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Kidney health during critical illness or upon major surgery

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Acute kidney injury (AKI) remains one of the most common types of organ failure in intensive care units and after major surgery. For years, we have known that an episode of AKI is not a transient laboratory abnormality but a turning point in kidney health, associated with higher risks of chronic kidney disease (CKD), kidney failure and mortality. In the absence of effective 'anti-AKI' drugs, this recognition underscores the importance of strategies that either prevent AKI from occurring or actively promote kidney recovery once injury has ensued, placing the optimization of supportive care at the centre of current management. In this context, two new randomized controlled trials—'A preventive care strategy to reduce moderate or severe acute kidney injury after major surgery (BigpAK-2); a multinational, randomized clinical trial' [1] in high-risk surgical patients and 'A conservative dialysis strategy and kidney function recovery in dialysis-requiring acute kidney injury: the liberation from acute dialysis (LIBERATE-D) randomized clinical trial' [2] in patients with dialysis-requiring AKI (AKI-D)—offer much-needed evidence that structured, kidney-focused care aimed at optimizing kidney physiology and avoiding additional insults can both prevent AKI and promote renal recovery.

The BigpAK-2 trial, building on previous smaller trials that provided proof of principle, randomized 1180 adults across eight European countries undergoing major surgery to a post-operative AKI prevention strategy versus usual care. The majority of participants (90%) underwent elective procedures, of which the two most common categories were cardiac and abdominal surgeries (approximately one-third of cases each). Participants were required to have one or more risk factors for AKI and also have a positive urinary AKI biomarker within 18 h of surgery [TIMP-2 × IGFBP7 concentration of at least 0.3/1000 (ng/mL)^2]. The intervention was intended to be applied as soon as possible after randomization and had several components aimed at optimizing kidney physiology and avoiding renal tubular cell injury. These comprised: fluid boluses based on straight leg–raise assessments of fluid responsiveness; maintaining mean arterial pressure ≥65 mmHg and cardiac index ≥2.5 mL/min/m^2; cessation of renin–angiotensin–aldosterone inhibitors (RAASi) and avoidance of nephrotoxic medications; and maintaining blood glucose levels between 5.5 and 8.3 mmol/L. The primary outcome was AKI stage 2/3 within 72 h defined using serum creatinine and urine output criteria. Blinding of the clinical teams to treatment allocation was not possible due to the nature of the intervention.

The primary outcome of AKI stage 2/3 was significantly reduced in patients randomized to the intervention, occurring in 14.4% versus 23.2% in the usual care group [odds ratio (OR) 0.57, $P < .001$]. This was seen whether AKI was diagnosed with urine or serum creatinine criteria, with non-significant trends towards fewer persistent AKI episodes and AKI of all stages. However, these findings are somewhat tempered by no differences in any secondary endpoints including recovery of kidney function and

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major adverse kidney events at Day 30 or 90, or in biomarker levels.

The results of BigpAK-2 are important, showing that a structured application of physiology-targeted interventions can reduce moderate and severe AKI in high-risk surgical patients. The integration of a biomarker enrichment strategy is a key strength, moving away from relying on static (possibly non-modifiable) risk factors for identification of those with incipient tubular cell injury. Targeting patients who are more likely to benefit from this type of early intervention may explain the positive results of BigpAK-2 that contrast with negative trials of peri-operative RAASi cessation or hypotension avoidance on AKI rates [3, 4]. Some may argue that cost or availability of AKI biomarkers are a barrier to widespread adoption of this approach, but the flip side of this argument is that more trials like BigpaK-2 are needed to show the value of biomarker-guided management and change the status quo. It is here that more conclusive evidence on whether a reduction in moderate–severe post-operative AKI affects rates of subsequent CKD or other adverse long-term outcomes would be particularly valuable.

It is also notable that these results were achieved with only 47% of the intervention group receiving all elements of the prevention bundle—we can only speculate as to whether higher levels of implementation would result in a greater magnitude of benefit. Also relevant to clinical translation is knowing which elements of the intervention were done most reliably, which showed greatest difference between groups and ultimately which were the most valuable. To the authors' credit, they describe this, as well as an analysis that suggested that avoidance of hypotension and RAASi cessation were the elements most strongly associated with the reduction in AKI stage 2/3. The largest difference in process measures between groups was seen with haemodynamic monitoring which was performed in 79% of intervention group and 9% of controls (compared with nephrotoxin administration which occurred in 11% versus 15.4%, respectively).

If BigpAK-2 speaks to prevention, LIBERATE-D addresses a different, equally neglected question: how aggressively should we dialyse patients once AKI is severe enough to require kidney replacement therapy (KRT).

In many centres, particularly in North America, practice for AKI-D in haemodynamically stable patients often mirrors that for chronic kidney failure, with conventional thrice-weekly intermittent haemodialysis and discontinuation once creatinine and urine output suggest recovery. This routine, schedule-based approach persists despite long-standing concerns that each dialysis session may subject a vulnerable kidney to further ischaemia, hypotension and membrane-related inflammation—amounting to a form of 'dialysis trauma' and potentially delaying recovery at a time when the renal tubular cells are attempting to re-enter the cell cycle, clear cellular debris and restore epithelial polarity.

LIBERATE-D tested the hypothesis that 'less can be more' for carefully selected patients with AKI-D. In this multicentre, unblinded, superiority trial, 220 adults with AKI-D, a baseline estimated glomerular filtration rate (eGFR) >15 mL/min/1.73 m² and haemodynamic stability with planned intermittent haemodialysis were randomized at four US centres. Participants had already been on KRT for a median of 9 days at randomization.

Patients assigned to the conservative strategy received dialysis only when pre-specified metabolic or clinical triggers were met—for example, serum urea nitrogen >112 mg/dL, hyperkalaemia despite medical therapy, severe metabolic acidosis or refractory pulmonary oedema. The control group continued with conventional thrice-weekly dialysis until recovery criteria based on urine output or creatinine clearance were achieved.

By hospital discharge, 64% of patients in the conservative arm had recovered kidney function (alive, off dialysis and dialysis-free for ≥14 days) compared with 50% in the conventional arm (absolute difference 13.8%; unadjusted OR 1.76, 95% confidence interval 1.02–3.03; $P = .04$). Conservative management also resulted in substantially fewer dialysis sessions (median 1.8 vs 3.1 per week), more dialysis-free days by Day 28 and fewer episodes of dialysis-associated hypotension. After adjustment, the confidence intervals widened and statistical significance for the primary outcome was lost, underlining the need for larger confirmatory trials. Still, the signal is consistent with the underlying hypothesis: avoiding unnecessary sessions may limit 'dialysis trauma' and give the injured kidney a better chance of recovering function.

LIBERATE-D provides the first randomized evidence that a dialysis delivery strategy can improve the chance of coming off dialysis in AKI-D. Notably, because KRT had already been ongoing for a median of 9 days at randomization, LIBERATE-D primarily informs management of persistent AKI-D, and applicability to early AKI is uncertain. This study aligns with other trials (AKIKI (Artificial Kidney Initiation in Kidney Injury) [5], IDEAL-ICU (Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit) [6], STARRT-AKI (Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury) [7]) suggesting that, in stable patients, delaying or individualizing KRT intensity is safe and may be beneficial, while also highlighting the dangers of excessive delay seen in trials such as AKIKI-2 [8]. Moreover, a secondary analysis of STARRT-AKI found that accelerated RRT initiation was associated with a higher risk of 90-day dialysis dependence among patients with pre-existing CKD [9].

Taken together, BigpAK-2 and LIBERATE-D argue for a quiet but important shift in our thinking: away from polishing kidney lab values, towards more assertive kidney-protective management that minimizes dialysis-associated complications and avoids iatrogenic delay in renal recovery. Both trials are grounded in a shared physiological principle, namely that protecting the injured kidney through haemodynamic optimization and avoidance of nephrotoxic or treatment-related stress is central to both prevention and recovery. BigpAK-2 now provides perioperative teams with randomized evidence that listening to the 'stressed kidney' and shielding it from avoidable haemodynamic and nephrotoxic insults can prevent moderate and severe AKI. LIBERATE-D reminds nephrologists and intensivists caring for patients with AKI-D that every dialysis session is a non-neutral act that carries the risk of additional injury—a form of 'dialysis trauma' to an organ that is attempting to recover. In carefully selected, haemodynamically stable patients, a conservative, trigger-based approach to dialysis delivery may therefore reduce treatment-related complications and create more favourable conditions for kidney repair.

BigpAK-2 requires long-term follow-up to determine whether preventing moderate to severe postoperative AKI truly translates into better kidney health in subsequent years. LIBERATE-D calls for replication and extension in larger and more heterogeneous intensive care unit populations, including patients on continuous renal replacement therapies. Future trials should more systematically include kidney-health outcomes—such as eGFR slope, CKD incidence and dialysis dependence—rather than stopping at in-hospital creatinine changes. Ultimately, these new randomized trials underscore that kidney health during critical illness is not an accidental consequence of 'good general care', but a modifiable outcome in its own right (Fig. 1).

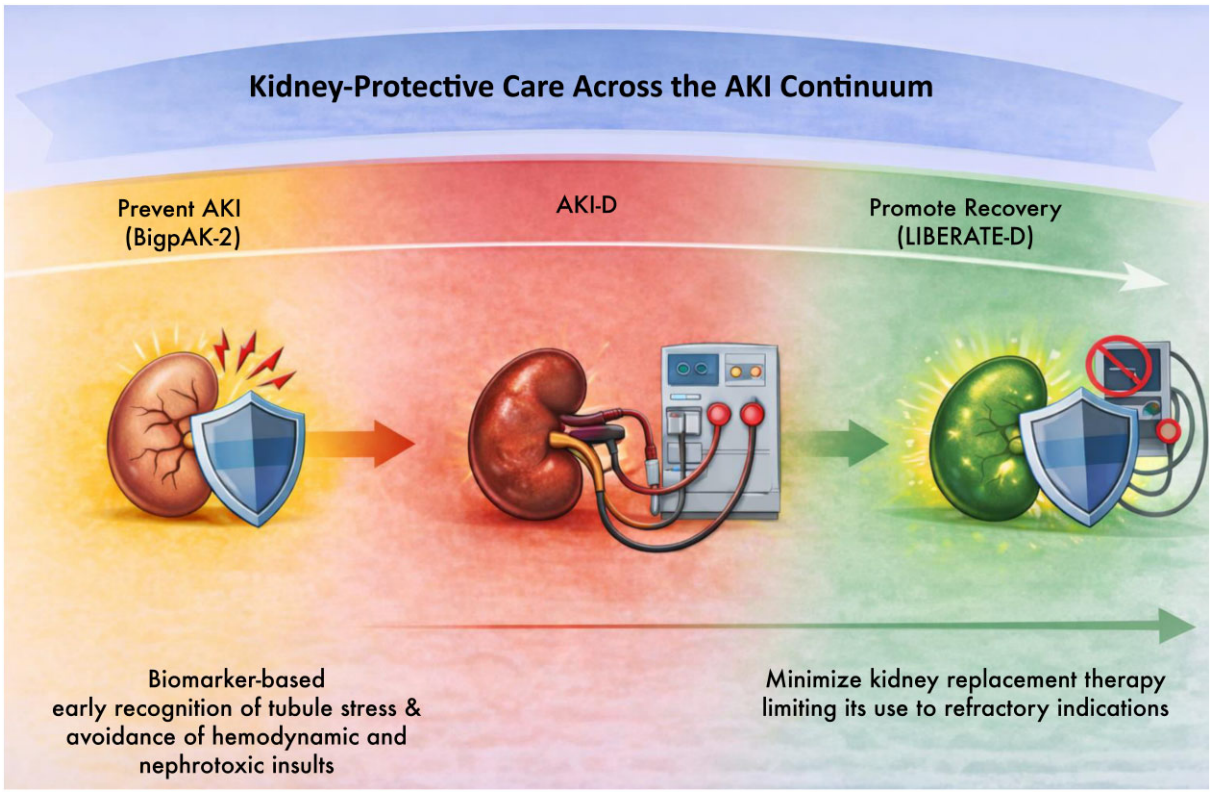

Figure 1: Protecting the stressed kidney: prevention, dialysis and recovery in AKI. A draft conceptual schematic was generated with assistance from an artificial intelligence–based image-generation tool and subsequently reviewed, edited and validated by the authors.

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AUTHORS' CONTRIBUTIONS

T.S. and N.M.S. wrote the manuscript. All other authors read, revised and contributed to the text.

CONFLICT OF INTEREST STATEMENT

M.O: received research funding from Biomerieux. All other authors declare no conflict of interests.

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