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*Editorial Comments*

# The importance of a correct evaluation of progression in studies on chronic kidney disease

Anne-Lise Kamper

Department of Nephrology, Rigshospitalet, University of Copenhagen, Denmark

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When studying the effect of therapeutic interventions on the progression of chronic kidney disease (CKD), the most relevant end points are death and development of end-stage renal disease (ESRD). However, since the rate of progression is often rather slow, the effect parameter that is usually monitored is one of the markers of glomerular filtration rate (GFR). The gold standard for determination of GFR is the renal clearance of inulin, administered as a constant intravenous infusion. This method, however, is rarely used, mainly due to its time-consuming chemical assay procedure. Alternative methods are radiolabelled markers and creatinine, as well as estimates of GFR [1,2]. In long-term studies on progressive CKD some patients usually develop ESRD during the study, while others disappear from the study due to non-renal causes. It is important to take this into account when selecting the research methods for evaluation of GFR. The authors of a recently published meta-analysis were apparently not aware of this problem [3], and therefore came to conclusions that might be questioned. Given this background, it seems relevant to call attention to the pitfalls that may be made in the handling of GFR data, when studying the progression of CKD. Specific problems connected with the use of creatinine-based markers will not be discussed.

## The handling of GFR data

When evaluating the progression of CKD, the GFR data may be handled in one of the following ways.

*Correspondence and offprint requests to*: Anne-Lise Kamper, Department of Nephrology P2132, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Email: anne.lise.kamper@rh.dk

*Sequential measurements of GFR with comparison of values between the study groups or with comparison of changes between groups*

These methods require that all patients complete the study, since withdrawal due to ESRD cannot be adequately accounted for (Figure 1). The significance of these different analytic methods is exemplified in the constructed data, presented in Table 1. This example shows that the comparison of GFR and plasma creatinine values between two groups may result in the impression of a better outcome in a treatment group where some patients develop ESRD before the end of study. Similarly, comparison of changes in these parameters between the groups may lead to a wrong conclusion, since it does not include any information on how fast a specific change has developed. As shown in Table 1, identical mean changes in plasma creatinine two groups may be associated with different mean

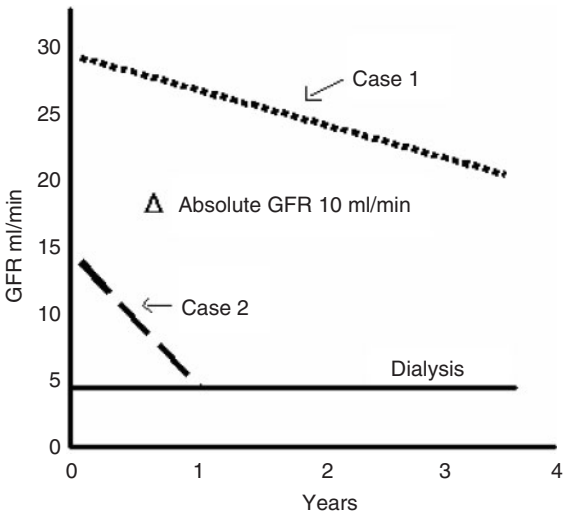


**Fig. 1.** Evaluation of progression of CKD. The absolute decline in GFR is 10 ml/min in both cases but the rate of decline in GFR is 2.5 ml/min/year in case 1 and 10 ml/min/year in case 2. Comparison of changes does not take into account that the observation time is different; this is done when rate of decline in GFR is evaluated. Changes in markers of renal function are only comparable when follow-up time is identical in all patients, which is rarely seen.

**Table 1.** Constructed data of a study comparing the renoprotective effect of treatment A and B in chronic kidney disease

| | Plasma creatinine (μmol/l) | | | | GFR (ml/min) | | | | GFR slope ml/min/year |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 3 months | 12 months | Change | Baseline | 3 months | 12 months | Change | |
| A1 | 200 | – | 325 | 125 | 30 | – | 20 | −10 | 10 |
| A2 | 200 | – | 400 | 200 | 30 | – | 15 | −15 | 15 |
| A3 | 200 | – | 400 | 200 | 30 | – | 15 | −15 | 15 |
| A4 | 400 | – | 500 | 100 | 15 | – | 12 | −3 | 3 |
| A5 | 500 | – | 700 | 200 | 12 | – | 8 | −4 | 4 |
| Mean | 300 | – | 465 | 165 | 23 | – | 14 | −9 | 9 |
| B1 | 200 | – | 300 | 100 | 30 | – | 23 | −7 | 7 |
| B2 | 200 | – | 200 | 0 | 30 | – | 30 | 0 | 0 |
| B3 | 200 | – | 250 | 50 | 30 | – | 27 | −3 | 3 |
| B4 | 400 | $775^{\text{end-stage}}$ | – | 375 | 15 | $6^{\text{end-stage}}$ | – | −9 | 36 |
| B5 | 500 | $800^{\text{end-stage}}$ | – | 300 | 12 | $5^{\text{end-stage}}$ | – | −7 | 28 |
| Mean | 300 | | 250 | 165 | 23 | | 27 | −5 | 15 |

Comparison of plasma creatinine and GFR values, changes in plasma creatinine and GFR, and rate of GFR decline demonstating the importance of correct methodology when evaluating progression. Treatment A is better than B as the mean decline in GFR is 9 and 15 ml/min/year, respectively. This conclusion is not achieved by the other parameters. As judged by 12-months mean values of plasma creatinine and GFR, treatment B is the best, and as judged by changes in plasma creatinine the treatments are equal whereas changes in GFR indicate a benefit of treatment B.

changes in GFR and, most importantly, the GFR changes may be contrary to the rate of decline in GFR.

The aforementioned meta-analysis on the renal effect of ACE inhibitors and the aforementioned angiotensin-II receptor blockers [3] questions the well-established benefit of these agents [4–15]. Although a significantly reduced risk of developing ESRD by inhibition of the renin–angiotensin system was demonstrated in the meta-analysis [3], it did not demonstrate any difference in secondary end-point variables: serum creatinine and GFR. That resulted in a strong reservation about a specific renal protective effect of inhibition of the renin–angiotensin system. The study of these parameters was however, performed by comparing changes in the variables between the randomized groups, with calculation of the differences by subtraction of the mean change in the variable in the reference group (follow-up value minus baseline value) from the corresponding mean change in the experimental group [3]. According to the example in Table 1, such a handling of GFR data might very well explain the discrepancy between primary and secondary end points in this meta-analysis and might have resulted in incorrect conclusions.

### *Sequential measurement of plasma creatinine with doubling of baseline plasma creatinine as an end point and comparison of number of patients reaching this end point*

In recent years this method has been used in several large clinical trials examining the effect of inhibitors of the renin–angiotensin system [5,6,8–10,12,15]. Usually the end point, doubling of baseline plasma creatinine, is used in combination with ESRD and death [6,8–10,12,15]. Using doubling of plasma creatinine as the only end point will require that all patients are at risk for reaching that end point and this is not the case if GFR is severely impaired at baseline. Consequently, failure to combine the end point with ESRD might lead to wrong results, since some patients may develop ESRD before reaching a doubling of the plasma creatinine (Table 2). In the meta-analysis by Casas *et al*. [3] doubling of serum creatinine was one of the primary end points and it was found not to be influenced by blockade of the renin-angiotensin system. The reason for that could easily be failure to combine this end point with ESRD.

**Table 2.** Constructed data as in Table 1

| | Plasma creatinine (μmol/l) | | |
|---|---|---|---|
| | Baseline | 3 months | 12 months |
| A1 | 200 | – | 325 |
| A2 | 200 | – | $400^{\text{doubling}}$ |
| A3 | 200 | – | $400^{\text{doubling}}$ |
| A4 | 400 | – | 500 |
| A5 | 500 | – | 700 |
| - | | – | |
| B1 | 200 | – | 300 |
| B2 | 200 | – | 200 |
| B3 | 200 | – | 250 |
| B4 | 400 | $775^{\text{end-stage}}$ | – |
| B5 | 500 | $800^{\text{end-stage}}$ | – |

Comparison of patients reaching the end points ESRD and doubling of baseline plasma creatinine (μmol/l). In severe renal failure, ESRD may be developed before doubling of plasma creatinine leading to discrepancy between these end points.

### *Sequential measurement of GFR with calculation of the individual linear slopes of the GFR vs time plot and comparison of slopes between the study groups*

These methods are advantageous in studies where observation time varies due to the development of ESRD or due to withdrawal for non-renal reasons.

It is generally accepted as the optimal way to evaluate kidney function in studies on progressive CKD and it is therefore widely used [4,7,11,13,14]. The marked significance of this method is demonstrated in Figure 1 and Table 1 as only the rate in decline in GFR correctly expresses progression of renal failure.

The present knowledge on treatment of progressive CKD must continuously be extended. This implies the application of correct research methodology in clinical trials and meta-analyses. Failure to do so may at worst lead to exclusion of a potentially beneficial treatment.

*Conflict of interest statement*. None declared.

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# Secondary rise of albuminuria under AT1-receptor blockade—what is the potential role of aldosterone escape?

Lars Christian Rump

Klinikum der Ruhr-Universität Bochum, Marienhospital Herne, Bochum, Germany

**Keywords:** ACE inhibition; albuminuria; aldosterone escape; angiotensin II; AT1-receptor blockade

*Correspondence and offprint requests to*: Prof. Dr L. C. Rump, Klinikum der Ruhr-Universität Bochum, Medizinische Klinik I, Marienhospital Herne, Hölkeskampring 40, 44625 Herne, Germany. Email: christian.rump@ruhr-uni-bochum.de

## Introduction

Inhibition of the renin–angiotensin system is the recommended standard therapeutic regimen in chronic kidney disease. The reasons for this choice are obvious. On the one hand angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs)