

# Meta-analysis of frusemide to prevent or treat acute renal failure

Kwok M Ho and David J Sheridan

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# Meta-analysis of frusemide to prevent or treat acute renal failure

Kwok M Ho, David J Sheridan

Editorial by Bennett-Jones

## Abstract

renal failure in adults.

Intensive Care Unit, Royal Perth Hospital, Perth, Western Australia 6000 Kwok M Ho consultant David J Sheridan resident medical officer Correspondence to: K M Ho kwok.ho@

health.wa.gov.au

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Objective To investigate the potential beneficial and adverse effects of frusemide to prevent or treat acute

Design Meta-analysis of randomised controlled trials. Data sources Cochrane controlled trials register (2005 issue 4), Embase, and Medline (1966 to 1 February 2006), without language restrictions. Review methods Two reviewers checked the quality of the studies and independently extracted data. **Results** Nine randomised controlled trials totalling 849 patients with or at risk of acute renal failure were included. Outcome measures not significantly different after frusemide treatment were in-hospital mortality (relative risk 1.11, 95% confidence interval 0.92 to 1.33), risk for requiring renal replacement therapy or dialysis (0.99, 0.80 to 1.22), number of dialysis sessions required (weight mean difference -0.48 sessions, -1.45 to 0.50), and proportion of patients with persistent oliguria (urine output < 500ml/day: 0.54, 0.18 to 1.61). Stratifying studies that used frusemide to prevent or treat acute renal failure did not change the results on mortality (relative risk ratio 2.10, 95% confidence interval 0.67 to 6.63) and the risk for requiring dialysis (4.12, 0.46 to 37.2). Evidence suggested an increased risk of temporary deafness and tinnitus in patients treated with high doses of frusemide (relative risk 3.97, 95% confidence interval 1.00 to 15.78).

Conclusions Frusemide is not associated with any significant clinical benefits in the prevention and treatment of acute renal failure in adults. High doses may be associated with an increased risk of ototoxicity.

#### Introduction

Several small randomised controlled studies evaluating the use of frusemide to either prevent or treat acute renal failure have produced negative results.<sup>w1-w4</sup> Frusemide is frequently used to facilitate fluid and electrolyte management of acute renal failure,1 yet its potential benefits, adverse effects, and cost effectiveness to prevent or treat this condition remain uncertain. We carried out a meta-analysis to assess the potential beneficial and harmful effects of frusemide in acute renal failure and whether effects differ when used to prevent or to treat acute renal failure.

### Methods

We searched the Cochrane controlled trials register, Embase, and Medline for randomised controlled clinical trials comparing frusemide with placebo in adults (see bmj.com for exploded MeSH terms). We also included studies of single dose frusemide compared with prolonged continuous infusion (see bmj.com for exclusions).

Two reviewers independently recorded the trial characteristics, outcomes, and quality of identified studies (Jadad score), using a predesigned data abstraction. Grading of allocation concealment was based on the Cochrane approach. One study that published data in two publications2 w5 was combined to represent one trial.

We chose in-hospital mortality and the proportion of patients requiring renal dialysis or replacement therapy as the main outcomes because they are the most relevant clinical outcomes in patients with acute renal failure. Other outcomes were the proportion of patients remaining oliguric (urine output <400-500 ml/day), proportion of patients who developed ototoxicity, number of dialysis sessions required until recovery, and length of hospital stay.

#### Statistical analyses

Using a random effect model we report the differences in categorical outcomes between the treatment and placebo or control groups as relative risks with  $\hat{95\%}$ confidence intervals. We further stratified the effects of frusemide on mortality and the need for dialysis after frusemide treatment into studies using frusemide to prevent or to treat acute renal failure, and we tested this interaction by relative risk ratio.3 Using a random effect model we report the differences in length of hospital stay and the number of dialysis sessions required as weighted mean differences. We used the  $\chi^2$  statistic to assess heterogeneity between trials and the I<sup>2</sup> statistic to assess the extent of inconsistency.<sup>4</sup> One study reported tinnitus and deafness in several patients after frusemide treatment but did not specify the number.<sup>w5</sup> We therefore estimated that at least three patients would have tinnitus or deafness in the frusemide group. One study reported the duration of continuous renal replacement therapy until recovery.<sup>w4</sup> We pooled the results of this study with others that reported the total number of dialysis sessions required until recovery of renal function. We carried out sensitivity analyses by excluding one study that compared a single dose of frusemide with prolonged continuous infusion<sup>w6</sup> or by including only studies that had adequate allocation concealment.<sup>w1-w3 w7</sup> Publication bias was assessed by funnel plot using mortality as an end point. We considered a P value less than 0.05 as significant.

#### Results

Nine of 23 potentially eligible studies,<sup>w1-w9</sup> totalling 849 patients, were included (see bmj.com). Three used frusemide to prevent acute renal failure<sup>w1-w3</sup> and six used frusemide to treat acute renal failure.<sup>w4-w9</sup> The

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mbspital mortality       effect) (95% C)       (%)       effect) (95% C)         Transmide to prevent acute deterioration in renal function isger <sup>24</sup> 662       559       1       1       90       0.51 to 7.26         asanigg <sup>211</sup> 441       1/40       99       0.75       3.90 (0.46 to 33.4)         call all enersit: 01 (fursamide), 4 (placebo)       103       99       99       97       3.90 (0.46 to 33.4)         first for hattrogenetic, y=0.31, d=1, P=0.58, /*=0%, first for hattrogenetic, y=0.43, d=1, P=0.58, /*=0%,       18/28       16/28       91       36.16       17.17 (0.86 to 15.2)         antaroxich <sup>207</sup> 59/166       50/164       77.3       9.01       1.08 (0.78 to 7.22       0.88 (0.44 to 17.6         Sintaroxich <sup>207</sup> 67/15       77/13       9.01       1.08 (0.58 to 7.20)       9.01       1.08 (0.58 to 7.20)         Sintaroxich <sup>207</sup> 20.32       17/30       9.01       1.08 (0.58 to 7.20)       9.01       1.08 (0.58 to 7.20)       9.01       1.08 (0.58 to 7.20)       9.01       1.00 (0.70 to 1.7.26)       9.01		No with event,	/No in group			
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Test for overall effect: 2-1.46, P=0.15         Fragemide to treat acute renal failure         arranovich <sup>197</sup> 59/166         Santarovich <sup>197</sup> 59/166         Santarovich <sup>197</sup> 9/19         Santarovich <sup>197</sup> 9/19         Santarovich <sup>197</sup> 0.88 (0.44 to 172         Santarovich <sup>197</sup> 0.713         Santarovich <sup>197</sup> 0.722         Santarovich <sup>197</sup> 0.713         Santarovich <sup>197</sup> 0.713         Santarovich <sup>197</sup> 0.722         Santarovich <sup>197</sup> 0.722         Santarovich <sup>197</sup> 0.722         Santarovich <sup>197</sup> 0.723         Santarovich <sup>197</sup> 0.722         Santarovich <sup>197</sup> 0.722         Santarovich <sup>197</sup> 0.723         Santarovich <sup>197</sup> 0.723         Santarovich <sup>197</sup> 0.723         Santarovich <sup>197</sup> 0.723         Santarovich <sup>197</sup> 0.733         Santarovich <sup>197</sup> 0.728         Field terrogeneity: x <sup>12</sup> -1.46, df-5, P=0.92, l <sup>12</sup> =0%         Fies for overall effect: z-1.08, P=0.28         Requirement for renal replacement therapy or dialysis         Framewide to treat acute renal failure         Santarovich <sup>197</sup>	Total events: 10 (frusemide), 4 (placebo)					
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Santarovich <sup>v0</sup> 6/15       7/13       7/1       7/1       0.74 (0.33 to 1.65         Geinkneu <sup>th6</sup> 13/33       12/23       9.01       1.08 (0.58 to 2.01       20.22       17.80         Shutbal (95% Cl)       293       281       20.32       17.80       20.22       1.10 (0.73 to 1.67         Fest for hetrogeneity: y=1.46, df=5, P=0.92, J <sup>2</sup> =0%       Fest for werall effect: z=0.35, P=0.39       96       380       100.00       1.11 (0.92 to 1.33         Fotal (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33       1.08 (0.92 to 1.33         Fotal (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Fotal (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Fotal (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Fotal (95% Cl)       128       127       0.47       4.88 (0.24 to 98.60         Agem <sup>21</sup> 2/41       0/40       4.88 (0.24 to 98.60       0.43       3.35 (0.14 to 78.60         Solutotal (95% Cl)       128       127       1.04 (0.97 to 1.11       1.16       0.14 to 72.60         Fest for overall effect: z=1.27, P=0.21       Fraemide to treat acute renal failure       37.33       31.33       31	Cantarovich <sup>w7</sup>	59/166	50/164	+-	36.16	1.17 (0.86 to 1.59)
Geinknecht <sup>46</sup> 13/33       12/33       12/33         Shillday <sup>44</sup> 20.32       17/30       20.29       1.10 (0.73 to 1.57         Subtotal (95% Cl)       293       281       9.01       1.00 (0.58 to 2.01         Test for heterogeneity: $\chi^2 = 1.46$ , df=5, P=0.92, l <sup>2</sup> =0%       100.00       1.11 (0.73 to 1.57       97.33       1.09 (0.90 to 1.31         Total (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Total (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Total (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Test for overall effect: z=1.08, P=0.28       P=0.83, l <sup>2</sup> =0%       100.00       1.11 (0.92 to 1.33         Subtotal (95% Cl)       293       281       0/59       1.04 (0.97 to 1.11         Ager <sup>472</sup> 0/62       0/59       0.43       3.55 (0.14 to 7.86         Subtotal (95% Cl)       128       127       0.43       3.55 (0.14 to 7.86         Subtotal (95% Cl)       128       127       0.90       4.08 (0.46 to 35.96         Subtotal (95% Cl)       0.33 (f=1, P=0.86, l <sup>2</sup> =0%       111       1.6       0.14 (0.02 to 0.96         Subtotal (95% Cl)       0.90 (0.80 to 1.22       77.10	Cantarovich <sup>w9</sup>	9/19	7/13	-	7.22	0.88 (0.44 to 1.76)
Shilliday <sup>v4</sup> 20/32 17/30 Subtolal (95% CI) 293 281 Fotal events: 125 (frusemide), 109 (placebo) Fest for heterogeneity: $\chi^{-1}$ 4.6, df-5, P=0.92, J <sup>2</sup> =0% Fest for overall effect: z=0.85, P=0.92 Fotal (95% CI) 396 380 Fotal events: 135 (frusemide), 113 (placebo) Fest for heterogeneity: $\chi^{-2}$ 3.53, df=7, P=0.83, J <sup>2</sup> =0% Fest for overall effect: z=1.08, P=0.28 Requirement for renal replacement therapy or dialysis Fresenide to prevent acute deterioration in renal function Hage <sup>m2</sup> 0/62 0/59 Subtolal (95% CI) 128 127 Frasemide to prevent acute deterioration in renal function Hage <sup>m2</sup> 0/62 0/59 Subtolal (95% CI) 128 127 Framewide to prevent acute deterioration in renal function Hage <sup>m2</sup> 2/41 0/40 Subtolal (95% CI) 128 127 Framewide to treat acute renal failure Shilliday <sup>v4</sup> 1/10 7/10 Cfal events: 71 (frusemide), 77 (placebo) Fest for heterogeneity: $\chi^{-2}$ 1.68, d=3, P=0.09 Fest for heterogeneity: $\chi^{-2}$ 1.68, d=3, P=0.00 Fest for heterogeneity: $\chi^{-2}$ 1.68, d=3, P=0.09 Fest for heterogeneity: $\chi^{-2}$ 1.68, d=3, P=0.09 Fotal (95% CI) 231 228 001 0.1 100 100 Fest for heterogeneity: $\chi^{-2}$ 1.69, d=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.39 Fest for heterogeneity: $\chi^{-2}$ 1.69, d=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.39 Fest for overall effect: z=0.12, P=0.39 Fest for heterogeneity: $\chi^{-2}$ 1.69, d=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.39 Fest for heterogeneity: $\chi^{-2}$ 1.69, d=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.39 Fest for heterogeneity: $\chi^{-2}$ 1.69, d=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.39 Fest for overall effect: z=0.12, P=0.39 Fest for heterogeneity: $\chi^{-2}$ 1.69, d=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.39 Fest for heterogen	Cantarovich <sup>w9</sup>	6/15	7/13		5.41	0.74 (0.33 to 1.65)
Subtolal (95% Cl)       293       281       97.33       1.09 (0.90 to 1.31         Total events: 125 (frusemide), 109 (placebo)       396       380       100.00       1.11 (0.92 to 1.33         Total events: 125 (frusemide), 113 (placebo)       396       380       100.00       1.11 (0.92 to 1.33         Feat for overall effect: z=0.85, P=0.39       396       380       100.00       1.11 (0.92 to 1.33         Fotal (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Fotal (95% Cl)       396       380       0.62       0.759         Frest for heterogeneity: $\chi^2 = 3.53$ , df=7, P=0.83, l²=0%       128       127       0.43       3.35 (0.14 to 78.60         Solutoral (95% Cl)       128       127       0.43       3.35 (0.14 to 78.60       0.90       4.08 (0.46 to 35.96         Fest for netrogeneity: $\chi^2 = 0.03$ , l²=0%       128       127       1.14 (0.97 to 1.11       1.16       0.14 (0.97 to 1.11         Gainvents: 3 (frusemide), 0 (placebo)       128       1270       47.31       1.04 (0.97 to 1.11       1.16       0.14 (0.02 to 0.56       42.66       1.00 (0.88 to 1.13       7.96       0.78 (0.40 to 1.54       9.10       0.94 (0.71 to 1.26       9.10       0.94 (0.71 to 1.26       9.10       0.94 (0.71 to 1.26       9.10       0.9	Kleinknecht <sup>w5</sup>		12/33	+	9.01	1.08 (0.58 to 2.01)
Total events: 125 (frusemide), 109 (placebo) Test for heterogeneity: $\chi^{k=1}$ 46, df=5, P=0.92, l <sup>2</sup> =0% Fest for overall effect: z=0.85, P=0.39 Total (95% Cl) 396 380 Total events: 125 (frusemide), 113 (placebo) Test for heterogeneity: $\chi^{k=3}$ 53, df=7, P=0.83, l <sup>2</sup> =0% Test for overall effect: z=1.08, P=0.28 <b>Requirement for renal replacement therapy or dialysis</b> Trusemide to prevent acute deterioration in renal function tager <sup>92</sup> 0/62 0/59 Not estimable 0.62 0/59 Not estimable 0.62 0/59 Not estimable 0.47 4.88 (0.24 to 98.66 0.43 3.35 (0.14 to 78.66 0.90 4.08 (0.46 to 35.96 For overall effect: z=1.27, P=0.21 Frusemide to treat acute renal failure Trusemide to frest or overall effect: z=1.27, P=0.21 Frusemide to frest acute renal failure Trusemide to renal effect: z=0.39, P=0.69 Total (95% Cl) 231 228 Total (95% Cl) 231 228 Total (95% Cl) 231 228 Total events: 73 (frusemide), 77 (placebo) Test for heterogeneity: $\chi^{2}=1.3.8, df=3, P=0.0.2, l2=64.2% Test for overall effect: z=0.12, P=0.91 Total events: 73 (frusemide), 77 (placebo) Test for heterogeneity: \chi^{2}=1.3.9, df=5, P=0.0.2, l2=64.2% Test for overall effect: z=0.12, P=0.91 Total events: 73 (frusemide), 77 (placebo) Test for overall effect: z=0.12, P=0.91 Total events: 73 (frusemide), 77 (placebo) Test for overall effect: z=0.12, P=0.91 Total events: 73 (frusemide), 77 (placebo) Tes$	-			+		1.10 (0.73 to 1.67)
Fest for heterogeneity: $\chi^{+}=1.46$ , df=5, P=0.92, I <sup>2</sup> =0%         Fest for overall effect: z=0.85, P=0.39         fotal (95% Cl)       396       380         fotal events: 135 (frusemide), 113 (placebo)       100.00       1.11 (0.92 to 1.33         fest for heterogeneity: $\chi^{+}=2.53$ , df=7, P=0.93, I <sup>2</sup> =0%       rest for overall effect: z=1.08, P=0.28       Not estimable         Requirement for renal replacement therapy or dialysis       rest for overall effect: z=1.08, P=0.28       Not estimable         Arger <sup>m2</sup> 2/41       0/40       0.47       4.88 (0.24 to 98.60         Solutotal (95% Cl)       128       127       0.48       0.44 to 8.60         Solutotal (95% Cl)       128       127       0.48       0.46 to 35.96         Fest for heterogeneity: $\chi^{+}=0.03$ , df=1, P=0.86, l <sup>2</sup> =0%       Fest for heterogeneity: $\chi^{+}=0.03$ , df=1, P=0.86, l <sup>2</sup> =0%       7/28       47.31       1.04 (0.97 to 1.11         Shilliday <sup>M4</sup> 10/32       12/30       116       0.14 (0.02 to 0.96       42.66 (1.00 (0.88 to 1.13       7.96       0.78 (0.40 to 1.54       99.10       0.94 (0.71 to 1.26         Shilliday <sup>M4</sup> 10/32       12/30       100.00       0.99 (0.80 to 1.22       0.01       0.1       10       100       0.99 (0.80 to 1.22         Shilliday <sup>M4</sup> 10/32       12/30	Subtotal (95% CI)	293	281	*	97.33	1.09 (0.90 to 1.31)
Fest for overall effect: $z=0.35$ , $P=0.39$ Fotal (95% Cl)       396       380         Total (95% Cl)       100.00       1.11 (0.92 to 1.33         Frisemide to prevent acute deterioration in renal function       100.00       1.11 (0.92 to 1.33         Ager <sup>er<sup>2</sup></sup> 0/62       0/59         Subtotal (95% Cl)       128       127         Fotal events: 3 (frusemide), 0 (placebo)       128       127         Fest for overall effect: z=1.27, P=0.21       28/28       27/28         Subtotal (95% Cl)       128       127         Frisemide to treat acute renal failure       31/33       31/33         Simum <sup>46</sup> 28/28       27/28         Grayannopoulos <sup>470</sup> 1/10       7/10         Kleinknecht <sup>465</sup> 31/33       31/33         Shiltiday <sup>464</sup> 10/32       12/30         Fest for overall effect: z=0.39, P=0.69       103       101         Fotal events: 70 (frusemide), 77 (placebo)       231       228         Fest for overall effect: z=0.39, P=0.69       100.00       0.99 (0.80 to 1.22         Fotal (95% Cl)       231       228       100.00       0.99 (0.80 to 1.22         Fotal (95% Cl)       231       228       100.00       0.99 (0.80 to 1.22 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>						
Fold (95% Cl)       396       380       100.00       1.11 (0.92 to 1.33         Fold events: 135 (frusemide), 113 (placebo)       110.00       1.11 (0.92 to 1.33         Fest for versal effect: z=1.08, P=0.28 $P=0.28$ Not estimable         Requirement for renal replacement therapy or dialysis $0.62$ 0/59         Frusemide to prevent acute deterioration in renal function $0.47$ 4.88 (0.24 to 98.6C)         Agen <sup>w2</sup> 0/62       0/59 $0.47$ 4.88 (0.24 to 98.6C)         Solomon <sup>w3</sup> 1/25       0/28 $0.47$ 4.88 (0.24 to 98.6C)         Total events: 3 (frusemide), 0 (placebo)       128       127 $0.43$ 3.35 (0.14 to 78.6C)         Fest for heterogeneity: $\chi^{*}=0.03$ , $d=1$ , P=0.86, $l^{*}=0\%$ 101.0       710 $0.90$ 4.08 (0.46 to 35.96         Gleinknecht <sup>100</sup> 1103       101       7.96       0.78 (0.40 to 1.54       99.10       0.94 (0.71 to 1.26         Subtotal (95% Cl)       103       101       10       100.00       0.99 (0.80 to 1.22         Subtotal (95% Cl)       103       101       10       100       0.91       0.1       10       100.00       0.99 (0.80 to 1.22         Forker Growerall effect: z=0.39, P=0.69       231       228						
Total events: 135 (frusemide), 113 (placebo) Test for heterogeneity: $\chi^2$ =3.53, df=7, P=0.83, l <sup>2</sup> =0% Test for overall effect: z=1.08, P=0.28 Requirement for renal replacement therapy or dialysis Frusemide to prevent acute deterioration in renal function Tager <sup>m2</sup> 0/62 0/59 Lassnigg <sup>v1</sup> 2/41 0/40 0.47 4.88 (0.24 to 98.60 0.43 3.35 (0.14 to 78.60 0.90 4.08 (0.46 to 35.96 0.43 3.35 (0.14 to 78.60 0.90 4.08 (0.46 to 35.96 0.43 3.35 (0.14 to 78.60 0.90 4.08 (0.46 to 35.96 0.90 4.08 (0.46 to 35.96 10.90 4.08 (0.46 to 35.96 10.1 1.11 1.16 0.14 (0.02 to 0.96 42.66 1.00 (0.88 to 1.13 7.96 0.78 (0.40 to 1.54 31/13 31/133 31/13 31/13 31/13 31/13 31/13 31/14 10/10 10.1 1.1 10 100 10.1	Test for overall effect: z=0.85, P=0.39					
Fest for heterogeneity: $\chi^2$ =3.53, df=7, P=0.83, l <sup>2</sup> =0% Fest for overall effect: z=1.08, P=0.28 <b>Requirement for renal replacement therapy or dialysis</b> Frusemide to prevent acute deterioration in renal function tage <sup>rv2</sup> 0/62 0/59 Again 2/41 0/40 Solomon <sup>v3</sup> 1/25 0/28 Subtotal (95% CI) 128 127 Total events: 3 (frusemide), 0 (placebo) Fest for heterogeneity: $\chi^2$ =0.03, df=1, P=0.86, l <sup>2</sup> =0% Fest for overall effect: z=1.27, P=0.21 Frusemide to treat acute renal failure 3rown <sup>v6</sup> 28/28 27/28 Glain kent <sup>v6</sup> 31/33 31/33 Shilliday <sup>v84</sup> 10/32 12/30 Total events: 70 (frusemide), 77 (placebo) Fest for heterogeneity: $\chi^2$ =2.18, df=3, P=0.001, l <sup>2</sup> =86.2% Fest for overall effect: z=0.39, P=0.69 Total (95% CI) 231 228 Total (95% CI) 77 (placebo) Fest for heterogeneity: $\chi^2$ =13.85, df=5, P=0.02, l <sup>2</sup> =64.2% Fert for overall effect: z=0.12, P=0.91 Total events: 73 (frusemide), 77 (placebo) Fest for heterogeneity: $\chi^2$ =13.85, df=5, P=0.02, l <sup>2</sup> =64.2% Favours control	Total (95% CI)	396	380	•	100.00	1.11 (0.92 to 1.33)
Fest for overall effect: $z=1.08$ , P=0.28         Requirement for renal replacement therapy or dialysis         Frusemide to prevent acute deterioration in renal function         Hager <sup>#2</sup> 0/62       0/59         Solomon <sup>W3</sup> 1/25       0/28         Subtotal (95% Cl)       128       127         Frusemide to treat acute renal failure       0.47       4.88 (0.24 to 98.60         Stort events: 3 (frusemide). 0 (placebo)       128       127         Fest for overall effect: $z=1.27$ , P=0.21       7/10         Frusemide to treat acute renal failure       7/10         Geinknecht <sup>166</sup> 31/33         Shilliday <sup>164</sup> 10/32       12/230         Groun <sup>166</sup> 28/28       27/28         Subtotal (95% Cl)       103       101         Shilliday <sup>164</sup> 10/32       12/30         Fest for overall effect: $z=0.39$ , P=0.69       231       228         Fotal (95% Cl)       231       228         Favours       Favours       Favours	Total events: 135 (frusemide), 113 (placebo)					
Requirement for renal replacement therapy or dialysis         Frusemide to prevent acute deterioration in renal function $4age^{rv2}$ $0/62$ $0/59$ $asoringg^{v1}$ $2/41$ $0/40$ $0.47$ $4.88$ ( $0.24$ to $98.64$ Solomon <sup>v3</sup> $1/25$ $0/28$ $0.43$ $3.35$ ( $0.14$ to $78.66$ Subtotal (95% Cl)       128 $127$ $0.90$ $4.08$ ( $0.46$ to $35.96$ Frusemide to treat acute renal failure $7.96$ $28/28$ $27/28$ Arrown <sup>v6</sup> $28/28$ $27/28$ $47.31$ $1.04$ ( $0.97$ to $1.11$ Schwnw <sup>v6</sup> $31/33$ $31/33$ $31/33$ $31/33$ $31/33$ $31/33$ Subtotal (95% Cl)       103       101 $7.96$ $0.90$ $0.90$ ( $0.80$ to $1.22$ Subtotal (95% Cl)       103       101 $0.1$ $10$ $100$ $0.99$ ( $0.80$ to $1.22$ Total events: 73 (frusemide), 77 (placebo)       231       228 $0.01$ $0.1$ $100$ $100$ $0.99$ ( $0.80$ to $1.22$ Total (95% Cl)       231       228 $6.01$ $0.1$ $100$ $100.00$ $0.99$ ( $0.80$ to $1.22$	Test for heterogeneity: $\chi^2$ =3.53, df=7, P=0.83, $I^2$ =0%					
The semide to prevent acute deterioration in renal function       Notestimable $4ager^{m/2}$ 0/62       0/59 $assnigg^{m1}$ 2/41       0/40         Solomon <sup>w3</sup> 1/25       0/28         Subtotal (95% Cl)       128       127         Fresemide to treat acute renal failure       0.90       4.08 (0.46 to 35.96         Solomon <sup>w3</sup> 1/25       0/28         Solomon <sup>w3</sup> 1/25       0/28         Fresemide to treat acute renal failure       0.90       4.08 (0.46 to 35.96         Fresemide to treat acute renal failure       9.90       0.90       4.08 (0.46 to 35.96         Solomon <sup>w6</sup> 28/28       27/28       47.31       1.04 (0.97 to 1.11         Karayannopoulos <sup>w9</sup> 1/10       7/10       7.96       0.78 (0.40 to 1.54         Subtotal (95% Cl)       103       101       9.10       0.94 (0.71 to 1.26         Fotal events: 70 (frusemide), 77 (placebo)       231       228       100.00       0.99 (0.80 to 1.22         Favours       Favours       Favours       Favours       Favours       Favours         fotal (95% Cl)       231       228       7.96       0.99 (0.80 to 1.22         fotal (95% Cl)       231       228	Test for overall effect: z=1.08, P=0.28					
Hager <sup>W2</sup> $0/62$ $0/59$ Not estimable         Lassnigg <sup>w1</sup> $2/41$ $0/40$ $0.47$ $4.88$ ( $0.24$ to $98.60$ Solomon <sup>W3</sup> $1/25$ $0/28$ $0.47$ $4.88$ ( $0.24$ to $98.60$ Subtotal (95% CI)       128       127 $0.43$ $3.35$ ( $0.14$ to $78.60$ Total events: 3 (frusemide), 0 (placebo)       Frest for heterogeneity: $\chi^2=0.03$ , df=1, P=0.86, l <sup>2</sup> =0% $47.31$ $1.04$ ( $0.97$ to $1.11$ Frest for heterogeneity: $\chi^2=0.03$ , df=1, P=0.86, l <sup>2</sup> =0% $28/28$ $27/28$ $47.31$ $1.04$ ( $0.97$ to $1.11$ Garwan <sup>66</sup> $28/28$ $27/28$ $47.31$ $1.04$ ( $0.97$ to $1.11$ $1.16$ $0.14$ ( $0.02$ to $0.96$ Karayannopoulos <sup>W9</sup> $1/10$ $7/10$ $7/10$ $7.96$ $0.78$ ( $0.40$ to $1.54$ $99.10$ $0.94$ ( $0.71$ to $1.26$ Subtotal (95% CI)       103       101 $99.10$ $0.94$ ( $0.71$ to $1.26$ $99.10$ $0.99$ ( $0.80$ to $1.22$ Total events: 70 (frusemide), 77 (placebo)       231       228 $0.01$ $0.1$ $10$ $100.00$ $0.99$ ( $0.80$ to $1.22$ Total events: 73 (frusemide), 77 (placebo)       231       228 $0.01$ </td <td>Requirement for renal replacement therapy or dia</td> <td>lysis</td> <td></td> <td></td> <td></td> <td></td>	Requirement for renal replacement therapy or dia	lysis				
Lassnigg <sup>w1</sup> $2/41$ $0/40$ $0/47$ $4.88 (0.24 to 98.60)$ Solomon <sup>w3</sup> $1/25$ $0/28$ $0/43$ $3.35 (0.14 to 78.60)$ Subtotal (95% CI)128127 $0.43$ $3.35 (0.14 to 78.60)$ Total events: 3 (frusemide), 0 (placebo)128127 $0.43$ $3.35 (0.14 to 78.60)$ Fersemide to treat acute renal failure $0.90$ $4.08 (0.46 to 35.96)$ Brown <sup>w6</sup> 28/2827/28 $47.31$ $1.04 (0.97 to 1.11)$ Karayanopoulos <sup>w9</sup> $1/10$ $7/10$ $42.66$ $1.00 (0.88 to 1.13)$ Shilliday <sup>w4</sup> $10/32$ $12/30$ $42.66$ $1.00 (0.88 to 1.13)$ Subtotal (95% CI)103101 $99.10$ $0.94 (0.71 to 1.26)$ Total events: 70 (frusemide), 77 (placebo)231228 $0.01$ $0.1$ $100.00$ Fest for overall effect: z=0.39, P=0.69 $0.01$ $0.1$ $100.00$ $0.99 (0.80 to 1.22)$ Total events: 73 (frusemide), 77 (placebo)231228 $728$ $728$ Fest for overall effect: z=0.12, P=0.91 $77$ $786$ $780 urs$ $780 urs$ Favours frusemide $780 urs$ $780 urs$ $780 urs$ $780 urs$ Fest for overall effect: z=0.12, P=0.91 $770 (200, 1/2 = 64.2%)$ $780 urs$ $780 urs$		n				
Solomon W3 1/25 0/28 0.43 3.36 (0.14 to 78.60 Subtotal (95% Cl) 128 127 0.90 4.08 (0.46 to 35.96 Frest for heterogeneity: $\chi^2$ =0.03, df=1, P=0.86, l <sup>2</sup> =0% Fest for overall effect: z=1.27, P=0.21 Frusemide to treat acute renal failure Brown W6 28/28 27/28 47.31 1.04 (0.97 to 1.11 Karayannopoulos <sup>W0</sup> 1/10 7/10 Kleinknecht <sup>W5</sup> 31/33 31/33 Shilliday <sup>W4</sup> 10/32 12/30 Subtotal (95% Cl) 103 101 Fotal events: 70 (frusemide), 77 (placebo) Fest for heterogeneity: $\chi^2$ =21.68, df=3, P<0.0001, l <sup>2</sup> =86.2% Fest for overall effect: z=0.39, P=0.69 Fotal (95% Cl) 231 228 0.01 0.1 10 100 Fest for heterogeneity: $\chi^2$ =13.95, df=5, P=0.02, l <sup>2</sup> =64.2% Fest for overall effect: z=0.12, P=0.91 Frusemide to reat acute renal fest control		0/62	0/59			Not estimable
Subtotal (95% Cl) 128 127 Total events: 3 (frusemide), 0 (placebo) Fest for heterogeneity: $\chi^2$ =0.03, df=1, P=0.86, $l^2$ =0% Fest for overall effect: z=1.27, P=0.21 Frusemide to treat acute renal failure Brown <sup>v6</sup> 28/28 27/28 A7.31 1.04 (0.97 to 1.11 1.16 0.14 (0.02 to 0.96 42.66 1.00 (0.88 to 1.33 Shilliday <sup>w4</sup> 10/32 12/30 Shilliday <sup>w4</sup> 10/32 12/30 Shilliday <sup>w4</sup> 10/32 12/30 Shilliday <sup>w4</sup> 10/32 12/30 Fotal events: 70 (frusemide), 77 (placebo) Fest for overall effect: z=0.39, P=0.69 Fotal (95% Cl) 231 228 Fotal events: 73 (frusemide), 77 (placebo) Fest for overall effect: z=0.12, P=0.91 Events for overall effect: z=0.12, P=0.91 Event for overall effect: z=0.12, P=0.91 Event for overall effect: z=0.12, P=0.91 Event for overal					0.47	4.88 (0.24 to 98.60)
Total events: 3 (frusemide), 0 (placebo) Test for heterogeneity: $\chi^2=0.03$ , df=1, P=0.86, l <sup>2</sup> =0% Test for overall effect: z=1.27, P=0.21 Frusemide to treat acute renal failure Brown <sup>w6</sup> 28/28 27/28 A7.31 1.04 (0.97 to 1.11 1.16 0.14 (0.02 to 0.96 Kleinknecht <sup>w5</sup> 31/33 31/33 Shilliday <sup>w4</sup> 10/32 12/30 Shilliday <sup>w4</sup> 10/32 12/30 Shilliday <sup>w4</sup> 10/32 12/30 Total events: 70 (frusemide), 77 (placebo) Test for heterogeneity: $\chi^2=21.68$ , df=3, P<0.0001, l <sup>2</sup> =86.2% Test for overall effect: z=0.39, P=0.69 Fotal (95% Cl) 231 228 Total events: 73 (frusemide), 77 (placebo) Test for heterogeneity: $\chi^2=13.95$ , df=5, P=0.02, l <sup>2</sup> =64.2% Test for overall effect: z=0.12, P=0.91 Ext for overall effect: z=0.12, P=0.9						3.35 (0.14 to 78.60)
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Test for overall effect: z=0.39, P=0.69         Total (95% Cl)       231       228       100.00       0.99 (0.80 to 1.22         Total events: 73 (frusemide), 77 (placebo)       0.01       0.1       1       10       100         Test for heterogeneity: $\chi^2$ =13.95, df=5, P=0.02, $I^2$ =64.2%       0.01       0.1       1       10       100         Fest for overall effect: z=0.12, P=0.91       Favours frusemide       Favours control       Favours control		/				
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Favours     Favours     Favours       Fest for overall effect: z=0.12, P=0.91     frusemide     control			C	0.01 0.1 1 10 1	00	
				avours Favou	IIS	
Fig 1 Effect of frusemide on in-hospital mortality and proportion of patients requiring renal replacement therapy or dialysis						

three preventive studies included patients who infusion<sup>w1 w2</sup> or a sing

underwent cardiac surgery, cardiac angiography, and major general or vascular surgery. In two of these studies all participants had mild pre-existing renal impairment.<sup>w1 w2</sup> Five of the six treatment studies included patients with acute renal failure without chronic renal failure and one study included patients who had either acute renal failure or acute on chronic renal failure.<sup>w9</sup> infusion<sup>w1</sup> <sup>w2</sup> or a single intravenous bolus dose of 80 mg.<sup>w3</sup> In the treatment group doses ranged from 600-3400 mg/day in studies of established acute renal failure. In one of these<sup>w6</sup> the control group also received one dose of frusemide (1 g) while the treatment group received prolonged frusemide infusion (3.4 g/day) until the serum creatinine level fell to less than 300 µmol/l. Two different doses of frusemide were assessed in two separate treatment groups in one study.<sup>w8</sup> The criteria for dialysis were described in three

Doses of frusemide used to prevent acute renal failure were 1 mg/h or 2.5 mg/h by intravenous

Study or subcategory	No of participants	Frusemide mean (SD)	No of participants	Control mean (SD)			mean di effect) (		•	Weight (%)	Weighted mean difference (random effect) (95% CI)
Brown <sup>w6</sup>	10	6.21 (2.81)	12	7.13 (3.64)		_				13.01	-0.92 (-3.62 to 1.78)
Cantarovich <sup>w7</sup>	166	6.50 (5.40)	164	6.90 (5.30)			-			71.04	-0.40 (-1.55 to 0.75)
Cantarovich <sup>w9</sup>	19	6.80 (NA)	13	8.80 (NA)							Not estimable
Cantarovich <sup>w9</sup>	15	2.80 (NA)	13	8.80 (NA)							Not estimable
Kleinknecht <sup>w5</sup>	20	5.50 (3.22)	22	6.09 (5.39)		-				13.40	-0.59 (-3.25 to 2.07)
Shilliday <sup>w4</sup>	32	13.40 (13.70)	30	13.20 (10.70)						2.55	0.20 (-5.90 to 6.30)
Total (95% CI)	262		254				-			100.00	-0.48 (-1.45 to 0.50)
Test for heterogeneity:	χ <sup>2</sup> =0.18, df=3,	P=0.98, 12=0%	)		-10	-5	0	5	10		
Test for overall effect: z=0.96, P=0.34				Favours frusemide		Favour contr					

Fig 2 Number of dialysis sessions required after frusemide or control treatments

studies.<sup>w5-w7</sup> Jadad scores ranged from 1 to 5 (mean 2.6). Allocation concealment was adequate in four studies.<sup>w1-w3</sup> <sup>w7</sup> Double blinding was used in four studies.<sup>w1 w2 w4 w7</sup> Three studies reported the proportion of patients who were randomised but lost to follow-up. (See bmj.com for characteristics of included studies.)

No significant heterogeneity was found for in-hospital mortality and ototoxicity but heterogeneity was significant for other outcomes. No significant reduction after frusemide treatment was found for in-hospital mortality (relative risk 1.11,95% confidence interval 0.92 to 1.33, P = 0.28,  $I^2 = 0\%$ ; fig 1), risk for requiring renal replacement therapy or dialysis (0.99, 0.80 to 1.22, P = 0.91,  $I^2 = 64.2\%$ ; fig 1), number of dialysis sessions required (weighted mean difference -0.48 sessions, -1.45 to 0.50, P = 0.34,  $I^2 = 0\%$ ; fig 2), or proportion of patients with persistent oliguria (urine output <400-500 ml/day; 0.54, 0.18 to 1.61, P=0.27,  $I^2 = 90.8\%$ ; fig 3). Regardless of whether frusemide was used to prevent or to treat acute renal failure no significant difference was found on mortality (relative risk ratio 2.10, 95 confidence interval 0.67 to 6.63, P = 0.20) and the proportion of patients requiring dialysis (4.12, 0.46 to 37.2, P=0.21). High dose frusemide (1-3.4 g daily) was associated with a suggestion of an increased risk of temporary deafness and tinnitus (relative risk 3.97, 95% confidence interval 1.00 to 15.78, P = 0.05,  $I^2 = 0\%$ ; fig 3). The length of hospital stay was reported in two preventive studies.<sup>w1 w2</sup> Frusemide was associated with an increase in hospital stay (weighted mean difference 3.57 days, 95% confidence interval 0.02 to 7.12, P = 0.049,  $I^2 = 0\%$ ). None of the studies reported a formal cost effectiveness analysis. The funnel plot showed a small possibility of publication bias, with absence of small studies showing a reduction in mortality after frusemide treatment (see bmj.com).

#### Sensitivity analyses

The magnitude and significance of the results was not changed after excluding one study that used a single bolus of frusemide in the control  $\text{group}^{w_6}$  or studies without adequate allocation concealment.<sup>w4-w6 w8 w9</sup>

#### Discussion

Meta-analysis showed that frusemide is not effective in the prevention and treatment of acute renal failure in

	'No in grou	p								
Study or subcategory	Frusemide	Control	-	Relative risk (random			Weight (%)	Relative risk (random		
Patients who remained oliguric				effect) (95% CI)				(70)	effect) (95% CI)	
Brown <sup>w6</sup>	4/28	26/28						23.85	0.15 (0.06 to 0.38)	
Cantarovich <sup>w8</sup>	8/19	6/13		-	_ <b>_</b>			24.89	0.91 (0.41 to 2.01)	
Cantarovich <sup>w8</sup>	4/15	6/13					-	22.88	0.58 (0.21 to 1.61)	
Kleinknecht <sup>w5</sup>	28/33	31/33			-			28.38	0.90 (0.76 to 1.07)	
Total (95% CI)	95	87						100.00	0.54 (0.18 to 1.61)	
Total events: 44 (treatment), 69 (control)										
Test for heterogeneity: $\chi^2$ =32.63, df=3, P<0.0001,	, / <sup>2</sup> =90.8%									
Test for overall effect: z=1.11, P=0.27										
Patients who mentioned deafness or tinnitus										
Brown <sup>w6</sup>	2/28	0/28						21.25	5.00 (0.25 to 99.67)	
Cantarovich <sup>w8</sup>	3/166	1/164		-				37.49	2.96 (0.31 to 28.20)	
Kleinknecht <sup>w5</sup>	3/33	0/33		-		-	->	22.24	7.00 (0.38 to 130.41)	
Shilliday <sup>w4</sup>	1/32	0/30						19.02	2.82 (0.12 to 66.62)	
Total (95% CI)	259	255						100.00	3.97 (1.00 to 15.78)	
Total events: 9 (treatment), 1 (control)						10	100			
Test for heterogeneity: $\chi^2$ =0.28, df=3, P=0.96, $I^2$ =0%			0.01	0.1	1	10	100			
Test for overall effect: z=1.96, P=0.05				avours usemide			avours control			

Fig 3 Proportion of patients remaining oliguric (urine output <400-500 ml/day) after frusemide or control treatments and those mentioning tinnitus or deafness

adults. It did not reduce in-hospital mortality, the requirement for dialysis, the number of dialysis sessions required until recovery of renal function, the proportion of patients remaining oliguric (urine output <400-500 ml/day), and the length of hospital stay. Furthermore, high doses may be associated with an increased risk of ototoxicity.

It has been argued that, especially at high doses, frusemide may convert oliguric acute renal failure to non-oliguric acute renal failure and thus reduce the requirement for dialysis.<sup>w7 w14</sup> We found no such potential benefits. As frusemide is largely excreted unchanged in the urine, it is the urinary excretion of the drug, not its plasma concentration, that determines the efficacy of its diuretic action.<sup>5</sup> <sup>6</sup> Non-oliguric acute renal failure is in general associated with a better prognosis than oliguric acute renal failure.7 Studies have shown that patients who have diuretic responses to frusemide have less severe acute renal failure.<sup>w4</sup> Therefore, a positive diuretic response to frusemide may indicate that patients have a milder form of acute renal failure rather than frusemide being capable of converting a more severe form of acute renal failure to a less severe form and improve the outcome.<sup>w4 8</sup> Our results agree with this hypothesis.

We did not find any significant increase in mortality after frusemide treatment. High doses (1-3.4 g daily) may, however, be associated with an increased risk of ototoxicity. Frusemide is primarily excreted by the kidneys and high doses can increase its serum concentration substantially in acute renal failure,6 w8 hence the higher risk of ototoxicity.

#### Limitations of the study

In the pooled studies only four trials had adequate allocation concealment  ${}^{\scriptscriptstyle w1 \cdot w3 \ w7}$  and four had a Jadad score of 3 or more.<sup>w1 w2 w4 w7</sup> The magnitude and direction of the results were not changed in sensitivity analysis by including only the studies with adequate allocation concealment. Furthermore, the number of patients we included may be inadequate to exclude small but significant clinical benefits of frusemide. With the sample size of this meta-analysis, a positive protective effect of frusemide on the risk for requiring dialysis can only be shown if the associated relative risk reduction exceeds 30%. If frusemide can reduce the relative risk for requiring dialysis by only 20%, a sample size of 400 patients would show such an effect if the

#### What is already known on this topic

Frusemide, a potent loop diuretic, can induce diuresis in some patients with acute renal impairment

#### What this study adds

Frusemide is not associated with any clinical benefits when used to prevent and treat acute renal failure in adults

High doses of frusemide may be associated with an increased risk of ototoxicity

baseline risk for requiring dialysis is 70% in the control group. Secondly, with the absence of small studies showing a reduction in mortality after frusemide treatment small publication bias was possible (see bmj.com). The asymmetrical shape of the funnel plot could be the result of the small number of included studies rather than to true publication bias.9 Finally, although our results were largely consistent across the included studies, significant differences were found in how frusemide was given. The benefits of a particular dose or mode of administration remain uncertain.

Contributors: See bmj.com.

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#### The hazards of being an unemployed SHO

Being an unemployed senior house officer can lead to feelings of frustration, anxiety, and poor self worth. But by far the greatest hazard is in the constant search for adrenaline rushes alternative to those provided when carrying the crash bleep or learning a new clinical skill.

Last Sunday a friend took me to try an extreme sport called dirt surfing. This involves standing on a metal frame similar in shape to a giant skateboard with a BMX cycle wheel at the front and back and hurtling down a steep downhill dirt track. If you can build up enough speed the contraption becomes surprisingly stable, and you can practise using your body weight to steer while enjoying the incredible rush of hurtling downhill at speed on a sunny day. What a glorious activity.

Unfortunately, as far as I can gather, the only way to stop at the end of your ride is to fall off, and that's how I ended up with dirt in my hair, a bruise on my bottom, and a broken ankle.

The following day I had a previously arranged appointment for an unrelated medical problem, and I hobbled into the clinic in my newly acquired cast below the knee with my newly acquired crutches. The consultant saw me arrive and understood immediately the implications of my situation. He looked me up, down, then square in the eye, and said, "You really need to get yourself a job.

Belinda Hirsh unemployed SHO, Borehamwood (binihirsh@unforgettable.com)