a reduction in cystatin C in the 10 mg dose group might have been significant if more patients had been studied. The primary end point of the study was to evaluate the maximum reduction in pulmonary capillary wedge pressure from baseline over the first 12 hours, regardless when this reduction occurred. This approach is somewhat unorthodox as most hemodynamic studies use time-dependent analyses to assess changes across multiple dose groups. Comparing individual group data over time (see Results, Figure 5 of reference 9); however, it is clear that SLV320 lacks systemic effects (relative to placebo), an important and novel observation for this class of drugs whose primary target is the kidney. Finally, the authors present data with correction for multiple comparisons and consider significant unadjusted pair-wise comparisons only if the overall treatment effect is significant. This correct approach may explain the relatively neutral findings of this report in comparison with more optimistic renal data presented in the original abstract and attests to the importance of peer and statistical review. In the current era of enhanced public oversight of medical research, unbiased peer review is particularly important to eliminate any perceived conflict of interest in a sponsor-initiated or -reported study or both.

**Taking a Fork in the Road**

Taken together with other recent studies of adenosine receptor antagonists in heart failure, the data reported by Mitrovic et al raise a critical question: where do we go from here? Drug development in chronic and acute heart failure is notable as much for its failures as its successes. Recent disappointments with tumor necrosis factor-α inhibitors, endothelin blockers, and immunomodulation therapy highlight the importance of pivotal studies to confirm or refute encouraging phase II results. In other instances, early clinical data have been positive, but observed benefits are overshadowed by worrisome safety signals in larger cohorts. Although SLV320 seemed safe in the population studied, other adenosine A1 receptor antagonists have been associated with seizures. Adenosine, acting via A1 receptors located in the central nervous system, modulates seizure threshold. In phase II studies of rololofylline, 2 seizures occurred in at-risk individuals, and preliminary data from the PROTECT study appear to confirm this risk. Although patients at risk for seizures were not excluded from the current study, the absence of seizures may be due to lack of exposure (only 67 patients received a 1-hour infusion of SLV320), pharmacokinetics, or unique properties of SLV320 that make it less susceptible to causing seizures. Going forward, novel positron emission tomography techniques may allow the isolation of compounds that are highly selective for the renal A1 receptor but do not cross the blood-brain barrier. In the meantime, it is concerning that 2 other large multicenter studies of intravenous adenosine A1 antagonists in acute heart failure have recently been suspended (RENO-DEFEND; SLV320) or cancelled (TRIDENT-1; tonapofylline).

If safer adenosine A1 receptor antagonists can be developed, what are the most appropriate clinical targets for therapy? Before the recent presentation of the PROTECT study results, conventional wisdom was that patients with acute heart failure and renal dysfunction would benefit not only in terms of renal protection but also with improved clinical outcomes. Perhaps, sicker patients with refractory heart failure and acute or recent worsening renal function or those demonstrating resistance to high dose or combination diuretics would be better targets of therapy. Comorbid conditions that contribute to renal dysfunction such as diabetes might also identify more “responsive” subjects. Post hoc analyses from PROTECT may shed light on these issues. Other questions such as optimal study design (placebo versus active controlled), duration, and end points (renal versus clinical) need to be addressed. If the development of adenosine A1 receptor antagonists for acute heart failure is abandoned, the focus should turn to chronic heart failure. To this end, the POSEIDON study is currently enrolling 300 ambulatory patients with moderate to severe heart failure and an estimated glomerular filtration rate between 20 and 70 mL/min into a 12-week safety and tolerability study of oral tonapofylline (BG9928). Potential mechanisms of benefit of
chronic inhibition of myocardial A1 receptors include limitation of ischemia-reperfusion injury and attenuation of myocardial fibrosis. The value of long-term diuretic sparing also cannot be underestimated. Positive results would provide a strong rationale for a phase III study in patients with heart failure and chronic kidney disease.

Beyond heart failure, other potential targets of adenosine A1 blockade include drug-induced renal injury (eg, due to antibiotics [gentamicin], immunosuppressive agents [cyclosporine], or chemotherapy [cisplatin]) and acute kidney injury after cardiopulmonary bypass. Recent studies with low-dose natriuretic peptides in patients undergoing cardiac surgery suggest that renal protection may translate into fewer postoperative complications, shorter length of stay, and possibly improved survival. These studies have also offered novel insights into the role of markers of acute kidney injury for early diagnosis and management of renal dysfunction. Finally, adenosine A1 receptors may play an important pathophysiologic role in mediating radiocontrast-induced nephropathy, and experimental data suggest protection with adenosine A1 blockade. Given the increasing dimension of this problem in cardiac patients undergoing diagnostic and interventional procedures, as well as the lack of definitive therapies, there is a clear need for further study in this area.

Disclosures

Dr Givertz has participated in clinical investigations of adenosine receptor antagonists sponsored by Merck & Co, Inc, and Biogen Idec.

References


Key Words: adenosine receptor antagonist ■ heart failure ■ kidney ■ hemodynamics ■ diuretics
Adenosine A₁ Receptor Antagonists at a Fork in the Road
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Circ Heart Fail. 2009;2:519-522
doi: 10.1161/CIRCHEARTFAILURE.109.916072
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/2/6/519

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