Acute kidney injury (AKI) occurs frequently in hospitalized patients, especially at the intensive care unit (ICU), and is associated with a high morbidity, mortality and cost [1,2]. The disappointing quest for a golden bullet to treat or prevent AKI during the 1990s has been replaced by a crusade to develop (early) biomarkers of AKI [3]. The underlying reasoning for this change in research perspective is that the single-shot therapies that worked so well in the rat models do not work in humans because we lag behind with accurate, early diagnosis. As a result, several biomarkers have been identified and tested over the last decade in an attempt to diagnose AKI earlier. In a recent issue of *Kidney International*, Endre et al. [4] report the negative results of a trial using biomarkers to guide administration of rHuEPO to prevent or attenuate AKI. Most of the interest in this study is that the biomarkers used were not at all able to establish an accurate diagnosis of AKI, although they have been claimed previously to be accurate [5]. History seems to repeat itself: whereas some of these biomarkers seem to work properly in well-controlled conditions and restricted populations, such as in children post-cardiac surgery [6], their performance decreases in mixed or more complex populations [3], and confidence intervals for sensitivity and specificity become wide [7]. Although Endre et al. [4] have to be congratulated for their courage in setting up this study, it is exemplary for the difficulties faced by all initiatives in the field of AKI: as long as a coherent and meaningful definition of AKI is lacking, all attempts for early diagnosis, prevention or treatment are bound to fail.

The several initiatives undertaken over the last years to harmonize the definition of AKI [8–10] must be greatly credited for having brought the problem of AKI to the attention of non-nephrologists. However, although the principles of RIFLE and AKIN are well accepted, most papers use a ‘convenience’ format of RIFLE or AKIN in real practice. Also, the boundaries of the diagnostic criteria, especially in relation to the baseline value of creatinine, seem to change continuously [8,11,12]. Most attempts to come up with one definition neglect the simple truth that ‘the’ AKI as a single entity does not exist. For the clinician, AKI is the reduction in glomerular filtration rate, when most likely the kidney has already been damaged substantially, while for the experimental physiologist, harm to even a few tubular cells as evidenced by biomarkers is enough to establish the diagnosis. AKI is a multifaceted condition, in terms of severity, underlying disease and circumstances, and sequence of events. By creating stages of AKI, both RIFLE [10] and AKIN [9] tried to tackle this problem. It has been demonstrated that these stages correlate with outcome [13,14]. This has been accepted as validation of these definitions. But here loom a number of conceptual problems. First, in order to define a change in creatinine, a baseline value is needed, changing the problem of definition of AKI into a problem of defining a baseline value of creatinine, which might lead to different classifications [15]. In the study of Endre et al. [4], although all patients complied with one definition of AKI based on baseline creatinine, this ‘baseline’ creatinine was defined according to a pre-specified algorithm, consisting of five different definitions, de facto resulting in five different types of AKI. It has been demonstrated that the selection of baseline creatinine influences the categorization of AKI [15]. Second, besides the difference between a baseline and a second value, also the further kinetics of the evolution of serum creatinine should be taken into account. The current definitions of RIFLE and AKIN take into account neither the kinetics of creatinine nor the duration of an increase. When a patient with an established normal kidney function comes in with acute dehydration, his creatinine on admission might be several folds his baseline value, but will decrease rapidly by rehydration. This is cardinal for the concept of ‘fluid responsiveness’ [16], and the best marker to be followed here is the rise in urinary output, a neglected parameter in many studies. In a septic patient, declining urinary output despite fluid loading is often the first sign of impending AKI, but creatinine will only rise slowly in the beginning. The distinction between renal and pre-renal, from the therapeutic viewpoint the most crucial distinction to be made, can only be made by evaluating fluid responsiveness or the effect of increasing renal perfusion, not by a definition based on single changes from baseline in serum creatinine or a biomarker [17]. Third, relative risk rather than predictive value is used to indicate the increase
in risk for a certain outcome when serum creatinine changes, e.g. in ‘R’ of RIFLE, the risk of getting ‘I’ or ‘F’ was doubled. This means that if the absolute risk is 1% (general hospitalized patient) or 15% (ICU patient), it goes up to 2% or 30%, respectively, in patients who comply with the ‘R’ criteria. These are impressive numbers indeed, but it still means that 98% and 70% will be misclassified as having ‘true’ AKI when we use ‘R’ as a definition of AKI. Using these low thresholds will thus lead to a plethora of clinically irrelevant AKI cases. If we use these definitions to guide therapy, it will also lead to exposure of potentially harmful therapies to patients who will never benefit from it because they do not have the disease in the first place. Last, it can be doubted whether changes in serum creatinine and/or urinary output have the same impact in a patient on a ward, or with sepsis, or after cardiac surgery, adding to the multifaceted aspect of AKI.

There is great belief that ‘biomarkers’ will solve all these problems. This belief is fuelled partly by our inclination to rely on ‘hard numbers’ rather than on (subjective) clinical conditions, and partly by industry, because commercialization of biomarkers is a rapidly growing market. There is a looming danger that the desire to believe that biomarkers can work is decreasing our scientific steadfastness. Although, e.g. the numbers in recent reviews demonstrate that biomarkers at present lack evidence of benefit, most authors still conclude that they might have great potential [3]. Endre et al. [4] used gamma-glutamyl transpeptidase (γ-GT) and alkaline phosphatase (AP) as biomarkers. The cut-off levels and accuracy of these markers were based on a single study with only four cases of AKI [5]. Misclassification of AKI by these biomarkers in the new cohort was substantial and resulted in a 3-fold increase in the speculative diagnosis of AKI, and a substantial part of AKI patients were missed. The most impressive example today of what biomarkers can do is the use of ‘cardiac markers’ in myocardial ischaemia. Can we, however, reasonably expect that biomarkers will ever play the same role for AKI? Unfortunately, this is rather doubtful, making the current enthusiasm precocious. First, as AKI is not a single entity, it will take many different markers to distinguish the different conditions, a fact recognized by many authors, who plead for a ‘panel’ of biomarkers. But even such a panel is not going to solve the problem, as the most important distinction is that between the so-called ‘pre-renal’ and ‘renal’ causes of AKI. As a biomarker for pre-renal AKI is unlikely, a therapeutic dilemma is created when a positive biomarker for renal AKI is found: should we fluid-load the patient to enhance renal perfusion or not? It can be feared that many clinicians will be inclined to start a ‘targeted’ (most likely expensive) therapy for ‘AKI’ and will forget to restore renal perfusion pressure. The same problem arises in the distinction between pre-existing chronic and acute kidney injury. As there is a rising incidence of ‘acute-on-chronic’ kidney injury, biomarkers will need to be able to distinguish between these two conditions. Neutrophil gelatinase-associated lipocalin (NGAL) has been claimed to detect AKI but seems also to be associated with severity of chronic kidney disease [18] and inflammation [19], and potentially also to urinary tract infection and even obstruction, compromising its diagnostic accuracy for AKI. A second, even more fundamental problem is which golden standard will be validated by these biomarkers. Most studies in this field use the RIFLE or AKIN criteria as golden standard, but this is circular reasoning because if these are the golden standard, biomarkers are no longer necessary as diagnostic tools. Third, in contrast with myocardial ischaemia, insults to the kidney, especially in ICU patients, are more protracted over time and come from different sources, such as inflammation, hypoperfusion or toxicity, and a single hit is rare. Biomarkers have been promoted to diagnose AKI earlier, but most biomarkers have a very small ‘window of opportunity’. NGAL, for example, had a reasonable (80% AUC in ROC) diagnostic accuracy at 18 h after coronary bypass, but far lower at 12 and 24 h [20]. These peaks can be variable in height and timing in different patients [18]. The timing strategy for the use of these biomarkers is thus unclear, as is also the target population. Most problematic AKI cases start in patients still on the ward, and the ‘window of opportunity’ is lost before these patients arrive at the ICU. As a consequence, to guide early intervention, several tests per day would be needed in all patients, which is neither practical nor financially realistic. In the study by Endre et al. [4], only 529 of the available 3966 patients were enrolled, the majority of the exclusions being because patients had already established AKI or a bad prognosis based on clinical grounds, so the biomarkers could only be useful in 16% of the patients. Fourth, to be beneficial, biomarkers should provide additional information on top of what already can be derived from other available parameters, such as urinary sediment analysis, diuresis or clinical conditions. Siew et al. [21] recently demonstrated that the additional information derived from NGAL to diagnose AKI on top of a set of clinical parameters was poor. Most studies, however, do not assess the discriminative or predictive capacity of biomarkers on top of diuresis [11] and/or clinical evaluation. This is more remarkable as urinary output can be considered as a sensitive and continuous ‘biomarker’. Koyner et al. [22] demonstrated that although NGAL was not better than creatinine in predicting AKI, it did predict the need for renal replacement therapy (RRT). However, when looking to the clinical conditions of the patients involved, it was clear even without the biomarker that these patients were bound to end up on RRT, and the additional value of the biomarker was non-existent. IL-18 has been related to outcome, both in terms of AKI and mortality, but this is not a real surprise, as it is a marker of inflammation and sepsis, by themselves prognostic factors. It has been argued that the benefit of biomarkers is that they can be used as a diagnostic criterion even by non-experts. However, as is clear from the above, biomarkers cannot replace clinical evaluation, and interpretation of sets of biomarkers in specific conditions will still rely on expertise to result in meaningful interpretations.

Finally, technical concerns also remain, such as correction of urinary markers to creatinine to correct for concentration, which cut-off values to use, and whether these cut-offs are comparable for different brands of biomarkers, etc. All these issues need to be solved before bio-
markers can really start to be used in clinical practice. Endre et al. [4] were very brave to set up their study but maybe a bit too precocious.

Looking for a definition for AKI is like playing hide-and-seek in a dark forest: there are many shadows and noises, many of which may appear to be the person you are looking for. It is appealing to scream out the name of every one of your playmates at every moving object, hoping eventually, one might be correct. Unfortunately, in the case of AKI, some players appear well disguised, and we do not even know all the players taking part. In view of the complexity of the issue of AKI, it is highly unlikely that we will eventually, one might be correct. Unfortunately, in the case of AKI, some players appear well disguised, and we do not even know all the players taking part. In view of the complexity of the issue of AKI, it is highly unlikely that we will come up with one single definition for this condition, nor will there be a consensus? Nephrol Dial Transplant 2010; 25: 107–118

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