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EDITORIAL

Advantages of sacubitril/valsartan beyond blood pressure control in arterial hypertension

Gema Ruiz-Hurtado[1] and Luis M. Ruilope[1,2,3]*

[1]Laboratorio Traslacional Cardiorenal and Unidad de Hipertensión, Instituto de Investigación imas12, Hospital Universitario 12 de Octubre; [2]Departamento de Medicina Preventiva y Salud Pública, Universidad Autónoma de Madrid; and [3]Escuela de Estudios Postdoctorales e Investigación, Universidad de Europa de Madrid, Madrid, Spain

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This editorial refers to 'The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study'†, by R.E. Schmieder *et al.*, on page 3308.

In the current issue of *European Heart Journal*, Schmieder *et al.*[1] compare the capacity of sacubitril/valsartan to olmesartan on arterial stiffness and left ventricular (LV) remodelling in a group of 114 hypertensive patients. The dual action drug decreases LV mass index significantly more at 12 and 52 weeks of follow-up. These differences remained after adjusting for changes in systolic blood pressure (BP). This was also accompanied by a larger reduction in central pulse pressure obtained in the sacubitril/valsartan group. The authors consider that these findings indicate that the addition of sacubitril to an angiotensin receptor blocker (ARB), valsartan, has valuable advantages compared with the ARB olmesartan administered alone. Furthermore, these positive changes did not seem to depend on the systolic BP drop and could be considered as independent of the BP-lowering capacity of sacubitril/valsartan.

Since the publication of the first comparison of sacubitril/valsartan to valsartan in a proof of concept trial,[2] it has been clearly established that compared to monotherapy with other ARBs, fundamentally valsartan and olmesartan[3] and with amlodipine,[4] the dual combination is superior. These results created great expectations on the use of sacubitril/valsartan in arterial hypertension by considering that the combination with amlodipine, and if needed with a diuretic, would significantly improve the percentage of patients attaining an adequate control of BP to values below 140/90 mmHg. In this sense, recent publications in Asian populations have shown the good effect of sacubitril/valsartan in salt-sensitive hypertension,[5] severe hypertension,[6] and hypertension accompanying chronic kidney disease (CKD).[7] More recent data, in the PARAMETER (Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Measuring Arterial Stiffness in the Elderly) study, investigated the effects on central aortic pressure of sacubitril/valsartan compared to olmesartan in elderly patients with systolic hypertension and pulse pressure above 60 mmHg. The results demonstrated a greater reduction in clinic and ambulatory central aortic and brachial pressure in patients with stiff arteries, which could provide a therapeutic advantage.[8] Regression of different types of target organ damage accompanying arterial hypertension, including LV hypertrophy, albuminuria, carotid plaques, and increased pulse wave velocity, are considered as positive strategies to improve the prognosis of cardiovascular and renal disease in arterial hypertension.[9] *Take home figure* outlines the effect of sacubitril/valsartan on the four main classes of target organ damage. The data of the paper to which this editorial is dedicated,[1] together with those of Williams *et al.*,[8] indicate that sacubitril/valsartan improves the prognosis of hypertensive patients through an improvement in the heart and big arteries. No data are available with respect to changes in carotid plaques during the administration of sacubitril/valsartan. On the other hand, the potential capacity of sacubitril/valsartan for renal protection has been poorly investigated in humans. Data from a study performed in Japan showed a reduction of urine albumin/creatinine ratio by 15.1%,[7] which is inferior to what is required for renal and cardiovascular protection.[10] A small but significant increase in urine albumin/creatinine ratio with the administration of sacubitril/valsartan in heart failure with preserved ejection fraction (HFpEF) patients has also been described.[11] Ongoing studies will answer the question of the capacity of the dual action drug to diminish albuminuria to an adequate degree while protecting from the progression of CKD.

In the meantime, the publication of the PARADIGM (Prospective Comparison of ARNI to Determine Impact of Global Mortality and Morbidity in Heart Failure Trial) study[12] has shown the excellent capacity of sacubitril/valsartan, when compared to enalapril, to very significantly improve the prognosis of patients with heart failure with reduced ejection fraction (HFrEF),

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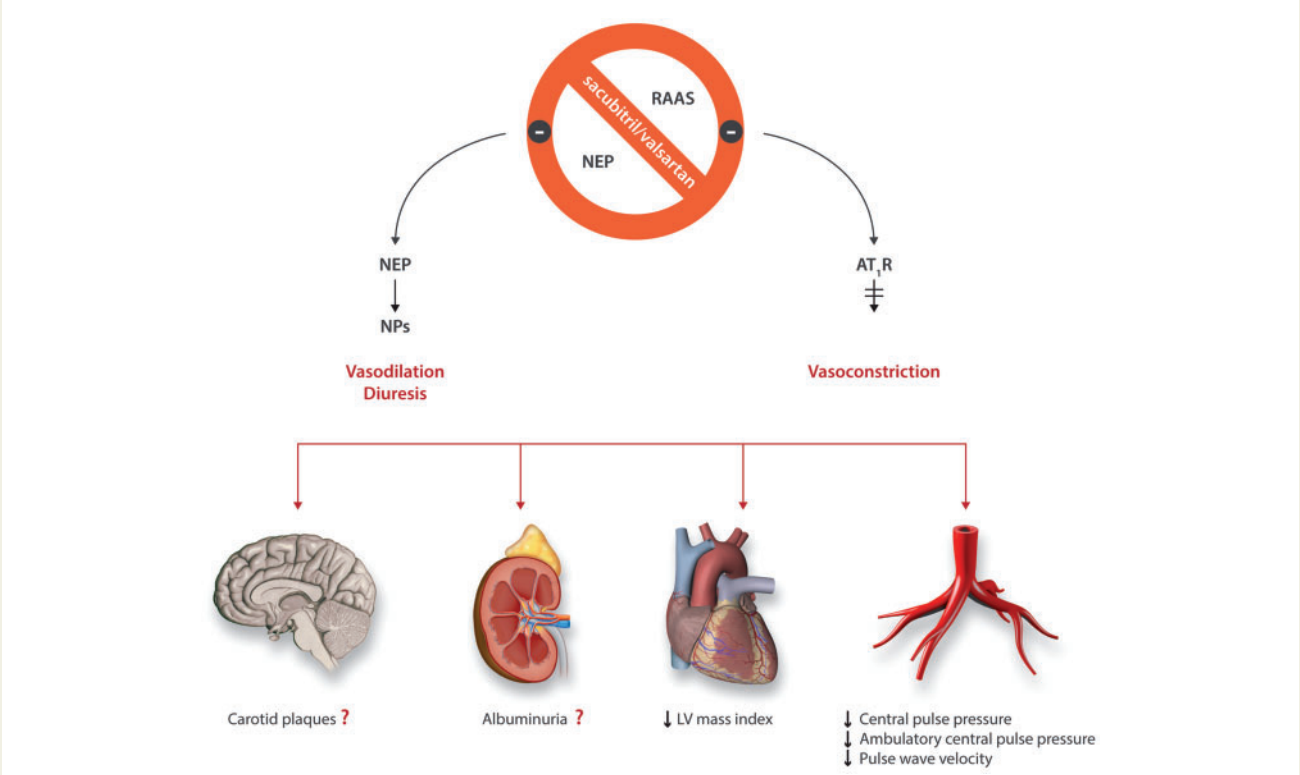
* Corresponding author. Centro de Investigación. Instituto de Investigación imas12, Hospital Universitario 12 de Octubre, Avenida de Córdoba s/n, 28041, Madrid, Spain. Tel: 34 913 908 284, Fax: 34 915 765 644, Email: ruilope@icloud.com



Take home figure Sacubitril/valsartan effects on four principal forms of target organ damage in arterial hypertension (LV hypertrophy, albuminuria, carotid plaques, and pulse wave velocity). RAAS, renin-angiotensin-aldosterone system; NEP, neutral endopeptidase; AT1R, angiotensin II type 1 receptor; NPs, natriuretic peptides; LV, left ventricle.

which allowed the dual action drug to obtain the indication for the treatment of this clinical entity in the USA and Europe. The ongoing PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial[13] will complete the investigation of sacubitril/valsartan in heart failure (HF) that constitutes the main area of utilization of this drug.

In contrast, the development of sacubitril/valsartan in the field of arterial hypertension did not progress due to concerns regarding potential side effects because of neutral endopeptidase (NEP), the substance inhibited by sacubitril, which is involved in the degradation of many peptides including amyloid beta 1-42 ($A\beta_{1\text{-}42}$). Inhibition of NEP accounts for an increase in these substances and, in particular, the aggregation of $A\beta_{1\text{-}42}$ is considered to be significantly involved in Alzheimer's disease.[14] The potential risk of Alzheimer's disease development should be significantly higher in diseases like arterial hypertension with greater longevity than in HFrEF. This explains why development in the use of sacubitril/valsartan in arterial hypertension was discontinued.

In any case, the data available provide evidence that sacubitril/valsartan and other forthcoming similar drugs could greatly contribute to facilitating the control of blood pressure in arterial hypertension and the simultaneous regression of cardiorenal disease. Secondarily, this would translate into diminished cardiovascular morbidity and mortality in arterial hypertension.

Conflict of interest: G.R.-H. has no conflict of interest. L.M.R. has served as a speaker/advisor for Novartis.

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