What is the best method of proteinuria measurement in clinical trials of antiproteinuric drugs?

Jonathan Towler, Neeraj Dhaun, Iain MacIntyre, Jane Goddard, David Webb. University of Edinburgh, BHF Centre of Research Excellence, QMRI, EH16 4TJ, United Kingdom.

Introduction Proteinuria is an independent risk factor for chronic kidney disease (CKD) which can be targeted with antiproteinuric drugs. Monitoring and comparing reduction in proteinuria in clinical trials requires an accurate, unbiased and repeatable assay for urine protein. In this study we test the hypothesis that protein-creatinine ratio (PCR) or albumin-creatinine ratio (ACR) are suitable replacements for 24h urine protein in the measurement of proteinuria in clinical trials of antiproteinuric drugs.

Methods Data were gathered in a randomised, double-blind, placebo controlled study of the ET_A selective endothelin antagonist sitaxsentan 100mg and active control in 27 patients with stable CKD (Dhaun *et al.* 2011). The three assays for urine protein were compared in terms of their agreement, variability, ability to predict reduction in proteinuria from baseline and requirement for repeat measurements to obtain accurate results.

Results In the placebo phase, the median coefficient of variation was lower for PCR than 24h urine protein (28.1% vs. 24.5%) but the range was greater (8.3 – 78.1% vs. 12.9 – 60%). When converted into the same units, the mean difference of all three assays is negligible. However, Bland-Altman plots show that scatter increases with mean proteinuria, such that agreement falls substantially above 1.5g/day. The limits of agreement (±2SD) span a large range which is clinically significant (-1.66 – 1.68g/day, 24h urine protein vs. PCR). According to two factor within-subjects ANOVA, the assay used was not a significant source of variation in the data (p=0.641, 24h urine protein vs. PCR). Using three repeat measurements resulted in a larger reported reduction in proteinuria with both 24h urine protein and PCR. This effect was not found to be significant using two factor within-subjects ANOVA (p=0.528, p=0.475 respectively). With three repeats, baseline proteinuria correlates equally well with change in proteinuria using 24h urine protein and PCR (r=-0.799, r=-0.781 respectively).

Discussion These results demonstrate that PCR is equivalent to 24h urine protein in all areas of comparison. In view of its greater convenience and lower cost, this indicates that PCR may be a suitable replacement for 24h urine protein in the clinical trial context. Less data was available for ACR, although it matched 24h urine protein in terms of agreement and prediction of change in proteinuria. A randomised control trial comparing all three assays in a larger and more diverse population is necessary before 24h urine protein can be appropriately substituted.

Dhaun N, MacIntyre IM, Kerr D, et al. (2011). Selective endothelin-a receptor antagonism reduces proteinuria, blood pressure and arterial stiffness in chronic proteinuric kidney disease. *Hypertension* **57:** 772-779.