# Renal replacement therapy in the ICU: when should we STARRT?

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When critically ill patients develop severe acute kidney injury (AKI) despite appropriate resuscitation measures, one of the key questions for clinicians is when to start renal replacement therapy (RRT).[1-3] The reason for this issue being of major significance is that RRT is an invasive procedure that carries risks and costs. Therefore, clinicians rightly want to consider whether the benefits that RRT might confer are greater than the risks associated with its deployment. The potential benefits of RRT in critically ill patients with severe AKI include greater control of electrolytes (eg, potassium), greater control of acid-base status (eg, correction of metabolic acidosis), greater control of volume status (eg, prevention or correction of fluid overload), and control of azotaemia (eg, prevention or control of uraemic complications). The potential harms of RRT are related to its invasiveness (eg, catheter insertion-related complications and catheter-related bloodstream infection), the need for anticoagulation to maintain the patency of the extracorporeal circuit (eg, bleeding or heparin-induced thrombocytopenia or citrate accumulation, coagulopathy and metabolic acid-base disorders with regional citrate anticoagulation), and RRT-associated electrolyte and volume complications (eg, hypokalaemia, hypophosphataemia and excessive or excessively rapid volume removal).

Whether the risk–benefit balance is favourable in a given patient remains a matter of clinical judgment. At a population level, however, this issue can only be resolved by well executed randomised controlled trials (RCTs). In this regard, three significant RCTs have been completed in the past 3 years and have been published in major journals. The first and largest is the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial.[4] The AKIKI investigators randomly allocated 620 patients to so called early RRT versus delayed RRT. They found that delayed RRT halved the use of RRT — as some patients recovered without receiving such treatment and others died without it — and the number of patients with catheter-related bloodstream infections without any effect on mortality (48.5% *v* 49.7%). A superficial analysis of the study may lead one to conclude that early RRT is a costly and undesirable approach. In reality, however, a deeper look reveals serious problems with the AKIKI trial. First, the AKIKI definition of early was the presence of Kidney Disease: Improving Global Outcomes (KDIGO) stage 3 criteria (a trebling of serum creatinine or the presence of severe oliguria for ≥ 24 h or anuria for > 12 h), a definition that many intensivists in Australia and New Zealand would classify as late. Thus, from the Australian and New Zealand perspective, AKIKI can be seen as a comparison of late versus very late RRT. Second, the modality of first RRT in these critically ill patients (86% were mechanically ventilated) was primarily intermittent haemodialysis (IHD) in 55% of patients. This was despite the fact that 82% of patients were receiving vasopressor therapy at a mean norepinephrine dose of 70 μg/min combined with a mean epinephrine dose of 46 μg/min. Almost all Australian and New Zealand intensivists would see this as simply extraordinary and totally outside of their usual practice, as such a degree of haemodynamic instability would typically mandate the use of continuous RRT (CRRT) in this setting. Moreover, such an approach is not aligned with the KDIGO clinical practice guidelines for AKI, which suggest using CRRT in preference to IHD for the management of severe AKI in haemodynamically unstable and vasopressor-supported patients.[5] Finally, the catheter-related bloodstream infection rate at 3.4/1000 catheter days was three times the rate reported in a recent case series of 458 patients treated with CRRT in an Australian academic centre.[6] Thus, it remains unclear whether the findings of AKIKI have relevance to current intensive care practice in Australia and New Zealand or indeed in most centres in Canada, the Unites States and the United Kingdom.

Less than a month after the publication of the AKIKI findings, the Early versus Delayed Initiation of RRT (ELAIN) trial was published.[7] Conducted in a surgical ICU in a single academic centre in Germany, ELAIN reflected Australian and New Zealand practice much more closely than AKIKI by defining "early" as KDIGO stage 2 (doubling of serum creatinine or oliguria ≥ 12 h) and initially using CRRT in all patients. In contrast to AKIKI, the ELAIN study found a significant survival benefit from early RRT. However, ELAIN has several characteristics that affected its external validity. In particular, it was limited in size (231 patients); it comprised predominantly surgical patients, with 50% being post-cardiac surgery patients; and was conducted in a single academic centre in Germany. The contradictory findings of AKIKI and ELAIN left clinicians with significant uncertainty about the best approach to the timing of RRT.

More recently, in October 2018, another French trial, the Initiation of Dialysis Early versus Delayed in Intensive Care Unit (IDEAL-ICU), was published.[8] This study focused on patients with septic shock, and randomised 488 patients to early versus late RRT. Like AKIKI, it found no difference

in survival between the two groups, and found a decreased use of RRT in patients randomised to late RRT. However, like AKIKI, the definition of early and late reflected the use of the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criterion of failure (essentially identical to KDIGO stage 3) to define early RRT. Therefore, once again, the comparison was between what many clinicians would call "late" and "very late". Incredibly, in patients with an 88% incidence of mechanical ventilation and a 100% use of vasopressor therapy, 44% of patients received IHD as their first modality of RRT and 34% only received IHD throughout their ICU stay.

From the point of view of intensivists in Australia and New Zealand, it is really difficult to draw any conclusions or implications for practice at a population level about when to start RRT in ICU from the above trials because they so poorly relate to local practice — although the findings of ELAIN may be useful to inform decision making in post-cardiac surgery and surgical patients. Hence, uncertainty remains.

Luckily, there is help on the way in a multicentre RCT that is the most ambitious and now the largest RCT of acute RRT ever conducted: the STARRT-AKI trial.[9] Initiated by Canadian investigators and conducted in close collaboration with investigators from France, Australia and New Zealand, it has now expanded to randomly allocate patients from 164 ICUs in 15 countries from America, Oceania, Asia and Europe, making its external validity the greatest of any similar trial ever conducted. STARRT-AKI is about to reach its target of 3000 patients (last patient randomisation just completed), and its detailed statistical analysis plan is presented in this issue of *CCR*.

Beyond the above extraordinary achievements, what is so very special about STARRT-AKI? The answer is this: its design and methodology and its careful pre-published statistical analysis plan, now presented in this issue of *CCR*.[9] Developed as a structured program of research in a step by step process of initial design, pilot work,[10] refinement[11] and, finally, execution, STARRT-AKI has quite correctly accepted that in some patients (eg, a 20-year-old with anuria, septic shock, a lactate level of 10 mmol/L and high dose vasopressor therapy), RRT must occur immediately and delaying therapy is essentially unjustifiable (lack of equipoise for any delay). In the opposite direction, it has quite correctly accepted that in some patients early RRT is similarly unjustified; for example, in a post-cardiac surgery patient with diabetes who weighs 140 kg, with a urinary output of 20 mL/h, whose creatinine has doubled, but who has a platelet count of $35 \times 10^9$/mL, is receiving 2 L/min of nasal oxygen and is off all cardiovascular support, with normal vital signs, sitting out of bed, having breakfast, and watching television. STARRT-AKI focuses on the group of patients for whom there is clinical equipoise for either early (KDIGO stage 2) or delayed RRT. This milestone study will likely see its final 90-day patient follow-up by early November 2019. Once published in 2020, STARRT-AKI will profoundly influence global RRT practice in the ICU.

## Competing interests

I am a member of the STARTT-AKI Investigators and the Editor-in-Chief of *Critical Care and Resuscitation*.

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