

# Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis

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Acute renal failure (ARF) affects an estimated 6% of patients admitted to intensive care<sup>1</sup> and is associated with increased morbidity, mortality and utilisation of health resources.<sup>2-5</sup> The use of diuretics is common practice — in about 60% of critically ill patients with ARF.<sup>6</sup>

Furosemide and other loop diuretics can reduce oxygen demand in the medullary thick ascending loop of Henle by inhibiting the Na<sup>+</sup>/K<sup>+</sup>/Cl<sup>-</sup> pump on the luminal cell membrane surface. Thus, timely administration of loop diuretics might attenuate renal injury and reduce the severity of ARF.<sup>7,8</sup> Similarly, loop diuretics may have additional benefit in patients with ARF by increasing urine output and thereby facilitating fluid, acid–base and potassium control.

Numerous small, clinical studies of loop diuretics for the treatment of ARF have been reported without consistent clinical benefits.<sup>9-20</sup> Moreover, two large observational studies in critically ill patients have reported discrepant findings on the effect of loop diuretics on mortality and renal recovery after ARF.<sup>6,21</sup> A recent meta-analysis concluded that furosemide was not associated with any significant clinical benefit and perhaps increased risk of harm.<sup>22</sup> Unfortunately, this meta-analysis included studies where furosemide was administered to both prevent and treat ARF, and one study where furosemide was given to both the treatment and control groups. Further, it included duplicated control data from a study with three treatment groups, and estimated the rates of toxicity in another. Consequently, evidence on the role of diuretics in the management of ARF, in particular in critically ill patients, remains uncertain.

In an attempt to overcome the above limitations and as part of a larger initiative to understand the therapeutic role of loop diuretics in the management of ARF, we conducted an up-to-date systematic review and meta-analysis. We assessed the impact of loop diuretics on mortality, need for renal replacement therapy and renal recovery after ARF. We also examined the effect of loop diuretics on physiological variables, such as urine output, duration of ARF or renal replacement therapy (RRT), hospital length of stay, and the occurrence of toxicity. Finally, we applied a critical care perspective to the current literature on the use of loop diuretics in the management of ARF.

## ABSTRACT

**Background:** Loop diuretics are commonly used in critically ill patients with acute renal failure (ARF), but their effect on clinical outcome remains uncertain. We systematically reviewed the literature comparing loop diuretics with control in the management of ARF.

**Methods:** Studies were identified by search of MEDLINE, EMBASE, and the Cochrane Controlled Clinical Trials Register, and review of proceedings from selected scientific meetings and clinical trial registries, and bibliographies of retrieved citations. We selected randomised controlled trials (RCTs) comparing loop diuretics with control in patients with ARF. Data were extracted in duplicate by two independent reviewers on study characteristics, quality and outcomes. Primary outcomes were mortality, need for renal replacement therapy (RRT) and renal recovery. Secondary outcomes were change to urine output, serum potassium level and acid–base status, duration of ARF or RRT, length of hospital stay and toxicity.

**Results:** Of 62 studies reviewed, five RCTs, enrolling 555 patients, were eligible and analysed. These trials enrolled a mix of patients, but only two included critically ill patients. Overall trial quality was low. There was no statistical difference in mortality (odds ratio [OR], 1.28; 95% CI, 0.89–1.84; *P* = 0.18) or renal recovery (OR, 0.88; 95% CI, 0.59–1.31; *P* = 0.5) with use of loop diuretics compared with control. However, loop diuretics were associated with a shorter duration of RRT (weighted mean difference, –1.4 days; 95% CI, –0.2 to –2.3 days; *P* = 0.02), shorter time to spontaneous decline in serum creatinine level (weighted mean difference, –2.1 days; 95% CI, –0.4 to –3.7 days; *P* = 0.01) and a greater increase in urine output from baseline (OR, 2.6; 95% CI, 1.4–4.9; *P* = 0.004). Insufficient data were available on acid–base status, hospital length of stay or health costs. Four studies reported toxicity, most commonly transient tinnitus and deafness.

**Conclusions:** Loop diuretics were not associated with improved mortality or rate of independence from RRT, but were associated with shorter duration of RRT and increased urine output. However, these findings have limited relevance to critically ill patients. The relative paucity of high-quality data assessing the value of loop diuretics in ARF for the critically ill suggests a need for a suitably powered randomised trial.

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**Methods**

**Search strategy**

Randomised controlled trials (RCTs) of loop diuretics in the management of ARF were identified by electronic and manual search strategies. This search was supplemented by scanning the bibliographies of retrieved articles and review articles, reviewing conference proceedings of selected scientific meetings and clinical trial registries, and contacting experts in the field. All languages and types of publications were considered eligible. The comprehensive search was performed in April 2006, and an updated verification search in November 2006.

The databases MEDLINE, EMBASE and the Cochrane Controlled Clinical Trials Register (from inception to April 2006 for all three) were searched via OVID using an approach recommended for systematic reviews of randomised trials.<sup>23</sup> MEDLINE was also searched through PubMed.<sup>24</sup> Three comprehensive search themes were derived, which were then combined using the Boolean operator “AND”. The first theme used a recommended highly sensitive RCT filter.<sup>25</sup> The second theme, diuretic, was created by a search using an exploded medical subject headings (MeSH) and textword search for “diuretic” or “frusemide” or “furosemide” or “lasix” or “loop”. The third theme, acute renal failure, was created using the Boolean search term “OR” to search for the following terms appearing as both exploded MeSH and text words: “acute renal failure” or “acute renal insufficiency” or “oliguria”.

**Study selection**

Identified abstracts were initially screened independently by two of the authors (SMB and AD) to confirm that they reported original data on the use of loop diuretics in the management of ARF. The full text articles were retrieved and assessed to determine if they fulfilled pre-determined eligibility criteria. The same two authors independently applied the inclusion criteria to all retrieved articles, with any disagreements resolved by discussion. A third reviewer (MH) assessed articles published in German or Russian to determine eligibility. To be eligible for inclusion, the article had to fulfil all the following criteria:

- study design — randomised clinical trial;
- target population — adult patients with established ARF;
- intervention — loop diuretics compared with control; and
- outcome — reported at least one of need for RRT, death or renal recovery.

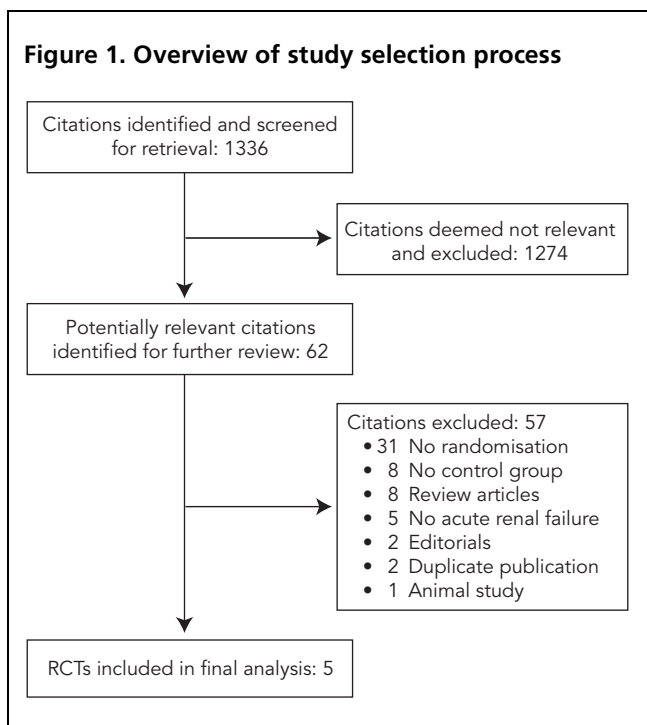
**Assessment of methodological quality**

The methodological quality and validity of the included studies were assessed using criteria defined *a priori*. Each study was assessed for allocation concealment, blinding, reporting of losses to follow-up or missing outcome assessments, evidence of important baseline differences between the groups, analysis on an intention-to-treat basis and use of a sample size calculation.<sup>26,27</sup> When the details of the methods for allocation concealment were not specified or could not be clarified, it was assessed as absent. Two authors (SMB and AD) independently assessed methodological quality of the included studies, with any disagreements resolved through discussion. We did not calculate quality scores, as many of their components were not available, and the validity of adjustment in meta-analyses by such quality scores, rather than simple description, has been questioned.<sup>28</sup>

**Data abstraction**

Data were abstracted onto standardised data collection forms independently by SMB and AD. Any discrepancies in extracted data were resolved by discussion. Data extracted included details of study protocol and regimen for administration of loop diuretics, baseline demographic, clinical and laboratory characteristics of the study population, aetiology of ARF, and the primary outcomes of need for RRT, death and renal recovery.

Secondary outcome data, when available, were abstracted on change in urine output, change in renal function, duration of ARF or duration of need for RRT, hospital length of stay, and occurrence of drug toxicity. Additional information was sought if available on acid-



**Table 1. Study features and patient characteristics at time of trial enrolment**

Study	Year	No. of patients	Mean age (years)	Male (%)	Baseline kidney function	Oliguria (%)	Renal replacement therapy (%)
Cantarovich <sup>29</sup>	1971	47	na	na	na	47 (100%)*	47 (100%)
Karayannopoulos <sup>36</sup>	1974	20	na	na	na	na	na
Kleinknecht <sup>37</sup>	1976	66	na	31 (47%)	na	66 (100%)†	na
Shilliday <sup>30</sup>	1997	92	58.8	51 (55%)	Creatinine clearance < 10 mL/min	na	0
Cantarovich <sup>35</sup>	2004	330	58.5	223 (68%)	Serum creatinine, 406 µmol/L Urea, 12.8 mmol/L‡	145 (44%)	330 (100%)

\* Oliguria defined as urine output < 400 mL/day. † Oliguria defined as urine output < 500 mL/day or < 20 mL/h after volume expansion. ‡ Mean values. Year = year of publication. na = not available or not reported. ◆

base status, serum potassium levels, oxygenation or need for mechanical ventilation, and health care costs. In one study where a loop diuretic was administered by two different regimens, outcome data were pooled and compared with the control.<sup>29</sup> In another study, both frusemide and torasemide were used, and, as they are reportedly equipotent, data were pooled for these arms and compared with the control.<sup>30</sup>

**Quantitative data synthesis**

Agreement on the inclusion of full text studies was assessed by the  $\kappa$  statistic. The presence of heterogeneity across trials for all variables was evaluated using the  $\chi^2$  test for homogeneity and the  $I^2$  statistic, with an  $I^2$  value > 50% indicating at least moderate statistical heterogeneity.<sup>31</sup> Dichotomous data were combined to estimate the pooled odds ratio (OR) with 95% CIs using weighted fixed-effects or random-effects models when appropriate.<sup>32</sup> Continuous outcomes were pooled using standardised mean differences. The potential for publication bias was assessed using both Egger’s test and a visual assessment of funnel plots for asymmetry.<sup>33,34</sup> All statistical analyses were performed using Stata version 8.2 (Stata-Corp, College Station, Tex, USA).

**Results**

**Study selection**

Database searches generated 1336 citations. Sixty-two full text articles were retrieved and reviewed in detail, with five RCTs fulfilling all eligibility criteria for inclusion.<sup>29,30,35-37</sup> All five RCTs were identified by the electronic search strategy. There was excellent agreement between reviewers for study inclusion (raw agreement = 0.94, chance-corrected agreement  $\kappa$  = 0.89 [SE, 0.16]). The studies included and reasons for exclusion are shown in Figure 1.

**Study description**

A total of 555 patients were studied, with 305 allocated to receive loop diuretics, and 250 to control groups. Two RCTs enrolled critically ill patients, but the proportion admitted to an intensive care unit was not specified.<sup>30,35</sup> The mean ( $\pm$ SD) age of patients enrolled was 58.7 ( $\pm$ 0.16) years,<sup>30,35</sup> and 57% were male.<sup>30,35,37</sup> The characteristics of the five trials are shown in Table 1.

The overall methodological quality and reporting of the trials was poor, as shown in Table 2. Adequate concealment of allocation was reported in only one trial, but this trial had significant differences between groups at baseline in terms

**Table 2. Summary of key indicators of trial methodological quality**

Study	Allocation concealment	Blinding	Placebo-controlled	Analysis by intention-to-treat	Baseline imbalance	Pre-defined outcomes	Loss to follow-up	Sample size calculation
Cantarovich <sup>29</sup>	No	No	No	No	na	No	na	No
Karayannopoulos <sup>36</sup>	No	No	No	No	na	No	na	No
Kleinknecht <sup>37</sup>	No	No	No	No	na	No	No	No
Shilliday <sup>30</sup>	No	Yes	Yes	No	No	Yes	No	No
Cantarovich <sup>35</sup>	Yes	Yes	Yes	No	Yes	Yes	No	Yes

na = not available or not reported. ◆

**Table 3. Details of protocol for administration of loop diuretics in acute renal failure**

Study	Loop diuretic	Protocol for diuretic administration	Target diuresis	Additional interventions
Cantarovich <sup>29</sup>	Furosemide	Fixed furosemide (600 mg/24 h IV*) v progressive furosemide (100–3200 mg/24 h IV*) v placebo	≥ 2000 mL/24 h	All received mannitol and conventional intermittent haemodialysis
Karayannopoulos <sup>36</sup>	Furosemide	1000 mg IV, titrated to a maximum 3000 mg × 7 days	na	na
Kleinknecht <sup>37</sup>	Furosemide	3 mg/kg IV bolus, then 1.5–6.0 mg/kg every 4 h	≥ 20–100 mL/h	Mannitol and renal replacement therapy
Shilliday <sup>30</sup>	Furosemide or torasemide	3 mg/kg IV over 1 h every 6 h × 21 days and tapered with evidence of recovery	na	Dopamine 2 µg/kg/min and mannitol 20% 100 mL every 6 h × 3 days
Cantarovich <sup>35</sup>	Furosemide	25 mg/kg/day IV or 35 mg/kg/day orally and tapered with evidence of recovery	> 2000 mL/24 h	Renal replacement therapy

\* Furosemide was administered IV over a duration of 30 min to 10 h, depending on the prescribed dose. IV = intravenous. na = not reported or not available. ◆

**Table 4. Summary of primary and secondary outcomes**

Study	Need for RRT (%)		Mortality (%)		Renal recovery (%)		Increased urine output (%)		Duration of ARF (days)	
	Loop	Control	Loop	Control	Loop	Control	Loop	Control	Loop	Control
Cantarovich <sup>29</sup>	34/34 (100)	13/13 (100)	15/34 (44)	7/13 (54)	na	na	22/34 (65)*	7/13 (54)*	na	na
Karayannopoulos <sup>36</sup>	1/10 (10) <sup>†</sup>	7/10 (70) <sup>†</sup>	na	na	na	na	na	na	na	na
Kleinknecht <sup>37</sup>	56/66 (85)		13/33 (39)	12/33 (36)	na	na	10/33 (30) <sup>‡</sup>	6/33 (18) <sup>‡</sup>	19.5 <sup>§</sup>	22.1 <sup>§</sup>
Shilliday <sup>30</sup>	21/62 (34)	12/30 (40)	42/62 (68)	15/30 (50)	14/62 (23) <sup>¶</sup>	7/30 (23) <sup>¶</sup>	32/62 (52)	7/30 (23)	5.66 <sup>§</sup>	7.6 <sup>§</sup>
Cantarovich <sup>35</sup>	166/166 (100)	164/164 (100)	59/166 (36)	50/164 (30)	82/166 (49)	87/164 (53)	na	na	11.4 <sup>§</sup>	12.4 <sup>§</sup>

\* Urine output increased to ≥ 400 mL/24 h. † RRT was peritoneal dialysis. ‡ Urine output increased to ≥ 500 mL/24 h.

§ Duration of ARF defined by time to reach a spontaneous decline in serum creatinine or serum urea level without further need for RRT.

¶ Recovery defined as spontaneous fall in serum creatinine level without further need for RRT.

RRT = renal replacement therapy. ARF = acute renal failure. Loop = loop diuretic. na = not available or not reported. ◆

of severity of kidney dysfunction and the proportion of participants with sepsis.<sup>35</sup>

The aetiology of ARF was categorised as medical in 367 patients (66%), surgical in 130 (23%), obstetric in 37 (7%), and unspecified in 21 (4%). A total of 189 (34%) patients had sepsis as a potential contributing factor for ARF. One trial reported that 38% of patients had sepsis, most of whom had septic shock.<sup>35</sup>

Baseline kidney function was reported in two trials.<sup>30,35</sup> However, in three trials<sup>29,35,37</sup> most patients were already receiving RRT at the time of enrolment. This suggests that nearly all patients had established and severe ARF. Oliguria was variably defined and present in 58% of patients across three trials.<sup>29,35,37</sup> The average duration of oligo-anuria before enrolment was 2.9 days in one trial,<sup>29</sup> whereas another reported that 53% of patients had oliguria for ≥ 2 days before trial entry.<sup>37</sup>

### Administration of loop diuretics

The details of how loop diuretics were administered are shown in Table 3. Furosemide was administered in all

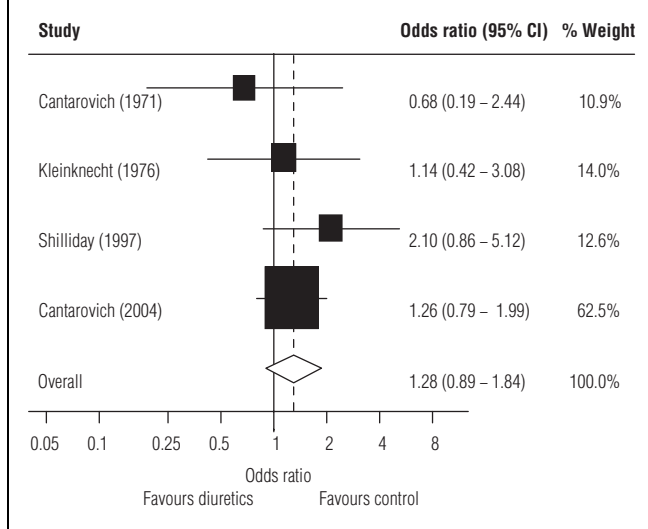
trials. One trial compared torasemide with furosemide and placebo.<sup>30</sup> Loop diuretics were generally administered as a bolus dose by the intravenous route. In two studies, the bolus infusion was given over several hours when the dose was large.<sup>29,35</sup> The average daily dose of loop diuretic delivered varied and was estimated between 600 mg and 3200 mg or 12 mg/kg.<sup>29,30,35,36</sup> Four trials had confounding co-interventions in addition to loop diuretics, including mannitol,<sup>29,30,37</sup> dopamine<sup>30</sup> or RRT.<sup>29,35</sup> Only three trials set a target diuresis range. This varied from 20 to 100 mL/h.<sup>29,35,37</sup>

### Evidence synthesis

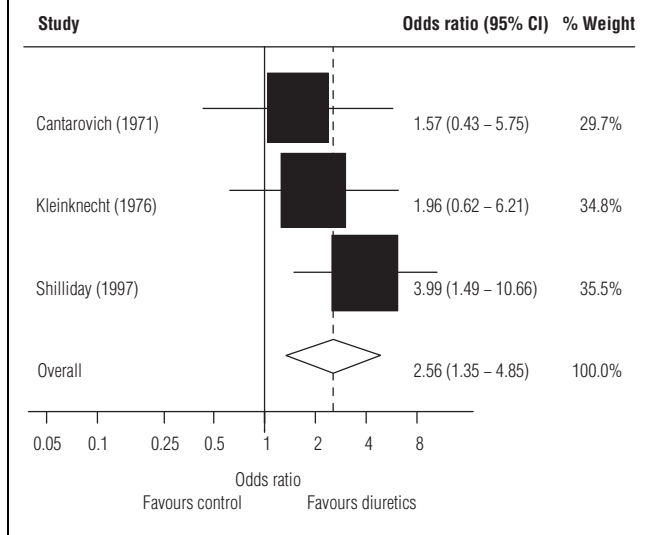
#### Mortality

Overall mortality was 40% (213/535)<sup>29,30,35,37</sup> (one study did not report mortality<sup>36</sup>) (Table 4). The odds for death was slightly higher with loop diuretics compared with the control, but the pooled OR was not statistically different (OR, 1.28; 95% CI, 0.89–1.84; *P* = 0.18) (Figure 2). There was no evidence of statistical heterogeneity across studies

**Figure 2. Forest plot for mortality associated with loop diuretics compared with control from four randomised controlled trials**



**Figure 3. Forest plot for urine output associated with loop diuretics compared with control from three randomised controlled trials**



( $\chi^2 P=0.5$ ;  $I^2=0$ ), or publication bias by either Egger's test (coefficient = 0.4;  $P=0.5$ ) or funnel plot asymmetry.

*Need for renal replacement therapy*

Renal replacement therapy was received by 85% (474/555) of enrolled patients (Table 4). The predominant modality of RRT was conventional intermittent haemodialysis, in 78% ( $n=371$ ), whereas 20% ( $n=95$ ) received continuous or

daily intermittent haemodialysis, and 2% ( $n=8$ ) received peritoneal dialysis.

It should be emphasised that, in two of the five trials, all patients were already receiving RRT at the time of randomisation,<sup>29,35</sup> while in another trial, 85% received RRT, although the timing of initiation and what proportion were allocated to loop diuretic or control were not specified.<sup>37</sup> Thus, the need for RRT after enrolment could be formally assessed in only two of the five trials, one of which used peritoneal dialysis alone.<sup>36</sup>

In those two studies, RRT was received by 37% (41/112). There was a reduced odds for receiving RRT with loop diuretics compared with control, but the pooled OR was not statistically significant (OR, 0.50; 95% CI, 0.23–1.10;  $P=0.09$ ).<sup>30,36</sup> Further, these trials showed evidence of statistical heterogeneity ( $\chi^2 P=0.04$ ;  $I^2=77\%$ ). One trial reported a lack of significant statistical difference in the time to initiation of RRT (5.2 days for loop versus 2.8 days for placebo,  $P=0.35$ ), despite an apparent > 2 day difference in delay in those receiving loop diuretics.<sup>30</sup>

*Renal recovery*

The definitions of renal recovery differed between trials. Only two trials reported the proportion of patients recovering renal function.<sup>30,35</sup> In these trials, renal recovery was defined as a spontaneous decrease in serum creatinine level independent from RRT.<sup>30,35</sup> The odds of renal recovery was slightly lower in patients receiving loop diuretics compared with control, but the resulting pooled OR was not statistically different (OR, 0.88; 95% CI, 0.59–1.31;  $P=0.5$ ). There was no evidence of statistical heterogeneity ( $\chi^2 P=0.9$ ;  $I^2=0$ ).

However, loop diuretics were associated with a shorter time to spontaneous decline in either serum creatinine<sup>30</sup> or urea<sup>37</sup> level, or a reduction in serum creatinine level to <200  $\mu\text{mol/L}$ <sup>35</sup> compared with the control (weighted mean difference, -2.1 days; 95% CI, -0.4 to -3.7 days;  $P=0.01$ ). There was no evidence of statistical heterogeneity ( $\chi^2 P=0.9$ ).

Additionally, loop diuretics were associated with a shorter duration of RRT (weighted mean difference, -1.4 days; 95% CI, -0.2 to -2.3 days;  $P=0.02$ ) compared with control.<sup>30,35</sup> There was no evidence of statistical heterogeneity ( $\chi^2 P=0.12$ ). Two trials also reported fewer sessions of RRT with loop diuretics compared with control (5.0–5.5 sessions for loop diuretics versus 6.1–8.0 sessions for control).<sup>29,37</sup>

*Secondary outcomes*

Both the definition and method of measuring urinary output varied across trials. Loop diuretics were associated with an increase in urine output, defined as diuresis  $\geq 400$ –500 mL/day, when compared with control (OR, 2.6; 95% CI,

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1.4–4.9;  $P=0.004$ ).<sup>29,30,37</sup> There was no evidence of statistical heterogeneity ( $\chi^2 P=0.5$ ;  $I^2=0$ ) (Figure 3). Similarly, three trials showed that time to achieve a urine output goal  $\geq 1.5$ – $2.0$  L/day was shorter with loop diuretics compared with control (weighted mean difference of  $-3.1$  days; 95% CI,  $-1.0$  to  $-5.3$  days;  $P=0.005$ ).<sup>29,35,37</sup> However, there was evidence of statistical heterogeneity ( $\chi^2 P=0.02$ ). During renal recovery, one trial described higher measures in both serum creatinine and urea levels in those allocated loop diuretics compared with control.<sup>35</sup>

Adverse or toxic effects were reported in four trials<sup>29,30,35,37</sup> (Table 5). However, reporting was inconsistent, and valid estimates of occurrence could not be determined. While two trials described transient episodes of tinnitus, deafness and vertigo following large intravenous doses of loop diuretics, neither provided data on rates of occurrence.<sup>29,37</sup> In the two largest studies ( $n=422$ ), four episodes of deafness were described, but tinnitus was either not described or did not occur.<sup>30,35</sup>

Additional effects described included a higher occurrence of seizures,<sup>30</sup> polyuria<sup>35</sup> and trend toward hypokalaemia<sup>35</sup> in patients receiving loop diuretics. No trial described changes in acid–base status. Likewise, no trial described the impact of diuretics on oxygenation or on the need for, or weaning from, mechanical ventilation. Finally, insufficient data were available for analysis or comment on length of hospitalisation or health care costs.

### Discussion

We performed a systematic review and meta-analysis of all randomised controlled trials describing the use of loop diuretics compared with control in the management of ARF. Our primary objective was to determine whether, in established ARF, loop diuretics influence mortality, the need for

RRT or the rate of renal recovery. We found that loop diuretics failed to show a significant reduction in mortality or increase in renal recovery, while assessment of the need for RRT was limited, and this need could not be reliably determined. On the other hand, our findings suggest that loop diuretics may be associated with a reduction in time to spontaneous decline in serum creatinine or urea level, reduced duration of RRT and promotion of a modest increase in urine output. However, these findings require careful interpretation as we also identified a number of limitations to the available literature on this topic. Specifically, few studies fulfilled our eligibility criteria, and those that did were generally small, several were published over three decades ago, few enrolled critically ill patients, and all had noteworthy methodological weaknesses or shortcomings.

The observed 40% hospital mortality across these trials is considerably lower than the more recent estimates of 60% mortality for ARF in critically ill patients.<sup>1,38,39</sup> This may indicate that patients in these trials had a lower severity of illness, or isolated renal injury rather than ARF in the setting of critical illness and multiorgan system failure (MOSF), as is now more commonly seen.<sup>1</sup> Importantly for critical care physicians, the trials published over three decades ago did not enrol critically ill patients. The remaining two trials did not report the proportion of enrolled patients admitted to an ICU.<sup>30,35</sup> Furthermore, it is plausible to consider that the use of loop diuretics alone will by no means result in a direct increase in survival in ARF in the setting of severe sepsis or MOSF. Survival may not be an appropriate primary outcome measure for loop diuretics; a more relevant outcome might rather be absolute need for, and duration and timing of RRT.

While 85% of patients included in this meta-analysis received RRT, most in the form of conventional intermittent haemodialysis, it should be highlighted that nearly all

**Table 5. Summary of reported adverse effects**

Adverse effect	Cantarovich <sup>29</sup>	Karayannopoulos <sup>36</sup>	Kleinknecht <sup>37</sup>	Shilliday <sup>30*</sup>	Cantarovich <sup>35*</sup>
Tinnitus	Yes <sup>†</sup>	na	Yes <sup>†</sup>	na	No
Hypoacusia	na	na	Yes <sup>†</sup>	Loop (1) v control (0)	Loop (3) v control (1)
Vertigo	na	na	Yes <sup>†</sup>	na	No
Allergic reaction	na	na	na	na	Loop (1) v control (2)
Seizures	na	na	na	Loop (12) v control (1)	No
Polyuria	na	na	No	na	Loop (7) v control (0)
Hypokalaemia	na	na	na	na	Loop (11) v control (4)
Agranulocytosis	na	na	na	na	Loop (1) v control (0)

\* Reported as absolute number(s) with adverse effect. † Tinnitus was reported, but no data were presented on rate of occurrence. It was reported as common in patients receiving intravenous frusemide 3200 mg in less than 4 h. Toxicity resolved without sequelae.

‡ Tinnitus, deafness and vertigo were reported, but no data were presented on rate of occurrence. Symptoms were reported to occur temporally a few hours after frusemide administration. Ototoxicity may have been confounded by concomitant use of aminoglycosides. No long-term sequelae were reported. na = not reported or not available.

patients were receiving RRT at the time of randomisation. This is of concern because early intervention would likely be key to deriving clinical benefit from any therapy. Moreover, we are unable to conclude from our findings whether loop diuretics are an appropriate alternative to the timely implementation of RRT in ARF. Available evidence shows that delay in the provision of RRT can result in higher mortality and delayed or lower likelihood for recovery of renal function.<sup>38,40</sup> Several studies included in this meta-analysis described prolonged durations of oligoanuria or delay after the diagnosis of ARF before initiation of RRT, which would not occur in modern ICU practice. On the other hand, patients who require RRT because of severe ARF have been identified as having a higher mortality.<sup>41,42</sup> However, whether loop diuretics can obviate the need for RRT, and thus have the potential to reduce morbidity (eg, need for catheter insertion and anticoagulation) and mortality cannot be reliably determined from our findings. This may, in part, account for the association between loop diuretics and higher mortality found in a large observational study.<sup>21</sup> The use of loop diuretics to avert initiation of RRT when the latter is indicated may increase renal injury, metabolic derangement and fluid balance complications, and contribute to higher mortality and non-recovery of renal function.<sup>21</sup> Overall, these trials failed to adequately address whether loop diuretics can obviate or delay the need for RRT.

Likewise, the assorted definitions of renal recovery after ARF resulted in significant uncertainty about the influence of loop diuretics on this outcome. For example, while the pooled estimate of the proportion of patients recovering function suggested no benefit, use of loop diuretics was found to be associated with shorter duration and absolute number of sessions of RRT, and shorter time to achieve a spontaneous decline in surrogate markers of renal function in patients not yet receiving RRT.

Our study also examined several secondary outcomes of interest. Specifically, loop diuretics were found to promote both an absolute increase in urine output from baseline and a shorter time to achieve diuresis. We were unable to establish whether these physiological changes carried any non-renal clinical benefits, such as shorter duration of mechanical ventilation or ICU stay. While toxicity was described with use of loop diuretics, most often tinnitus and temporary deafness, no reliable estimates of occurrence could be determined. Toxicity was generally uncommon and appeared restricted to patients receiving large intravenous doses in short periods of time. Likewise, no data were available on the effect of loop diuretics on length of hospital stay or associated health care costs.

Two previous systematic reviews evaluated diuretics in ARF.<sup>22,43</sup> One review focused largely on dopamine in ARF

and was unable to include more recent publications.<sup>43</sup> In the recent meta-analysis by Ho and Sheridan, there were several concerns: study selection, the pooled analysis and the global inferences based on their data.<sup>22</sup> In particular, this meta-analysis pooled data from trials assessing loop diuretics for both prevention and treatment of ARF. Further and importantly, the global conclusions from this meta-analysis do not appear firmly supported by the available data because of limitations in individual trial quality and poor reporting.<sup>22</sup> Our study highlights the weakness of the available body of evidence and the dubious nature of any firm conclusions on the efficacy of loop diuretics in ARF.

Two large observational studies have now reported differing conclusions as to the effect of loop diuretics in critically ill patients with ARF. One study suggested the use of frusemide resulted in an increased risk of death, but this finding was not corroborated by the second larger study.<sup>6,21</sup> The contrasting findings in these prospective cohort studies may be the consequence of residual confounding, despite propensity-adjusted and multivariate analysis, or information bias, or may simply reflect significant differences in patterns of practice. These conflicting findings suggest there is evidence of genuine equipoise on whether loop diuretics have a role in the management of ARF. As such, our findings support a very different and more careful global conclusion when compared with the meta-analysis of Ho and Sheridan. Specifically, we can only comment that, based on the available data, it is not possible to draw any strong conclusions about how loop diuretics may modify outcome in ARF. Two small pilot RCTs are underway that will assess the impact of a frusemide infusion on kidney function early in ARF and after discontinuation of RRT, both in critically ill patients. It is hoped these studies will provide further insight on the potential role of diuretics in ARF and a rationale for a larger study.

Our study had limitations. First, there were few trials, each with methodological and quality concerns. Second, several outcomes were variably defined or inconsistently reported, which could unduly influence event rates and effect estimates. Third, patients included in these trials generally had low severity of illness, and few were admitted to an ICU. Fourth, findings from these trials are likely confounded by concomitant co-interventions, such as mannitol or dopamine. Fifth, loop diuretics were predominantly administered by large intravenous boluses rather than continuous infusion and, in several trials, were not titrated to a physiological end-point or target urine output. Finally, many trials had evidence of a prolonged period of oliguria before intervention with loop diuretics. In total, these observations strongly suggest a lack of generalisability to critically ill patients.

To overcome these limitations and obtain high-quality evidence on whether loop diuretics have a role in the management of ARF, a suitably powered multicentre RCT is needed. This trial should ideally incorporate clinically relevant and patient-centred outcomes, such as need for RRT, or renal recovery, as well as important secondary outcomes focused on issues of harm, dose response and physiological end-points (eg, urinary output). The trial should also include stratification for the presence of septic ARF, early intervention specifically in patients at risk or with evidence of acute renal injury,<sup>44</sup> and continuous and physiologically targeted infusion of loop diuretic or placebo with close hourly monitoring of urine output and fluid balance. Ideally, the study would focus on critically ill patients. If such a trial were to use need for RRT as a primary outcome, assuming an estimated 15% need for RRT in such patients,<sup>45</sup> with a 90% power to detect a 5% absolute reduction, about 2000 patients would need to be enrolled. Considering the low cost of loop diuretics and the high cost of RRT, such a difference would likely have clinical relevance.

## Conclusions

In summary, there is a paucity of reliable and high-quality data assessing the value of loop diuretics in the management of ARF. As a result, the findings in this systematic analysis have uncertain significance and require cautious interpretation. Loop diuretics failed to improve mortality or RRT independence. Yet, use of loop diuretics was associated with a modest increase in urine volume and a shorter duration of RRT. Importantly for ICU clinicians, these studies have limited relevance to critically ill patients, who were not included in many of these trials, and who are both unlikely to receive such delayed intervention, and more likely to receive loop diuretics by continuous infusion. This uncertainty surrounding a seemingly common intervention suggests the urgent need for a suitably powered RCT focused on a critically ill population.

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