# Primary Aldosteronism: At the Tipping Point

In their article, Brown and colleagues (1) report a study of the prevalence of unrecognized primary aldosteronism that is a game changer. The study shows that the single spot measurement of plasma aldosterone concentration, which clinicians have used for decades to screen for primary aldosteronism, is not merely useless but actually misleading. The authors caution readers about the uncertain representativeness of the study population for the U.S. population, but I believe that the findings are generalizable to the United States and elsewhere.

Yet no study is perfect. Study participants from Boston, Massachusetts; Charlottesville, Virginia; and Salt Lake City, Utah, included few African Americans, whereas more than half of participants from Birmingham, Alabama, were African American. A surprisingly high proportion of potential participants (>17%) were excluded despite a high sodium balance, probably reflecting the cutoffs used for suppressed renin (<1.0 μg/L per hour seated or <0.6 μg/L per hour supine). Patients in the Birmingham group with resistant hypertension continued to receive a wide range of medications, except mineralocorticoid receptor antagonists and epithelial sodium-channel blockers, whereas medications were completely withdrawn at the other study sites. African American patients are considerably more responsive to aldosterone than white patients, so relatively low values for aldosterone are compatible with primary aldosteronism. Yet, despite these caveats, the findings provide the basis for a radical reappraisal of how we manage patients with primary aldosteronism.

The central problem is that plasma aldosterone concentration is a very poor index of total daily aldosterone secretion. A single morning spot measurement of plasma aldosterone cannot take into account ultradian variation in aldosterone secretion. Commonly unrecognized is that adrenocorticotropic hormone is at least as potent a secretagogue for aldosterone (albeit briefly) as for cortisol (2). Cortisol is more highly bound than aldosterone in plasma and has a longer half-life; episodic secretion of adrenocorticotropic hormone thus produces much higher peaks and lower troughs in plasma aldosterone than in cortisol. In response to the innumerable short stresses of a normal day, there are additional spikes of aldosterone secretion that a single spot measurement of plasma aldosterone concentration cannot reflect.

The authors report that when normotensive patients and those with higher blood pressure have suppressed renin and are screened on the basis of their 24-hour urinary excretion of aldosterone, their prevalence of primary aldosteronism is 3- to 5-fold that found with conventional spot testing of plasma aldosterone concentration. The authors set the bar for urinary excretion of aldosterone at 12 μg/24 h, the upper limit of normal with a modest sodium intake but not necessarily that when challenged with a sodium suppression regimen of 200 to 300 mmol/d. In Table 2, they report levels even more telling for primary aldosteronism (for example, in about 60% of patients with resistant hypertension) with the bar set at 10 μg/24 h.

A recent study found urinary excretion of aldosterone above 12 μg/24 h in 29 of 210 normotensive participants; only 6 of the 29 tested positive for primary aldosteronism on conventional spot screening of plasma aldosterone concentration (3). Forty years ago, a study assigned 3 groups of patients—normotensive persons, those with essential hypertension, and those with confirmed primary aldosteronism—to a sodium intake of 175 mmol for 6 days; investigators then measured urinary excretion of aldosterone in each group (4). All normotensive control participants had rates at or below 6 μg/24 h; the primary aldosteronism group predictably had rates above 6 μg/24 h—as did 36 of the 100 participants with "essential hypertension." Challenged with spironolactone, systolic blood pressure in the 64 hypertensive participants with aldosterone levels in the normal range decreased by 9 mm Hg, and predictably by 21 mm Hg in those with confirmed primary aldosteronism; in the 36 with "essential hypertension" and elevated aldosterone levels, the decrease in systolic blood pressure averaged 23 mm Hg. This suggests that Brown and colleagues' observations represent the more florid end of the spectrum. Were a line to be drawn across Figure 2 (*top*) at 6 μg/24 h to complement the existing line at 12 μg/24 h, it would show a rather higher prevalence of primary aldosteronism in all 4 groups of patients (1).

Other studies support a considerably higher prevalence of primary aldosteronism in hypertension. Gouli and colleagues (5) studied 72 normotensive patients with normal adrenal glands on imaging and had them undergo the 4-day fludrocortisone plus sodium test for primary aldosteronism, enhanced by 1 mg of dexamethasone on the final evening (fludrocortisone–dexamethasone suppression test). In this group, the upper limit (97.5% of participants) of plasma aldosterone concentration was 74 pmol/L and that of the aldosterone–renin ratio was 32 pmol/L per mU/L. When the authors similarly tested 180 "essential hypertensives" using fludrocortisone–dexamethasone suppression, they found 31% to have both plasma aldosterone concentration and aldosterone–renin ratio above the previously established normal range. Subsequently, Markou and colleagues (2) studied aldosterone and cortisol responses to ultralow adrenocorticotropic hormone infusion in 61 normotensive and 113 hypertensive participants with negative results on fludrocortisone–dexamethasone suppression testing; 30 of 113 were hyperresponsive in terms of elevating aldosterone but not cortisol secretion. Taken together, these data suggest that the prevalence of primary aldosteronism in hypertensive patients may be on the order of 45% to 50%.

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Where to from here? In both Germany and the United Kingdom, only 1 in 1000 hypertensive patients is ever screened for primary aldosteronism (Reincke M. Personal communication) (6). This reflects the reluctance of primary care physicians—or others treating hypertensive patients—to refer them for investigation, given the taxing nature of the current work-up and the possible expense of adrenal venous sampling. Instead, physicians just try to control blood pressure. One in 1000 is an appallingly low capture rate, and the risk profile for patients without appropriate levels of targeted therapy is at least 3 times higher than that for patients with essential hypertension matched on age, sex, and blood pressure (7). Much of the present guideline (8) needs to be jettisoned, and radically reconstructed recommendations should be developed to guide clinicians treating hypertensive patients. With their study, Brown and colleagues sound a call to arms and start the process of bringing the management of primary aldosteronism into the 21st century. For this, the authors deserve congratulations, thanks, and unstinting praise.

*John W. Funder, MD, PhD*
Hudson Institute of Medical Research
Wandin East, Victoria, Australia

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**Corresponding Author:** John W. Funder, MD, PhD, Hudson Institute of Medical Research, 64 Parker Road, Wandin East, Victoria 3139, Australia; e-mail, john.funder@hudson.org.au.

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