Atrial Natriuretic Peptide for Management of Acute Kidney Injury: A Systematic Review and Meta-analysis

Sagar U. Nigwekar,* Sankar D. Navaneethan,† Chirag R. Parikh,‡ and John K. Hix§

*Department of Internal Medicine, Rochester General Hospital and University of Rochester School of Medicine, Rochester, New York; †Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio; ‡Section of Nephrology, Yale School of Medicine, New Haven, Connecticut; and §Department of Nephrology, Rochester General Hospital and University of Rochester School of Medicine, Rochester, New York

Background and objectives: Randomized controlled trials (RCTs) with atrial natriuretic peptide (ANP) have shown inconsistent effects for renal end-points. The authors aimed to systematically review these trials to ascertain the benefit of ANP in prevention and treatment of acute kidney injury (AKI).

Design, setting, participants, & measurements: The authors searched MEDLINE, EMBASE, and Cochrane Renal Health Library that investigated ANP in adult patients considered with or at risk for AKI. Outcomes were analyzed separately for prevention and treatment of AKI.

Results: Nineteen RCTs (11 prevention, 8 treatment) involving 1861 participants were included. Pooled analysis of prevention trials showed a trend toward reduction in renal replacement therapy in the ANP group (OR = 0.45, 95% CI, 0.21 to 0.99) and good safety profile, but no improvement in mortality. For the treatment of established AKI, ANP, particularly in high doses, was associated with a trend toward increased mortality and more adverse events. Subgroup analysis of AKI after a major surgery (14 RCTs, 817 participants) showed a significant reduction in renal replacement therapy requirement in the ANP group (OR = 0.49, 95% CI, 0.27 to 0.88). Included RCTs were mostly low- or moderate-quality, underpowered studies.

Conclusions: There are an insufficient number of high-quality studies to make any definite statement about the role of ANP in AKI. Analysis of the existing literature suggests ANP might be associated with beneficial clinical effects when administered in patients undergoing major surgery such as cardiovascular surgery. Its use, in low doses, should be explored further in this setting.


Acute kidney injury (AKI) is common in hospitalized patients and is associated with significant morbidity and mortality (1). Despite recent advances, outcomes from AKI have not substantially changed in the last four decades and incidence of AKI is on the rise (2). There is an urgent need to explore novel therapeutic agents and revisit some older agents to explore their role in management of AKI.

Atrial natriuretic peptide (ANP) is a 28-amino acid peptide predominantly synthesized in the atrial myocyte (3). During the initiation phase of AKI, ANP causes vasodilatation of the preglomerular artery, inhibition of the angiotensin axis, and prostaglandin release. During the reflow period of AKI, its natriuretic effect could be useful in preventing tubular obstruction (4). In animal studies, ANP has been shown to directly increase GFR (5) and to have direct diuretic and natriuretic effects on the distal nephron (6). Thus, ANP may be an ideal agent to counteract two proposed pathophysiological mechanisms of decreased GFR, namely, reduced glomerular perfusion and tubular obstruction.

There have been multiple clinical trials involving the experimental use of ANP or one of its synthetic analogues in AKI. These were prevention or treatment studies, done in different settings (medical or surgical), that used different dosages and analogues of ANP and demonstrated conflicting results. The purpose of this review was to undertake a systematic analysis of clinical trials to ascertain the therapeutic potential of ANP in management of AKI. The terminology used when referring to ANP or one of its synthetic analogues is not standardized. For this systematic review, the term “ANP” was used to refer to the circulating peptide and its synthetic analogues used in the clinical trials.

Materials and Methods

Search Strategy

Using sensitive Cochrane search methodology (Appendix), we searched MEDLINE (1966 to December 2007), EMBASE (through December 2007) and Cochrane Renal Health Library (Issue 4, 2007) for randomized controlled trials (RCTs) that investigated the use of ANP in prevention and treatment of AKI.
To retrieve the eligible studies, we used the following search terms: atrial natriuretic factor, ANF, atrial natriuretic peptide, ANP, urodilatin, anaritide, urapidil, atriopeptin, acute kidney injury, AKI, acute renal failure, acute kidney failure, ARF, acute renal insufficiency, acute kidney insufficiency, acute tubular necrosis, and ATN.

In addition, we studied reference lists and bibliographical data from all retrieved articles and reviews for any additional relevant material. There was no language restriction. A protocol for this review was developed and approved by the Cochrane Renal Group (7).

Study Selection

We included RCTs comparing any dose or form of ANP to placebo or standard treatment (e.g. furosemide) or no treatment, given before or after the development of AKI in adult (age ≥18 yr) hospitalized patients. For the purpose of this review, established AKI was defined per the recently proposed Acute Kidney Injury Network (AKIN) guidelines (8), as an abrupt (within 48 h) reduction in kidney function expressed as an absolute increase in serum creatinine of ≥ 0.3 mg/dl (≥ 26.4 μmol/L), a percentage increase in serum creatinine of ≥ 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of < 0.5 ml/kg per hr for > 6 hr).

To study the role of ANP in prevention category, we included all trials that analyzed the effectiveness of ANP as a prophylactic agent to prevent AKI after an insult known to cause AKI. Trials involving participants on chronic renal replacement therapy (RRT) were excluded.

Outcomes

Primary outcomes included (1) need for RRT and (2) mortality during the hospitalization or within 30 d. Secondary outcomes were (1) lengths of intensive care unit (ICU) and hospital stay (in days); (2) change in renal function during the trial measured by serum creatinine (mg/dl), creatinine clearance (ml/min) and/or estimated GFR (ml/min/1.73 m²); and (3) end-of-trial renal function measured by serum creatinine (mg/dl), creatinine clearance (ml/min), and/or estimated GFR (ml/min/1.73 m²). Adverse events attributed to intervention (hypotension, arrhythmias) were analyzed. Outcomes were analyzed separately for the prevention and treatment study cohorts.

Data Extraction

Two authors independently assessed the studies for eligibility and extracted relevant data regarding study design and setting, type of intervention, participant characteristics, and outcome measures, using a standardized data extraction form. Studies that used multiple intervention arms were combined through weighted means into single intervention arm. Any discrepancy between the two reviewers was resolved by discussion with an arbitrator. We contacted the corresponding investigators of all of the included studies to request unpublished data needed for a quantitative meta-analysis; only one corresponding investigator responded to this request.

Data Analysis

Analyses were performed separately for the prevention and treatment cohorts. Dichotomous data outcomes from individual studies were analyzed according to the Mantel-Haenszel model to compute individual odds ratios (ORs) with 95% confidence intervals (CI), and a pooled summary effect estimate was calculated by means of a random-effects model. Where continuous scales of measurement were used to assess the effects of treatment, the weighted mean difference (WMD) was used. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. The method of all included studies was rated by the Jadad scale (9), which considers randomization, blinding, and withdrawal/dropouts.

We assessed how robust the findings from the primary analysis were to the effects of study population and baseline risk of any of the primary outcomes through a series of sensitivity analyses, including a fixed-effects model, and by withdrawing one study at a time. To analyze the effect of quality of the included studies, we performed sensitivity analyses that were restricted to those studies with high and moderate quality and to only those studies with high quality.

Statistical heterogeneity was analyzed with the heterogeneity χ² (Cochrane Q) statistic and the I² test (10). I² values of 25%, 50%, and 75% correspond to low, medium, and high levels of statistical heterogeneity. If significant heterogeneity was found, then we explored the possible sources of heterogeneity (dose of ANP, characteristics of participants, and study quality). We constructed funnel plots for the primary outcomes to explore publication bias. All analyses were performed with RevMan 4.2.10.

We performed two predefined subgroup analyses to address the effectiveness of ANP in major surgery associated AKI and in oliguric AKI. For these subgroup analyses, we analyzed only the primary outcomes because sufficient information to compute secondary outcomes was not available.

Results

Search Results

Details of the flow of study identification are reported in Figure 1. Database searches and snowballing yielded 171 citations. Excluding 142 nonrelevant titles and abstracts, we retrieved 29 studies in complete form and assessed them according to the selection criteria. A total of 10 studies were further excluded for the following reasons: six lacked a control group (11–16), three lacked randomization process (17–19), and one included participants on chronic RRT before the initiation of study (20). Our analysis finally identified 19 eligible studies that included 1861 participants (1021 ANP group, 840 control

Figure 1. Flow chart of study identification.
group) (21–39). Eleven studies involving 818 participants satisfied our review criteria for the prevention of AKI category (21,23–25,27,28,30,35–38). Eight studies involving 1043 participants were included under the treatment of AKI category (22,26,29,31–34,39). Individual study setting, participant characteristics, type of intervention, and list of reported outcomes are summarized in Tables 1 and 2. Dose, duration, and preparations of ANP varied among studies. Six studies used urodilatin preparations (23,26,29,30,32,33), and other studies used human ANP preparation. Most of the prevention studies were conducted with low-dose ANP preparations (21,24,25,27,30,35–38). One prevention study designed to assess the effectiveness of ANP in radiocontrast nephropathy was a dose-response trial that involved administration of both low and high doses of ANP (28). Among the treatment studies, one was a dose-response trial that used both low and high doses of ANP (33), five used low-dose preparations (26,29,32,34,39), two used high-dose preparations (22,31), and one used intrarenal administration (34). Four studies in the treatment cohort included participants with established oliguric AKI (22,31–33). One study (22) included a subgroup of patients with oliguric AKI, whereas three other studies (31–33) included all participants with oliguria. Fourteen studies (817 participants) evaluated effects of ANP after major surgery (transplantation, cardiac surgery, aortic surgery, and major abdominal surgery) (21,23,24–26,29,30,32,33,35–39).

Quality of all included studies was rated with the Jadad scale (9), which considers randomization, blinding, and withdrawal/dropouts (Table 3). In the prevention cohort, five studies were of low quality (24,25,30,37,38), five were of moderate quality (21,27,28,35,36), and one was of high quality (23). Among the treatment studies, one was of low quality (34), four were of moderate quality (26,29,32,33), and three were of high quality (22,31,39).

**Prevention of AKI**

Pooled analysis of studies in the prevention cohort showed a trend toward reduction in the need for RRT in the ANP group (OR = 0.45, 95% CI = 0.21 to 0.99, P for effect = 0.05, P for heterogeneity = 0.79, I² = 0%) (Figure 2). Restricting the analysis to studies that used low dose ANP preparations did not change the overall effect for this outcome.

There was no significant difference noted between the ANP and control groups for mortality in the prevention category (OR = 0.67, 95% CI = 0.19 to 2.35, P for effect = 0.53, P for heterogeneity = 0.62, I² = 0%). Restricting the analysis to studies that used low dose ANP preparations did not change the overall effect for this outcome.

Data on secondary outcomes and adverse events on the prevention category studies are summarized in Table 4. Lengths of ICU and hospital stay were reported in only 4 and 3 studies respectively and they were significantly shorter in the ANP group compared with the control group.

**Treatment of AKI**

Pooled analysis of studies in the treatment cohort did not show any significant difference for RRT requirement between the ANP and control groups (OR = 0.59, 95% CI = 0.32 to 1.08, P for effect = 0.12, P for heterogeneity = 0.006, I² = 69.1%). There was a moderate statistical heterogeneity among the studies. We explored this heterogeneity by categorizing studies into low dose and high dose groups. This analysis (Figure 3) showed that low dose ANP preparations were associated with significant reduction in the RRT requirement (OR = 0.34, 95% CI = 0.12 to 0.96, P for effect = 0.04, P for heterogeneity = 0.04, I² = 63.6%) whereas high dose ANP preparations were not associated with reduction in RRT requirement (OR = 0.87, 95% CI = 0.52 to 1.46, P for effect = 0.60, P for heterogeneity = 0.09, I² = 57.6%). Classifying studies as per the dose of ANP reduced the heterogeneity among the studies but did not eliminate it completely. Differences in study setting, methodological quality, participant characteristics (such as baseline renal function) and sample sizes may have contributed to the remaining significant heterogeneity that was observed among these studies.

There was no significant difference noted between the ANP and control groups for mortality in the treatment category (8 RCTs, 1043 participants, OR = 1.01, 95% CI = 0.72 to 1.43, P for effect = 0.89, P for heterogeneity = 0.26, I² = 23.1%), with no significant statistical heterogeneity among the studies. After classifying studies according to the dose of ANP, we did not find low-dose ANP to be associated with any significant difference in mortality (OR = 0.61, 95% CI = 0.29 to 1.29, P for effect = 0.20, P for heterogeneity = 0.28, I² = 22.1%). Similarly, high-dose ANP was not associated with any significant difference in mortality (OR = 1.05, 95% CI = 0.92 to 1.69, P for effect = 0.15, P for heterogeneity = 0.43, I² = 0%).

Data on secondary outcomes and adverse events on the treatment category studies are summarized in Table 4. Length of ICU stay was reported in only one study (39), and it was significantly better in the ANP group compared with the control group (59 participants, WMD = −2.30 d, 95% CI = −3.40 to −1.20). None of the treatment studies reported length of hospital stay. End of trial serum creatinine was reported in three trials and was not different between the ANP and control groups. None of the studies in the treatment category reported change in renal function outcome.

Incidence of hypotension was higher in the ANP group compared with the placebo group when ANP was administered for the treatment of AKI (OR = 3.63, 95% CI = 1.76 to 7.46). When studies were characterized on the basis of ANP dose, incidence of hypotension was not different between the ANP and control groups for low-dose studies (OR = 1.55, 95% CI = 0.84 to 2.87), whereas it was significantly higher in the ANP group compared with the control group in the high-dose ANP studies (OR = 4.13, 95% CI = 1.38 to 12.41). Similarly, incidence of arrhythmias was higher in the ANP group compared with the placebo group (OR = 2.21, 95% CI = 1.33 to 3.66); however, when studies were categorized on the basis of ANP dose, this tachycardia was not increased in the ANP group compared with the control group (Table 4).
<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Setting</th>
<th>Renal function at enrollment (intervention/control)*</th>
<th>Intervention</th>
<th>Control</th>
<th>No. of participants (intervention/control)</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akamatsu 2005 (21)</td>
<td>Liver transplantation</td>
<td>48 ± 22/51 ± 18*</td>
<td>Synthetic human ANP infusion 0.05 to 0.1 μg/kg/min for 5 days</td>
<td>Furosemide bolus with potassium canrenoate</td>
<td>19/18</td>
<td>Need for RRT, mortality, length of stay (hospital, ICU), end of study creatinine, change in creatinine, and adverse events</td>
</tr>
<tr>
<td>Brenner 1995 (23)</td>
<td>Heart transplantation</td>
<td>147 ± 30/102 ± 19*</td>
<td>Urodilatin 40 ng/kg/min for 6 days</td>
<td>Placebo</td>
<td>12/12</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Hayashi 2003 (24)</td>
<td>Elective infra-renal aortic aneurysm repair</td>
<td>1.17 ± 0.49/1.25 ± 0.56</td>
<td>h-ANP at 0.025 μg/kg/min for 3 days</td>
<td>None mentioned</td>
<td>24/26</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Hayashida 2000 (25)</td>
<td>Mitral valve surgery</td>
<td>51 ± 8*/46 ± 5*</td>
<td>h-ANP at 0.05 μg/kg/min for 6 h</td>
<td>None mentioned</td>
<td>9/9</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Kurnik 1990 (27)</td>
<td>CKD patients undergoing cardiac catheterization</td>
<td>2.4 ± 0.7/2.5 ± 0.80</td>
<td>ANP (8-33 MET-ANF) at 50 μg bolus then 1 μg/min infusion for 2 h</td>
<td>Mannitol at 15% at 100 ml/h</td>
<td>10/10</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Kurnik 1998 (28)</td>
<td>CKD patients undergoing contrast requiring radiographic procedure</td>
<td>2.1 ± 0.50/2.1 ± 0.56</td>
<td>One of the 3 doses of Anaratide- 0.01 μg/kg/min or 0.05 μg/kg/min or 0.1 μg/kg/min for maximum duration of 3 h along with 0.45% normal saline</td>
<td>5% dextrose water along with 0.45% normal saline</td>
<td>60/187</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Langrehr 1997 (30)</td>
<td>Liver transplantation</td>
<td>1.18 ± 0.14/1.02 ± 0.08</td>
<td>Urodilatin at 20 ng/kg/min for 7 days</td>
<td>Placebo</td>
<td>33/37</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Sezai 2000 (35)</td>
<td>Elective CABG</td>
<td>Normal renal function in both groups</td>
<td>h-ANP between 0.03 to 0.05 μg/kg/min for 24 h</td>
<td>Placebo</td>
<td>20/20</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Sezai 2006 (36)</td>
<td>Elective CABG</td>
<td>Normal renal function in both groups</td>
<td>h-ANP at 0.02 μg/kg/min from the initiation of CPB; after surgery dose reduced to 0.01 μg/kg/min for 12 h</td>
<td>Placebo</td>
<td>75/73</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Sezai 2006a (37)</td>
<td>Thoracic aortic surgery requiring cardiopulmonary bypass</td>
<td>Normal renal function in both groups</td>
<td>h-ANP infusion from the initiation of CPB at 0.02 μg/dl/min for 12 h</td>
<td>None mentioned</td>
<td>20/20</td>
<td>Need for RRT, mortality, length of stay (hospital, ICU), end of study creatinine, and adverse events</td>
</tr>
<tr>
<td>Sezai 2007 (38)</td>
<td>Emergent CABG for acute coronary syndrome</td>
<td>Normal renal function in both groups</td>
<td>h-ANP infusion at 0.02 μg/dl/min from the initiation of CPB; after surgery dose reduced to 0.01 μg/dl/min for approximately 24 h</td>
<td>Placebo</td>
<td>63/65</td>
<td>Need for RRT, mortality, length of stay (hospital, ICU), and adverse events</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide; CKD, chronic kidney disease; CABG, coronary artery bypass graft; ICU, intensive care unit; RRT, renal replacement therapy.

*Baseline renal function was measured by serum creatinine (mg/dl), except those with asterisks, which are creatinine clearance values (ml/min)
<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Setting</th>
<th>Renal function at enrollment (intervention/control)(^a)</th>
<th>Intervention</th>
<th>Control</th>
<th>No of participants (intervention/control)</th>
<th>Outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allgren 1997 (22)</td>
<td>ATN caused by ischemic or nephrotoxic insults</td>
<td>4.40 ± 1.70 (oliguric subgroup), 4.40 ± 1.40 (nonoliguric subgroup)</td>
<td>Anaritide infusion at 0.05 to 0.20 μg/kg/min for 24 h</td>
<td>Placebo</td>
<td>243/225</td>
<td>Need for RRT, mortality, end of study creatinine, and adverse events</td>
</tr>
<tr>
<td>Herbert 1999 (26)</td>
<td>ATN after major abdominal surgery</td>
<td>2.80 ± 0.24/2.93 ± 0.38</td>
<td>Urodilatin infusion at 20 ng/kg/min for 4-6 days</td>
<td>Placebo</td>
<td>6/6</td>
<td>Need for RRT, mortality, end of study creatinine, and adverse events</td>
</tr>
<tr>
<td>Kuse 1996 (29)</td>
<td>Liver transplantation (recipients with refractory oliguria, increase of serum creatinine to at least 200% of preoperative values, and BUN levels ≥70 mg/dl)</td>
<td>2.02 ± 1.43/2.30 ± 1.14</td>
<td>Urodilatin at 20 ng/kg/min for 7 h</td>
<td>Placebo</td>
<td>5/4</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Lewis 2000 (31)</td>
<td>Oliguric ATN</td>
<td>8/5.1 (SD not available)</td>
<td>Anaritide infusion at 0.05 to 0.20 μg/kg/min for 24 h</td>
<td>Placebo</td>
<td>108/114</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Meyer 1997 (32)</td>
<td>Cardiac surgery (patients post surgery with oliguria)</td>
<td>2.58 ± 0.70/2.77 ± 0.15</td>
<td>Urodilatin at 20 ng/kg/min for 7 days</td>
<td>Placebo</td>
<td>7/7</td>
<td>Need for RRT, mortality, end of study creatinine, and adverse events</td>
</tr>
<tr>
<td>Meyer 1999 (33)</td>
<td>After major (cardiac, transplantation) surgery (patients with oliguria)</td>
<td>9 ± 8/10 ± 16*</td>
<td>One of the 4 Ularitide doses (5 or 20 or 40 or 80 ng/kg/min) for 5 days</td>
<td>Placebo</td>
<td>114/58</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Rahman 1994 (34)</td>
<td>ATN</td>
<td>9 ± 2/9 ± 2*</td>
<td>h-ANP either intrarenal (0.08 μg/kg/min for 4 h) or intravenous (0.20 μg/kg/min for 24 h) along with intravenous furosemide or mannitol</td>
<td>Intravenous furosemide or mannitol</td>
<td>30/23</td>
<td>Need for RRT, mortality, and adverse events</td>
</tr>
<tr>
<td>Sward 2004 (39)</td>
<td>AKI after cardiopulmonary bypass</td>
<td>1.23 ± 0.04/1.24 ± 0.04</td>
<td>Recombinant h-ANP at 50 ng/kg/min given for approximately 5 days</td>
<td>Placebo</td>
<td>29/30</td>
<td>Need for RRT, mortality, length of ICU stay, and adverse events</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide; ATN, acute tubular necrosis; BUN, blood urea nitrogen; ICU, intensive care unit; RRT, renal replacement therapy.

\(^a\)Baseline renal function are measured by serum creatinine (mg/dl), except those with asterisks, which are creatinine clearance values (ml/min).
increased incidence was observed only in high-dose studies (OR = 2.03, 95% CI = 1.23 to 3.25), and no difference was noted in studies using low-dose ANP preparations (OR = 1.65, 95% CI = 0.87 to 3.12).

**Subgroup Analyses**

**Major Surgery**

Analysis of trials designed to study the role of ANP in AKI after a major surgery (14 RCTs, 817 participants) showed that ANP was associated with significant reduction in the need for RRT (OR = 0.49, 95% CI = 0.27 to 0.88, P for effect = 0.02, P for heterogeneity = 0.27, I² = 19.1%) (Figure 4). There was no difference between the ANP and control groups in mortality in the surgical setting (OR = 0.91, 95% CI = 0.53 to 1.54, P for effect = 0.72, P for heterogeneity = 0.39, I² = 3.1%).

Eight studies in this subgroup were performed in the cardiovascular surgical setting (24, 25, 32, 35–39), and analysis re-
stric ted to these studies showed that ANP was associated with significant reduction in the need for RRT (OR = 0.24, 95% CI = 0.10 to 0.58, P for effect = 0.002, P for heterogeneity = 0.73, I² = 0%); however, there was no difference in mortality between the ANP and control groups.

**Oliguric AKI**

Pooled analysis of studies that examined oliguric AKI did not show any significant benefit from ANP in terms of RRT require ment (OR = 0.46, 95% CI = 0.19 to 1.12, P for effect = 0.09, P for heterogeneity = 0.03, I² = 67.0%) and mortality (OR = 0.94, 95% CI = 0.62 to 1.43, P for effect = 0.79, P for heterogeneity = 0.19, I² = 33.2%).

**Sensitivity Analysis**

Sensitivity analyses performed by switching from random-effect to fixed-effect models, computing relative risks and excluding one study at a time, confirmed the robustness of observed outcomes. Restricting the analysis to high- and moderate-quality studies did not change the overall effect on the observed results for either the prevention or treatment cohort. There was only one high-quality study (23) in the prevention cohort, and in this study, ANP did not have any beneficial effects over the placebo and was not associated with adverse events such as hypotension or arrhythmias. There were three high-quality studies (22,31,39) in the treatment cohort. Two of the treatment studies (22,31) administered high-dose ANP preparations and did not have any beneficial effects from ANP compared with placebo; in both of these, ANP was associated with increased incidence of hypotension and arrhythmias. The only high-quality study in the treatment cohort that administered low-dose ANP was associated with a reduction in the incidence of RRT, requirement without any significant difference in mortality and adverse events.

Assessment of validity and robustness of the primary outcome findings by means of a funnel plot analysis showed asymmetrical funnel plots. Although this asymmetry may be due to publication bias, our sensitive search strategy was designed to identify the relevant conference abstracts from major nephrology conferences, and we did not identify any such abstracts aside from the included published studies. Asymmetrical funnel plots could have been due to other reasons, such as poor methodological quality and small size of the studies.

**Discussion**

Beneficial effects seen in animal models of AKI led researchers to conduct clinical trials with different ANP preparations. Early clinical trials were underpowered and showed mixed results. Subsequently, Allgren *et al.* conducted a large trial of ANP in critically ill patients with acute tubular necrosis (22). The administration of ANP in this study did not improve the overall rate of dialysis-free survival; however, some benefits were observed in a subgroup of patients with oliguria. Since the publication of this study, there have been multiple clinical trials evaluating ANP for prevention and treatment of AKI. We conducted a comprehensive review of the existing literature on this topic. Our results show that there are a too few large, high-
quality studies on this topic to make any definite statement regarding the efficacy of ANP in the management of AKI. However, analysis of the existing studies shows that ANP, when used in low doses for prevention of AKI, is well tolerated and may be associated with some improvement in clinical outcomes (requirement of RRT, lengths of ICU stay, and hospitalization). Its effects are most robust when analyzed in a postsurgery setting (such as cardiovascular surgery). High-dose ANP in the treatment of established AKI was not associated with any significant clinical improvements. By causing hypotension, high-dose ANP preparations may jeopardize renal perfusion, particularly in AKI that is characterized by loss of auto regulatory capacity, and further negate the possible benefits of ANP.

Benefits of ANP observed in animal models (5,6) have not been consistently translated into clinical benefits. Pathogenesis of clinical AKI is complex (2); it can be argued that studies focused on postsurgery AKI are more similar to experimental models in that the timing of the potential renal insult is often known and the setting is one in which careful observation, administration of therapy, and data gathering is possible. This is in contrast to studies of established AKI in an unselected population of critically ill patients, who may come to medical attention at varying times after the initial renal insult and thus may be at different stages of renal injury.

Postoperative AKI is a recognized cause of significant postoperative morbidity and mortality (40). A recent systematic review by Zacharias et al. (40) did not find any reliable evidence from the available literature to suggest that interventions during surgery can protect the kidneys. This review analyzed dopamine, diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors, and hydration fluids but did not address the role of ANP. In our review, a predefined subgroup analysis looking at the surgical setting showed that the use of...
ANP might be associated with reduction in RRT requirement. Several factors, including uniform definition of AKI, a predictable injury setting, and high incidence of AKI, are needed to study the role of any intervention in the prevention of AKI (41). A major surgical setting, in particular cardiovascular, provides one such opportunity, and given the possible benefit from ANP that our review shows, its role needs to be further explored.

Our systematic review has limitations. The paucity of high-quality and adequately powered studies in our review necessitates the confirmation of these findings by future, better conducted studies. Our online clinical trial registries search (http://clinicaltrials.gov) showed one phase II ongoing trial studying ANP in the prevention of AKI after bone marrow transplantation (42), and further research is needed to establish the safety and efficacy of ANP in management of AKI. We did not find any phase IV data to verify the incidence of adverse effects caused by the ANP preparations. Even although we performed this review in compliance with the Cochrane Collaboration and QUOROM guidelines (43) and followed a comprehensive search strategy, publication bias is possible, as suggested by the funnel plots. Because of the lack of adequate information, we could not effectively assess the impact of chronic kidney disease on the efficacy of ANP. It is possible that the use of ANP may have differential effects in different AKIN-proposed stages. Unfortunately, we could not analyze effects of ANP for these different stages without potentially misclassifying studies into different stages. Future studies should prospectively classify their participants according to AKIN staging. There are no uniform indications for the initiation of RRT in clinical practice; in the included trials, the decision to initiate RRT was left to the participating physicians. This may explain the wide variation in the incidence of RRT in the included studies and could have introduced a type I error. Mortality and RRT can be competing outcomes in the critically ill population with or at risk for AKI, and it is possible that some patients with AKI did not survive to require RRT. To overcome this limitation, we performed a post hoc analysis for a composite outcome of mortality or RRT requirement during the study period and/or within 30 d. The information required to compute this composite outcome was available in 16 studies (21–31,35–39), and results were generally similar to those observed regarding the need for RRT outcome for both prevention and treatment cohorts. We contacted the original study authors of the three studies for which the information needed to analyze this composite outcomes was not available (32–34); however, none of the authors could provide this information. Despite these limitations, our results provide the most comprehensive review to date of benefits and harms of ANP administration in the management of AKI.

Researchers should consider assessing the safety and efficacy of ANP in the cardiovascular surgical setting and should analyze the efficacy according to outcomes such as the standard AKI definition suggested by the AKIN (8) or a composite outcome such as dialysis-free survival. The researchers should, instead of proceeding with more small-scale trials, form the collaborative networks needed for a definitive large trial and consider studying a population that is at a higher risk for postsurgery AKI, such as patients with pre-existing chronic kidney disease (44). In comparison with serum creatinine, novel biomarkers such as NGAL, IL-18, and others may help in earlier identification of established AKI (45,46) and could be used as enrollment criteria for future clinical trials. There are two common designs for use of the biomarker in a clinical trial (47). In the first, patients are randomized to have the biomarker measured, and anyone with an elevated level is treated with the intervention. In the second design, all patients have the biomarker measured, and those with elevated levels are randomized to therapy or no therapy.

In conclusion, there are a limited number of high quality studies to make any definite statement about the role of ANP in management of AKI. Current available evidence suggests that the use of ANP may be associated with beneficial clinical effects when administered in patients undergoing major surgery such as cardiovascular surgery. These observations need to be confirmed in a prospective multi-center study using low dose ANP preparations.

Appendix

Search methods of identification of studies

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 4, 2007), MEDLINE (1966 to December 2007), and EMBASE (through December 2007). We used the search strategies given below:

1. The Cochrane Renal Groups Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, (Issue 4, 2007) were searched using the following terms:
   
   #1. Kidney Failure, Acute explode all trees in MeSH products
   #2. acute kidney failure* in All Fields
   #3. acute renal failure* in All Fields
   #4. AKI* in All Fields
   #5. acute renal insufficiency* in All Fields
   #6. acute kidney insufficiency* in All Fields
   #7. acute tubular necrosis* in All Fields
   #8. acute kidney tubular necrosis* in All Fields
   #9. akn* in All Fields
   #10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
   #11. Atrial Natriuretic Factor explode all trees in MeSH products
   #12. atrial natriuretic peptides* or ANP* or ANF* in All Fields
   #13. urodilatin* in All Fields
   #14. anaritide* in All Fields
   #15. uraliritide* in All Fields
   #16. atriopeptin* in All Fields
   #17. (natriuretic* and (peptide* or factor*)) in All Fields
   #18. natriuretic* peptide* in All Fields
   #19. natriuretic* factor* in All Fields
   #20. (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #18 OR #19)
   #21. #10 and #20

   CENTRAL and the Renal Groups Specialized Register contain the hand-searched results of conference proceedings from general and specialty meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective
and prospective (http://www.cochrane.us/masterlist.asp). Therefore, we did not specifically search conference proceedings.

2. MEDLINE (1966 to December 2007), in the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Coordinators, was searched for the following terms:

1. exp kidney failure, acute/ or exp kidney tubular necrosis, acute/
2. acute renal failure.tw.
3. acute kidney failure.tw.
4. AKI.tw.
5. acute renal insufficiency.tw.
6. acute kidney insufficiency.tw.
7. acute tubular necrosis.tw. or ATN.tw
8. acute kidney tubular necrosis.tw
9. or/1 to 8
10. exp Atrial Natriuretic Factor/
11. (atrial natriuretic peptide$ or ANP or ANF).tw.
12. urodilatin$.tw.
13. anaritide$.tw.
14. uraliritide$.tw.
15. atriopeptin$.tw.
16. (natriuretic$ and (peptide$ or factor$)).tw.
17. or/10 to 16
18. and/9,17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized controlled trials/
22. random allocation/
23. double blind method/
24. single blind method/
25. or/19 to 24
26. animals/ not (animals/ and human/)
27. 25 not 26
28. clinical trial.pt.
29. exp clinical trials/
31. crossover procedure/
32. double blind procedure/
33. single blind procedure/
34. prospective study/
35. major clinical study/
36. exp comparative study/
37. placebo/
38. [e]valuation and follow up”/
39. follow up/
40. randomization/
41. or/17 to 29
42. controlled study/ not case control study/
43. or/30 to 31
44. (clinic$ adj5 trial$).ti,ab.
45. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
46. placebos/
47. placebo$.ti,ab.
48. random$.ti,ab.
49. or/28 to 37
50. 38 not 26
51. 27 or 39
52. and/18,40

3. EMBASE (through December 2007), in the same strategy described above for MEDLINE, was searched for the following terms:

1. *acute kidney failure/ or *acute kidney tubule necrosis/
2. acute renal failure.tw.
3. acute kidney failure.tw.
4. AKI.tw or ATN.tw
5. acute renal insufficiency.tw.
6. acute kidney insufficiency.tw.
7. or/1 to 6
8. exp natriuretic factor/ or atrial natriuretic factor alpha/ or atriopeptin i/ or atriopeptin ii/ or atriopeptin iii/ or brain natriuretic peptide/ or cardiodilatin/ or digitalis like factor/ or isothial natriuretic peptide/ or natriuretic peptide type c/ or urodilatin/
9. (atrial natriuretic peptide$ or ANP or ANF).tw.
10. (natriuretic$ and (peptide$ or factor$)).tw.
11. urodilatin$.tw.
12. anaritide$.tw.
13. uraliritide$.tw.
14. atriopeptin$.tw.
15. or/8 to 14
16. and/7,15
17. exp clinical trial/
18. evidence based medicine/
19. outcomes research/
20. crossover procedure/
21. double blind procedure/
22. single blind procedure/
23. prospective study/
24. major clinical study/
25. exp comparative study/
26. placebo/
27. [e]valuation and follow up”/
28. follow up/
29. randomization/
30. or/17 to 29
31. controlled study/ not case control study/
32. or/30 to 31
33. (clinic$ adj5 trial$).ti,ab.
34. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
35. placebos/
36. placebo$.ti,ab.
37. random$.ti,ab.
38. or/33 to 36
39. 32 or 37
40. limit 38 to human
41. and/16,39

4. We studied reference lists and bibliographical data from all retrieved articles and reviews for any additional relevant material.
5. We also sent letters seeking information about unpublished or incomplete trials to investigators known to be involved in included trials.

Acknowledgments
This work was done as part of the Cochrane Renal Group review.

Disclosures
None.

References


31. Lewis J, Salem MM, Chertow GM, Weisberg LS, McGrew F, Marbury TC, Allgren RL: Atrial natriuretic factor in


