4. Mandic A, Hansson J, Linder S *et al.* Cisplatin induces endoplasmic reticulum stress and nucleus-independent apoptotic signaling. *J Biol Chem* 2003; **278**: 9100–9106.
5. Kitamura M. Endoplasmic reticulum stress and unfolded protein response in renal pathophysiology: Janus faces. *Am J Physiol Renal Physiol* 2008; **295**: F323–F334.

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Response to 'Autophagy: a protective mechanism against nephrotoxicant-induced renal injury'

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We thank Dr. Pallet and Dr. Anglicheau for their interest in our recent publication reporting autophagy in cisplatin nephrotoxicity and its cytoprotective role.[1] We are pleased to learn that their latest work has also demonstrated autophagy as a protective mechanism against cyclosporine toxicity in renal cells and tissues.[2] Interestingly, whereas we showed the regulation of cisplatin-induced autophagy by p53, BcL-2, and related mechanisms, Pallet *et al.* further emphasized the involvement of ER stress in autophagy during cyclosporine toxicity. Although we did not examine ER stress in the cisplatin model, we believe this is a possibility that deserves consideration and further investigation. As correctly pointed out, cisplatin can induce ER stress. In this regard, Liu and Baliga[3] showed evidence for ER stress during cisplatin treatment of renal tubular cells. Nevertheless, multiple stresses and signaling pathways are induced or activated during cisplatin nephrotoxicity.[4] Notably, cisplatin induces pathological alterations in several subcellular sites or organelles including mitochondria, ER, and the nucleus. As a result, cellular responses, either cytoprotective or injurious, may be mediated by multiple rather than a single mechanism.[4] Certainly, a specific stress or pathway may have a major role in the induction of autophagy; whether it is ER stress remains to be determined. In addition, the signaling pathways activated by cisplatin may also cross talk and be integrated, resulting in an impressive renal pathology. The recent studies by this and other laboratories have suggested that autophagy is a renoprotective mechanism during cisplatin and cyclosporine nephrotoxicity.[1,2,5] However, whether this conclusion can be generalized to other kidney injury models (for example renal ischemia-reperfusion) remains to be investigated, as excessive autophagy can lead to cell death. Thus we have to agree with Dr. Lieberthal that 'the extent to which autophagy can ameliorate kidney injury caused by other types of renal insults remains to be determined'.[6] It is hoped that these studies have provided impetus for investigation of autophagy in renal pathophysiology.

1. Periyasamy-Thandavan S, Jiang M, Wei Q *et al.* Autophagy is cytoprotective during cisplatin injury of renal proximal tubular cells. *Kidney Int* 2008; **74**: 631–640.
2. Pallet N, Bouvier N, Legendre C *et al.* Autophagy protects renal tubular cells against cyclosporine toxicity. *Autophagy* 2008; **4**: 783–791.
3. Liu H, Baliga R. Endoplasmic reticulum stress-associated caspase 12 mediates cisplatin-induced LLC-PK1 cell apoptosis. *J Am Soc Nephrol* 2005; **16**: 1985–1992.
4. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. *Kidney Int* 2008; **73**: 994–1007.
5. Yang C, Kaushal V, Shah SV *et al.* Autophagy is associated with apoptosis in cisplatin injury to renal tubular epithelial cells. *Am J Physiol Renal Physiol* 2008; **294**: F777–F787.
6. Lieberthal W. Macroautophagy: a mechanism for mediating cell death or for promoting cell survival? *Kidney Int* 2008; **74**: 555–557.

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Telmisartan is more effective than losartan in reducing proteinuria

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To the Editor: We read with interest the paper that Telmisartan is more effective than losartan in reducing proteinuria in patients with Diabetic Nephropathy recently published in *Kidney International* by Bakris *et al.*[1] where the effects of telmisartan 80 mg was compared with losartan 100 mg in 860 patients with type 2 diabetes treated for 52 weeks. The authors showed that with telmisartan, proteinuria decreased from 1.42 to 0.95 g per g creatinine ($P<0.0001$) and with losartan, proteinuria decreased from 1.39 to 1.05 g per g creatinine ($P<0.0001$) at the end of the study. They also documented a trend in favor of telmisartan where there was a difference of 4.2 mm Hg difference in systolic blood pressure compared to losartan. We would like to comment on the dose of telmisartan and losartan used in Bakri's study. From our observation, comparing telmisartan 80 mg with losartan 100 mg would favor telmisartan with regards to clinical efficacy in particular with respect to reduction of proteinuria.

We would like to share our own experience in a clinical trial involving patients with IgA nephritis treated with losartan 100 mg ($n=45$) compared to those treated with losartan 200 mg ($n=61$) over a 6-year period from 2001 to 2007.[2] In the losartan 100 mg group, proteinuria decreased from 2.1 ± 1.0 to 1.7 ± 1.0 g/day compared to losartan 200 mg group where proteinuria decreased from 2.1 ± 0.8 to

1.0 ± 0.8 g/day ($P<0.001$). There was no significant difference in the systolic blood pressure between the two groups before and after the study ($P=0.447$). Neither was there a difference in the diastolic blood pressure ($P=0.159$). The decrease in the estimated glomerular filtration rate (eGFR) was 3.5 ml/min/year for the losartan 100 mg group compared to 0.7 ml/min/year for the losartan 200 mg group ($P<0.0005$) and there were significantly less patients with chronic kidney disease (CKD) 4 and 5 in the losartan 200 mg group compared to the 100 mg group ($P<0.005$) at the end of 6 years.

From our experience, dose for dose, losartan is probably equipotent to telmisartan, that is if prescribed in the dose of losartan 150 mg versus telmisartan 80 mg. Telmisartan, because of its longer half-life in terms of blood pressure control[3] has the advantage of offering better renoprotection in hypertensive CKD patients (whether diabetic or IgA nephropathy). But for patients who do not have hypertension associated with CKD, losartan may be more appropriate as it is a relatively weaker hypotensive drug[4] and one can prescribe larger doses without the side effects of giddiness and hypotension. In the long term, what is of paramount importance is preservation of renal function and prevention of renal failure. In this respect, data for telmisartan 80 mg[5] and our own studies on losartan 200 mg[2] have shown that after 5 years therapy there is a gain in eGFR for both of these drugs which has yet to be demonstrated by other angiotension receptor blocker (ARBs) or angiotension converting enzyme inhibitor (ACEI).

1. Bakris G, Burgess E, Weir M *et al.* Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int* 2008; **74**: 364–369.
2. Woo KT, Chan CM, Wong KS *et al.* High dose ARB and ACE gene polymorphism in IgA nephritis (*Abstract*). *Nephrology* 2008; **13**: A21.
3. Burnier M. Angiotensin II type 1 receptor blockers. *Circulation* 2001; **103**: 904–912.
4. Xi GL, Cheng JW, Lu GC *et al.* Meta-analysis of randomised controlled trials comparing telmisartan with losartan in the treatment of patients with hypertension. *Am J Hypertens* 2008; **21**: 546–552.
5. Barnett A. Prevention of loss of renal function over time in patients with diabetic nephropathy. *Am J Med* 2006; **119**: 405–415.

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Response to 'Telmisartan is more effective than losartan in reducing proteinuria'

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We read with interest your letter in response to our trial. We very much appreciate the issue of dose equivalence between losartan and telmisartan. There are clearly differences between these two agents with regard to AT1 receptor binding at the doses we used.[1,2] The doses selected, however, resulted from those most commonly used in the United States. They are also the maximum approved doses by the Food and Drug Administration. The dose escalation of losartan and results on proteinuria reduction mirror those seen with other angiotensin receptor blocker (ARBs). Dose escalation studies with candesartan have also shown similar findings on proteinuria without substantial additional blood pressure reductions.[3,4] Thus, we appreciate your observations and do not find them surprising. It is clear that increasing ARB dose above the current guideline recommendations to reduce proteinuria further is warranted; this should also be considered by regulatory agencies. The one interesting finding in the study was that the decline in estimated glomerular filtration rate (eGFR) was less at the higher dose. This is important and needs confirmation in longer-term studies.

1. Burnier M. Angiotensin II type 1 receptor blockers. *Circulation* 2001; **103**: 904–912.
2. Maillard MP, Wurzner G, Nussberger J *et al.* Comparative angiotensin II receptor blockade in healthy volunteers: the importance of dosing. *Clin Pharmacol Ther* 2002; **71**: 68–76.
3. Weinberg AJ, Zappe DH, Ashton M *et al.* Safety and tolerability of high-dose angiotensin receptor blocker therapy in patients with chronic kidney disease: a pilot study. *Am J Nephrol* 2004; **24**: 340–345.
4. Weinberg MS, Kaperonis N, Bakris GL. How high should an ACE inhibitor or angiotensin receptor blocker be dosed in patients with diabetic nephropathy? *Curr Hypertens Rep* 2003; **5**: 418–425.

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Adiponectin in chronic kidney disease: Dr Jekyll and Mr Hyde

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To the Editor: We read with interest the commentary by Costacou and Orchard[1] on the hypothesis that elevated adiponectin levels may occur as a protective response to vascular damage. Although such changes may be operative in CKD, we believe that the putative involvement of adiponectin in the process of protein-energy wasting also needs consideration. As adiponectin is produced in inverse proportion to fat mass, wasted patients who have lost body weight would, as a consequence, have higher plasma adiponectin values.[2] Thus, it is not unexpected that adjustment for body mass index resulted in the loss of impact on mortality by adiponectin in patients with chronic heart failure.[3] Also, a nested case–control study showed that adiponectin reflects the degree of systemic wasting that precedes death.[4] On the other hand, as intracerebroventri-