HHS Public Access

Author manuscript

Ann Intern Med. Author manuscript; available in PMC 2020 October 13.

Published in final edited form as:

Ann Intern Med. 2018 May 15; 168(10): 755–756. doi:10.7326/L18-0027.

The Spectrum of Subclinical Primary Aldosteronism and Incident Hypertension

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Dr. Spence notes that a low-renin phenotype may also suggest a phenotype of Liddle syndrome and wonders how this implication may have influenced our results in the context of racial differences. Data to address both of these issues are available in our study. The low-renin phenotype has been the focus of investigation for decades and may reflect a heterogeneous mixture of underlying mechanisms (1). The focus of our study was the potential for excessive mineralocorticoid receptor activation due to autonomous aldosterone secretion, characterized by suppressed renin and inappropriately high (albeit potentially normal) aldosterone levels; in the study, this phenotype was associated with the highest risk for incident hypertension. When renin and aldosterone are both suppressed, many potential phenotypes may be considered: appropriate and physiologic suppression due to a high sodium balance; suppression due to other mineralocorticoids, such as in mild hypercortisolism or decreased activity of 11β-hydroxysteroid dehydrogenase isoenzyme-2; or suppression caused by a variant of Liddle syndrome (1). Figure 1 provides insight into Dr. Spence's comments. Among participants with a suppressed renin phenotype, those who had the highest aldosterone levels (hypothesized to be enriched for a PA-like phenotype) had the highest incident rates of hypertension. In contrast, those with suppressed aldosterone in the context of suppressed renin (which may reflect a mixture of phenotypes) had a lower incident rate of hypertension. We also report in Table 1 that participants with a suppressed renin phenotype were more likely to be African American.

Drs. Inoue and Nishikawa suggest that aldosterone suppression and adrenocorticotropic hormone stimulation tests may be needed to define subclinical PA. As described in the Discussion section, our study did not include confirmatory testing or assess the influence of cortisol on the mineralocorticoid receptor; however, prior studies with detailed phenotyping (sodium loading and fludrocortisone-dexamethasone suppression) have confirmed PA in normotensive patients (2, 3). We did not measure adrenocorticotropic hormone levels or use it in stimulation tests in this cohort; however, we agree that this hormone is an important regulator of aldosterone secretion and that such stimulation may help determine the phenotype of autonomous aldosterone secretion in normotensive patients.

Drs. Inoue and Nishikawa and Dr. Gkaliagkousi and colleagues question our use of the term *subclinical PA*. We realize that these semantics may not be preferred by all, particularly because PA has generally been regarded as a binary or categorical condition for decades.

Disclosures: Disclosures can be viewed at http://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-0882.

However, rather than focusing on the specific terminology, we suggest emphasizing the pathophysiology that suggests an apparent continuum in the severity of renin-independent aldosterone secretion, with classical PA representing only the most severe or overt form. Because milder (or, alternatively, subclinical or nonclassical) forms of autonomous aldosterone secretion are increasingly being recognized (1–3), experts have noted that “the strict definition of [PA] is no longer tenable” (4) and that future progress involves recognizing “the true prevalence of [PA] to include ‘dysregulated aldosterone secretion’ and ‘inappropriate aldosterone production’” (4). The objective of our study was not to rigorously define or characterize potential diagnostic thresholds for subclinical or normotensive PA but to investigate whether such an entity or continuum exists and, if so, what clinical effect it may have longitudinally.

Vasan and associates first reported an association between higher aldosterone levels (within the physiologic range) and higher blood pressures and risk for hypertension (5). They postulated that 1 explanation may be that “some of the study participants had subclinical hyperaldosteronism at baseline and that hypertension subsequently developed” and subsequently showed that a low-renin phenotype may have driven this finding. Our study validates these observations by showing that the association between higher aldosterone levels in normotensive patients and the risk for incident hypertension is most apparent in the context of renin suppression. These observations were true independent of age, and we reviewed the risk for misclassifying renin or aldosterone phenotypes due to dietary sodium intake. We agree that better methods to characterize mild or subclinical autonomous aldosterone secretion will be needed before it can be used clinically; however, in the meantime, an important step forward may involve simply recognizing the extension of the severity spectrum of autonomous aldosterone secretion and parallel continuum of risk for cardiovascular disease.

More studies—particularly longitudinal ones using rigorous phenotyping protocols—will be needed to better define subclinical and normotensive PA (or dysregulated and nonclassical autonomous aldosteronism as an alternative terminology), how it may affect future cardiovascular risk, and the most efficient way to recognize and address it.

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