The Authors Reply: We are responding to Dr David Naimark's letter[1] regarding our warfarin-related nephropathy (WRN) paper.[2] With respect to Dr Naimark's comment regarding the section regimen, we agree that our selection process was biased to include those with 'acute illnesses'. We point out that our selection process likely identified the sickest of the patients. However, it would be highly improbable that this accounts for the cases of 'presumptive WRN'. That would have required that all of the cases of unexplained AKI (presumptive WRN) by chance alone occurred all within 1 week after an increase in international normalized ratio (INR) to >3.0, but not before or after the increase, as shown in Figure 1. Note that there was no evidence that AKI occurred before the increase in INR to >3.0. The fact that the unexplained AKI instances are strongly and temporally related to an INR increase >3.0 suggests a mechanistic link between the INR increase >3.0 and the case of AKI. Further evidence that the INR increase >3.0 is mechanistically related to the episodes of AKI is our previous work in humans[1,2] and our animal model in 5/6 nephrectomy rats.[3] Taken together, we suggest that we have provided compelling evidence that our study of 'presumptive WRN' is, in fact, a study of WRN.

Regarding the comment on the mortality hazard associated with 'WRN,' we suggest that Dr Naimark's interpretation is implausible and refer to Figure 5. Panels c and d show, respectively, the hazard ratio for death in the WRN versus no-WRN patients unadjusted and adjusted for all of the relevant covariates (those that were significantly different between the WRN and no-WRN patients). As shown, the unadjusted and the adjusted hazard ratios were comparable and were not significantly different. This indicates that the greater mortality rate in the WRN patients was not related to their greater degree of co-morbidity. Indeed, in the covariate model, the only variable that significantly predicted the increased mortality rate was whether the patient developed presumptive WRN after the INR increase >3.0.

We agree with the remarks that the alternative hypothesis could explain why drugs expected to both increase and decrease glomerular hydrostatic pressure was associated with WRN and address as such in our paper. The study was designed to study patients new to warfarin therapy, and the issue of whether WRN tends to occur early in the course of the patient's disease is discussed and based on our detailed retrospective analysis of 113 patients with chronic kidney disease. We also point out that WRN can recur in the same patient.

With regard to Dr Naimark's contention that the present results may have been confounded by patients' illnesses, we would remark that it is highly improbable.

1. Naimark D. Warfarin-related nephropathy. *Kidney Int* 2012; **81**: 322.
2. Brodsky SV, Nadasdy T, Rovin BH *et al.* Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int* 2011; **80**: 181–189.
3. Ware K, Brodsky P, Satoskar AA *et al.* Warfarin-related nephropathy modeled by nephron reduction and excessive anticoagulation. *J Am Soc Nephrol* 2011; **22**: 1856–1862.

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Kidney International (2012) **81,** 323; doi:10.1038/ki.2011.386

The therapeutic tradeoff between the adverse impacts of a lower GFR and long-term renal protection

To the Editor: The recent demonstration of a slower rate of decline in estimated glomerular filtration rate (eGFR), in those losartan-treated diabetic patients with the larger acute fall in eGFR, by Holtkamp *et al.*[1] did not consider the adverse effects of the lower eGFR in this group, which was still present at 39 months, despite this group recording twice the number of adverse renal events (doubling of plasma creatinine level or end-stage renal disease) when compared to the losartan treated patients with an acute rise in eGFR.[1]

Although renal failure may be asymptomatic down to a glomerular filtration rate (GFR) of circa 20 ml/min, physiological changes of pathological importance occur much earlier. Examples include increasingly low levels of 1,25-dihydroxyvitamin D as the GFR falls to <80 ml/min,[2] and changes in physical function in the elderly, as assessed by the Short Form-36, with an eGFR <45 ml/min.[3]

An additional concern, in assessing the impact of lowering GFR, is the patient's actual GFR, given the imprecision of eGFR, with coefficients of variation against measured GFR being circa 20–30%.[4] That is, with a starting eGFR of 40 ml/min some 16% of the patients will have an actual GFR <30 ml/min, with an acute reduction of 30% post treatment resulting in an actual GFR of circa 20 ml/min.

The actual GFR achieved post treatment is important in assessing the short-term risks. There should be a lower limit for acceptable acute post-treatment eGFR, based on the significance and risk of possible adverse events, as well as life expectancy. What that lower limit should be awaits further study. But 30 ml/min would seem a practicable starting point for a debate on this issue.

1. Holtkamp FA, de Zeeuw D, Thomas MC *et al.* An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* 2011; **80**: 282–287.
2. Levin A, Bakris GL, Molitch M *et al.* Prevalence of abnormal serum vitamin D, PTH, calcium and phosphorus in patients with chronic kidney