Editorial: Aldosterone-Renin Ratios in the Context of Primary Care

When Jerome Conn first described primary aldosterone, he predicted that this syndrome may account for 20% of all essential hypertension. For the next 40 yr, conventional wisdom (and medical school teaching) reduced this figure to less than 1%. Over the last decade, however, studies from around the world have progressively revised the figure upward, toward (or in several cases beyond) the 20% level Conn predicted. In this issue of JCEM, Olivieri et al. (1) present their findings on an unselected population of hypertensives from a northern Italian general practice population. They find an elevated aldosterone to renin ratio (ARR), evidence for autonomous aldosterone secretion, in almost one third (32.4%) of their cases. In the process, the authors of this study raise a number of important questions in the area.

Before these questions are considered, it is important to point out a number of features of the Bussolengo study (1). First, the authors make a convincing case that their sample is representative, despite a surprisingly high 30% of established hypertensives declining venepuncture “for personal (business, working or family) reasons”; the extent to which 4 wk of medication withdrawal (except for verapamil and α-blockers) contributed to this fallout is not stated. Second, the criteria for establishing hypertension and the protocols used for blood sampling appear more than adequate. Third, the use of a plasma aldosterone to direct active renin ratio (AARR) rather than the more common plasma aldosterone to plasma renin activity ratio (ARR) appears to have been exhaustively validated by two previous studies involving direct comparison (n = 120) and case matching (AARR, n = 165; AAR, n = 309). Fourth, although the cut-off for AAR in other studies varies from 27 upward, the authors chose a conservative cut-off value, equivalent to more than 50 for AAR, as an index of elevated aldosterone to renin levels. Finally, the authors are careful to distinguish between elevations in aldosterone to renin ratio and primary aldosteronism; only a minority of the 32.4% of patients in fact had aldosterone levels above the normal range, to the extent to which such a range is useful.

In terms of commentary, there are a number of things to say. First, although Hiramatsu et al. (2) introduced the ARR as a diagnostic too, the pioneering work of Dick Gordon (3, 4) is difficult to overestimate. His careful studies over time of measuring ratios followed by radiologically guided adrenal venous catheterization to lateralize (or otherwise) the autonomous secretion have shown adenoma to be a minority cause of Conn’s syndrome, and that hypokalemia is very much not a diagnostic criterion of primary aldosteronism, particularly in the case of bilateral hyperplasia. Their values of 8–12% of hospital-referred hypertensives are at the lower end of the scale compared with subsequent hospital-based studies in which values of 10–40% were recorded in terms of high ARRs. In the single previous primary care study in Scotland, Lim et al. (5) found 14% of hypertensive patients from a single general practitioner to have an elevated ratio. These studies are very usefully summarized in tabular form in Ref. 1.

The inferences from the Bussolengo study are potentially far-reaching. First, the relatively high percentage of elevated ARR in this population of modestly hypertensive patients (mean systolic blood pressure, less than 150 mm Hg; diastolic blood pressure, 90 mm Hg) suggests that aldosterone as a contributor to elevated blood pressure may be more common in moderate (e.g., general practitioner-treated) hypertensives than in those referred to specialist clinics. This is of particular piquancy, given the common criticism of the initial hospital-based studies, that a sample was inadvertently selected for referral with a factitiously high percentage (in terms of the total population of essential hypertensives) of patients with autonomous aldosterone production. Second, the doubling of the female-to-male ratio in the high aldosterone-to-renin group, in a general practice context, is of considerable interest, given the current therapeutic options and the mean age (59 yr) in a group with an age cut-off of 74 yr. Third, as the authors point out, whether or not their 32.4% of hypertensives are or are not “true” cases of primary aldosteronism, there appears to be an incontrovertible case for inclusion of spironolactone in their antihypertensive medication, with minimal side effects anticipated on a population basis given the female preponderance and average age. Such therapy would optimally be low dose (25 mg/d), given the importance of titration-to-effect in the clinical use of mineralocorticoid receptor antagonists (6). One potential drawback of such a shotgun approach—and of the even more radical suggestion of including spironolactone in all antihypertensive treatment regimes—is that it may in fact delay the diagnosis and surgical treatment of aldosterone-producing adenoma or even of autonomous aldosterone production from bilateral hyperplasia, which commonly requires much higher doses of antagonist.

Although some 20% of more severe hypertensives (mean systolic blood pressure, ~160 mm Hg; diastolic blood pressure, 100 mm Hg) had minimal antihypertensive responses to 200 mg eplerenone (6), animal studies have shown profound vascular protection by mineralocorticoid receptor blockade, even without a significant fall in elevated blood pressure (7). Whether or not an outcome trial of mineralocorticoid receptor blockade in hypertension will ever be mounted, either publicly or privately funded, remains moot.

Abbreviations: AARR, Aldosterone to active renin ratio; ARR, aldosterone to renin ratio.

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In the absence of trial-based clinical evidence, we need to rely on surrogate measures; and the recently published studies on eplerenone (8), particularly in combination with angiotensin-converting enzyme inhibition, strongly point to the superiority of such combined therapy for endpoints such as left ventricular hypertrophy and albuminuria. In short, the study from Bussolengo adds further weight to the contention that inappropriate levels of aldosterone may be of pathogenetic importance in essential hypertension, as recently suggested by longitudinal analyses of patients in the Framingham study (9). Given the very low cost of spironolactone, the eventual availability of more selective mineralocorticoid receptor antagonists like eplerenone, and the minimal risk of hyperkalemia when such agents are titrated to effect (6), it would now seem possible to make a case for the use of mineralocorticoid receptor blockade in hypertension across the board.

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