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FULL REVIEW

Differences in acute kidney injury ascertainment for clinical and preclinical studies

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ABSTRACT

Background. Acute kidney injury (AKI) is a common clinical condition directly associated with adverse outcomes. Several AKI biomarkers have been discovered, but their use in clinical and preclinical studies has not been well examined. This study aims to investigate the differences between clinical and preclinical studies on AKI biomarkers.

Methods. We performed a systematic review of clinical and preclinical interventional studies that considered AKI biomarkers in enrollment criteria and/or outcome assessment and described the main differences according to their setting, the inclusion of biomarkers in the definition of AKI and the use of biomarkers as primary or secondary end points.

Results. In the 151 included studies (76 clinical, 75 preclinical), clinical studies have prevalently focused on cardiac surgery (38.1%) and contrast-associated AKI (17.1%), while the majority of preclinical studies have focused on ether ischemia–reperfusion injury or drug-induced AKI (42.6% each). A total of 57.8% of clinical studies defined AKI using the standard criteria and only 19.7% of these studies used AKI biomarkers in the definition of renal injury. Conversely, the majority of preclinical studies defined AKI according to the increase in serum creatinine and blood urea nitrogen, and 32% included biomarkers in that definition. The percentage of both clinical and preclinical

studies with biomarkers as a primary end point has not significantly increased in the last 10 years; however, preclinical studies are more likely to use AKI biomarkers as a primary end point compared with clinical studies [odds ratio 2.31 (95% confidence interval 1.17–4.59); P = 0.016].

Conclusion. Differences between clinical and preclinical studies are evident and may affect the translation of preclinical findings in the clinical setting.

Keywords: acute kidney injury, biomarkers, end points, methods

INTRODUCTION

Acute kidney injury (AKI) is a common and serious clinical condition with an overall incidence estimated to be ∼2–3/1000 population, a rate very similar to that for myocardial infarction [1]. Critically ill patients who develop AKI have worse outcomes, such as higher mortality, prolonged hospitalization and increased risk for progression to cardiovascular events and chronic kidney disease (CKD) [2, 3]. Even small increases in serum creatinine may greatly impact long-term outcomes [4]. Despite intense investigation, therapeutic interventions to limit the development and impact of AKI have not been successful. This may be related, at least in part, to the difficulties in identifying patients who are at high risk for AKI or to detect kidney damage early when it may be more treatable [5]. Current AKI definitions are based on changes in serum creatinine and urine output—the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria [6] for example. However, serum creatinine is a late indicator of AKI and is often influenced by factors such as age, muscle mass, protein intake and gender [7]. Urine output may be more sensitive but is less specific for AKI unless severely decreased. Over the last decade, there has been extensive research for novel biomarkers of kidney injury for timely identification of AKI, to allow appropriate interventions and to improve outcomes [8]. The most promising biomarkers can be separated into different classes: (i) tubular cell enzymes released after renal injury, (ii) inflammatory mediators or cytokines released by kidney-specific cells or by inflammatory cells after damage and (iii) low molecular weight proteins, which either are filtered freely in the glomeruli and not adequately reabsorbed or digested by injured tubular cells or are released by injured tubular cells following acute damage. More recently, cell cycle arrest biomarkers, like tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7) have been validated as indicators of renal damage and their product can predict the onset of severe AKI within 12 h better than other known biomarkers [9]. AKI biomarkers may help explain the molecular mechanisms of AKI and could perhaps be used as phenotyping tools in clinical practice to identify patients with specific AKI etiologies or to predict long-term outcomes [8, 10]. The adoption of novel AKI biomarkers into clinical practice may depend in part on whether therapies can be directly linked to biomarker signals. As such, it is vital to understand whether these markers are being incorporated into clinical and preclinical studies. The purpose of this systematic review is to evaluate the use of AKI biomarkers in preclinical and clinical studies, analyzing the differences in how these markers were used in different settings.

MATERIALS AND METHODS

Data source and search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Two different databases (PubMed and Ovid MEDLINE) were searched for articles without language restriction up to February 2016 through a focused search strategy (Supplementary data, Table S1). References from relevant studies published on the same topic were screened to identify additional studies. The search was designed and performed by two authors (M.F. and J.A.K.).

Study selection

We included any clinical and preclinical interventional study in which novel AKI biomarkers were used for enrollment criteria and/or for outcome assessment. Preclinical interventional studies were defined as studies that tested a drug, procedure or other medical treatment using *in vivo* (animals) or *in vitro* models (cell culture) before trials were carried out in humans. Clinical interventional studies are identified as prospective studies or randomized clinical trials designed to test the safety and effectiveness of a new drug, device or treatment in humans. Studies were excluded if (i) AKI biomarkers were evaluated as diagnostics, (ii) they did not focus on AKI, (iii) they dealt with AKI but did not report data about AKI biomarkers and (iv) they were not an interventional design. Case reports, reviews, editorials and letters were excluded as well. Study selection was independently performed by two authors (M.F. and G.C.) using the EndNote bibliography manager to screen the citations based on titles and abstracts and then to evaluate the full text of the articles previously screened. Discrepancies in judgment were solved collegially.

Data extraction and synthesis

Data extraction and analysis were performed by two authors (M.F. and J.A.K.). The selected studies were divided into preclinical and clinical and in each study we analyzed the following key questions: (i) Are biomarkers used in the definition of AKI? (ii) Are there differences in the setting in which clinical and preclinical studies were based? (iii) Are biomarkers used as primary or secondary end points in these studies? We also compared studies with similar exposures and/or interventions but with divergent outcomes between the preclinical and clinical setting. From each study, the following information was extracted: first author, year of publication, sample size, population or animal setting, definition of AKI and what biomarker was evaluated and how (primary or secondary end point). We evaluated the proportions of studies that answered these specific questions and the comparison of their proportion between clinical and preclinical studies, using the χ^2 test and logistic regression. Statistical analyses were performed using SPSS (version 21; IBM, Armonk, NY, USA).

RESULTS

Search results

The flow diagram of the study selection process is shown in Figure 1. The primary search revealed 5622 publications from the two databases (22 additional articles were found by searching bibliographies), which were evaluated for eligibility by title and abstract. First, 4996 articles were excluded because of search overlap ($n = 2435$); because they were case reports, reviews, editorials or letters ($n = 1147$) or because they did not deal with AKI topics ($n = 1017$) or AKI biomarkers ($n = 397$). There were 626 publications evaluated in detail. Among these, 475 were excluded because they were not based on an interventional design. A total of 151 studies were therefore included in this analysis (76 clinical, 75 preclinical studies). The majority of preclinical studies focused on animals [$n = 72$ (96%)], while only three studies (45) were performed using *in vitro* models [11–13].

Time frame and settings of clinical and preclinical studies

The majority of selected clinical trials or prospective studies were dated after 2007, while only four studies before this date considered AKI biomarkers in their analysis. Conversely, preclinical studies are more equally distributed over time. The settings in which the selected studies are focused varied significantly between clinical and preclinical studies and are summarized in Tables 1 and 2, respectively. Clinical trials and prospective studies were mainly focused on surgical patients, particularly in patients undergoing cardiac surgery [14–22] (cardiopulmonary bypass [23–29], coronary artery bypass graft [30–37], valvular heart surgery [38–40] or other invasive procedures [41–43]), accounting for 38.1% of the selected clinical studies. Contrast-associated AKI was the next most common focus of prospective studies or clinical trials (17.1%). Trials in contrast-associated AKI examined volume expansion [74, 75], *N*-acetylcysteine [50, 76] or sodium bicarbonate [42, 77] in preventing or reducing AKI after procedures [78, 79] such as coronary angiography [41, 80–85]. Other clinical studies focused on drug-induced AKI (7.9%), particularly related to the nephrotoxic effects of chemotherapic drugs (cisplatin, methotrexate) [44–49] in critically ill patients [61–65], particularly septic patients (13.1 and 2.6%, respectively) [56, 66–70], kidney and liver transplantation (7.8%) [51–55] or after specific procedures (13.1) [58–60, 70–73, 86–89].

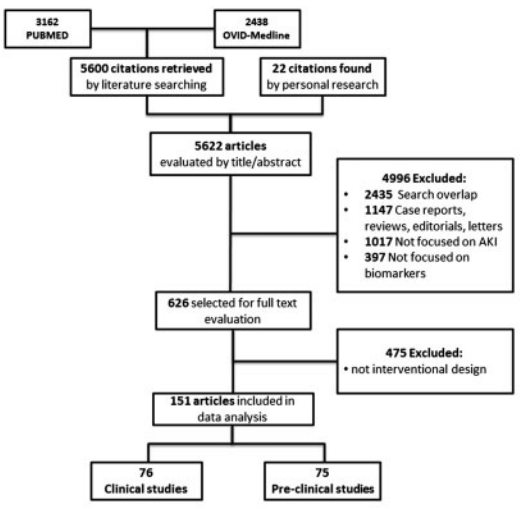

FIGURE 1: Flow diagram for the study selection process.

In contrast, animal models of AKI were frequently focused on several models of renal ischemia–reperfusion injury (42.6% of selected preclinical studies) [12, 13, 90–119]. The number of preclinical studies using AKI models induced by nephrotoxic agents (cisplatin, paraquat, gentamicin, vancomycin, herbicide, anesthetic drugs, ketoprofen and other toxics) is significantly greater than in clinical studies (42.6 versus 7.9%; $P < 0.001$) [105, 112, 114, 120–149]. Similarly, a greater proportion of preclinical studies focused on sepsis-associated AKI compared with clinical studies (10.6 versus 2.6%; $P = 0.04$) [150–157]. However, relatively few preclinical studies considered AKI biomarkers in the surgical setting (5 versus 39%; $P < 0.001$) [158, 159] or in contrast-induced models of AKI (2.6 versus 17.1%; $P = 0.003$) [160, 161].

Definition of AKI

The definition of AKI was highly variable between interventional studies in the clinical and preclinical setting. As described in Table 3, 57.8% of clinical studies defined AKI according to international consensus criteria, such as the KDIGO guideline criteria [6], Risk, Injury, Failure. Loss and End-stage kidney disease (RIFLE) criteria [162] or Acute Kidney Injury Network (AKIN) criteria [163]. A few clinical studies (23.6%) defined AKI by the increment of blood urea nitrogen (BUN) or serum creatinine that did not meet these criteria. The aim of these studies was to evaluate the possible role of these biomarkers in specific settings in which AKI diagnosis was performed using the standard criteria. The use of AKI biomarkers in the definition of renal damage was limited to 19.7% of these studies and neutrophil gelatinase–associated lipocalin (NGAL) was the main biomarker used in these studies to define AKI (11.3%). Balkanay *et al.* [32] investigated the positive effect of dexmedotomidine on renal injury in patients after coronary artery bypass graft (CABG): in the early postoperative period, the development of AKI, as determined by measurements of blood NGAL levels (>149 ng/mL), was significant and dose dependent. Sahraei *et al.* [55] analyzed the protective effects of *N*-acetylcysteine alone or in combination with vitamin C to alleviate kidney injury in living donor kidney transplantation by measuring interleukin-18 (IL-18) and NGAL levels: no significant differences in delayed graft function (DGF) or NGAL values were found between the two groups. Coca *et al.* [14] analyzed the relationship between preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and AKI in patients undergoing cardiac surgery. The authors defined AKI as functional (based on changes in serum creatinine) or structural [diagnosed by postoperative levels of four urinary biomarkers of tubular damage, NGAL, IL-18, kidney injury molecule-1 (KIM-1) and liver-type fatty acid–binding protein (L-FABP)] and described that across three different levels of drug exposure there was an increase in functional AKI while no differences in structural AKI were found. Yousefshahi *et al.* [34] evaluated the effect of

Table 1. Summary of settings for clinical interventional studies

Clinical studies							
Setting	Study	Year	No. of patients	Setting	Study	Year	No.
Cardiac surgery	Coca *et al.* [14]	2013	1594	**Drug-induced AKI**	Gaspari *et al.* [44]	2010	24
	De Seigneux *et al.* [15]	2012	80		Lin *et al.* [45]	2013	33
	Ejaz *et al.* [16]	2013	26		Seker *et al.* [46]	2015	42
	Foroughi *et al.* [17]	2014	159		Shahbazi *et al.* [47]	2015	24
	Lipcsey *et al.* [18]	2014	83		Ylinen *et al.* [48]	2014	20 (children)
	Prowle *et al.* [19]	2012	100		Shinke *et al.* [49]	2015	11
	Tasanarong *et al.* [20]	2013	100	**Transplantation**	Ataei *et al.* [50]	2015	80
	Wagener *et al.* [21]	2008	369		Ojeda *et al.* [51]	2013	20
	Zarbock *et al.* [22]	2015	240		Sureshkumar *et al.* [52]	2012	72
	Matata *et al.* [23]	2015	199		Tsuchimoto *et al.* [53]	2014	31
	Basu *et al.* [24]	2014	345 (children)		Coupes *et al.* [54]	2015	40
	Meersch *et al.* [25]	2014	51 (children)		Sahraei *et al.* [55]	2015	84
	Haase *et al.* [26]	2013	350				
	Adademir *et al.* [27]	2012	85				
	Ricci *et al.* [28]	2011	80 (children)				
	Westhuyzen *et al.* [29]	1994	21				
	Deininger *et al.* [30]	2015	120				
	Gallagher *et al.* [31]	2015	86				
	Balkanay *et al.* [32]	2015	295				
	Dardashti *et al.* [33]	2014	75				
	Yousefshahi *et al.* [34]	2013	40				
	Barkhordari *et al.* [35]	2011	28				
	Oh *et al.* [36]	2012	71				
	Song *et al.* [37]	2015	117				
	Choi *et al.* [38]	2011	76				
	Kim *et al.* [39]	2013	98				
	Torregrosa *et al.* [40]	2015	60				
	Xinwei *et al.* [41]	2009	228				
	Brulotte *et al.* [42]	2013	34				
	Pedersen *et al.* [43]	2012	113 (children)				
Sepsis	Leaf *et al.* [56]	2014	67	**General surgery**	Lahoud *et al.* [58]	2015	49
	Pickkers *et al.* [57]	2012	36		Orsolya *et al.* [59]	2015	40
					Kharasch *et al.* [60]	1997	73
Critically ill patients	Boldt *et al.* [61]	1996	28	**Shockwave lithotripsy**	Daggulli *et al.* [70]	2016	29
	Lahiri *et al.* [62]	2014	52		Kardakos *et al.* [71]	2014	37
	Nymo *et al.* [63]	2012	1415		Fahmy *et al.* [72]	2013	60
	Yang *et al.* [64]	2010	100		Hatipoglu *et al.* [73]	2014	60
	Oh *et al.* [65]	2014	95				
	Schilder *et al.* [66]	2014	42				
	Srisawat *et al.* [67]	2011	76				
	Endre *et al.* [68]	2010	529				
	Mayeur *et al.* [69]	2010	10				
Contrast-induced AKI	Xinwei *et al.* [41]	2009	228	**Others**	Boertien *et al.* [86]	2015	27
	Brulotte *et al.* [42]	2013	34		Fassett *et al.* [87]	2012	82
	Ribichini *et al.* [74]	2013	38		Junglee *et al.* [88]	2013	10
	Torigoe *et al.* [75]	2013	122		Oboho *et al.* [89]	2013	132
	Ataei *et al.* [50]	2015	80				
	Poletti *et al.* [76]	2007	87				
	Kooiman *et al.* [77]	2015	511				
	Duan *et al.* [78]	2013	60				
	Gok *et al.* [79]	2013	144				
	Akrawinthawong *et al.* [80]	2015	63				
	Katoh *et al.* [81]	2014	25				
	Tasanarong *et al.* [82]	2013	130				
	Yin *et al.* [83]	2013	204				
	Igarashi *et al.* [84]	2013	60				
	Ling *et al.* [85]	2008	150				

hypertonic saline infusion versus normal saline on serum NGAL and cystatin C levels in 40 patients undergoing CABG: in this study, AKI was defined by a >0.3 mg/dL increase in serum creatinine, by serum cystatin C levels >1.16 mg/dL, or by a significant increase in serum NGAL (>400 ng/mL). The authors did not describe significant differences in NGAL levels between the hypertonic saline group and the normal saline group. Ejaz *et al.* [16] defined the effect of rasburicase, uric acid–lowering

Table 2. Summary of settings for preclinical interventional studies

Preclinical studies							
Setting	Study	Year	No.	Setting	Study	Year	No.
Ischemia–reperfusion injury	Zang *et al.* [12]	2014	NRK-52E cells	**Drug-induced AKI**	Zager *et al.* [105]	2012	84 rats
	Koga *et al.* [13]	2012	Rats		Dennen *et al.* [112]	2010	Mice
	Zhang *et al.* [90]	2015	50 rats		Zhou *et al.* [114]	2006	167 rats
	Youssef *et al.* [91]	2015	30 rats		Kim *et al.* [120]	2016	18 rats
	Visnagri *et al.* [92]	2015	Rats		Shin *et al.* [121]	2014	Rats
	Speir *et al.* [93]	2015	24 rats		Tan *et al.* [122]	2015	Rats
	Mei *et al.* [94]	2015	30 piglets		Luo *et al.* [123]	2014	15 rats
	Duan *et al.* [95]	2105	52 swine		Wunnapuk *et al.* [124]	2014	16 rats
	Calistro Neto *et al.* [96]	2015	40 rats		Cardenas *et al.* [125]	2013	36 rats
	Si *et al.* [97]	2014	24 rats		Hanna *et al.* [126]	2013	18 rats
	Oron *et al.* [98]	2014	54 rats		Maguire *et al.* [127]	2013	120 rats
	Koo *et al.* [99]	2014	C57BL/6 mice		Chen *et al.* [128]	2013	18 rats
	Hang *et al.* [100]	2014	32 piglets		Sinha *et al.* [129]	2013	18 rats
	Gardner *et al.* [101]	2014	30 pigs		Nozaki *et al.* [130]	2012	21 mice
	Bussmann *et al.* [102]	2014	32 rats		Vinken *et al.* [131]	2012	50 rats
	Woodson *et al.* [103]	2013	58 rats		Efrati *et al.* [132]	2012	94 rats
	Sohotnik *et al.* [104]	2013	21 rats		Hosolata *et al.* [133]	2012	24 rats
	Zager *et al.* [105]	2012	84 rats		Efrati *et al.* [134]	2012	88 rats
	Sanchez-Pozos *et al.* [106]	2012	62 rats		Groebler *et al.* [135]	2012	Rats
	Hosgood *et al.* [107]	2012	Pigs		Pawar *et al.* [136]	2012	8 mice
	Jochmans *et al.* [108]	2011	6 porcine		Dodiya *et al.* [137]	2011	Rats
	Ko *et al.* [109]	2010	9 mice		Lee *et al.* [138]	2011	Mice
	Kim *et al.* [110]	2010	30 rats		Raekallio *et al.* [139]	2010	12 sheep
	Hu *et al.* [111]	2010	Rats		Kramer *et al.* [140]	2009	64 rats
	Dennen *et al.* [112]	2010	Mice		Zhou *et al.* [141]	2008	Rats
	He *et al.* [113]	2008	IL-18 BP Tg mice		Naghibi *et al.* [142]	2007	Rats
	Zhou *et al.* [114]	2006	167 rats		Negishi *et al.* [143]	2007	Mice
	Nitescu *et al.* [115]	2006	53 rats		Mishra *et al.* [144]	2004	35 mice
	Baker *et al.* [116]	2006	42 pigs		Ziai *et al.* [145]	2003	Rats
	Burne-Taney *et al.* [117]	2003	Mice		Usuda *et al.* [146]	1998	Rats
	Gueler *et al.* [118]	2002	54 rats		Xie *et al.* [147]	2001	10 mice
	Seth *et al.* [119]	2000	24 rats		Yanagisawa *et al.* [148]	1998	30 rats
					Guo *et al.* [149]	2015	84 rats
Sepsis	Otto *et al.* [150]	2015	191 rats	**General surgery**	Li *et al.* [158]	2015	90 rabbits
	Wang *et al.* [151]	2015	12 mice	**Cardiac surgery**	Patel *et al.* [159]	2011	24 pigs
	Lee *et al.* [152]	2013	20 rats				
	Zhou *et al.* [153]	2014	60 rats				
	Han *et al.* [154]	2012	48 rats				
	Knotek *et al.* [155]	2001	Mice				
	Li *et al.* [156]	2008	30 mice				
	Wang *et al.* [157]	2006	17 pigs				
Contrast-induced AKI	Li *et al.* [160]	2014	54 rats	**Others**	Bobek *et al.* [11]	2010	*In vitro*
	Schultz *et al.* [161]	1992	44 rabbits		Guo *et al.* [149]	2015	84 rats

therapy, on the prevention of AKI in patients undergoing cardiovascular surgery: AKI was defined according to AKIN criteria or by the increases in urinary NGAL levels and urinary IL-18. While no differences in serum creatinine were found between the two groups (rasburicase versus placebo), active treatment resulted in less evidence of renal structural damage as shown by urinary NGAL concentrations.

Cystatin C, IL-18 and KIM-1 were included in the AKI definition in several clinical studies. Yin *et al.* [83] described the incidence of contrast-associated AKI, defined as an increase in serum cystatin C concentration of $\geq$10% from the baseline value within 72 h after coronary intervention, and the preventive effect of probucol in this setting. Kardaros *et al.* [71] investigated the impact of shockwave lithotripsy on acute renal damage, considering the variations in NGAL, cystatin C and IL-18 levels before and after the procedure as indicators of AKI. Finally, a clinical trial analyzed the effect of remote ischemic preconditioning in alleviating contrast-induced AKI in patients with moderate CKD, using urinary L-FABP as an AKI indicator [84].

When considering preclinical interventional studies (Table 4), we found differences in the definition of AKI compared with that in clinical studies. The majority of preclinical studies, in fact, did not include standard AKI definitions previously reported (KDIGO, RIFLE or AKIN criteria) (9.3 versus 57.8%; $P < 0.001$ comparing preclinical versus clinical studies) and 80% of these studies defined AKI by an unspecified increment of serum creatinine or BUN [13, 90–93, 97–99, 105, 112–

Table 3. AKI definition among clinical interventional studies

Clinical studies							
	Study	Year	No. of patients		Study	Year	No.
International consensus criteria							
RIFLE criteria	Foroughi *et al.* [17]	2014	159	**BUN**	Shinke *et al.* [49]	2015	11
	Prowle *et al.* [19]	2012	100	**AKI biomarkers**			
	Meersch *et al.* [25]	2014	51 (children)	NGAL	Coca *et al.* [14]	2013	1594
	Ricci *et al.* [28]	2011	80 (children)		Ejaz *et al.* [16]	2013	26
	Dardashti *et al.* [33]	2014	75		Adademir *et al.* [27]	2012	85
	Torregrosa *et al.* [40]	2015	60		Balkanay *et al.* [32]	2015	295
	Pedersen *et al.* [43]	2012	113 (children)		Yousefshahi *et al.* [34]	2013	40
	Ataei *et al.* [50]	2015	80		Gaspari *et al.* [44]	2010	24
	Lin *et al.* [45]	2013	33		Seker *et al.* [46]	2015	42
	Yang *et al.* [64]	2010	100		Sahraei *et al.* [55]	2015	84
	Mayeur *et al.* [69]	2010	10		Kardakos *et al.* [71]	2014	37
	Orsolya *et al.* [59]	2015	40				
AKIN criteria	De Seigneux *et al.* [15]	2012	80	IL-18	Ejaz *et al.* [16]	2013	26
	Ejaz *et al.* [16]	2013	26		Adademir *et al.* [27]	2012	85
	Wagener *et al.* [21]	2008	369		Ojeda *et al.* [51]	2013	20
	Deininger *et al.* [32]	2015	120		Kardakos *et al.* [71]	2014	60
	Barkhordari *et al.* [35]	2011	28	Cystatin C	Yousefshahi *et al.* [34]	2013	40
	Song *et al.* [37]	2015	117		Torigoe *et al.* [75]	2013	122
	Choi *et al.* [38]	2011	76		Poletti *et al.* [76]	2007	87
	Brulotte *et al.* [42]	2013	34		Yin *et al.* [83]	2013	204
	Ataei *et al.* [50]	2015	80		Kardakos *et al.* [71]	2014	37
	Gok *et al.* [79]	2013	204				
	Shahbazi *et al.* [47]	2015	24				
	Pickkers *et al.* [57]	2012	36				
	Tsuchimoto *et al.* [53]	2014	31				
	Orsolya *et al.* [59]	2015	40				
	Junglee *et al.* [88]	2013	10				
KDIGO criteria	Coca *et al.* [14]	2013	1594	KIM-1	Ojeda *et al.* [51]	2013	20
	Tasanarong *et al.* [20]	2013	100		Hatipoglu *et al.* [73]	2014	60
	Zarbock *et al.* [22]	2015	240	L-FABP	Igarashi *et al.* [84]	2013	60
	Matata *et al.* [23]	2015	199				
	Basu *et al.* [24]	2014	345 (children)				
	Gallagher *et al.* [31]	2015	86				
	Yousefshahi *et al.* [34]	2013	40				
	Kim *et al.* [39]	2013	98				
	Ribichini *et al.* [74]	2013	60				
	Duan *et al.* [78]	2013	38				
	Akrawinthawong *et al.* [80]	2015	63				
	Katoh *et al.* [81]	2013	130				
	Tasanarong *et al.* [82]	2013	130				
	Nymo *et al.* [63]	2012	1415				
	Leaf *et al.* [56]	2014	67				
	Lahoud *et al.* [58]	2015	49				
Serum creatinine	Haase *et al.* [26]	2013	350	**Not reported**	Lipcsey *et al.* [18]	2014	83
	Westhuyzen *et al.* [29]	1994	21		Lahiri *et al.* [62]	2014	52
	Xinwei *et al.* [41]	2009	228		Nymo *et al.* [63]	2012	1415
	Torigoe *et al.* [75]	2013	122		Oh *et al.* [65]	2014	95
	Poletti *et al.* [76]	2007	87		Schilder *et al.* [66]	2014	42
	Kooiman *et al.* [77]	2015	511		Srisawat *et al.* [67]	2011	76
	Ling *et al.* [85]	2008	150		Fahmy *et al.* [72]	2013	60
	Gaspari *et al.* [44]	2010	24		Boertien *et al.* [86]	2015	27
	Ylinen *et al.* [48]	2014	20 (children)		Fassett *et al.* [87]	2012	88
	Shinke *et al.* [49]	2015	11		Oboho *et al.* [89]	2013	132
	Boldt *et al.* [61]	1996	28				
	Endre *et al.* [68]	2010	529				
	Sureshkumar *et al.* [52]	2012	72				
	Coupes *et al.* [54]	2015	40				
	Kharasch *et al.* [60]	1997	73				

Table 4. AKI definitions among preclinical interventional studies

Preclinical studies							
	Study	Year	No.		Study	Year	No.
Serum creatinine	Koga *et al.* [13]	2012	Rats	**BUN**	Koga *et al.* [13]	2012	Rats
	Zhang *et al.* [90]	2015	50 rats		Zhang *et al.* [90]	2015	50 rats
	Youssef *et al.* [91]	2015	30 rats		Youssef *et al.* [91]	2015	30 rats
	Visnagri *et al.* [92]	2015	Rats		Visnagri *et al.* [92]	2015	Rats
	Speir *et al.* [93]	2015	24 rats		Speir *et al.* [93]	2015	24 rats
	Si *et al.* [97]	2015	24 rats		Si *et al.* [97]	2015	24 rats
	Oron *et al.* [98]	2014	54 rats		Oron *et al.* [98]	2014	54 rats
	Koo *et al.* [99]	2014	C57BL/6 mice		Koo *et al.* [99]	2014	C57BL/6 mice
	Gardner *et al.* [101]	2014	30 pigs		Zager *et al.* [105]	2012	84 rats
	Bussmann *et al.* [102]	2014	32 rats		Dennen *et al.* [112]	2010	Mice
	Sanchez-Pozos *et al.* [106]	2012	62 rats		He *et al.* [113]	2008	IL-18 BP Tg mice
	Hosgood *et al.* [107]	2012	Pigs		Zhou *et al.* [114]	2006	167 rats
	Jochmans *et al.* [108]	2011	6 pigs		Baker *et al.* [116]	2006	42 pigs
	Dennen *et al.* [112]	2010	Mice		Tan *et al.* [122]	2015	Rats
	He *et al.* [113]	2008	IL-18 BP Tg mice		Efrati *et al.* [134]	2012	88 rats
	Zhou *et al.* [114]	2006	167 rats		Lee *et al.* [138]	2011	Mice
	Nitescu *et al.* [115]	2006	53 rats		Zhou *et al.* [141]	2008	Rats
	Baker *et al.* [116]	2006	42 pigs		Naghibi *et al.* [142]	2007	Rats
	Burne-Taney *et al.* [117]	2003	Mice		Li *et al.* [158]	2015	90 rabbits
	Gueler *et al.* [118]	2002	54 rats	**AKI biomarkers**			
	Tan *et al.* [122]	2015	Rats	NGAL	Zang *et al.* [12]	2014	NRK-52E cells
	Wunnapuk *et al.* [124]	2014	16 rats		Mei *et al.* [94]	2015	30 pigs
	Cardenas *et al.* [125]	2013	36 rats		Calistro Neto *et al.* [96]	2015	40 rats
	Hanna *et al.* [126]	2013	18 rats		Si *et al.* [97]	2014	24 rats
	Chen *et al.* [128]	2013	18 rats		Woodson *et al.* [103]	2013	58 rats
	Sinha *et al.* [129]	2013	18 rats		Sohotnik *et al.* [104]	2013	21 rats
	Groebler *et al.* [135]	2012	Rats		Kim *et al.* [110]	2010	30 rats
	Lee *et al.* [138]	2011	Mice		Luo *et al.* [123]	2014	15 rats
	Kramer *et al.* [140]	2009	64 rats		Efrati *et al.* [132]	2012	94 rats
	Naghibi *et al.* [142]	2007	Rats		Pawar *et al.* [136]	2012	8 mice
	Ziai *et al.* [145]	2003	Rats		Mishra *et al.* [144]	2004	35 mice
	Usuda *et al.* [146]	1998	Rats		Guo *et al.* [149]	2015	84 rats
	Yanagisawa *et al.* [148]	1998	30 rats		Otto *et al.* [150]	2015	191 rats
	Guo *et al.* [149]	2015	84 rats		Lee *et al.* [152]	2013	20 rats
	Otto *et al.* [150]	2015	191 rats		Han *et al.* [154]	2012	48 rats
	Knotek *et al.* [155]	2001	Mice		Li *et al.* [160]	2014	54 rats
	Li *et al.* [156]	2008	30 mice				
	Li *et al.* [158]	2015	90 rabbits				
	Patel *et al.* [159]	2011	24 pigs				
International consensus criteria							
RIFLE criteria	Duan *et al.* [95]	2015	52 swine	KIM-1	Sohotnik *et al.* [104]	2013	21 rats
	Hang *et al.* [100]	2014	32 piglets		Luo *et al.* [123]	2014	15 rats
	Dennen *et al.* [112]	2010	Mice		Vinken *et al.* [131]	2012	50 rats
	Wang *et al.* [151]	2015	17 pigs		Lee *et al.* [138]	2013	20 rats
	Zhou *et al.* [153]	2014	60 rats		Li *et al.* [158]	2012	90 rabbits
AKIN criteria	Hang *et al.* [100]	2014	32 piglets	L-FABP	Negishi *et al.* [143]	2007	Mice
	Kim *et al.* [120]	2016	18 rats				
KDIGO criteria	Hang *et al.* [100]	2014	32 piglets	Klotho	Hu *et al.* [111]	2010	Rats
Cystatin C	Mei *et al.* [94]	2015	30 pigs	**Not reported**	Bobek *et al.* [11]	2010	*In vitro*
	Si *et al.* [97]	2014	24 rats		Ko *et al.* [109]	2010	9 mice
	Oron *et al.* [98]	2014	54 rats		Shin *et al.* [121]	2014	Rats
	Woodson *et al.* [103]	2013	58 rats		Maguire *et al.* [127]	2013	120 rats
	Efrati *et al.* [132]	2012	94 rats		Nozaki *et al.* [130]	2012	21 mice
	Efrati *et al.* [134]	2012	88 rats		Hosolata *et al.* [133]	2012	24 rats
					Dodiya *et al.* [137]	2011	Rats
					Raekallio *et al.* [139]	2010	12 sheeps
					Xie *et al.* [147]	2001	10 mice
					Wang *et al.* [151]	2006	12 mice

NA, not available.

114, 116, 122, 134, 138, 141, 142, 150, 158]. Renal histology was used in 59 preclinical studies (78.6%) to assess the presence and the severity of renal damage. About one-third of preclinical studies included novel biomarkers in the definition of AKI, although this difference compared with clinical studies did not reach statistical significance (32 versus 19.7%; P = 0.06). Calistro-Neto *et al.* [96] evaluated the effect of parecoxib on renal function by measuring serum NGAL in an ischemia-induced AKI model in the rat. Luo *et al.* [123] analyzed gentamicin-induced nephrotoxicity in rats, focusing on the expression of KIM-1 and NGAL: repeated administration of gentamicin resulted in a dose- and time-dependent increase in these two markers of acute renal damage and a correlation between histopathological alterations and changes in gene and protein expressions was found. Han *et al.* [154] investigated the temporal variations in NGAL levels in a rat model of AKI induced by lipopolysaccharide, showing a significant up-regulation in NGAL mRNA that correlated with urinary NGAL and the degree of renal injury. Bussmann *et al.* [102], by measuring plasma NGAL, urinary NGAL, KIM-1, IL-18 and serum creatinine, did not find a protective effect of allopurinol on kidney function in uninephrectomized rats subjected to ischemia–reperfusion injury. Sohotnik *et al.* [104] demonstrated the nephroprotective effects of tadalafil, a phosphodiesterase-5 inhibitor, in an experimental model of renal ischemia–reperfusion injury, showing significant differences in functional (glomerular filtration rate, urinary NGAL and KIM-1) and histological parameters of acute kidney damage between untreated and treated groups.

Furthermore, preclinical studies mainly evaluated the differences in biomarker levels between baseline and after specific interventions and did not use specific cut-offs to define AKI. Conversely, about half of clinical studies reported specific cut-off values, although cut-offs were not consistent between studies. For example, Balkanay *et al.* [32] defined AKI as serum NGAL >149 ng/mL [32], while Yousefshahi *et al.* [34] used a cut-off that was much higher (>400 ng/mL).

We also compared preclinical and clinical studies in specific settings; in studies on sepsis (eight preclinical, two clinical), only three preclinical studies included biomarkers in the definition of AKI [150, 152, 154]. Among studies focused on a specific drug exposure (cisplatin-associated AKI; 13 preclinical and 5 clinical), only 3 preclinical studies considered AKI biomarkers in the AKI definition [131, 143, 144] and no clinical study did. Focusing on studies on contrast-associated AKI with the same exposure (iodinated contrast media) and interventions (hydration and *N*-acetylcysteine for preventing AKI; one preclinical and four clinical), we found that two clinical and one preclinical study addressed this point [75, 76, 160]. Among these studies, focusing on studies that analyzed the same biomarker (urinary NGAL) and with divergent outcomes (one preclinical [160] and two clinical studies [77, 82]), differences in the definition of AKI are evident (the two clinical studies used serum creatinine and KDIGO criteria to define AKI, while the preclinical study included urinary NGAL).

Overall, the number of studies including biomarkers in the definition of AKI increased in the last 6 years in both the clinical and preclinical setting, reaching 20–30% of the selected studies by year (Figure 2). The odds of including biomarkers in the definition of AKI in preclinical studies is 2.14 times higher than in clinical studies [95% confidence interval (CI) 1–4.6; P = 0.04], while no significant increase over the years was described.

Use of AKI biomarkers as primary or secondary end points

The incidence of AKI, AKI mortality and recovery at specified time points were often used as primary end points in clinical trials or prospective studies focusing on AKI. In these studies, AKI biomarkers were often included in secondary outcomes (48.6% of selected studies) to test their associations with specific conditions, such as cardiac surgery–associated AKI and sepsis-induced AKI. Zarbock *et al.* [22] investigated whether remote ischemic preconditioning reduced the rate and severity of AKI in cardiac surgical patients: the primary end point was the rate of AKI, while secondary end points were need of dialysis, mortality and change in AKI biomarkers. They found that remote ischemic preconditioning significantly reduced AKI incidence as well as ameliorated the increase in NGAL and TIMP-2 × IGFBP7 after cardiac surgery. Similarly, Gallagher *et al.* [31] investigated the effect of remote ischemic preconditioning in 86 patients with AKI undergoing cardiac surgery, evaluating the incidence of AKI as the primary end point and the comparison with several biomarkers of renal injury as the secondary outcome. Tasanarong *et al.* [20] examined the role of erythropoietin (EPO) in reducing the incidence of cardiac surgery–associated AKI and evaluated possible reductions in urinary NGAL levels in patients who received the treatment. Prowle *et al.* [164] tested whether short-term perioperative atorvastatin administration could reduce AKI incidence: the primary outcome was the detection of a limited increase in postoperative serum creatinine after atorvastatin therapy, while secondary outcomes included AKI incidence, changes in urinary NGAL, the need for renal replacement therapy (RRT), length of hospitalization and mortality.

More than half of clinical interventional studies included AKI biomarkers in the primary end point of the study (51.4% of selected studies) (Table 5). Kooiman *et al.* [77] analyzed KIM-1 and NGAL in patients with CKD enrolled in a trial on hydration regimens to prevent contrast-induced AKI and found that the excretion of these biomarkers was unaffected by contrast medium in patients with and without AKI. DeSeigneux *et al.* [15] tested the hypothesis that different doses of EPO administered to patients in the intensive care unit after cardiac surgery would reduce the incidence of AKI: the primary outcome was the change in urinary NGAL concentration from baseline and 48 h after EPO administration, while secondary outcomes were changes in traditional renal function markers (serum creatinine). Oh *et al.* [65] analyzed the effect of high-dose statin in patients hospitalized for acute heart failure: the primary outcome was the change in the level of biomarkers related to inflammation and renal injury (cystatin C). Choi *et al.* [38] found no significant differences in AKI incidence in 76 patients undergoing valvular heart surgery randomly assigned to either remote ischemic preconditioning or a control group. In this study, the primary end points were

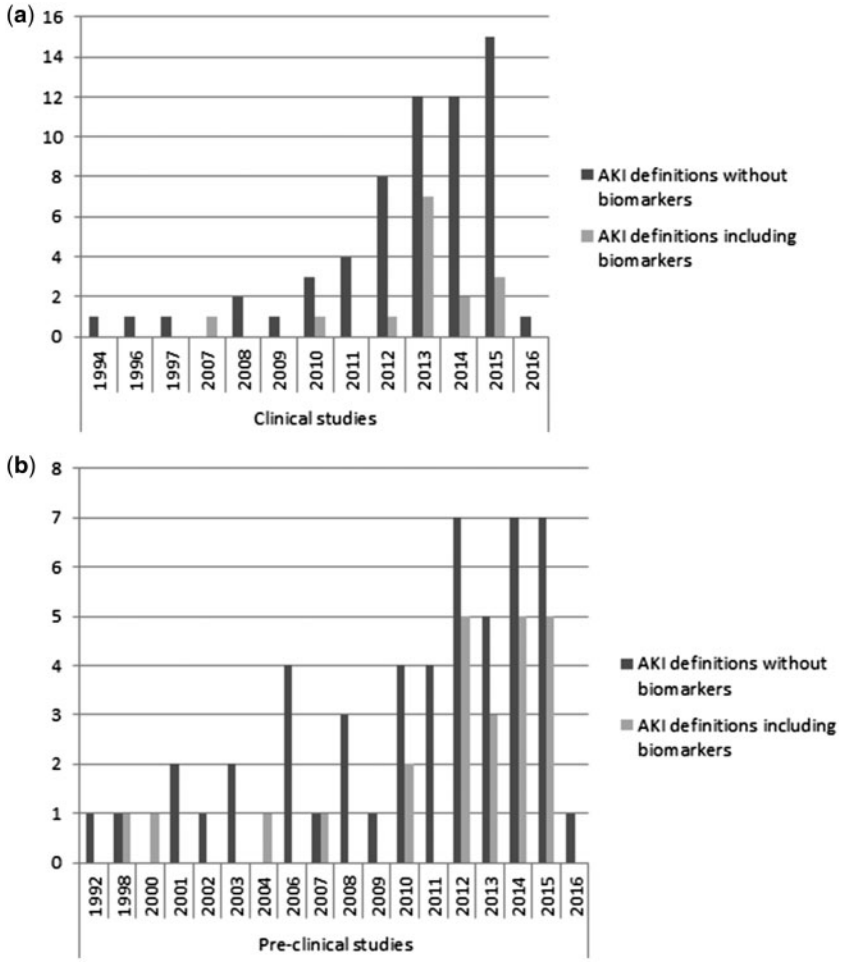

FIGURE 2: Number of studies including biomarkers in the definition of AKI in (**a**) clinical and (**b**) preclinical studies.

comparison of biomarkers of renal injury, including serum creatinine, cystatin C and NGAL, while the secondary end points were the evaluation of myocardial enzyme release and pulmonary parameters.

A higher percentage of preclinical interventional studies included AKI biomarkers in the primary end point compared with clinical studies (68 versus 51.4%; P = 0.03) (Table 6). Recently, Kim *et al.* [120] investigated the role of urinary Klotho and NGAL for differentiating pre renal (volume-depleted model) and intrinsic AKI (obtained by injections of cisplatin) in rats and showed a significant reduction of urinary Klotho in pre renal AKI and no differences in NGAL levels between the two groups. Wang *et al.* [151] analyzed the different expressions of NGAL and other pro-inflammatory cytokines (IL-6, TNF-α) between septic (obtained by cecal perforation) and nonseptic AKI in 17 pigs. Pawar *et al.* [136] determined that NGAL expression in renal tissue, as well as urinary levels, was significantly higher in mice with nephrotoxic nephritis as compared with control mice and a tight correlation was observed between these levels and renal histopathology.

We also compared preclinical and clinical studies in specific settings: comparing studies on sepsis (eight preclinical and two clinical studies), the majority of preclinical studies (87.5%) used biomarkers as the primary end point [150–152, 154–157], while the two clinical studies used them as the secondary end point [56, 57]. In 18 studies on cisplatin-associated AKI (13 preclinical and 5 clinical), 11 preclinical [105, 112, 114, 120, 121, 128, 130, 131, 133, 143, 144] and all the clinical studies [44–47, 49] used AKI biomarkers as the primary end point. Conversely, among five studies focusing on contrast-associated AKI with the same exposure and specific strategy to prevent AKI (hydration and *N*-acetylcysteine; one preclinical and four clinical), one preclinical [160] and three clinical studies [75, 77, 82] used the biomarkers as the primary end point. Considering studies that analyzed the same biomarker (urinary NGAL), but with divergent outcomes (one preclinical and two clinical studies [77, 82]), the three studies used the biomarker as the primary end point.

Overall, there was not an increasing trend in the number of studies using AKI biomarkers as the primary end point in the last 10 years and the percentage of these studies has ranged from 20 to 55.6% of the selected studies by year (Figure 3). Preclinical studies are more likely to use biomarkers as the primary end point compared with clinical studies [odds ratio 2.31 (95% CI 1.17–4.59); P = 0.016].

DISCUSSION

Failure to translate basic discoveries in AKI pathophysiology into clinical treatments has been a major impediment to

Table 5. Use of AKI biomarkers as primary or secondary end points in clinical interventional studies

	AKI biomarker	Study	Year	AKI biomarker	Study	Year	AKI biomarker	Study	Year
Primary end point	**NGAL**	Coca *et al.* [14]	2013	**NGAL**	Bobek *et al.* [11]	2010	**KIM-1**	Coca *et al.* [14]	2013
		Lipcsey *et al.* [18]	2014		De Seigneux *et al.* [15]	2012		Ribichini *et al.* [74]	2013
		Balkanay *et al.* [32]	2015		Adademir *et al.* [27]	2012		Kooiman *et al.* [77]	2015
		Dardashti *et al.* [33]	2014		Ricci *et al.* [28]	2011		Duan *et al.* [78]	2013
		Yousefshahi *et al.* [34]	2013		Barkhordari *et al.* [35]	2011		Shinke *et al.* [49]	2015
		Ribichini *et al.* [57]	2013		Choi *et al.* [38]	2011		Lahiri *et al.* [62]	2014
		Kooiman *et al.* [77]	2015		Gaspari *et al.* [44]	2010		Daggulli *et al.* [70]	2016
		Akrawinthawong *et al.* [80]	2015		Yang *et al.* [64]	2010		Fahmy *et al.* [72]	2013
			2013		Fassett *et al.* [87]	2012		Lahoud *et al.* [58]	2015
		Tasanarong *et al.* [82]	2013	**NAG**	Shinke *et al.* [49]	2015	**Cystatin C**	Ricci *et al.* [28]	2011
		Lin *et al.* [45]	2015		Lahiri *et al.* [62]	2014		Dardashti *et al.* [33]	2014
		Seker *et al.* [46]	2015		Daggulli *et al.* [70]	2016		Yousefshahi *et al.* [34]	2013
		Shahbazi *et al.* [47]	2014		Fahmy *et al.* [72]	2013		Choi *et al.* [38]	2011
		Ylinen *et al.* [48]	2015		Oboho *et al.* [89]	2013		Torigoe *et al.* [75]	2013
		Shinke *et al.* [49]	2014	**L-FABP**	Coca *et al.* [14]	2013		Duan *et al.* [78]	2013
		Schilder *et al.* [66]	2015		Katoh *et al.* [81]	2014		Ylinen *et al.* [48]	2014
		Sahraei *et al.* [55]	2016		Igarashi *et al.* [84]	2013		Oh *et al.* [65]	2014
		Daggulli *et al.* [70]	2014		Daggulli *et al.* [70]	2016		Mayeur *et al.* [69]	2010
		Kardakos *et al.* [71]	2015	**Cytokines**	Mayeur *et al.* [69]	2010		Kardakos *et al.* [71]	2014
		Lahoud *et al.* [58]	2015					Fassett *et al.* [87]	2012
		Orsolya *et al.* [59]	2013						
		Junglee *et al.* [88]	2013						
		Oboho *et al.* [89]							
Secondary end point	**NGAL**	Ejaz *et al.* [16]	2013	**NGAL**	Wagener *et al.* [21]	2008	**IL-18**	Ejaz *et al.* [16]	2013
		Foroughi *et al.* [17]	2014		Ling *et al.* [85]	2008		Gallagher *et al.* [31]	2015
		Prowle *et al.* [19]	2012		Srisawat *et al.* [67]	2011		Brulotte *et al.* [42]	2013
		Tasanarong *et al.* [20]	2013	**TIMP2 × IGFBP7**				Ling *et al.* [85]	2008
		Zarbock *et al.* [22]	2015		Zarbock *et al.* [22]	2015		Pickkers *et al.* [57]	2012
		Matata *et al.* [23]	2015		Meersch *et al.* [25]	2014		Sureshkumar *et al.* [52]	2012
		Basu *et al.* [24]	2014					Coupes *et al.* [54]	2015
		Deininger *et al.* [30]	2015	**KIM-1**	Deininger *et al.* [30]	2015	**Cystatin C**	Basu *et al.* [24]	2014
		Gallagher *et al.* [31]	2015		Gallagher *et al.* [31]	2015		Gallagher *et al.* [31]	2015
		Oh *et al.* [36]	2012		Brulotte *et al.* [42]	2013		Song *et al.* [37]	2015
		Kim *et al.* [39]	2013		Leaf *et al.* [56]	2015		Kim *et al.* [39]	2013
		Brulotte *et al.* [42]	2013		Pickkers *et al.* [57]	2012		Pedersen *et al.* [43]	2012
		Pedersen *et al.* [43]	2012		Coupes *et al.* [54]	2015		Poletti *et al.* [76]	2007
		Ataei *et al.* [50]	2015		Hatipoglu *et al.* [73]	2014		Gok *et al.* [79]	2013
		Gok *et al.* [79]	2013		Boertien *et al.* [86]	2015		Yin *et al.* [83]	2013
		Nymo *et al.* [63]	2012					Srisawat *et al.* [67]	2011
		Leaf *et al.* [56]	2015	**L-FABP**	Deininger *et al.* [30]	2015	**GGT**	Endre *et al.* [68]	2010
		Pickkers *et al.* [57]	2012		Boertien *et al.* [86]	2015			
		Ojeda *et al.* [51]	2013	**NAG**	Brulotte *et al.* [42]	2013	**Cytokines**	Westhuyzen *et al.* [29]	1994
		Sureshkumar *et al.* [52]	2012		Gok *et al.* [79]	2013		Xinwei *et al.* [41]	2009
		Tsuchimoto *et al.* [53]	2014		Kharasch *et al.* [60]	1997		Boldt *et al.* [61]	1996
		Coupes *et al.* [54]	2015					Leaf *et al.* [56]	2015
		Boertien *et al.* [86]	2015					Pickkers *et al.* [57]	2012

NAG, N-acetyl-glucosaminidase; α-GST, alpha-glutathione S-transferase; MCP-1, monocyte chemotactic protein 1; TIMP-2, tissue inhibitor metalloproteinase 2; GGT, gamma-glutamyl transpeptidase; NA, not available.

progress in clinical medicine [164, 165]. Differences between clinical and preclinical studies may represent one of the most important barriers to successful translation into clinical practice. With the present study, we analyzed the differences between clinical and preclinical studies on AKI biomarkers based on the setting and the etiologies on which they are focused, the inclusion of biomarkers in the definition of AKI and their use as primary or secondary end points in interventional studies.

There is an important disconnect between studies concerning the setting in which they evaluated AKI. A significant percentage of clinical studies analyzed AKI in patients undergoing cardiothoracic surgery or with contrast-associated AKI, while ischemia–reperfusion injury and drug-associated AKI predominating in preclinical studies. These differences may help explain the limited reproducibility of results obtained by experimental analyses in clinical studies since AKI in the clinical setting is related to multiple conditions and may involve different pathogenic features. A host of cellular and molecular pathways involving injury, regeneration and repair have been implicated [164, 166, 167]. To be useful, a model organism must recapitulate the clinical and molecular (subclinical) features of the disease in question. For AKI, these features are limited to changes in function (e.g.

Table 6. Use of AKI biomarkers as primary or secondary end points in preclinical interventional studies

	AKI biomarker	Study	Year	AKI biomarker	Study	Year	AKI biomarker	Study	Year
Primary end point	**NGAL**	Zang *et al.* [12]	2014	**KIM-1**	Visnagri *et al.* [92]	2015	**Inflammatory cytokines**	Visnagri *et al.* [92]	2015
		Visnagri *et al.* [92]	2015		Bussmann *et al.* [102]	2014		Zager *et al.* [105]	2012
		Mei *et al.* [94]	2015		Sohotnik *et al.* [104]	2013		Hosgood *et al.* [107]	2012
		Duan *et al.* [95]	2015		Ko *et al.* [109]	2010		Dennen *et al.* [112]	2010
		Calistro Neto	2015		Shin *et al.* [121]	2014		Gueler *et al.* [118]	2002
		et al. [96]	2014		Luo *et al.* [123]	2014		Shin *et al.* [121]	2014
		Si *et al.* [97]	2014		Cardenas *et al.* [125]	2013		Hanna *et al.* [126]	2013
		Bussmann *et al.* [102]	2013		Chen *et al.* [128]	2013		Nozaki *et al.* [130]	2012
		Woodson *et al.* [103]	2013		Nozaki *et al.* [130]	2012		Yanagisawa	1998
		Sohotnik *et al.* [104]	2012		Vinken *et al.* [131]	2012		*et al.* [148]	2015
		Hosgood *et al.* [107]	2011		Hosolata *et al.* [133]	2012		Wang *et al.* [151]	2012
		Jochmans *et al.* [108]	2010		Kramer *et al.* [140]	2009		Han *et al.* [154]	2001
		Ko *et al.* [109]	2016		Zhou *et al.* [141]	2008		Knotek *et al.* [155]	2008
		Kim *et al.* [120]	2014		Lee *et al.* [152]	2013		Li *et al.* [156]	2006
		Shin *et al.* [121]	2014		Li *et al.* [158]	2015		Wang *et al.* [157]	
		Luo *et al.* [123]	2012	**IL-18**	Duan *et al.* [95]	2015	**L-FABP**	Duan *et al.* [95]	2015
		Hosolata *et al.* [133]	2012		Bussmann *et al.* [102]	2014		Jochmans *et al.* [108]	2011
		Pawar *et al.* [136]	2004		He *et al.* [113]	2008		Negishi *et al.* [143]	2007
		Mishra *et al.* [144]	2015		Nozaki *et al.* [130]	2012			
		Otto *et al.* [150]	2013	**Osteopontin**	Xie *et al.* [147]	2001	**uFetuin-A**	Zhou *et al.* [114]	2006
		Lee *et al.* [152]	2012	**α-GST**	Chen *et al.* [128]	2013	**Klotho**	Hu *et al.* [111]	2010
		Han *et al.* [154]	2015					Kim *et al.* [120]	2016
		Wang *et al.* [157]	2014	**Cystatin C**	Youssef *et al.* [91]	2015	**NAG**	Hosolata *et al.* [133]	2012
		Li *et al.* [160]			Mei *et al.* [94]	2015		Raekallio *et al.* [139]	2010
					Si *et al.* [97]	2014		Zhou *et al.* [141]	2008
					Oron *et al.* [98]	2014		Usuda *et al.* [146]	1998
					Woodson *et al.* [103]	2013	**GGT**	Naghibi *et al.* [142]	2007
					Wunnapuk *et al.* [124]	2014			
Secondary end point	**NGAL**	Speir *et al.* [93]	2015	**KIM-1**	Speir *et al.* [93]	2015	**Cystatin C**	Hang *et al.* [100]	2014
		Hang *et al.* [100]	2014		Hang *et al.* [100]	2014		Efrati *et al.* [132]	2012
		Gardner *et al.* [101]	2014		Sanchez-Pozos	2012		Efrati *et al.* [134]	2012
		Kim *et al.* [110]	2010		*et al.* [106]	2013		Zhou *et al.* [153]	2014
		Tan *et al.* [122]	2015		Maguire *et al.* [127]	2013			
		Sinha *et al.* [129]	2013		Sinha *et al.* [129]	2012			
		Efrati *et al.* [132]	2012		Groebler *et al.* [135]				
		Guo *et al.* [149]	2015	**IL-18**	Patel *et al.* [159]	2011			
		Zhou *et al.* [153]	2014	**uClusterin**	Dodiya *et al.* [137]	2011	**Inflammatory cytokines**	Koga *et al.* [13]	2010
				NAG	Hang *et al.* [100]	2014		Zhang *et al.* [90]	2015
					Baker *et al.* [116]	2006		Speir *et al.* [93]	2015
					Sinha *et al.* [129]	2013		Gardner *et al.* [101]	2014
					Ziai *et al.* [145]	2003		Nitescu *et al.* [115]	2006
					Schultz *et al.* [161]	1992		Burne-Taney	2003
				MCP-1	Koo *et al.* [99]	2014		*et al.* [117]	2000
								Seth *et al.* [119]	2015
								Tan *et al.* [122]	2012
								Efrati *et al.* [134]	2011
								Lee *et al.* [138]	2008
								Li *et al.* [156]	

NAG, N-acetyl-glucosaminidase; α-GST, alpha-glutathione S-transferase; MCP-1, monocyte chemotactic protein 1; TIMP-2, tissue inhibitor metalloproteinase 2; GGT, gamma-glutamyl transpeptidase; NA, not available; uClusterin, urinary clusterin; uFetuin-A; urinary fetuin-A.

increased serum creatinine) and evidence of damage (e.g. changes in biomarkers). Histologic changes are also relevant, but to a far lesser extent, because renal tissue is rarely obtained from humans with AKI.

As previously described [7, 8, 10], the AKI definition was an important source of heterogeneity. In our analysis, only ∼20% of all clinical interventional studies actually included novel biomarkers of renal injury, while about one-third of preclinical studies used them. Many studies deviated from standard criteria to define AKI and one of the most frequent deviations, was to ignore the urinary output criteria altogether. In most studies, particularly in the preclinical setting, AKI was based only on serum creatinine elevations, despite this marker's well-known deficiencies. Differences in biomarker results and 'AKI' may be explained in part by the lack of sensitivity for serum creatinine. Indeed, false positives (true tubular damage, but negative serum creatinine) or false negatives (no significant tubular injury, but an increase in serum creatinine related to prerenal AKI or due to other confounding variables) were observed. In such scenarios, it will be important for future studies to investigate

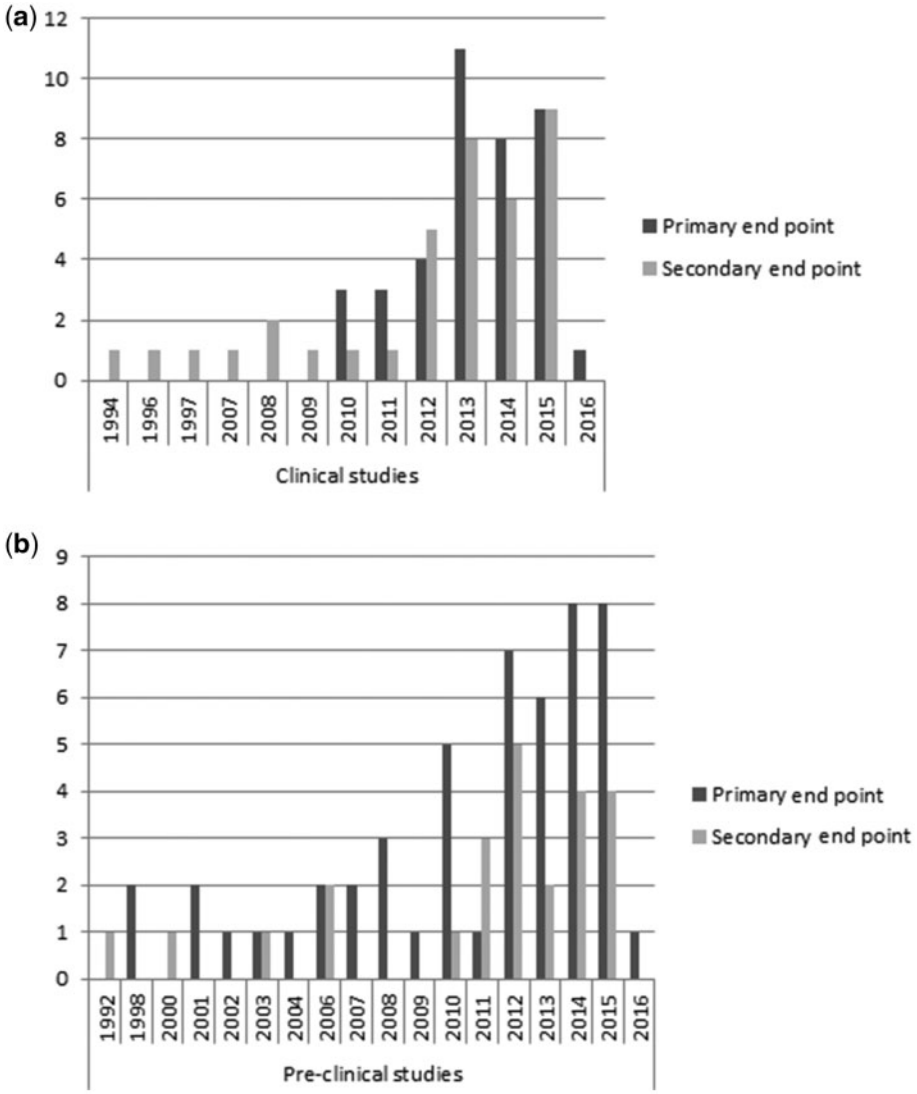

FIGURE 3: Percentages of (**a**) clinical and (**b**) preclinical studies with AKI biomarkers as primary and secondary end points.

clinical outcomes (including long-term outcomes) for patients who appear to develop subclinical AKI (biomarker positive but serum creatinine negative). AKI diagnosis and staging based on standard criteria developed for humans (e.g. RIFLE) have been applied to both laboratory animals [112, 153] and veterinary patients [100, 151]. NGAL and KIM-1 were first identified in animals and then validated in humans and, recently, the cell cycle arrest biomarker TIMP-2 × IGFBP7, the only FDA-approved biomarker for AKI, was validated in animals [168]. Thus we believe that AKI definitions and biomarkers can be used across species. The question is whether they have been and to what extent.

Overall, only a limited number of studies have investigated biomarkers for AKI severity and long-term outcomes (renal recovery, progression to CKI, cardiovascular events and mortality), mainly as secondary end points [43, 67, 68, 122, 164]. Few studies examining AKI biomarkers have suggested their potential role to distinguish patients at risk of severe AKI requiring RRT and the available data are not sufficient to conclude that biomarkers should be used for the clinical decision to begin RRT. For this reason, the identification of new biomarkers or novel ways to use known biomarkers, such as robust clinical prediction models that integrate biomarkers and clinical variables, need to be developed to increase their use in clinical practice. A critical need is to improve the design of preclinical and clinical studies in AKI settings to identify potential therapeutic targets and translate findings in preclinical studies in humans for the prevention and treatment of AKI. Future directions in preclinical research should aim to improve animal models to better reproduce human AKI and its characteristics. Table 7 summarizes the main findings of the present study, as well as recommendations for future AKI biomarkers research.

In conclusion, this study highlights the main differences in terms of settings and the inclusion of novel biomarkers in the definition of AKI and in the assessment of outcomes between clinical and preclinical interventional studies focused on AKI biomarkers. Overcoming this disconnect could be fundamental to improving our understanding of the pathophysiology of AKI and the potential therapeutic options.

Table 7. Main results and future recommendations

Differences in AKI ascertainment between clinical and preclinical studies: main results
• Different settings between clinical and preclinical studies (cardiac surgery–associated AKI and contrast-associated AKI in clinical studies; ischemia–reperfusion injury and drug-induced AKI in preclinical studies)
• Different definition of AKI and limited use of AKI biomarkers in the AKI definition (19.7% of clinical studies, 32% of preclinical studies)
• Preclinical studies are more likely to include AKI biomarkers in the primary end point of the study compared with clinical studies
Future directions
• Improve animal models of AKI to closely mimic human conditions (age, comorbidities) and allow the translation of preclinical findings in humans
• Need a better understanding of similarities and differences in molecular targets and pathophysiological pathways involved in different settings, as well as between animal and human AKI
• Standardize the AKI definition between preclinical and clinical studies
• Integrate AKI biomarkers with each other and with clinical parameters in clinical studies
• Define different phenotypes of patients with AKI and analyze biomarker behaviors among different phenotypes in clinical studies

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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AUTHORS' CONTRIBUTIONS

The contributions of the authors are as follows: M.F., J.A.K.: research idea, study design, data synthesis and writing of the article; G.C.: collaborated in study selection and data collection. All authors approved the final version of the submitted article

CONFLICT OF INTEREST STATEMENT

J.A.K. reports consulting and/or grant support from various companies developing AKI biomarkers, including Astute Medical, Alere and BioPorto. The remaining authors have declared no competing interests. The content is solely the responsibility of the authors. The results presented in this study have not been published elsewhere in whole or in part.

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