Comment

—to: Davis BJ, Forbes JM, Thomas MC et al. (2004) Superior renoprotective effects of combination therapy with ACE and AGE inhibition in the diabetic spontaneously hypertensive rat. *Diabetologia* 47:89–97

To the Editor: We read with interest the recent paper by Davis et al. [1] reporting the renoprotective effects of an ACE inhibitor, an AGE inhibitor and a combined ACE and AGE inhibitor on streptozotocin-induced diabetic spontaneously hypertensive rats. The level of renoprotection obtained by the ACE inhibitor, perindopril, was similar to that obtained by the AGE inhibitor, aminoguanidine, as measured by the prevention of albuminuria, glomerular and tubulointerstitial injury and TGF β 1 overexpression, and by the suppression of nephrin expression. Davis et al. claimed that they obtained superior renoprotection with combination therapy using ACE and AGE inhibitors. However, the mechanism by which it happened is unclear for several reasons. Firstly, the ACE inhibitor perindopril is not a specific inhibitor of ACE, but a combined ACE and AGE inhibitor [2]. A significant degree of inhibition of AGE formation by perindopril is also clear from the study by Davis et al. In spite of this, the authors were unable to demonstrate superior renoprotection of perindopril over AGE inhibitor aminoguanidine. Moreover, the addition of aminoguanidine with perindopril had no additional inhibitory effect on AGE formation. Therefore, it is not clear that the superiority of renoprotection after addition of aminoguanidine was a result of the inhibition of AGE formation. Secondly, ACE inhibitor perindopril was not used at a sufficient dose in the study by Davis et al., and the rats were still hypertensive after 24 weeks of therapy. Davis et al. argued that a maximal dose of ACE inhibitor would have prevented assessment of the superiority of dual blocking. We, however, are in doubt about the validity of this argument in this respect, as the superiority of combination therapy cannot be claimed over monotherapy without assessing the full potential of monotherapy. It is most likely that tight control of blood pressure by adequate dosing of ACE inhibitor would have abolished the superiority of combination therapy. This was taken into consideration, in part, by Davis et al. Tight control of blood pressure, as an effective measure of renopro-

tection, has recently been reported by our group in diabetic spontaneously hypertensive rats [3, 4]. In our studies, ACE inhibitor and non-ACE inhibitor antihypertensive agents showed similar levels of renoprotection. In fact, the beneficial effects of blood pressure reduction, independent of the renin–angiotensin system inhibition, had previously been suggested by the group of Davis et al. in studies of diabetic spontaneously hypertensive rats [5, 6].

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DOI 10.1007/s00125-004-1469-5

Received: 18 May 2004 / Accepted: 9 June 2004

Published online: 22 July 2004

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