

# Renin-angiotensin system blockade: time for a reappraisal?

Luis M. Ruilope\*

Instituto de Investigación, Unidad de Hipertensión, Hospital 12 de Octubre, Madrid, Spain

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**This editorial refers to ‘Aliskiren alone or with other anti-hypertensives in the elderly with borderline and stage 1 hypertension: the APOLLO trial’<sup>†</sup>, by K.K.Teo et al., on page 1743 and ‘Renin–angiotensin system antagonists and clinical outcomes in stable coronary artery disease without heart failure’<sup>‡</sup>, by E. Sorbets et al., on page 1760.**

A series of randomized clinical trials demonstrated that when compared with placebo, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were drugs able to improve the prognosis of patients with heart failure accompanied by low ejection fraction, patients with a myocardial infarction (MI), and patients with chronic kidney disease (CKD; most notably demonstrated by ARBs in diabetic nephropathy), allowing the recognition by Guidelines that blockade of the renin–angiotensin system (RAS) must be used in all these situations. The use of ACE inhibitors and also of ARBs was later expanded to patients with an increased global cardiovascular (CV) risk, patients with stable coronary artery disease (CAD), diabetic patients independently of the presence of established CV or renal disease, and hypertensive patients if clustering of CV risk factors or target organ damage was present. Table 1 lists the different clinical situations where RAS blockade is indicated according to Guidelines that led to the wide use of ACE inhibitors and ARBs in clinical practice; as an example, either alone or in combination, these drugs are prescribed in > 30–40% of the hypertensive population.<sup>1</sup>

Recently, the first orally active renin inhibitor was launched as an antihypertensive drug able theoretically to improve the degree of blockade of the RAS obtained with ACE inhibitors and ARBs.<sup>2</sup> This drug was shown to be a good antihypertensive even for resistant hypertensive patients,<sup>3</sup> but, when investigated in patients with heart failure, CKD, established CV disease, and progression of coronary atherosclerosis failed to show differences when added on top of an ACE inhibitor or an ARB.<sup>4–6</sup> This drug, aliskiren, was never given the opportunity to prove its capacities in a head to head comparison with either an ACE inhibitor or an ARB, and

was used as monotherapy or in combination preferentially with a diuretic or a calcium antagonist for the treatment of arterial hypertension. Only two studies were designed to investigate the capacity of aliskiren alone; in the first, the ATMOSPHERE study, it is compared with an ACE inhibitor or with the combination of the two in chronic heart failure with low ejection fraction,<sup>7</sup> and, the second, the APOLLO trial, was designed to investigate the capacity of aliskiren to reduce CV disease in elderly hypertensives with systolic blood pressure (SBP) between 130 and 159 mmHg through the administration of the drug alone or in combination using a stratified 2 × 2 factorial trial and added on top of other medications (48.2% were taking an ACE inhibitor or an ARB). Unfortunately, the second study was prematurely stopped at the request of the sponsor. Now the results of the tolerability and efficacy of aliskiren alone or in combination with hydrochlorothiazide or amlodipine and its antihypertensive efficacy in elderly hypertensives (72.1 ± 5.2 years) during the short duration of the study (0.6 year of follow-up) are presented.<sup>8</sup> The study confirmed the good antihypertensive efficacy of aliskiren that induced sizeable reductions in BP, with potential for substantial CV reduction, that were safely achieved in the elderly with high–normal or stage 1 hypertension. The final data of this study would have been of great interest for several reasons, among which the most relevant would have been to know: first, whether SBP < 160 mmHg can be safely treated in the elderly, including those with established CV disease; secondly, whether SBP levels between 130 and 139 mmHg can be treated; and, thirdly, and related to the previous two, whether the reduction of SBP below 130 mmHg—which the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension Guidelines do not recommend because of absence of evidence and a potential risk—is safe.<sup>9</sup> In this sense, in patients with SBP below 140 mmHg and with established CV disease, the administration of antihypertensive drugs for reasons other than lowering BP has been shown to have a positive effect.<sup>10</sup> We will not know the answers to any of these three questions because the study was stopped, and this probably occurred because of the previous

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\* Corresponding author. Tel: +34 913 908 284, Fax: +34 915 765 644, Email: ruilope@ad-hocbox.com

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**Table 1** Clinical situations where the use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker has demonstrated positive effects

Heart failure with low ejection fraction
Myocardial infarction
Chronic kidney disease with albuminuria
Stable coronary artery disease
High global cardiovascular risk
Arterial hypertension

failures of aliskiren and the risk of failing again in an area of interest but accompanied by a potentially high margin of risk if the BP was lowered too much. The ALTITUDE study<sup>5</sup> also contributed to the recognition by Guidelines that dual blockade of the RAS cannot be used in clinical practice.

A second study now published contains data from the Reduction of Atherothrombosis for Continued Health (REACH) registry that indicate that the use of an ACE inhibitor or an ARB was not associated with better outcomes in stable CAD.<sup>11</sup> These data do not replicate previous findings in randomized clinical trials. Results also obtained from the REACH registry in patients with CAD risk factors only, known prior MI, or known CAD without MI show similar results for the use of beta-blockers that were not accompanied by a lower risk of composite CV events.<sup>12</sup>

Other potential differences in the benefit of RAS blockade in reference to the recommendations of Guidelines based on randomized controlled trials (RCTs) have been published recently. Development of CKD characterized by the appearance of albuminuria, with predictive capacity for the development of CV events, during chronic RAS blockade has recently been described.<sup>13</sup> On the other hand, the use of ACE inhibitors or ARBs in hypertensive patients with and without CKD has been recently analysed by the Blood Pressure Lowering Treatment Trialists' Collaboration.<sup>14</sup> Blood pressure lowering was shown to be an effective strategy for preventing CV events among patients with moderately reduced estimated glomerular filtration rate (eGFR), but there was little evidence to support the preferential choice of particular drug classes, in particular that of RAS blockers. The demonstrated increase in risk for either MI or stroke<sup>15</sup> observed when eGFR is < 60 mL/min/m<sup>2</sup> apparently is not accompanied by a positive effect of RAS blockade according to these data. It seems that there could be a dissociation between results of RCTs showing the efficacy of ACE inhibitors or ARBs with the effectiveness observed in clinical practice. Why is this so? Answering this is not easy, but a plausible explanation could be that the doses of the RAS blockers are significantly higher in randomized trials than in clinical practice and also the fact that the most important factor in long-term CV and renal protection with pharmacological therapy is an adequate compliance<sup>16</sup> that is always recognized to be superior in randomized trials. It is probable that a reappraisal of the doses of RAS blockers used and more education on compliance and long-term adherence will be required to obtain in daily clinical practice outcomes similar to those seen in randomized controlled trials in our patients. As recognized by the authors the use of low

doses of RAS blockers or an inadequate compliance could explain the findings shown in the paper. Another possibility to explain the conflicting data could be the participation in the progression of cardiorenal disease of the escape of angiotensin II to the effect of RAS blockers followed by aldosterone breakthrough.<sup>17</sup> In the meantime, further studies with aldosterone antagonists that have been so positive in heart failure<sup>18</sup> on top of an ACE inhibitor or an ARB and the investigation of the use of dual neurohormonal intervention with LCZ696<sup>19</sup> are new ways to continue investigating the blockade of the RAS system in CV and renal disease. Finally, the data from APOLLO contribute to the consideration that aliskiren could still be used in clinical practice as a good antihypertensive.

**Conflict of interest:** L.M.R. has served as speaker and advisor for Novartis.

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## CARDIOVASCULAR FLASHLIGHT

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### Diagnosis of pheochromocytoma on physical examination

Marat Fudim\*, Eugene W. Ely, Cheryl L. Laffer, and Fernando Eliovich

Department of Medicine, Vanderbilt University Medical Center, D-3100, MCN, Nashville, TN 37232, USA

\* Corresponding author. Tel: +1 917 544 4377, Email: marat.fudim@vanderbilt.edu

A 37-year-old female presented with transient episodes of acute shortness of breath and no other complaints. On admission she was found to be hypertensive (160/115 mmHg) and tachycardic (145 min) with a respiratory rate of 28 min and an oxygen saturation of 84% on room air. Pertinent findings on initial examination included bilateral crackles on auscultation and abdominal fullness in the left upper quadrant with a palpable mass percussed to be >12 cm in span. Imaging of the lung demonstrated CXR findings of diffuse interstitial oedema and on CT scan of chest she had patchy ground-glass opacities with innumerable nodules stemming from bronchoalveolar bundles (Panel A). Initial symptoms resolved within hours but were followed by repeat episodes of shortness of breath over the next 24 h associated with systolic blood pressures >200 mmHg, one of which was provoked by palpation of the abdominal mass. Clinical presentation and the unexpected finding on abdominal examination raised suspicion for a pheochromocytoma. Computed tomography scans of the abdomen and pelvis (Panels B and C) showed a large abdominal multilocular cystic mass (14.8 cm in craniocaudal dimension) in the left abdomen presumably arising from the adrenal gland. Markedly increased levels of catecholamine metabolites in blood and urine confirmed the diagnosis [plasma metanephrine >50.00 nmol/L (normal range 0.00–0.49) and plasma normethanephrine 47.10 nmol/L (normal range 0.00–0.89)]. Sixteen days after admission, the tumour was resected (Panel D), showing the histological findings of basophilic, granular cells arranged in a typical zellballen growth pattern typical of a pheochromocytoma (Panel E). Two and a half months after the patient was discharged, her vital signs and catecholamine levels normalized and the repeat CT scan showed no evidence of the tumour.

