CHAPTER 226

End Points for Clinical Trials in Acute Kidney Injury

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OBJECTIVES

This chapter will:
1. Highlight some of the challenges inherent to studies of acute kidney injury (AKI).
2. Discuss the different renal and nonrenal end points in AKI trials.
3. Discuss methods to improve study outcomes in AKI intervention trials.

CHALLENGES INHERENT TO THE STUDY OF ACUTE KIDNEY INJURY

Despite advances in modern medicine, acute kidney injury (AKI) is associated with a heavy burden of morbidity and mortality. Even mild forms of AKI are associated with a sevenfold increase in 30-day mortality and increase the risk of multiorgan failure.[1] Severe AKI requiring renal replacement therapy (RRT) is associated independently with a 50% incidence of death among critically ill patients.[2] In spite of the rising incidence of AKI in hospitalized patients no effective therapies other than supportive care currently exist. End point selection is one of the most critical components of clinical trial design. The primary end point must be clinically relevant, important to patients and medical providers, quantifiable, and amenable to therapeutic interventions. The end point should be robust, with negligible confounding factors or bias. In addition, end point selection must be relevant to regulatory agencies (e.g., Food and Drug Administration and European Medicines Agency) if the trial involves a therapeutic agent. The choice of end point is further influenced by the target patient population (e.g., septic AKI vs. cardiac surgery–associated AKI) and treatment objective (e.g., reduction in need for dialysis and/or mortality vs. creatinine improvement) (Fig. 226.1).

Therapeutic clinical trials for AKI have been hampered by numerous barriers such as lack of agreement on the staging and diagnostic criteria for AKI, failure to diagnose AKI in a timely manner, lack of well-defined appropriate study end points, small observed effect size, and inadequate study size population.[3–5] The development and use of consensus criteria for AKI diagnosis have been an important step in improving the conduct of clinical trials across target patient populations.[6–8] The Acute Kidney Injury Network (AKIN) group, National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), and the Acute Dialysis Quality Initiative (ADQI) have made ongoing attempts to improve end points for AKI clinical trials.[9–14] However, some of the challenges inherent to studies of AKI therapeutics persist.[15] First, the event rates for AKI, particularly severe AKI, can be relatively low; to yield acceptable event rates to make clinical trials practical, the target population should be at high risk for AKI. Among 1219 adults who underwent cardiac surgery in the translational research in biomarker end points (TRIBE) study, 426 (34.9%) patients developed AKI after cardiac surgery; however, the incidence of severe AKI (doubling of serum creatinine or need RRT) was only 5%.[16] Therefore with this incidence rate and power of 0.9, and 30% effectiveness of

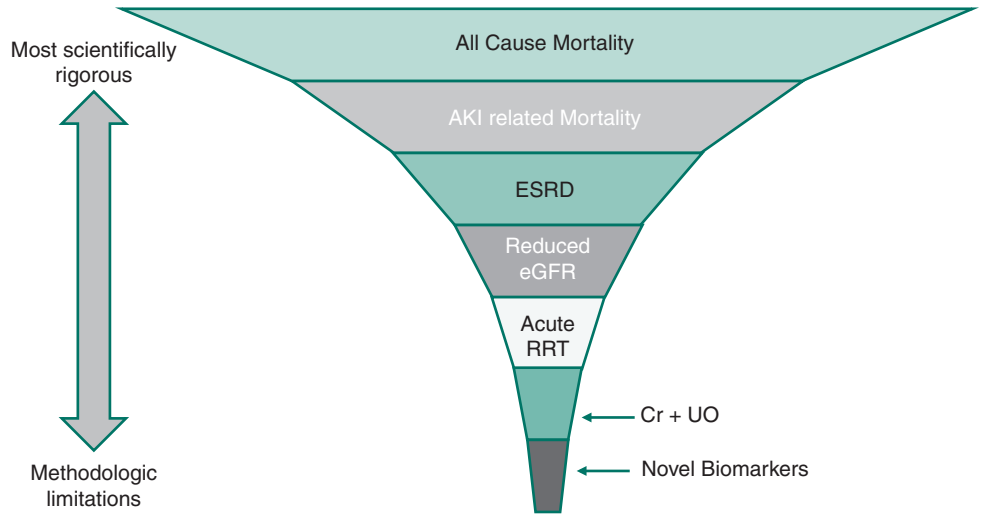

FIGURE 226.1 Schematic diagram of potential end points for acute kidney injury trials. The order ranking of the different end point options depends on the end point's relevance to a specific phase of clinical trial, target population, and treatment option. *Cr, creatinine; eGFR, estimated glomerular filtration rate; ESRD, end stage kidney disease; RTT, renal replacement therapy; UO, urinary output.*

an intervention (i.e., 30% relative reduction in the development of severe AKI from 5% to 3.5%), respectively, 3799 patients per intervention group would be needed to show therapeutic benefit with this event rate. No clinical trial in AKI, either preventative or interventional, has enrolled such high patient numbers to achieve adequate power. Without adequate power, results from clinical trials may be misleading and may misinform the medical provider.[5,17] In one published summary of preventative AKI trials, only 3 of 30 cardiac surgery trials and only 3 of 28 contrast studies were enrolling 800 or more adult patients total.[5]

Second, although selecting patients at highest risk of AKI increases the event rate, it may reduce the efficacy of the therapeutic intervention in these high-risk patients.[18] Third, other challenges to trial design in the field of critical care nephrology include the identification of study participants early enough such that they may benefit from treatment, the use of therapies that target only a single pathophysiologic process despite the multifactorial causes of some AKI events, and the relative heterogeneity of study populations.[19]

Finally, deciding on the appropriate study end point for phase of AKI clinical trial can depend on whether it is a preventative or intervention trial and can prove challenging. For instance, the use of short-term changes in serum creatinine (or other measures of glomerular filtration rate [GFR]) or changes in biomarker levels as secondary end points may be premature in phase 3 AKI management clinical trials.[15] Other randomized clinical trials in AKI have assessed other hard clinical end points, including death, and have been met with disappointment.[20] Important examples of clinical end points in AKI trials include creatinine- and urine output–based criteria for AKI diagnosis, risk prediction scores, functional and damage biomarkers, requirement for renal replacement therapy, onset of chronic kidney disease (CKD), persistent decline in estimated glomerular filtration rate (eGFR), progression to end-stage renal disease (ESRD), and death. We will discuss individually the different renal and nonrenal end points in AKI trials and discuss methods to improve study outcomes in AKI intervention trials.

CREATININE- AND URINE OUTPUT–BASED CRITERIA FOR ACUTE KIDNEY INJURY DIAGNOSIS

Trial end points that include reduced urinary output or reflect a rise in creatinine typically are applied in earlier phases of drug or device development to demonstrate dose responsiveness, support proof-of-concept, and/or provide preliminary evidence of safety and efficacy. Current consensus definitions of AKI including the Kidney Disease: Improving Global Outcomes (KDIGO) criterion rely on changes in either the level of serum creatinine or urinary output.[21] AKI severity has an important impact on enrollment in AKI prevention trial. A higher stage of AKI diagnostic criteria provides a more appropriate clinically significant AKI end point than less severe AKI diagnostic criteria. Enrollment of patients with early AKI (stage 1 KDIGO) is more sensitive to identification of AKI and will increase statistical power. For example, a therapy that reduces the relative risk of stage 1 AKI by 40% will require approximately 200 study participants (100 in the treatment group and 100 in the control group) if the baseline risk of stage 1 AKI is 40%. A therapy that reduces the relative risk of stage 2 AKI by 50% will require approximately 2200 study participants (1100 in the treatment group and 1100 in the control group) if the baseline risk of stage 2 AKI is 12%. Including participants with early AKI will increase the incidence of false-positive results and, as a result, attenuate the association of AKI with more important subsequent outcomes, such as worsened CKD and death.

Another explanation for the disappointment of interventional trials in AKI and the high mortality associated with AKI is the dependence on serum creatinine for diagnosis of AKI. The diagnosis of AKI may be delayed by the overreliance on serum creatinine as a functional marker, a surrogate for changes in GFR which often occur late in the time course of AKI. A subclinical AKI defined as a renal injury marked by a lack of change in serum creatinine despite changes in structural nephron damage biomarkers is increasingly being recognized as a clinically important type of AKI.[22,23] Injury biomarkers can detect AKI several hours to days before increases in serum creatinine and is discussed in more detail below.

Although decreased urine output is also incorporated as part of the AKI definitions, limited data exist as to whether early alterations in urine flow are a sensitive marker of AKI. Indeed, there is less certainty of the appropriateness of oliguria alone as a trial entry criterion. Clinical factors such as hydration status, nondiuretic use, cardiovascular hemodynamics, and the extent of early resuscitation measures can affect urine output.[24] Early changes in urinary output are not always true reflections of the decline of GFR and can lead to a misclassification as "mild" AKI. Despite this, some critically ill patients such as those with severe septic shock, consecutive oliguria may provide a valuable measure of AKI risk.[25,26]

ACUTE KIDNEY INJURY RISK SCORES

We currently lack the means to reliably determine which patients will develop AKI. A substantial subset of patients with AKI recover without any detrimental effects, whereas others who do not recover may progress to a more severe form of AKI.[27] Understanding an individual's AKI risk profile may offer the opportunity for prevention or early intervention.[28–32] Currently available risk scores to predict AKI have been proposed in cardiac surgery–associated AKI (CSA-AKI), contrast-induced AKI (CI-AKI), and nephrotoxicity studies.[32–34] These scoring systems rely on common clinical and biochemical parameters to assess a patient's risk or probability of developing AKI and/or the need for RRT.[34–36] One score that has excellent discriminatory capacity for predicting CI-AKI in patients with acute coronary syndrome who underwent coronary angiography is the Mehran risk score.[34] The Mehran risk score uses clinical characteristics as well as procedure-related parameters, such volume of contrast media used and presence of intraaortic balloon pump. The Mehran risk score for CI-AKI has been validated in many studies even several years after its publication.[37]

Despite the success of the Mehran risk score in predicting the risk of CI-AKI, some other risk prediction scores in particular in the area of CSA-AKI have been criticized for not being sensitive or specific enough to identify high risk individuals and may predict AKI progression poorly.[38–41] Potential explanations for the failure to translate into current clinical practice may be related to difficulty reproducing results in larger patient studies, the inability to account for patient heterogeneity, and a failure to calculate these complex scores at the bedside. Many of these risk scores require further refinement and validation.

More recently, a clinical model of renal angina (Renal Angina Index) was established to identify which critically

ill patients would be at the greatest risk for development of AKI.[42] This index uses patient demographic risk factors and clinical context in addition to signs of renal injury such as oliguria or fluid overload to develop a practice similar to acute coronary syndrome to identify patients at high risk for severe AKI and creates heightened vigilance in monitoring of renal function.[43] Interestingly, when combined with novel AKI biomarkers, it can improve risk prediction of AKI 3 days later.[44]

DAMAGE AND FUNCTIONAL BIOMARKERS

Although risk prediction scores, other than the Mehran score, seldom are used to predict which patients are at high risk for development of AKI, the use of functional and damage biomarkers over the last 10 years may have improved the identification of patients at high risk for development of AKI, the early diagnosis of AKI, and the enrichment the target population for interventions in AKI clinical trials.[45] Earlier detection of AKI with a kidney-specific biomarker that is released into the blood or urine by the injured kidney may identify patients at risk of AKI and help guide timing and nature of interventions. Injury biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), cystatin C, liver-fatty acid binding protein (L-FABP), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7) among many other AKI biomarkers can detect AKI several hours before increases in serum creatinine.[46–49] The appropriate enrollment of patients into AKI trials can be enhanced by the use of biomarkers and can be used to increase the effect population size even before a rise in creatinine is evident (Fig. 226.2).[50]

The most widely studied and validated biomarker of early AKI is NGAL.[51] After cardiac surgery, urine or plasma NGAL measurements were predictive of AKI and its severity in more than 6600 patients, with an overall area under the receiver operating characteristic (ROC) curve of 0.8 to 0.82.[51] In patients undergoing kidney transplantation, NGAL measurements predicted a delayed graft function with an overall area ROC curve of 0.88.[51] A large multicenter pooled analysis of existing NGAL studies confirmed the potential advantage of using this biomarker for the early diagnosis of AKI and its adverse outcomes.[52] Biomarker combinations have been used successfully to diagnose AKI after cardiac surgery.[53] NGAL was detectable within 2 hours of bypass pump initiation, urine L-FABP and IL-18 within 6 hours, and urine KIM-1 increased at the 12-hour time point. All markers correlated with AKI severity and clinical outcomes

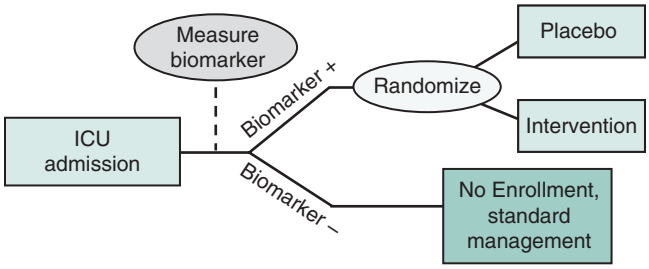

FIGURE 226.2 Schematic diagram of potential screening of acute kidney injury (AKI) patients using novel AKI biomarkers. The enrollment of patients into AKI trials can be enhanced by the use of biomarkers and can be used to increase the effect population size even before a rise in creatinine is evident.

improved the risk prediction for AKI over risk prediction models.

Unfortunately, despite the approval of combination TIMP-2 and IGFBP7 for use in the United States, the potential availability of NGAL in Europe and the approval of L-FABP in Japan, no universally recognized biomarker has entered routine clinical practice.[54] There has been only a small number of early AKI intervention trials guided by urinary biomarker elevation that have been published; however, many other trials are ongoing in this area.[55–58] AKI biomarker studies have focused heavily on the prediction of elevated creatinine for diagnosis of AKI and use of ROC curves to quantify biomarker performance. The emphasis on creatinine assumes biomarker detects only loss of function or fall in GFR rather than a modest renal injury or stress. At the present time, AKI biomarkers require more extensive evaluation and qualification before they can be used as study end points. Future studies in AKI biomarkers must focus on biomarker reference ranges and associate biomarkers with clinically meaningful outcomes, such as need for RRT, risk of CKD, and death.[59]

RENAL REPLACEMENT THERAPY

For patients with established AKI, the initiation of RRT (within a prespecified time point) is considered to be a meaningful trial end point; however, this outcome may have flaws. Absolute criteria for dialysis initiation in the intensive care unit do not exist. There is a wide range of clinical practice uncertainty regarding the optimal timing of initiation of dialysis despite the classical indications for dialysis. In one survey of 180 physicians and intensivists at 32 hospitals in Canada, factors that influenced the timing of initiation were the time of day that laboratory and clinical results became available, patient comorbidity and age, responsiveness to a diuretic challenge, and the specialty of the prescribing physician.[60] Even when there was consensus around starting RRT, there was no uniformity regarding rationale.

Many prevention trials of pharmacologic therapies in patients initiated on RRT have been disappointing.[61–63] The need for RRT as an outcome is measured easily using procedural and billing coding and undoubtedly represents a key event associated with morbidity, mortality, and health resource utilization. The difficulty is that this late stage of AKI is less common than early kidney injury stage end points and surrogate outcomes. Furthermore, these end points do not provide a good opportunity to treat patients early in the course of injury. Collectively, the composite outcome of death, new dialysis, and worsened renal function (expressed as a 25% or greater decline in eGFR) comprise the *major adverse kidney event* (MAKE) outcome.[64] MAKE30, MAKE60, and MAKE90 are assessed 30, 60, and 90 days after AKI diagnosis, respectively. MAKE90 may be the most appropriate end point because that is typically the time when CKD is diagnosed after AKI; therefore it may pick up a higher proportion of patients with a clinically meaningful outcome.

This is also the primary composite outcome for one of the largest prevention trials in AKI, known as the PRESERVE trial.[62] The Prevention of Serious Adverse Events following Angiography (PRESERVE) trial is a randomized, double-blind, multicenter trial that actively is enrolling 8680 patients undergoing coronary or noncoronary angiography to compare the effectiveness of IV isotonic sodium bicarbonate versus IV isotonic sodium chloride and oral N-acetylcysteine

versus oral placebo for the prevention of serious, adverse outcomes associated with contrast-induced AKI.

DECLINE IN ESTIMATED GLOMERULAR FILTRATION RATE

Little data exist that support a threshold of eGFR that would be a meaningful surrogate end point in the context of AKI and progression to ESRD. Prior studies have indicated that a 30% decline in eGFR may be a suitable surrogate for progression of CKD to ESRD rather than using the customary end point of doubling of serum creatinine levels.[65] One of the largest analyses to examine systematically the association between eGFR decline and risk of ESRD after onset of AKI (defined by KDIGO) was performed in a total of 19,025 AKI patients, and the risk of ESRD and mortality followed over a median of 3.8 years.[66] For patients with in-hospital AKI compared with those with no AKI and stable eGFR, a 30% decline in eGFR at 30, 60, and 90 days after discharge demonstrated adjusted hazard ratios (95% confidence intervals [CIs]) of ESRD of 5.60 (95% CI 4.06–7.71), 6.42 (95% CI 4.76–8.65), and 7.27 (95% CI 5.14–10.27), with corresponding estimates for 40% decline in eGFR of 6.98 (95% CI 5.21–9.35), 8.03 (95% CI 6.11–10.56), and 10.95 (95% CI 8.10–14.82). The authors propose that a 30% to 40% decline in eGFR measured 30 to 180 days after onset of AKI could be a useful intermediate end point for AKI clinical trials. However, additional studies are needed to analyze the magnitude of this effect between eGFR decline and ESRD in the context of a prospective clinical trial so that the impact of treatment on the intermediate outcomes of eGFR decline and the longer-term outcomes of ESRD and death can be tested. If the PRESERVE trial finds that falls in eGFR of 30% to 40% are connected with subsequent CKD progression, this trial would provide even stronger proof that such changes could be considered valuable clinical trial end points.[62]

DEATH

Mortality as a specific event is particularly challenging in not only AKI trials but also critical care trials. The causes of death in this population and whether these deaths are attributed to complications of AKI must be better defined. In the study by Grams et al., from a total of 161,185 patients who underwent major surgery at US Veterans Affairs hospitals, 19,025 AKI events defined by KDIGO were recorded,[66] 43,668 deaths occurred during a follow-up period compared with 787 cases of ESRD (the risk of death was more than 50-fold greater than the risk of ESRD).[66] This highlights the magnitude of the competing risk of death as a study end point. No therapeutic agent can be expected to affect all causes of death even if it has been shown to prevent or reverse kidney injury. A therapeutic agent may reduce all-cause mortality by reducing the chief cause or causes of death, but renal-specific deaths must be better delineated. The preference between all-cause events and AKI-specific events depends on whether the objective is only to reflect the benefit of the drug, in which case the end point should be as specific as expectations permit. However, if the purpose is to reflect net benefit, then a nonspecific (global cause) end point would better demonstrate that the benefit is not masked by adverse effects or noise from completely unrelated events. Although death is possibly the most vital patient-centered outcome, an AKI therapy that does not decrease the risk of death may have limited power to show benefit even in highly powered studies because of the degree of competing risk.

Key Points

1. In summary, several challenges exist for the vigorous design of end points for clinical trials in AKI. To improve outcomes for patients at risk of AKI or for patients with preexisting AKI we need to:
   a. Further develop AKI definitions to incorporate novel AKI biomarkers in conjunction with established markers of AKI, such as serum and urinary creatinine and urine output.
   b. Conduct clinical trials that trigger interventions on the basis of elevated injury biomarkers and in doing so, establishing the time course profile, reference ranges, and optimal utility of novel established biomarkers of AKI.
   c. Standardize novel biomarker elevations against robust clinical end points, including death, need for renal replacement therapy, and decline in estimated glomerular filtration rate.
   d. Incorporate new techniques such as Renal Angina Index and Furosemide Stress Test in the risk stratification of patients with AKI.
   e. Design pivotal large multicenter AKI trials to provide robust evidence that may support therapeutic effect and avoid smaller underpowered trials that may create only confusion among providers.
2. The international AKI community needs to unite in all aspects of trial design and implementation to ensure that barriers to AKI trials are overcome to beat this devastating disease.

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A complete reference list can be found online at ExpertConsult.com.

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