Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis
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CRD summary
The evidence suggested that early renal replacement therapy may be associated with improved survival, but the evidence was limited in study numbers and quality and conclusions could not be drawn. Given the poor quality of included studies and the presence of considerable clinical heterogeneity, the authors' cautious conclusions are appropriate.

Authors' objectives
To determine the impact of early initiation of renal replacement therapy on mortality in patients with acute renal failure.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials were searched from 1960 to October 2006. Search terms were reported. The proceedings of the American Society of Nephrology (1999 to 2006) and the Latin American and Caribbean Health Sciences Literature database were handsearched. Review articles and the references of relevant studies were handsearched. Articles in English, French, Spanish, Italian and Portuguese were included in the search.

Study selection
Studies of various designs comparing the effect of early versus late renal replacement therapy initiation on mortality in patients with acute renal failure were eligible for inclusion. Studies investigating dosage or frequency/intensity of renal replacement therapy (that is, without a control group) were excluded.

Included studies were of intermittent haemodialysis, continuous venovenous haemofiltration, continuous venovenous haemodialysis and continuous venovenous haemodiafiltration using a variety of dialyser types. A range of different definitions of early and late haemodialysis was used in the studies including varying cutoff points of blood levels of nitrogenous waste products, clinical deterioration, the presence of uremic symptoms or the diagnosis of septic shock. A variety of population settings were included in the review. Where reported, the percentage of males ranged from 51 to 100 per cent and the mean age ranged from 23 to 69 years. Outcomes included in the review were mortality and kidney function recovery. The follow up ranged from 28 to 180 days. The study period of the included studies ranged from 1950 to 2005. Studies were carried out in a variety of different countries.

The authors did not state how the studies were selected for the review.

Assessment of study quality
Validity was measured using a modified quality instrument with questions in the three domains of enrollment, intervention and outcomes (quality of randomisation, inclusion criteria, comparability of treatment arms, relevance of outcome variables and loss to follow up). Each question was rated on a scale of 1 to 5. Mean scores for each domain were calculated. An overall quality score was achieved by calculating the mean of the three domain scores. The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted on the number of deaths and the number of patients with kidney recovery for early versus late renal replacement therapy. Risk ratios with corresponding 95% confidence intervals were calculated for each group. Two reviewers independently extracted the data. Differences were resolved through discussion.

Methods of synthesis
Pooled risk ratios with corresponding 95% confidence intervals were calculated using a random-effects model weighted according to within-study variance and between-study heterogeneity. Heterogeneity was assessed using the $\chi^2$ statistic and explored using sensitivity and sub-group analyses. A random-effects meta-regression was performed to
investigate the relationship between several covariates and risk ratios.

Results of the review
Twenty three studies were included for the review (n=2,378): four randomised controlled trials (n=252); one quasi-randomised controlled trial (n=18); one prospective cohort study (n=243); 16 retrospective cohort studies (n=1,832); and one single-arm study with a historical control group (n=33). Thirteen studies scored between 2 and 2.9 on the validity assessment, eight scored between 3 and 3.9 and two scored 4 or more. There was no blinding in any of the randomised controlled trials. Sample sizes ranged from 18 to 320, with most studies including fewer than 100 patients.

There was no significant difference in mortality risk between early and late renal replacement therapy groups when only the randomised controlled trials and the quasi-randomised controlled trial were analysed (five studies, n=270). There was no evidence of significant statistical heterogeneity. When the cohort studies were analysed, early renal replacement therapy was associated with a 28 per cent reduction in the risk of mortality (18 studies, n=2,108; risk ratio 0.72, 95% confidence interval: 0.64, 0.82, p<0.001). However, there was evidence of significant statistical heterogeneity (p=0.005). Findings for early renal replacement therapy were more likely to be significant in studies with one hundred or more participants (p<0.001). Other sub-group and meta-regression analyses did not significantly alter the findings. There was no significant difference between early and late renal replacement therapy in the rate of recovery of kidney function (seven studies, n=404). There was no evidence of significant statistical heterogeneity.

Authors' conclusions
The evidence suggested that early renal replacement therapy may be associated with improved survival, but the evidence was limited in study numbers and quality and, therefore, conclusions could not be drawn.

CRD commentary
The review addressed a clear question. Inclusion criteria were clearly defined for outcomes. However, inclusion criteria for participants and intervention were broad and they were not defined for study design. Several relevant databases were searched. The search was restricted to five languages and did not appear to include unpublished material, therefore, language and publication bias could not be ruled out. Appropriate steps were taken in the data extraction process to rule out reviewer error and bias, but it was unclear whether similar steps were taken in the study selection and validity assessment and, therefore, the risk of reviewer error and bias could not be ruled out. A validity assessment was performed. Most included studies were of low or moderate quality and only a small number of randomised controlled trials were available for review, so the data included for analysis may be unreliable. There was considerable clinical and methodological heterogeneity between the included studies and some analyses indicated significant statistical heterogeneity, so the results may have been better treated in a narrative synthesis. Given these limitations, the authors' cautious conclusions were appropriate.

Implications of the review for practice and research
Practice: There was insufficient evidence at present to recommend early renal replacement therapy.

Research: The authors stated that further large-scale observational studies and an adequately-powered (n>1,106) randomised controlled trial was needed, using biomarkers not influenced by confounding factors such as diuretic therapy, to identify patients likely to benefit from early renal replacement therapy. Future research may benefit from using recent consensus criteria for the class and staging of acute renal function as a stratification tool for designing studies (see Other Publications of Related Interest 2).

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