REVIEW

Progress in the Management of Primary Aldosteronism

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Primary aldosteronism (PA) is now considered as one of leading causes of secondary hypertension, accounting for 5–10% of all hypertensive patients and more strikingly 20% of those with resistant hypertension. Importantly, those with the unilateral disease could be surgically cured when diagnosed appropriately. On the other hand, only a very limited portion of those suspected to have PA has been screened, diagnosed, or treated to date. With current advancement in medical technologies and genetic research, expanding knowledge of PA has been accumulated and recent achievements have also been documented in the care of those with PA. This review is aimed to have focused description on updated topics of the following; importance of PA screening both in the general and specialized settings and careful interpretation of screening data, recent achievements in hormone assays and sampling methods and their clinical relevance, and expanding knowledge on PA genetics. Improvement in workup processes and novel treatment options, as well as better understanding of the PA pathogenesis based on genetic research, might be expected to result in increased cure and better care of the patients.

Keywords: aldosterone; blood pressure; diagnosis; genetics; hypertension; primary aldosteronism; treatment.

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Following the isolation of aldosterone, originally reported as "electrocortin" by SA Simpson, JF Tait and their colleagues in 1953, the first case of primary aldosteronism (PA) due to aldosterone-producing adenoma (APA) was documented by JW Conn in 1955.[1] Although Conn had predicted relatively high prevalence of PA (approximately up to 20% in hypertension), most of the following studies had been unsuccessful in confirming his expectation, which was partly attributed to limited screening process based on overt clinical findings, such as hypokalemia, among hypertensive patients.

After the periods in which PA had been regarded as a rare cause of hypertension, Hiramatsu *et al.* first introduced aldosterone-to-renin ratio (ARR) as a screening test[2] and Gordon *et al.* subsequently reported estimated incidence of approximately 10% in those with "essential" hypertension.[3] With the advent of the Gordon's report, extensive research has been performed to investigate actual prevalence of PA and resulted in showing 5–10% in those with hypertension,[4] and remarkably 20% in those with resistant hypertension.[4,5] Based on this re-evaluated concept that PA is considered as one of the causes for secondary hypertension, novel findings have been extensively accumulated from both basic and clinical studies for the last 2 decades. This narrative review aims to describe recent advancement in the management of patients with PA with special emphasis on the following topics; ARR-based focused screening, new trends in assay and imaging studies and their clinical relevance, and expanding knowledge on the genetic research. Updated knowledge on confirmatory tests and pharmacological treatment in those with PA might be referred to the latest version of the comprehensive practice guideline[4] and specialized review articles,[6,7] due to limited space of this review.

EPIDEMIOLOGY AND SCREENING OF PA

As mentioned in the introduction, the Endocrine Society, in its latest guideline, documented the estimated prevalence of PA was more than 5% and 10% in primary care settings and referral centers, respectively.[4] As reported to date, results on the prevalence rate have been influenced at least by the following factors: design and size of study, characteristics of cohorts, difference in inclusion and confirmatory tests with their cutoff values, and so forth.[8–10] It is to be noted that, among these literatures, Käyser *et al.* revealed that reported estimates of the

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prevalence have been substantially variable and influenced by heterogeneity inherent in study designs by using meta-regression analysis, and indicated that a definite statistical conclusion is yet to be made.[8] In addition, we need to consider limitations in population-based screening of PA; we do not have enough data to show epidemiological or clinical benefits of the population-based screening, and consequently evidence obtained from cost-effectiveness analysis is still lacking.

As reported in the higher prevalence in those with resistant hypertension,[5] increasing evidence revealed that PA could be widely observed with varying degree of prevalence in those with normotension, prehypertension to resistant hypertension.[9] Mosso *et al.* first reported that the prevalence was proportionally increased with the stages of hypertension,[11] and Rossi *et al.* also revealed increased incidence of PA depending on the level of blood pressure in a prospective study of 1,125 patients.[12] Additionally, Monticone *et al.* recently reported that the prevalence was increased from 3.9% in those with stage 1 hypertension to 11.8% in stage 3 hypertensive patients.[13] In addition, Pappa *et al.* revealed that PA is found in 12% of normotensive patients with adrenal incidentalomas[14] and Ito *et al.* also reported that 6.8% of those with prehypertension was diagnosed to have PA.[15] Furthermore, Stowasser *et al.* revealed that those with type 1 familial hyperaldosteronism remained normotensive while they harbored aldosterone-induced cardiac remodeling.[16]

Another important issue remains to be resolved on focused screening in those at increased risk of PA, while screening of PA might be considered ideally at least once in the management of hypertension. The latest Endocrine Society guideline documented that focused screening on those with increased risk for PA showing the following conditions; sustainedly, elevated BP above 150/100 mm Hg, resistant hypertension, controlled hypertension (<140/90 mm Hg) with more than 3 antihypertensive agents, hypertension with hypokalemia regardless of diuretic use, hypertension with adrenal tumor, sleep apnea or family history of early onset hypertension or cerebrovascular event at age of younger than 40 years.[4] Additionally, based on the recently increasing evidence on familial type of PA, screening is recommended to all first-degree hypertensive relatives of PA patients.[4]

Although the introduction of ARR as a screening method[2] made considerable contribution for making contemporary estimation of PA prevalence, the issues on high rate of false-positives inherent to the ARR method have been documented.[17] Due to the mathematical fact that calculated ARR is dependent on its denominator, sensitivity of renin assay might have nonnegligible effect on the ratio, suggesting the importance of understanding each measured value of aldosterone and renin assays and the consequently calculated ARR value. In addition, another evidence that low renin activity or concentration was observed in a substantial proportion of hypertensive cohorts requires careful attention to interpret ARR values in those with so-called low renin hypertension, especially in cases with very low-to-undetectable levels of renin measurement and apparently low-to-normal levels of aldosterone concentration.[4] Interestingly, Adlin *et al.* reported that 2 peaks of aldosterone concentrations were observed in patients with low renin hypertension, as compared to a unimodal distribution of aldosterone concentrations in those with normotension and normal-renin hypertensive in cohorts of the Framingham Heart study.[18] When adjusted for age, sex, and urinary sodium excretion, the bimodally distributed aldosterone concentrations in the cohort with low renin hypertension were observed within normal range, suggesting a possibility that some proportion of patients with low renin hypertension might be likely to manifest autonomous secretion of aldosterone in the evolving process into clinically established state of PA.

MOVEMENT TOWARD NOVEL ASSAYS IN WORKUP OF PA

Another issue of clinical relevance to ARR screening is a shift of assays to active (or direct) renin concentrations. While assays for plasma renin activity have been employed in clinical laboratories for a long time, increasing demands for more rapid and sensitive assays of renin have brought us recent development of new-generation active/direct renin concentration (ARC/DRC) assays, and importantly, these newly developed chemiluminescent immunoassays (CLEIA) made it possible to measure both renin and aldosterone concentrations simultaneously in automated manners.[19–22] These rapid and highly sensitive assays are also expected to make a considerable contribution in the management of those with primary hypertension by supporting us in decision making of prescription based on their renin status, called as "PRA strategy" reported by Schwartz et al.[23]

In terms of assay methods, as already reported in various fields of medical research and practice, mass-spectrometry-based analytical methodology is also expanding in the area of hypertension.[24] Juutilainen et al. reported that combination of PAC measured by LC-MS/MS and DRC by automated CLEIA provided rapid screening ability comparable to combination of conventional immunoassays.[25] Additionally, some research groups reported LC-MS/MS-based measurement of aldosterone and related adrenocortical steroids in the diagnostic workup of PA.[26–28] Generally, LC-MS/MS approaches have been considered to have the following clinical benefits over conventional immunoassays; first, increased variability in immunoassay measurements has been reported especially in those with renal impairment, while the mass-spectrometry-based method is considered to be less influenced. Second, existence of heterophilic antibodies and exogenous confounders have been recognized as inevitable interference in immunoassays,[29] while the LC-MS/MS method is considered to be free from these interferences.

When focused in research of hybrid steroids in those with PA, although measurements of 18-hydroxycorticosterone, 18-hydroxycortisol, and 18-oxocortisol had long been considered to be useful in differentiation of unilateral APA from bilateral lesions, their sensitivities of conventional immunoassays were documented to be too low to measure plasma levels and their clinical utilities were limited, because these assays usually required 24-hour-collected urine samples. Recently, Mulatero et al. developed more sophisticated immunoassays with improved sensitivities and specificities and showed that measurements of these steroidogenic intermediates were well correlated with results of screening, confirmatory tests, and adrenal venous sampling (AVS),

proposing a clinical utility as a surrogate marker for unilateral disease.[30] Subsequently, we reported LC-MS/MS-based measurement of 18-oxocortisol levels in adrenal and peripheral venous samples and proposed it as a predictor for unilateral APA. [31,32] Biochemically overt PA patients with radiologically typical unilateral adrenocortical adenoma might have indication for adrenalectomy (ADX) without AVS, especially in relatively young patients who have less incidence to have clinically nonfunctioning tumors. In this context, measurement of these hybrid steroids, in combination with adrenal imaging, might be a help to prioritize which patients should have AVS, and consequently might be useful in raising pretest probability to diagnose unilateral PA.

ADVANCED IMAGING STUDIES AND SEGMENTAL AVS

Once a patient is diagnosed to have PA after a set of screening and confirmatory tests, adrenal imaging is required mainly for the following 2 reasons. First is to detect adrenal tumors, and the other is preparation for subsequent AVS indicated to those who are willing to have surgery. Malignancy of adrenocortical tumor is pathologically diagnosed based on the criteria proposed by Weiss,[33,34] and the incidence of aldosterone-producing cancer has been reported to account for only 2–3% of all adrenocortical carcinomas.[35] Although the proportion of bilateral APA has been reported to be small,[7] segmental AVS-based sparing surgery might be considered in those with bilateral APA.[36] Until recently, clinical diagnosis of bilateral APA has been based solely on presence of bilateral adrenal tumors and sampling from bilateral central veins. In contrast, combination of imaging studies and sampling from drainage veins of the tumors might enable us to show whether these tumors could be aldosterone-producing or not.[36]

A second purpose for detailed imaging study is to delineate adrenal vascular anatomy in order to improve success rate of AVS. Adrenal venous sampling has been still regarded as a gold standard to make indication for ADX,[4] although its technical difficulties have hindered widespread use in clinical practice. One of keys to successful AVS has been considered to lie in deep understanding of normal anatomy and variations of adrenal veins.[37–39] Since detailed review of current issues in protocol and interpretation of AVS might go beyond the scope of this article, a recently published expert consensus statement on AVS should be referred.[40]

In addition to the preprocedural anatomical knowledge, on-site efforts have been reported to be useful to improve success rate of the sampling. First, Rossi et al. reported that on-site assays of cortisol increased success rate when compared to their historical data.[41] Betz et al. documented that rapid, automated CLEIA of cortisol significantly improved their success rates from 55% to 85%.[42] Subsequently, Yoneda et al. developed a novel rapid cortisol assay specialized for AVS using immunochromatography and gold nanoparticles.[43] This new on-site assay made it possible to measure cortisol within 6 minutes and achieved 94% of success rate in their multicenter study.[43] Secondly, another intraprocedural approach using C-arm computed tomography (CT) to confirm appropriate cannulation was reported by Park and their colleagues.[44] They confirmed appropriate positioning of catheters into right adrenal veins radiographically employing C-arm CT scans and reached 95.2% of success rate.[44] Combination of these technical supports might be an additional help to both experienced and in-training angiographers in the practice of AVS.

Besides the considerable efforts to improve success rate of sampling, a novel technique has also been developed to gain a more detailed picture of aldosterone secretion within adrenal glands in those with PA. Catheters are conventionally placed at the central portion of bilateral adrenal veins, namely central veins. On the other hand, another approach involves multiple sampling from so-called branch veins, "tributary veins", by intentionally introducing microcatheters into adrenal segments. Satani et al. named this approach segmental AVS and revealed anatomical patterns of adrenal tributary veins and characterized major types of within-adrenal aldosterone secretion in those with PA.[39] Initial clinical experiences in our research group revealed some typical scenarios in which segmental AVS might provide additional diagnostic information, when compared to conventional "central" AVS.[45] First, those with unilateral APA located distal to the central vein might miss a surgical indication due to dilution effect (Figure 1).[45] A second case suitable for segmental AVS might be recurrence of APA in a patient whose contralateral gland was already resected (Figure 2).[45] Using the segmental sampling, we revealed that aldosterone secretion was suppressed at the nontumor segments, compared to the secretion from APA segment within the ipsilateral adrenal gland. Based on this difference in aldosterone secretion revealed by segmental AVS, we successfully performed segmental AVS-guided partial ADX in those with recurrent APA.[45] This approach of segmental sampling with sparing surgery could be applicable to those with bilateral APA (Figure 3)[36] and unilateral APA. Although further clinical utility of segmental AVS-based intervention should be confirmed in future studies, the following clinical issues are also required to be considered; refinement of microcatheters suitable for the segmental sampling, longer time, more costs, and higher incidence of complication than that reported in central sampling.[36,46]

Another achievement in imaging was development of metomidate positron emission tomography. Metomidate, first applied in practice as an anesthetic agent, was shown to bind to steroidogenic enzymes including CYP11B, enzymes involved in biosynthesis of cortisol and aldosterone, and adrenocortical functional imaging using radiolabeled metomidate was developed.[47] Following studies for clinical validation showed that 11C-metomidate/PET was useful in differentiation of adrenocortical lesions including APA from noncortical lesions and also revealed relatively high sensitivity and specificity in identification of APA when its size of the lesion is large (more than 10–15 mm) enough for accurate detection, using dexamethasone suppression in some cases.[48–52] Further studies to refine metomidate-based methods or to develop more suitable radiotracers are expected to improve specificity for CYP11B2 (aldosterone synthase) and sensitivity to detect smaller aldosterone-producing lesions, and might suggest a possibility that novel functional imaging modalities such as the metomidate be complementary to or a substitute for AVS in the future.

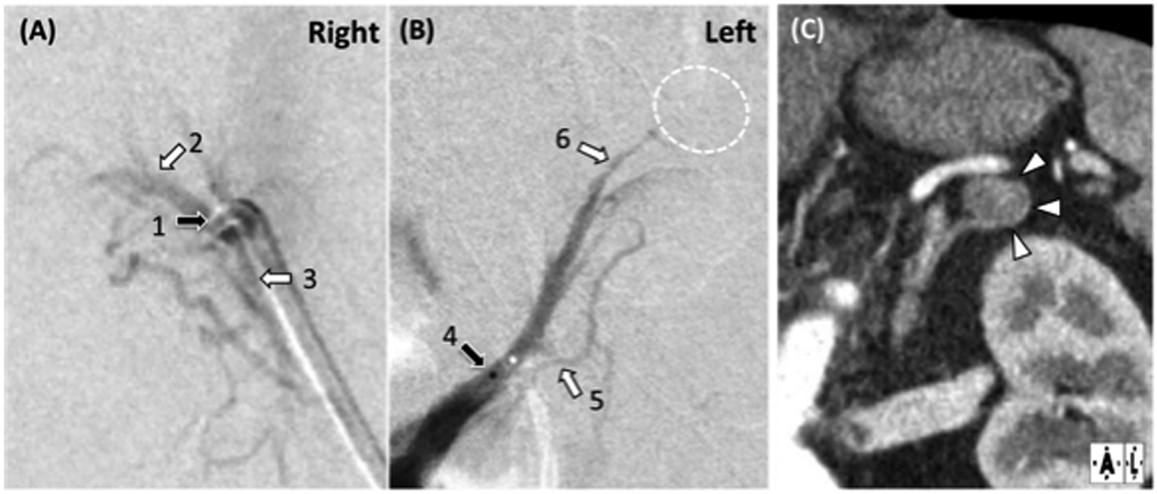

Figure 1. Adrenal venography performed to carry out segmental AVS (**A**, right side; **B**, left side) and coronal CT image of the left adrenal gland (**C**) in a 55-year-old woman who was finally diagnosed unilateral APA. The adrenal tumor was detected by CT (C, arrowheads) and projected into the venography (B, dotted circle). Sampling points from central veins are indicated by black arrows 1 and 4 in (A) and (B), respectively. Sampling points from tributary veins are indicated by white arrows 2 and 3 in (A) and 5 and 6 in (B). Abbreviations: APA, aldosterone-producing adenoma; CT, computed tomography.

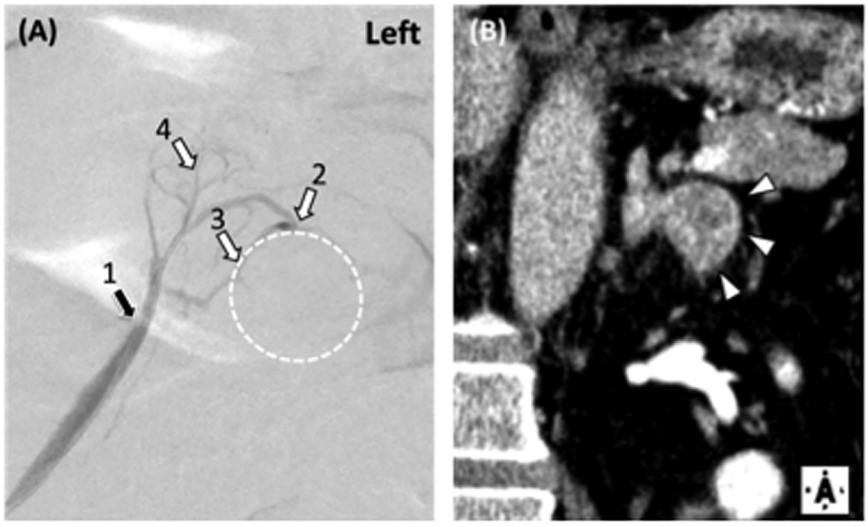

Figure 2. Adrenal venography performed to carry out segmental adrenal venous sampling (S-AVS) (**A**) and coronal CT image (**B**) of the left adrenal gland in a 56-year-old man who was finally diagnosed recurrent APA. The adrenal tumor was detected by CT (B, arrowheads) and projected into the venography (A, dotted circle). The sampling point from a central vein is indicated by black arrow number 1 (A). Sampling points from tributary veins are indicated by white arrows 2, 3, and 4 in (A). Abbreviations: APA, aldosterone-producing adenoma; CT, computed tomography.

TREATMENT OPTIONS AND UPDATED OUTCOMES

Once a patient is diagnosed to have unilateral PA, laparoscopic ADX is currently recommended. Laparoscopic ADX has been regarded as an established, less invasive approach, when compared to open surgery. Purposes of the surgical intervention are considered as follows; resolution of excess secretion of aldosterone and biochemical disturbances such as hypokalemia, cure or improved control of high blood pressure, and prevention or amelioration of aldosterone-induced end-organ damages. Until recently, various degrees of therapeutic (or adverse) effects had been reported in a number of surgical outcome studies as to long-term (more than 12 months) management of blood pressure,[53–55] cardiovascular complications,[53,55–61] cardiovascular and overall mortality,[62] potassium metabolism,[63,64] renal impairment.[61,65–69] Cure rate of hypertension has been reported to be 50% (ranging from 35% to 80% when defined as BP less than 140/90 mm Hg without antihypertensive medication) in those who underwent ADX for unilateral APA,[4] and several scoring models have been proposed to predict probability of cure and improvement.[70–72] In order to evaluate these overall outcomes from various cohort studies, systematic review and meta-analysis method was also employed.[59,73,74] More recently, Williams *et al.* first published an international, multicenter, retrospective outcome survey, Primary Aldosteronism Surgery Outcome (PASO) study, based on consensus panel-defined 6 outcome measures of both clinical and biochemical success.[75] They enrolled a cohort of 705 patients who underwent

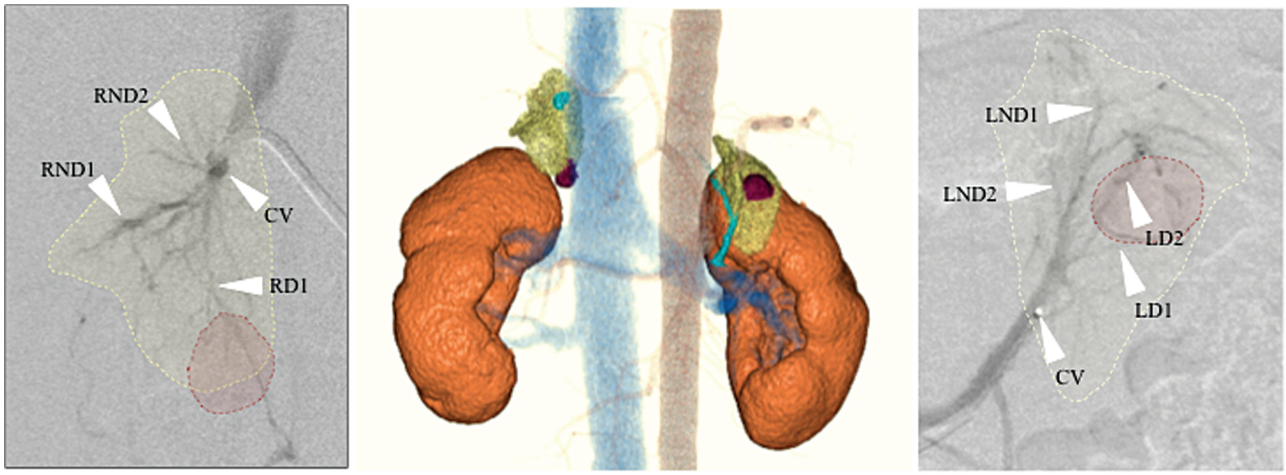

Figure 3. Illustration of bilateral APA by reconstructed 3D CT and segmental AVS. (**A**) Segmental sampling points from tumor (RD1) and nontumor segments (RND1 and RND2) of the right adrenal gland were superimposed on adrenal venography based on the 3D CT. The area circumscribed with a red dotted line delineates the tumor segment and that with a yellow dotted line indicates the outer line of the right adrenal gland. CV indicates a sampling point from a CV. (**B**) Reconstructed 3D CT showing the adrenal tumor (dark red) within each adrenal gland (yellow). Inferior vena cava, kidneys and abdominal aorta are depicted in blue, orange and light brown, respectively. (**C**) Segmental sampling points from tumor (LD1 and LD2) and nontumor segments (LND1 and LND2) of the left adrenal gland were superimposed on adrenal venography based on the 3D CT. The area circumscribed with a red dotted line delineates the tumor segment and that with a yellow dotted line indicates the outer line of the left adrenal gland. CV indicates a sampling point from a CV. Abbreviations: CT, computed tomography; CV, central vein.

laparoscopic unilateral ADX, and revealed complete success rates of 37% (range, 17–62%) and 94% (range, 83–100%) in clinical and biochemical evaluations, respectively.[75] The PASO study first provided internationally standardized outcome criteria based on the consensus reached by 31 experts of 12 tertiary PA centers worldwide employing Delphi process, and established a basis for scientific comparisons of the outcomes in those who underwent ADX for unilateral PA in future studies.[75]

Another emerging option, possibly as a future alternative for unilateral ADX, might be radio-frequency ablation of APA. To date, some research groups of interventional radiologists have reported clinical application of ablative methods to adrenocortical tumors including cortisol-producing adenomas[76,77] and adrenal metastatic lesions.[78,79] As clinical experiences of the adrenal ablation have been accumulated, initial experiences of CT-guided percutaneous radio-frequency ablation to unilateral APA was reported.[80–83]

In terms of the pharmacological treatment, mineralocorticoid receptor antagonists remain to be a mainstay. Recent advances have been reported in the development of nonsteroidal, third generation mineralocorticoid receptor antagonist, and aldosterone synthase inhibitors. Currently available steroidal mineralocorticoid receptor antagonists, spironolactone (first generation) and eplerenone (second generation), the former is more potent and the latter is more selective, have found their clinical use not only in hypertension but also in cardiovascular protection, especially in those with heart failure.

Extensive search was performed to discover compounds with higher potency and selectivity and clinically manageable property, and the following 3 agents have been evaluated in preclinical and clinical trials; apararenone (MT-3995), esaxerenone (CS-3150), and finerenone (BAY 94–8862). Unfortunately, concerning apararenone, no publication was available and some phase II clinical studies on diabetic nephropathy were reported to be in progress or completed according to clinical trial registration (https://clinicaltrials.gov). Esaxerenone was reported to have improved potency and selectivity *in vitro* and more potent antihypertensive effects in rat models, when compared to spironolactone and eplerenone.[84–86] Esaxerenone was reported to be under phase III trials in patients with PA, essential hypertension, and diabetes.[87] Finerenone, which was derived from dihydropyridine-based search and classified as a dihydronaphthyridine derivative, has already been extensively reviewed in recent articles on its basic and clinical data.[88–90] Briefly, finerenone was revealed to show balanced tissue distribution including heart and kidneys,[91] and Barkis *et al.* reported that add-on of finerenone in those with diabetic nephropathy significantly reduced albuminuria in dose-dependent manner in a randomized trial (ARTS-DN).[92] Subsequently, Filippatos *et al.* documented that finerenone decreased hospitalization for cardiovascular causes and mortality in those with heart failure with reduced ejection fraction complicated with diabetes and/or renal insufficiency in a randomized controlled study when compared to eplerenone (ARTS-HF).[93] Clinical utility of these third generation mineralocorticoid receptor antagonists in those with PA is to be extensively validated in future studies.

In addition, aldosterone synthase inhibitors have been investigated in recent clinical studies. Of them, LCI699 was an orally active inhibitor of both CYP11B2 and CYP11B1 and first evaluated clinically. In its early phase, LCI699 showed significant reduction in blood pressure in those with essential hypertension (dosage: 0.25–1.0 mg/day)[94] and reduction in both plasma aldosterone level and blood pressure in patients with PA (dosage: 1–2 mg/day)[95] with accepted

clinical tolerability. LCI699, on the other hand, was reported to show attenuated secretion of cortisol in cosyntropin stimulation in dose- and time-dependent manner in following studies.[96,97] Relatively high dosage of LCI699 (more than 2 mg/day) has been considered to cause hypocortisolism and concomitant feedback activation of HPA axis because of its inhibitory effect on CYP11B1. Subsequently, Amar *et al.* reported that high dosage of eplerenone (100–200 mg/day) showed better clinical profiles of blood pressure and potassium metabolism, when compared to relatively low dosage of LCI699 (1–2 mg/day) by sequential administration of these 2 agents.[98] According to the latest information on the trial registration, LCI699 has been clinically evaluated as an inhibitor of cortisol synthesis in those with excess secretion of cortisol. Further studies are expected to develop more selective inhibitors of CYP11B2 with less effect on cortisol synthesis and appropriate profile of tolerability and safety.[99,100]

GENETICS IN SPORADIC AND FAMILIAL FORMS OF PA

PA is a genetically heterogenous disease. Familial hyperaldosteronism accounts for 1–5% of PA and is classified into several forms based on clinical presentations and genetic alterations.[101] While some of the genetic alterations in familial hyperaldosteronism have been discovered over the past decades, those in sporadic PA have not been revealed until recently.

The recent advances of next-generation sequencing enabled several groups to identify recurrent somatic mutations in sporadic APA. Choi *et al.* first reported somatic mutations in *KCNJ5*, potassium voltage-gated channel subfamily J member 5, and other genes, including *CACNA1D*, *ATP1A1*, and *ATP2B3* (calcium voltage-gated channel subunit alpha1 D, ATPase Na+/K+ transporting subunit alpha 1, ATPase plasma membrane Ca2+ transporting 3, respectively), were also identified as somatically mutated in APA.[102–105] Through *in vitro* studies in adrenal cell lines, mutations in these genes have been demonstrated to increase intracellular calcium levels, resulting in CYP11B2 (aldosterone synthase) overexpression and aldosterone overproduction.[102–107] To date, approximately 40% and 70% of sporadic APA in Caucasian and Eastern Asian patients harbor somatic mutations in *KCNJ5*, respectively, while each of the other genes accounts for up to 10% of APA in these populations.[103,108–114] Whether the rest of APA, currently regarded as "wild-type", harbor abnormalities in other gene(s) and/or epigenetic modifications needs further experiments. In addition to these aldosterone-driver gene mutations, somatic mutations in *CTNNB1* (catenin beta 1) are also reported in up to 5% of APA,[103,110,111] but its involvement in tumorigenesis warrants further investigation.

In addition to the somatic alterations of APA described above, somatic mutations in non-APA PA adrenals are also being revealed. Similar to APA which has unilateral (more common) and bilateral (less common) forms, non-APA PA also has unilateral (less common) and bilateral (more common) forms. Although unilateral or bilateral non-APA PA do not present detectable masses by CT, hormonal measurement and adrenal vein sampling show excess levels of aldosterone secreted from unilateral or bilateral adrenals in non-APA PA, respectively. In 2017, we have reported that adrenals from unilateral non-APA PA, also known as unilateral multiple adrenocortical micronodules, have CT-undetectable multiple CYP11B2-positive lesions. These lesions, later collectively termed aldosterone-producing cell clusters (APCC), were considered sources of excess aldosterone because they expressed much more abundant CYP11B2 by immunohistochemistry than adjacent adrenals, like APA.[115] We then collected a large cohort of age-matched normotensive adrenals and demonstrated that the number of APCC is significantly increased in unilateral non-APA PA adrenals than normotensive adrenals, supporting the pathological role of APCC in clinical manifestation of hyperaldosteronism.[116] Furthermore, hypothesizing these APCC harbor somatic mutations similar to APA, we performed targeted next-generation sequencing on APCC from the unilateral non-APA cohort and the normotensive cohort, and showed that these APCC harbor somatic mutations in genes previously described as mutated in APA.[115,116] Interestingly, the most frequently mutated gene was *CACNA1D* in both cohorts as opposed to *KCNJ5* in APA, suggesting that APCC are not a major precursor for APA, but instead, there is a pathological increase of APCC number from normal adrenals to PA adrenals with maintained mutation spectrum could be the cause of unilateral non-APA PA. Whether more common bilateral non-APA PA, known as idiopathic hyperaldosteronism, is caused by the similar mechanism awaits further investigations. There are also several case reports where an APCC was observed adjacent to a small APA.[117–119] This may support APCC-APA progression but further confirmation with a larger number of such cases is warranted.

Taken together, applying next-generation sequencing techniques to adrenal glands (both PA and normal) has allowed making significant progress in understanding the underlying cellular and genetic mechanisms of PA, in the hope that further advances in basic and translational research would contribute to improving the current treatment strategies.

CONCLUSION AND PERSPECTIVES

After the decades in which PA had been nearly left behind as a rare cause of secondary hypertension, PA has currently been attracting growing interests from both basic and clinical standpoints. From a clinical standpoint in the management of hypertension, both general practitioners and specialists should share a common concept that PA might be rewarding if diagnosed and treated appropriately, especially in cases with surgically curable subtypes. We in addition need to consider 2 aspects of the disease; one dependent on blood pressure and the other induced by aldosterone (and salt) independently to blood pressure. More specifically, the following areas of PA clinical research are expected; first, appropriately designed, population-based screening of PA, second, studies on ethnicity-based differences in diagnosis, third, prospective studies on clinical outcomes such as blood pressure, target organ morbidities and mortalities, quality of life, and so forth. Finally, more detailed understanding of the pathophysiology and sophisticated care and cure of the

patients might be expected to make considerable contribution in lowering cardiovascular morbidity and mortality in those with hypertension and subsequent improvement in public health.

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DISCLOSURE

The authors declared no conflict of interest.

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