

End Points for Clinical Trials in Acute Kidney Injury

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Acute kidney injury (AKI) is an increasingly common and feared complication in hospitalized patients. The selection of appropriate primary and secondary end points is critical to the design and eventual success of clinical trials aimed at preventing and treating AKI. In this article, we provide an overview of AKI definitions and suggestions on the rational selection of end points for clinical trials in various settings, including the prevention of contrast-induced AKI, prevention of cardiac surgery-associated AKI, treatment of established AKI, and treatment of dialysis-requiring AKI.

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End points are critical in the design, execution, and eventual success of clinical trials for both early phases of drug development and eventual approval by regulatory agencies. In this article, we provide a brief history of the evolution of acute kidney injury (AKI) definitions and discuss considerations for kidney end points for interventional studies using 4 commonly encountered clinical scenarios.

AKI Epidemiology

A common and often devastating disorder, AKI complicates the hospital course of many patients.¹ Epidemiologic studies have consistently found that even small increases in serum creatinine (SCr) levels in hospitalized patients are associated with poor outcomes,^{2,3} whereas more severe AKI is associated with a markedly increased risk of death.^{2,4} Patients who survive an episode of AKI have prolonged lengths of stay⁵ and are at increased risk for rehospitalization,⁶ major adverse cardiac events,⁷ and chronic and end-stage kidney disease.⁸⁻¹¹ Thus, there is great interest in developing novel therapies to prevent and treat AKI. However, reaching a consensus on appropriate AKI definitions and kidney end points for clinical trials has proved challenging.

Markers Used in Renal and Nonrenal Acute Organ Failure

Definitions of AKI have consistently relied on acute changes in SCr levels and/or urine output. In [Table 1](#), we compare these “AKI” markers with markers used to define acute injury syndromes in nonrenal organs. Several parallels can be drawn comparing definitions of renal versus nonrenal organ injury. The P_{aO_2}/F_{iO_2} ratio (ratio of partial pressure of arterial oxygen to fraction of inspired oxygen), used to define acute respiratory distress syndrome, is a real-time physiologic marker, not unlike urine output. Similarly, international normalized ratio,

used to define acute liver failure, is a blood test that reflects abnormal organ function, not unlike an elevated SCr level. In contrast, neither physical examination nor imaging studies, both of which are critical in diagnosing acute stroke, are currently used in official definitions of AKI, and they are not likely to be used to define AKI in the near future. Similarly, elevated levels of direct injury markers (eg, troponin), the cornerstone of the definition of acute myocardial infarction, have not been incorporated into current AKI definitions, although this is an area of active research. Many experts have argued that the lack of a reliable direct injury marker used to define AKI—in other words, a “renal troponin”—is largely responsible for the dearth of progress made in AKI research as compared to acute myocardial infarction.^{12,13}

Novel AKI Biomarkers

A number of promising kidney injury biomarkers have been developed over the past decade, including urinary KIM-1 (kidney injury molecule-1), NGAL (neutrophil gelatinase-associated lipocalin), [TIMP-2] × [IGFBP7] (product of the urinary concentrations of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7), and others. Some of these biomarkers may have the potential to identify kidney injury earlier than changes in SCr levels (see reviews^{14,15}) and thus could be used to

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Table 1. Definitions of Acute Organ Injury

Organ System/ Clinical Syndrome	Definition of Injury	Major Injury Marker	Type of Marker
Cardiovascular/ acute MI	Increase and/or decrease of cardiac biomarker values with at least 1 value greater than the 99th percentile upper reference limit and at least one of the following: symptoms of ischemia, new significant ST-segment changes, or new LBBB; development of pathologic Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; intracoronary thrombus identified by angiography or autopsy ⁴⁶	Troponin	Direct injury
Pulmonary/ ARDS	Impairment of oxygenation ($PaO_2/FiO_2 \leq 300$) and all of the following: new or worsening respiratory symptoms during the past 7 d; bilateral opacities consistent with pulmonary edema on chest x-ray or computed tomographic scan; respiratory failure must not be fully explained by cardiac failure or fluid overload ⁴⁷	PaO_2/FiO_2	Physiologic
CNS/acute stroke	Brain, spinal cord, or retinal cell death attributable to ischemia based on: (1) pathologic, imaging, or other objective evidence of focal ischemic injury in a defined vascular distribution; or (2) clinical evidence of focal ischemic injury based on symptoms persisting ≥ 24 h or until death, and other causes excluded ¹¹	Magnetic resonance imaging + neurologic deficit	Imaging + physical exam
Hepatic/acute liver failure	Rapid deterioration of liver function, resulting in coagulopathy (INR ≥ 1.5) and encephalopathy in a patient without pre-existing liver disease ⁴⁸	INR + encephalopathy	Functional + physical exam
Renal/AKI	A SCr increase ≥ 0.3 mg/dL within 48 h or $\geq 50\%$ within 7 d, or need for RRT, or urine output < 0.5 mL/kg/h for ≥ 6 h ²⁰	Urine output + SCr	Physiologic + functional

Note: Conversion factor for SCr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CNS, central nervous system; exam, examination; FiO_2 , fraction of inspired oxygen; INR, international normalized ratio; LBBB, left bundle branch block; MI, myocardial infarction; RRT, renal replacement therapy; SCr, serum creatinine.

identify patients at risk for AKI. For the purpose of clinical trials, AKI biomarkers could be used as an enrichment strategy to maximize the AKI event rate and thereby facilitate clinical trial design (see¹⁶ for an example of one such biomarker strategy that was only modestly successful). Biomarkers can also serve as surrogate end points in clinical trials. Although low-density lipoprotein cholesterol level has been an acceptable surrogate end point for cardiovascular trials, the accumulated evidence base is massive, with tens of thousands of patients enrolled into randomized trials with low-density lipoprotein cholesterol measurements. For the purpose of a phase 3 trial in AKI prevention or treatment, the evidence base for AKI biomarkers is still far too premature to consider their use as surrogate end points. Thus, despite an increasing body of literature that these novel biomarkers are important predictors of adverse clinical outcomes,¹⁷ they cannot be endorsed at this time as primary kidney end points

for AKI trials, though their measurement as secondary end points or in early-phase studies should continue and will undoubtedly add to our understanding of AKI pathophysiology.

Heterogeneity of AKI Definitions

A number of consensus definitions have been proposed by expert panels (eg, RIFLE [Risk, Injury, Failure, Loss, End-stage renal disease],¹⁸ AKIN [AKI Network],¹⁹ and KDIGO [Kidney Disease: Improving Global Outcomes] criteria²⁰). Despite efforts at standardization, multiple AKI definitions continue to be used in clinical trials (Table 2). For example, contrast-induced AKI is often defined as a $\geq 25\%$ increase in SCr level within 48 hours,²¹ but several other definitions have been used in the epidemiology literature and in clinical trials.²² Furthermore, although consensus definitions of AKI include both SCr level and urine output-based criteria, most epidemiologic studies and AKI trials have focused exclusively on SCr levels, perhaps due to the difficulty of accurately

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