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What endpoints should not be used for clinical studies of acute kidney injury?

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In the accompanying commentary, Kellum and colleagues [1] opine that “...the easiest way to ruin a clinical trial is to choose the wrong endpoint.” We strongly agree with this view; here, we review pitfalls in endpoint selection for AKI trials. The development of novel AKI therapies is fraught with challenges, including the timing of renal injury relative to therapy (with the exceptions of post-operative, medication and contrast-associated AKI, it is impossible to provide therapy before AKI) and the heterogeneous nature of AKI, including the clinical entities that lead to AKI and the multiple tissue compartments (endothelium, epithelium, vasculature) that may be involved. Another consideration complicating endpoint selection is the (often implicit) paradigm that treats AKI as a discrete disease rather than a condition with multiple phenotypes. Designing studies using an endpoint that is not specific for the specific phenotype of interest may result in inconclusive or potentially misleading study results.

Endpoints should not be the same for prevention and treatment trials. In prevention trials, the development of AKI is the logical primary endpoint. How AKI is defined is therefore critical. Although consensus definitions of AKI rely on small changes in plasma creatinine (PCr) and short durations of oliguria [2], these parameters do not differentiate between functional (pre-renal) AKI and intrinsic kidney damage. Relying on small changes in PCr provides a sensitive index of AKI that may be appropriate as the primary endpoint for early phase (proof of concept trials) trials, but is fraught with risk of error and is not appropriate for definitive phase 3 clinical trials. In addition, the change in PCr used as an endpoint needs to be appropriate for the baseline level of kidney function. A change of 0.3 mg/dL may represent a significant decrease in glomerular filtration rate (GFR) for someone with normal kidney function; however, the same change may reflect physiologic variation for a patient with chronic kidney disease (CKD). Conversely, limitations to using relative changes in PCr to define AKI need to be recognized. In simulation studies [3], the kinetics with which a relative change in PCr is achieved varies based on baseline kidney function. When a 90% reduction in GFR is simulated, PCr increases by nearly 2.5-times baseline over 24 hours when baseline kidney function is normal but by less than 50% with Stage 4 CKD. Along the

same lines, therapeutic interventions may alter PCr independent of true nephroprotection. For example, the use of change in PCr as an endpoint for studies of renal replacement therapy (RRT) for the prevention of AKI [4] is problematic because the intervention results in direct lowering of PCr concentration.

Similarly, while reductions in urine output are associated with increased mortality and other adverse outcomes [5], changes in urine output are not sufficiently specific to be a robust endpoint for AKI prevention. For example, urine output may be increased by diuretics in patients and may have prognostic value [6], although it is established that diuretic administration has no role in prevention (or treatment) of AKI [7].

The lack of specificity inherent in the consensus definitions of AKI may be mitigated by the use of larger or sustained changes in PCr or urine output, however use of these more stringent criteria will reduce event rates and necessitate larger sample sizes. These deficiencies may also be addressed through clinical adjudication to ascertain the specific etiology of AKI, but this requires consensus among adjudicators [8]. In a recent biomarker study of patients after cardiac surgery, one adjudicator attributed 73.2% of AKI events to acute tubular necrosis (ATN), whereas a second adjudicator attributed just 20.9% of the same AKI events to ATN [9]. Thus, for studies of prevention, we suggest that endpoints should not focus solely on small changes in PCr, and that the magnitude of the change in PCr should be significant and needs to reflect underlying renal function. In the future, incorporation of validated biomarkers of cellular injury may improve the robustness of endpoints based on small changes in PCr and urine output.

Studies of AKI treatment, particularly for severe RRT-requiring AKI, have often used 60 or 90-day mortality as an endpoint [10, 11]. For studies of less severe AKI, AKI progression may be considered an endpoint for treatment trials. Although change in KDIGO AKI stage has been used, there are methodologic challenges with this endpoint, including differences in the magnitude of injury needed to achieve a given change in kidney function (as described previously) and the absence of a tight correlation between change in PCr and actual kidney function in non-steady-state conditions. This latter issue is of particular importance since changes in PCr lag behind changes in GFR, leading to the potential for progression of AKI stage despite actual improvement in kidney function, a shortcoming that could be overcome with the availability of real-time assessment of GFR. PCr lag as well as the differences in PCr kinetics associated with varying baseline kidney function (described previously) also complicate the use of duration of AKI as an endpoint for treatment trials, despite the association of longer duration AKI with adverse outcomes. Furthermore, there are no data that modifying the duration of AKI is associated with improved outcomes. Finally, the lack of consensus surrounding RRT initiation (as well as discontinuation) makes the use of RRT-requiring AKI a problematic endpoint, unless clear biochemical and physiologic criteria are used to define initiation and cessation of therapy.

While recovery of kidney function is an important outcome for treatment trials, it is problematic to define renal recovery based on PCr alone. PCr production decreases with acute illness [12] and with reduction in muscle mass, which is common in critically ill patients. Volume of distribution may affect PCr [13, 14]. Consequently, patients with full

recovery may achieve a new “baseline” PCr that is below their prior baseline, and recovery to within 50% of baseline may reflect significant ongoing renal dysfunction. Cystatin C has not been well-validated as an alternative endpoint. In the future, treatment trials may also incorporate novel biomarkers that are associated with either ongoing injury or early recovery; for the successful use of such biomarkers, it will be critical to confirm that these biomarkers are reliably elevated in the population of interest, and that the kinetics of biomarker change over time are understood. For trials of AKI requiring RRT, recovery to independence from RRT has been used, but there is no consensus on criteria for discontinuation of renal support. Recognition of recovery of kidney function may also be masked by treatment parameters, limiting the usefulness of time to recovery as an endpoint.

A composite endpoint of death, dialysis, and persistent kidney dysfunction (Major Adverse Kidney Events; MAKE) at a defined time-point after AKI (e.g., MAKE₃₀ at 30 days) has also been suggested [15]. One of the challenges of such an endpoint is that the relationship between short and long-term renal dysfunction is uncertain. In CORONARY (a large, multicenter, randomized trial of off-pump versus on-pump coronary artery bypass graft [CABG] surgery), although the use of off-pump CABG was associated with a lower risk of AKI within 30 days, there was not a lower risk of renal dysfunction at 1 year [16]. Thus, despite significant advances in our understanding of the epidemiology of AKI, how outcomes over the medium term (30–90 days) translate to outcomes over the long term (1 year or longer) have yet to be fully defined. Furthermore, an important consideration for the MAKE endpoint is the relative effect of the treatment on each of the components of the endpoint. Depending on the severity of concomitant illness, treatment of AKI may or may not have a significant impact on mortality. In post-operative populations with relatively low mortality risk, AKI is associated with a significant increase in the risk of death. The degree to which AKI in this setting is a marker for otherwise unrecognized mortality risk and not modifiable by treatment (as opposed to a mediator of mortality that is modifiable by treatment of AKI) is uncertain. In a population with multi-organ failure from sepsis, the impact of treatment of AKI on mortality is even less clear. However, even if the intervention has only a small effect on mortality, inclusion of mortality in a composite endpoint may be desirable, as death is a competing outcome for other AKI-relevant events including dialysis-dependence or persistent decline in kidney function. Intervening clinical events may also affect these longer-term outcomes, further diluting their usefulness as clinical endpoints. Despite these limitations, MAKE is a composite of multiple endpoints that are more clearly patient-centered than simple changes in PCr. The challenge is whether the effect of a given treatment on the MAKE components will be large enough to be detected among within the clinical “noise” created by competing risks. Patient-centered outcomes, including quality of life, have not been extensively studied in AKI, and further studies are needed as these are highly relevant and potentially very useful endpoints for clinical trials.

Finally, we note clinical trial endpoints depend on the phase of drug development, and cannot be fixed based on the study type (e.g. prevention vs. treatment). Phase 1 clinical trials are largely focused on safety. Phase 2 clinical trials often have multiple goals, all of which are critical steps toward a definitive Phase 3 trial. However, it is critical that the clinical endpoints for a Phase 2 trial (often needed to convince funding agencies/investors that a Phase 3 trial is warranted) not merely be underpowered Phase 3 endpoints (such as

mortality), as plausible biological effects will not be detectable given the small sample size [17]. Discussions with regulatory agencies at this stage can be helpful to frame the design of both the Phase 2 and subsequent Phase 3 trial. For example, an ongoing Phase 2 trial of alkaline phosphatase for the treatment of sepsis-associated AKI has prespecified the area under endogenous creatinine clearance curve as the primary endpoint, along with a number of secondary renal endpoints, including the incidence of RRT using prespecified criteria for RRT initiation [18]. Thus, this trial may allow the investigators to determine the relationship, if any, of their primary endpoint with “harder” AKI endpoints including the need for RRT. Similarly, endpoints for Phase 3 trials cannot merely be based on small changes in PCr, but rather must represent important, patient centered outcomes.

In sum, we have highlighted a number of potential considerations when selecting endpoints for clinical trials in AKI. Lest the reader despair, our intent is not to state that there are no appropriate endpoints for AKI clinical trials; rather, the endpoint must be driven by the intervention and its proposed effect, the population of interest, and the phase of clinical trial design.

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