

ANARITIDE IN ACUTE TUBULAR NECROSIS

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ABSTRACT

Background Atrial natriuretic peptide, a hormone synthesized by the cardiac atria, increases the glomerular filtration rate by dilating afferent arterioles while constricting efferent arterioles. It has been shown to improve glomerular filtration, urinary output, and renal histopathology in laboratory animals with acute renal dysfunction. Anaritide is a 25-amino-acid synthetic form of atrial natriuretic peptide.

Methods We conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial of anaritide in 504 critically ill patients with acute tubular necrosis. The patients received a 24-hour intravenous infusion of either anaritide (0.2 μg per kilogram of body weight per minute) or placebo. The primary end point was dialysis-free survival for 21 days after treatment. Other end points included the need for dialysis, changes in the serum creatinine concentration, and mortality.

Results The rate of dialysis-free survival was 47 percent in the placebo group and 43 percent in the anaritide group ($P=0.35$). In the prospectively defined subgroup of 120 patients with oliguria (urinary output, <400 ml per day), dialysis-free survival was 8 percent in the placebo group (5 of 60 patients) and 27 percent in the anaritide group (16 of 60 patients, $P=0.008$). Anaritide-treated patients with oliguria who no longer had oliguria after treatment benefited the most. Conversely, among the 378 patients without oliguria, dialysis-free survival was 59 percent in the placebo group (116 of 195 patients) and 48 percent in the anaritide group (88 of 183 patients, $P=0.03$).

Conclusions The administration of anaritide did not improve the overall rate of dialysis-free survival in critically ill patients with acute tubular necrosis. However, anaritide may improve dialysis-free survival in patients with oliguria and may worsen it in patients without oliguria who have acute tubular necrosis. (N Engl J Med 1997;336:828-34.)

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ACU TE tubular necrosis is an acute, severe, and sustained decrease in renal function that can result from both ischemic and nephrotoxic insults to the kidney. Despite the availability of dialysis, the morbidity and mortality are high.¹⁻³ Atrial natriuretic peptide, a hormone synthesized by the cardiac atria, increases the glomerular filtration rate and glomerular hydrostatic pressure by dilating afferent arterioles while constrict-

ing efferent arterioles.⁴ The hormone also blocks the tubular reabsorption of sodium and chloride,⁵ redistributes renal medullary blood flow,⁶ disrupts tubuloglomerular feedback,⁷ and reverses endothelin-induced vasoconstriction.⁸ Atrial natriuretic peptide has been shown to improve renal function (that is, to increase glomerular filtration and urinary output) and renal histopathology in laboratory animals with acute renal dysfunction.⁹⁻¹³ In a single-center, open-label, clinical study of 53 patients with acute tubular necrosis, infusion of atrial natriuretic peptide resulted in transient increases in creatinine clearance during the infusion of the peptide and a decreased need for dialysis.¹⁴ We conducted a multicenter, randomized, double-blind, placebo-controlled study of anaritide, a 25-amino-acid synthetic form of atrial natriuretic peptide, in patients with acute tubular necrosis.

METHODS

Patients

Patients at least 18 years of age with a clinical diagnosis of acute tubular necrosis due to recent ischemic or nephrotoxic insults were eligible for enrollment. The diagnosis of acute tubular necrosis was based on the patient's clinical history, physical examination, and laboratory values, including an analysis of urinary electrolytes and examination of urine sediment. Patients were also required to have a continuing increase in serum creatinine of at least 1 mg per deciliter (88 μmol per liter) in a period of less than 48 hours despite the optimization of fluid status. Patients were excluded from the study if they had acute renal dysfunction due to prerenal azotemia, vascular obstruction, postrenal obstruction, or systemic or intrinsic renal diseases other than acute tubular necrosis (such as vasculitis and glomerulonephritis); if they had already undergone dialysis for the current episode of acute tubular necrosis; if they were expected to require dialysis within the subsequent 24 hours or not to be candidates for dialysis; or if their underlying nonrenal medical condition was so severe that an improvement in renal function would not be expected to improve the clinical outcome. We also excluded patients who had a history of marked chronic renal insufficiency (usual serum creatinine con-

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centration [before acute tubular necrosis], >3.0 mg per deciliter [$265 \mu\text{mol}$ per liter]), previous renal transplantation, or a systolic blood pressure of less than 90 mm Hg despite the use of vasopressor therapy. The study protocol was approved by the institutional review board at each center, and all the patients gave informed consent.

Assignment and Administration of the Study Drug

To enroll a patient, a member of the staff at the study site telephoned an independent Study Randomization and Interim Analysis Center that randomly assigned eligible patients in a double-blind manner in a 1:1 ratio, stratified according to center, to receive an infusion of either anaritide (Auriculin, or human atrial natriuretic peptide, amino acid residues 102 to 126; Scios, Mountain View, Calif.) or an identical-appearing placebo (stored in coded vials). The infusion of anaritide (or an equal volume of placebo) was initially given at a dose of $0.05 \mu\text{g}$ per kilogram of body weight per minute intravenously. The dose was escalated to $0.20 \mu\text{g}$ per kilogram per minute over a 90-minute period and was continued at that level (or at the highest dose the patient tolerated) for the remainder of the 24-hour treatment period.

Study Protocol

Each patient's blood pressure and heart rate were monitored, and single-lead electrocardiography was performed, during the infusion of anaritide or placebo. A complete blood count and tests of serum chemistry were done before and after the administration of the drug. Urinary output and creatinine clearance were measured for at least four hours before the administration of anaritide or placebo; urinary output was measured for five days after treatment. Serum creatinine concentrations, requirements for dialysis, and mortality were followed for 21 days, and dialysis status and mortality were assessed again at day 60.

All the patients received full supportive care for their acute renal failure, including the optimization of fluid and nutritional status and necessary treatment for other medical problems, including the adjustment of doses of medication as appropriate for patients with renal dysfunction. Low-dose dopamine ($\leq 3 \mu\text{g}$ per kilogram per minute) or diuretic therapy was instituted or continued at the discretion of the investigator. The need for dialysis was determined by each patient's attending nephrologist on a case-by-case basis, with the need judged on the basis of the presence of volume overload, electrolyte imbalance, uremia, or acid-base disturbances not responsive to medical management.

Statistical Analysis

The primary end points were dialysis-free survival (the percentage of patients who survived through day 21 without requiring dialysis) and dialysis (the percentage of patients who underwent dialysis by day 14). Dialysis-free survival was analyzed by the Pearson chi-square test. Dialysis was studied by first estimating the curves for the time to the first dialysis with Kaplan-Meier methods, with death used as a censoring mechanism. We then used the point estimates at day 14 to test the null hypothesis that the incidence of dialysis was the same in both groups; Greenwood's formula was used to estimate the variances. All statistical tests were two-sided. Plus-minus values are means \pm SD.

Secondary end points included mortality from any cause and changes in the serum creatinine concentration at day 21. Analyses of multiple subgroups were prespecified in the protocol and were defined by the absence or presence of multiorgan failure, the cause of acute tubular necrosis (nephrotoxic or ischemic insult), the serum creatinine concentration at enrollment (≤ 4.0 mg per deciliter [$354 \mu\text{mol}$ per liter] vs. >4.0 mg per deciliter), the presence or absence of a history of chronic renal insufficiency (usual serum creatinine concentration, ≤ 1.8 mg per deciliter [$159 \mu\text{mol}$ per liter] vs. 1.8 to 3.0 mg per deciliter), and urinary output at enrollment (<100 ml per day vs. 100 to 399 ml per day [both considered oliguric] vs. ≥ 400 ml per day [nonoliguric]).

An independent Data Monitoring Committee reviewed issues of study execution and safety on an ongoing basis and conducted three interim analyses, in which data on 151, 294, and 366 patients were summarized. The objectives of the interim analyses included evaluating safety and determining whether there was sufficient evidence of efficacy or lack thereof to warrant an early termination of the study; any such decision was to be based on a prespecified guideline for stopping. At no time during the study did either the investigators or the sponsor have access to the randomization code or the unblinded results of the interim analyses. The final analysis was performed on an intention-to-treat basis, with SAS version 6.08, run on a VAX 4000-105A; it included all patients enrolled in the study.

RESULTS

Between January 1993 and February 1995, 504 patients with acute tubular necrosis were enrolled at 59 clinical centers in the United States and Canada. One patient in the placebo group was lost to follow-up on day 11 without having undergone dialysis. All the other patients were followed through day 21 or death.

Characteristics of the Patients

At enrollment, 425 patients (84 percent) were in the intensive care unit, and 253 patients (50 percent) were intubated for respiratory support. Acute tubular necrosis was attributed primarily to a nephrotoxic insult in 112 patients (22 percent), to an ischemic insult in 132 patients (26 percent), and to multiple causes in 255 patients (51 percent). The treatment groups were well matched with regard to base-line demographic variables, medical history, and the severity of renal dysfunction at enrollment (Table 1).

At enrollment, 120 of the 504 patients (24 percent) had oliguria (average urinary output, <400 ml per day), and 378 patients (75 percent) did not have oliguria (average urinary output, ≥ 400 ml per day); information on the base-line urinary output was not available for 6 patients (1 percent). The proportion of women was higher in the subgroup with oliguria than in the subgroup without oliguria (44 percent vs. 30 percent, $P=0.003$). The mean creatinine clearance at base line was significantly lower in the group with oliguria than in the group without oliguria (4 ± 6 vs. 13 ± 12 ml per minute, $P<0.001$). During the infusion of anaritide, the mean urinary output increased in the patients with oliguria but decreased in the patients without oliguria (Table 1).

During the infusion of the study drug, 167 patients (33 percent) received no dopamine, 170 patients (34 percent) received low-dose dopamine, and 167 patients (33 percent) received higher-dose dopamine for hemodynamic support; 303 patients (60 percent) received diuretics. The proportions treated with diuretics and dopamine were similar in the anaritide and placebo groups (data not shown). Concomitant diuretic therapy did not alter the responses to anaritide. There was a trend toward better out-

TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH OLIGURIA AND THOSE WITHOUT OLIGURIA IN THE ANARITIDE AND PLACEBO GROUPS.*

CHARACTERISTIC	PATIENTS WITH OLIGURIA		PATIENTS WITHOUT OLIGURIA	
	ANARITIDE (N=60)	PLACEBO (N=60)	ANARITIDE (N=183)	PLACEBO (N=195)
Age — yr	62±17	62±17	61±17	62±17
Sex — %†				
Male	57	55	73	68
Female	43	45	27	32
Chronic medical conditions — no. (%)				
Hypertension	34 (57)	35 (58)	109 (60)	116 (59)
Coronary artery disease	27 (45)	29 (48)	88 (48)	93 (48)
Diabetes mellitus	17 (28)	18 (30)	59 (32)	52 (27)
Congestive heart failure	17 (28)	21 (35)	48 (26)	53 (27)
Chronic renal insufficiency	16 (27)	16 (27)	40 (22)	44 (23)
Medical status at presentation — no. (%)				
In intensive care unit	49 (82)	52 (87)	156 (85)	165 (85)
Intubated for respiratory support	33 (55)	33 (55)	90 (49)	93 (48)
Acute medical conditions				
Infection	34 (57)	27 (45)	81 (44)	93 (48)
Sepsis	25 (42)	20 (33)	50 (27)	57 (29)
Thrombocytopenia	22 (37)	25 (42)	58 (32)	65 (33)
Coagulopathy†	16 (27)	13 (22)	26 (14)	26 (13)
Arrhythmia requiring therapy	13 (22)	17 (28)	45 (25)	56 (29)
Acute hepatic dysfunction†	11 (18)	20 (33)	24 (13)	30 (15)
Myocardial ischemia	9 (15)	8 (13)	35 (19)	29 (15)
Gastrointestinal bleeding	5 (8)	8 (13)	16 (9)	20 (10)
Adult respiratory distress syndrome	4 (7)	13 (22)	17 (9)	17 (9)
Pancreatitis	6 (10)	1 (2)	12 (7)	11 (6)
Renal function				
Creatinine clearance at enrollment — ml/min†	3±4	4±7	14±13	12±11
Urinary output — ml/day				
At base line†	187±125	151±119	2008±1396	1998±1554
During study-drug infusion	782±2104	305±329	1891±1576	2292±1583
Three days after infusion	943±1156	734±1098	2172±1573	2054±1315
Serum creatinine — mg/dl				
At enrollment	4.4±1.7	5.0±2.6	4.4±1.4	4.5±1.7
Day 21	2.8±1.9	4.1±2.6	2.8±2.0	2.7±2.1
Systolic blood pressure — mm Hg				
At base line†	121±24	126±26	132±25	130±23
Maximal decrease during drug infusion	28±18	25±18	36±23	24±19
Minimum during drug infusion	94±21	101±21	96±19	106±19
Laboratory values before dialysis				
Serum creatinine — mg/dl	6.5±1.5	6.9±2.6	6.8±2.0	6.5±2.1
Blood urea nitrogen — mg/dl	86±30	92±37	103±39	104±34
Central venous pressure — mm Hg	17±6	17±5	16±5	14±6

*Oliguria was defined as a urinary output of less than 400 ml per day. Plus-minus values are means ±SD. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for blood urea nitrogen to micromoles per liter, multiply by 0.357. Some patients had more than one of the medical conditions listed. Data on six patients without base-line measurements of urinary output are not included in this table.

†P<0.05 for the comparison between patients with oliguria and patients without oliguria.

comes in the patients with oliguria who received anaritide but not dopamine than in those who received anaritide plus dopamine. Because the patients were not randomly assigned to receive dopamine therapy, however, these findings could reflect the differential administration of dopamine to patients with a worse prognosis.

Among patients who underwent dialysis, there was no significant difference in the type of dialysis membrane used (that is, a cellulose membrane vs. a

noncellulose membrane), either between the oliguric and nonoliguric groups or between the anaritide and placebo groups. Serum creatinine and urea nitrogen values before the start of dialysis were also similar in the anaritide and placebo groups.

Measurements of Outcome

The rates of dialysis-free survival for 21 days in the anaritide and placebo groups were 43 and 47 percent, respectively (P=0.35). By day 14, 42 percent

of the patients in the placebo group and 44 percent of those in the anaritide group had undergone dialysis ($P=0.75$). The rates of death from any cause by day 21 were 26 percent in the placebo group (67 of 256 patients) and 29 percent in the anaritide group (73 of 248 patients, $P=0.41$). The mean serum creatinine concentration at day 21 in the placebo group was 3.0 ± 2.2 mg per deciliter (265 ± 194 μmol per liter); in the anaritide group, it was 2.8 ± 2.0 mg per deciliter (248 ± 177 μmol per liter, $P=0.98$).

Analyses of Subgroups

Table 2 shows rates of dialysis-free survival according to treatment group in the overall study population and all prospectively defined subgroups. Among the patients with oliguria, dialysis-free survival was 8 percent in the placebo group (5 of 60 patients) and 27 percent in the anaritide group (16 of 60 patients, $P=0.008$). Conversely, among the patients without oliguria, dialysis-free survival was 59 percent in the placebo group (116 of 195 patients) and 48 percent in the anaritide group (88 of 183 patients, $P=0.03$). When the study population was stratified further according to base-line urinary output, there was a trend toward improved dialysis-free survival after the administration of anaritide in the subgroups with base-line urinary output of less than 400 ml per

day, whereas in the subgroups with base-line urinary output of at least 400 ml per day, rates of dialysis-free survival tended to decrease (Fig. 1).

Among the anaritide-treated patients with oliguria, there was a strong association between conversion to nonoliguric status by day 3 and improved outcome; dialysis-free survival was 58 percent (15 of 26 patients) among those who converted to nonoliguric status and only 3 percent (1 of 34 patients) among those who continued to have oliguria. This association was less strong in the placebo group, in which dialysis-free survival was only 14 percent among the patients with oliguria who converted to nonoliguric status and 5 percent among those who continued to have oliguria.

Among the 120 patients with oliguria, 87 percent of those in the placebo group but only 64 percent of those in the anaritide group underwent dialysis by day 14 ($P=0.005$). Among the patients without oliguria, 30 percent of those in the placebo group and 38 percent of those in the anaritide group underwent dialysis ($P=0.12$). The mean serum creatinine concentration at day 21 was lower in the patients with oliguria who received anaritide than in those who received placebo (2.8 ± 1.9 mg per milliliter [248 ± 168 μmol per liter] vs. 4.1 ± 2.6 mg per milliliter [362 ± 230 μmol per liter], $P=0.06$).

TABLE 2. DIALYSIS-FREE SURVIVAL IN THE OVERALL STUDY POPULATION AND THE PROSPECTIVELY DEFINED SUBGROUPS.

VARIABLE	NO. OF PATIENTS*	ANARITIDE	PLACEBO	P VALUE
Study population	504	107 (43)	121 (47)	0.35
Failure of ≤ 1 nonrenal organ system	390	91 (48)	102 (51)	0.54
Cause of acute tubular necrosis				
Nephrotoxic	112	30 (59)	40 (66)	0.46
Ischemic	132	19 (28)	26 (41)	0.10
Multifactorial	255	57 (45)	52 (41)	0.49
Serum creatinine‡				
At base line				
≤ 4 mg/dl	240	54 (47)	55 (44)	0.73
> 4 mg/dl	264	53 (40)	66 (50)	0.11
Usual, before acute tubular necrosis				
≤ 1.8 mg/dl	339	75 (45)	82 (47)	0.68
1.8–3.0 mg/dl	118	27 (47)	25 (42)	0.59
Urinary output				
Oliguric (< 400 ml/day)	120	16 (27)	5 (8)	0.008
< 100 ml/day	43	3 (16)	2 (8)	0.45
100–399 ml/day	77	13 (32)	3 (8)	0.01
Nonoliguric (≥ 400 ml/day)	378	88 (48)	116 (59)	0.03

*Numbers of patients do not total 504 when base-line data needed to classify a patient were not available.

†Values shown are the numbers of patients in each treatment subgroup who survived for the 21 days after treatment without requiring dialysis and the corresponding percentages of the subgroup.

‡To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

There were no significant treatment-related differences in survival to day 60 in either the oliguric group or the nonoliguric group (Fig. 2). Among the patients with oliguria, the rates of death from any cause by day 21 were 45 percent in the placebo group (27 of 60 patients) and 40 percent in the anaritide group (24 of 60 patients, $P=0.58$). Among the patients without oliguria, the corresponding rates were 20 percent in the placebo group (39 of 195) and 26 percent in the anaritide group (48 of 183, $P=0.15$).

Safety

The administration of anaritide was generally tolerated well. Hypotension was reported in 18 percent of the placebo group and 46 percent of the anaritide group ($P<0.001$). The absolute and proportional declines in blood pressure during the infusion of anaritide were greater in patients who did not have oliguria than in those who did. Premature ventricular contractions during the infusion were noted in 6 percent of patients in the anaritide group and 2 percent of those in the placebo group ($P=0.009$); serious arrhythmias (such as heart block, ventricular tachycardia, and cardiac arrest) were infrequent (in 3 percent of patients or less) and were evenly distributed between the treatment groups. No other major adverse events and no adverse changes in laboratory values were found in the anaritide group.

DISCUSSION

We found that a 24-hour intravenous infusion of anaritide did not improve overall survival without dialysis in critically ill patients with acute tubular necrosis. The results of the subgroup analysis, however, suggest that anaritide infusion may have different effects in such patients according to their base-line urinary output, improving dialysis-free survival in those with oliguria but perhaps worsening it in those without oliguria.

The findings of subgroup analyses must always be interpreted with caution,¹⁵ particularly when multiple subgroups are tested, because the likelihood of false positive results is increased. To assess the possibility that the results in patients with oliguria were an artifact caused by the testing of multiple subgroups, we ran a computer simulation (data not shown). In each iteration, subgroup membership was randomly reassigned and the outcomes in the subgroups were reanalyzed. Only 15 of 5000 iterations (0.3 percent) yielded a result for the subgroup that was similar to the actual findings for the patients with oliguria in this trial, suggesting that these results would only rarely be obtained by chance.

The differing effects of anaritide treatment on dialysis-free survival according to base-line urinary output in patients with acute tubular necrosis were accompanied by differential trends in subsequent renal function (for example, in the serum creatinine con-

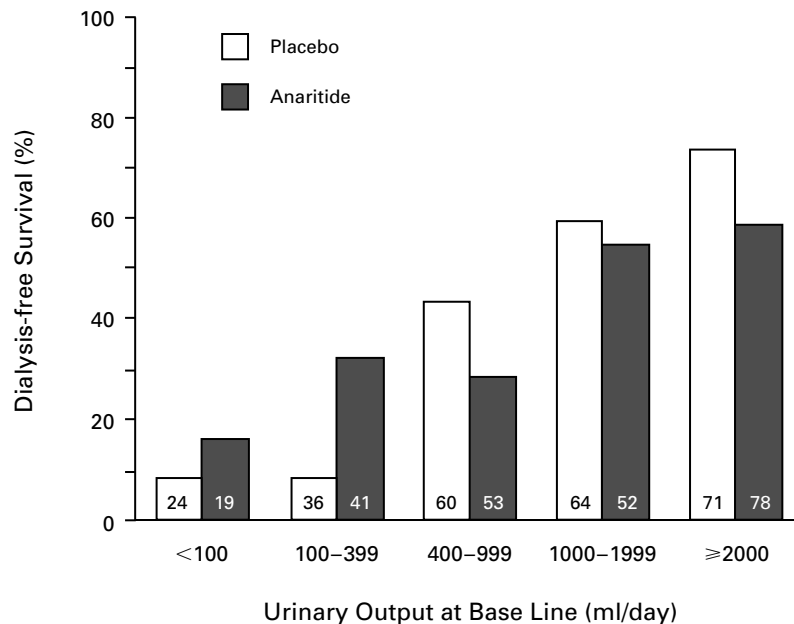
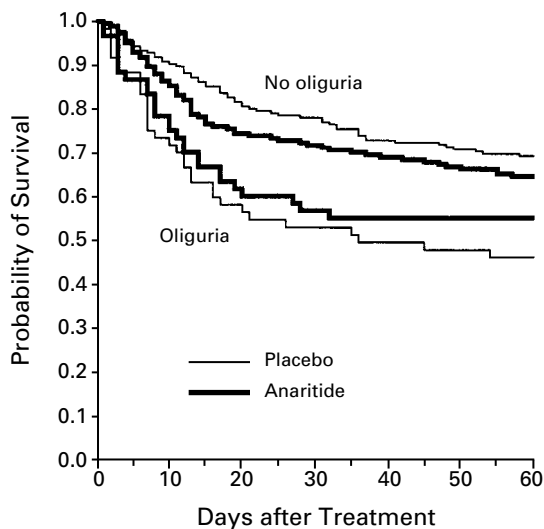


Figure 1. Dialysis-free Survival at 21 Days in the Anaritide and Placebo Groups, According to Base-Line Urinary Output.

The numbers inside the bars indicate the number of patients in each subgroup.



No oliguria				
Anaritide	183	136	126	118
Placebo	195	157	140	133
Oliguria				
Anaritide	60	36	33	33
Placebo	60	33	29	27

Figure 2. Kaplan-Meier Estimates of Survival for 60 Days after Treatment in the Anaritide and Placebo Groups, According to Base-Line Urinary Output.

The numbers below the figure indicate the number of patients in each subgroup.

centration and urinary output), the need for dialysis, and mortality. Parallel positive trends in outcome were also found in prospectively defined subgroups of patients with oliguria (that is, patients with a urinary output below 100 ml per day and those with an output of 100 to 399 ml per day). Among patients with oliguria, conversion to nonoliguric status after treatment with anaritide — but not placebo — correlated with improvement in dialysis-free survival.

Blood pressure during the infusion of anaritide decreased more in the patients who did not have oliguria than in those who did. This may have resulted in decreased renal blood flow and further ischemic injury in the patients without oliguria, thus worsening renal function.^{16,17} This finding is consistent with the observation that during the anaritide infusion the mean urinary output of the patients with oliguria increased, whereas in those without oliguria it decreased.

The differential responses to anaritide according to the level of urinary output may also reflect intrinsic differences between patients with oliguria and those without it with regard to the intrarenal mechanisms that regulate renal dysfunction. In a recent study of the effects of the biocompatibility of the dialysis membrane on the clinical outcome in patients with acute renal failure, the use of polymethyl meth-

acrylate membranes as compared with cuprophane membranes resulted in improved recovery of renal function and a trend toward decreased mortality in patients who did not have oliguria, but not in those who did.¹⁸ Thus, among patients with acute tubular necrosis, the extent of intrarenal vasoconstriction, immune-mediated disease, and glomerular and tubular dysfunction and the effectiveness of the kidney's regenerative capabilities may differ between patients with oliguria and those without it. The intrarenal pharmacologic actions of anaritide may improve renal function in patients with oliguria but may have no benefit — or may even have deleterious effects — in patients without oliguria.

Our findings are consistent with those of earlier studies indicating that patients with acute tubular necrosis who have oliguria have worse clinical outcomes than those who do not,^{1,2} and they suggest that the two groups of patients may respond differently to treatment with drugs such as anaritide. In future clinical studies of patients with acute tubular necrosis, consideration should be given to stratifying patients prospectively on the basis of their urinary output.

Supported by Scios, Inc. Drs. Allgren and Genter are employees of Scios, Inc.

Presented as an abstract at the 28th Annual Meeting of the American Society of Nephrology, San Diego, Calif., Nov. 5–8, 1995, and the 13th International Congress of Nephrology, Madrid, Spain, July 2–6, 1995.

We are indebted to the study coordinators and to the other study personnel at all the participating sites for their assistance in recruiting patients and conducting this study.

APPENDIX

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Center, San Antonio: C. Nolan; St. John's Mercy Medical Center, St. Louis: M. Ravenscraft; Wayne State University, Detroit: J. Sondheimer, H. Dries, J. Bandes; University of Texas Southwestern Medical Center, Dallas: R. Toto, J. Smart; Clinical Research Associates of Tidewater, Norfolk, Va.: D. Wombolt; Rhode Island Hospital, Providence: R. Endreny, M. Maher; University of Michigan, Ann Arbor: E. Young; St. Boniface General Hospital, Winnipeg, Man., Canada: A. Fine; San Francisco General Hospital, San Francisco: M. Humphreys; Tulane Medical Center, New Orleans: J. Puschett, S. DiLeo; West Roxbury Veterans Affairs Medical Center, West Roxbury, Mass.: G. Curhan; Brookdale Hospital Medical Center, Brooklyn, N.Y.: P. Faubert; State University of New York Health Sciences Center, Brooklyn, N.Y.: E. Friedman; Emory University School of Medicine, Atlanta: J.M. Sands; St. Louis University Health Sciences Center, St. Louis: K. Martin; University of Chicago Medical Center, Chicago: J. Umans; University of California at Irvine Medical Center, Orange: N.D. Vaziri, C. Kaupke; and Mt. Sinai Medical Center, Cleveland: T. Zipp.

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