Primary Aldosteronism: Where Are We Now? Where to from Here?

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ABSTRACT

The past nine years have seen major advances in establishing the etiology of unilateral primary aldosteronism, and very possibly that of bilateral hyperaldosteronism, in response to somatic mutations in aldosterone synthase expressing cells. Though there have been important advances in the management of primary aldosteronism, in small but convincing studies, they represent minor changes to current guidelines. What has been totally absent is consideration of the public health issue that primary aldosterone represents, and the public policy issues that would be involved in addressing the disorder. In his introduction to PiPA 6, Martin Reincke calculated that only one in a thousand patients in Germany with primary aldosteronism were treated appropriately, an astounding figure for any disease in the 21st century. Towards remedying this totally unacceptable public health issue, the author proposes a radical simplification and streamlining of screening for primary aldosteronism, and the management of most patients by general practitioners. The second bottle-neck in current management is that of mandatory adrenal venous sampling for all but 1–2 % of patients, a costly procedure requiring rare expertise. Ideally, it should be reserved – on the basis of likelihood, enhanced imaging, or peripheral steroid profiles – for a small minority of patients with clear evidence for unilateral disease. Only when costs are minimized and roadblocks removed will primary aldosteronism be properly treated as the public health issue that it is.

Background

The initial invitation to contribute to PiPA6 was flattering but implausible – as final speaker, to review the previous presentations (37 orals, 24 posters). To do them justice would take at least a week, in itself a Sisyphean task: in 25 min, impossible. The organizers responded generously to my protests, and we settled amicably on the above title. A number of presentations at PiPA 6 have informed both questions posed by the title: many were in the area of bench-top discovery science, with others translational and clinical. As was only tangentially addressed were the public health issues around primary aldosteronism, covered in some detail in 'Where to from Here?'.

Current obstacles to optimal management of PA and possible remedies for obstacles to current management are outlined in ▶ **Table 1**.

'Where Are We Now?', were it to be broken down into basic and clinical, would merit 4.5/5 for the former and a very generous 1.5/5 for the latter: in terms of the policy issues needed to address the public policy lacuna it scores a resounding 0/5. First, inevitably, is the good news. Over the past nine years we have witnessed major breakthroughs in the molecular mechanisms underpinning primary aldosteronism: not yet complete, more to come, but the future looks bright. The last nine years have been revolutionary in terms of discovery – a variety of somatic mutations underpinning aldosterone producing adenomas (APA); expansion of hyperaldosteronism (FH) familiar to FH-II, FH-III, and FH-IV to join the time honored FH-I; recognition of aldosterone producing cell clusters (APCCs) largely replacing the zona glomerulosa with age, and somatic mutations thereof almost certainly underpinning bilateral adrenal hyperplasia, at least to a major extent if not totally.

2011: What Started the Ball Rolling?

The trigger for this cornucopia was a study from the Lifton laboratory on a series of large APAs from around the world. The authors found that 8/22 had one of two somatic mutations (6 L168R , 2 G151R) in the gene encoding KCNJ5, a component of the Kir1.3.4 potassium channel [1]. The dam broke: within the same year (2011) at least five corroborative studies were submitted for publication, which extended and refined several aspects of the first [2–6]. A corollary of the initial study was the recognition that a previously described [7] fulminating version of BAH, necessitating bilateral adrenalectomy in the father and two infant daughters, reflected a germ-line mutation in *KCNJ5* – and so the second cause of familial hyperaldosteronism was established as FH-III. FH-II, of which more later, described kindreds of up to five generations with primary aldosteronism, and with – at the time – no known genetic cause [8].

...And it Kept Rolling

Somatic mutations in *KCNJ5* in Caucasian populations represent 35–40 % of all APA, with a clearly higher incidence in women than men; in Japan and China the overall percentage of *KCNJ5* mutations is reported as 65–80 % [9, 10]. A series of additional somatic mutations was rapidly defined – in *CACNA1D*, *CACNA1H*, *ATP1A1*, *ATP2A3*, *CTNNB* [11–15] – and more recently *CNCL2*, now recognized as causing FH-II [16, 17]: it should be noted that this covered some but not all of the kindred previously studied. Since these initial discoveries, the percentage of APAs classified as 'wild type' – like essential (or primary) hypertension an admission of ignorance – shrank to < 10 % reflecting technical improvements with identification of CYPIIB2 expressing cells by antibody staining of sections, and next generation rather than Sanger sequencing. Very recently, somatic mutations in *CACNA1H* [18] have been found in three of 75 patients undergoing next generation sequencing of CYP11B2 positive cells from APAs, further reducing the percentage of 'wild type' APAs.

On the basis of these data clear patterns have emerged, in terms of the different prevalence of the various mutations.

Yet to be Explained Variation

In men, *CACNA1D* is the most common mutation; in women, as noted earlier, it is *KCNJ5*. Patterns between Caucasian [19] and African-Americans [20] differ significantly: whether Africans from the West Coast of Africa, with putatively considerably less Caucasian genetic material, are even more different is to date moot. Some mutations are extremely rare: it thus seems likely that over the course of the next few years additional somatic mutations will be added to the present tally of 93–94 %: 'wild type' is perhaps better expressed as 'not yet identified'. One major difference between *KCNJ5* and the other mutations is the apparent cell of origin, with *KCNJ5* mutations being in fasciculata-type cells, where CYP11B2 is co-expressed with CYP11B1, the enzyme responsible for cortisol production.

It is Probably not just APAs

The other area in which somatic mutations appear potentially to be causative is that of bilateral adrenal hyperplasia. In studies on archival material, it was noted not only that the prevalence of APCCs increased with age [21], but that in material from putatively normotensive patients some APCC appeared positive for *CACNA1D*, and to a lesser extent *ATP1A1*/*ATP2B3* – but not *KCNJ5*[22]. There had been a series of suggestions for a driver of bilateral hypersecretion of aldosterone above and beyond the physiological stimuli (angiotensin II, elevated plasma [K^+], ACTH) – agonist anti-AT_1R antibodies, leptin, etc. The scene changed radically with the publication of a joint Brisbane/Sendai ANN ARBOR manuscript, which examined the adrenal unilaterally removed for a variety of reasons, not all annotated – from patients with bilateral adrenal hyperplasia [23]. Of 15 specimens one proved technically lacking; all the other 14 proved to harbor *CACNA1D* mutations in some but not all of the APCCs present. All 14 adrenals had at least one, and up to 10, mutation-bearing APCCs. There were a total of 27 different mutations: of which 9 were found more than once, of which one was novel, as were the 18 mutations occurring only once. Tellingly, the authors found a highly significant correlation between the number of mutation-bearing APCCs and the previously measured plasma aldosterone concentration.

Questions yet to be Answered

At this stage, to recapitulate. Over the past nine years a series of somatic mutations have been shown to underpin > 90 % of APAs, and the recognition of germline familial hyperaldosteronism (a much less common form of primary aldosteronism) extended. FH-II is caused by *CNCL2* mutation; FH-III by *KCNJ5* mutation, with severity varying with different mutation sites; FH-IV, very rare, reflecting germline mutations in *CACNA1*H. Somatic mutations at this point in time also appear as drivers of bilateral aldosterone secretion: given the proclivity of *KCNJ5* mutations to occur in zona fasciculata cells, it is perhaps not surprising that they are not found in APCCs. The male prevalence of *CACNA1D* mutations, contrasting with that of *KCNJ5* in females, and the different somatic mutation profiles between Caucasians/African Americans/East Asians remain to be resolved, as does the diminishing percentage of APAs with a currently unidentified somatic mutations. Whether *CACNA1D* mutations can be confirmed to cause FH-V – it certainly can be germline expressed – and the erstwhile FH-II lineages negative for *CNCL2* mutation shown to be FH-VI - remain to be established.

Advances Elsewhere: PA Remains a Cottage Industry

This is a truly remarkable advance: nothing remotely similar has occurred beyond the laboratory, in terms of screening, confirmation/exclusion, imaging, lateralization (or not), surgery (for APA), targeted medical therapy for BAH, follow-up or, as previously noted, public health. There have been isolated, incremental advances, most yet to be adopted into the canon. Before detailing these it needs to be stated front and center that the management of primary aldosteronism, by expert groups between centers and countries, is the medical equivalent of a cottage industry. For those not

▶ **Table 1** Current obstacles to optimal management of PA and possible remedies.

Current Obstacles to optimal management of PA are
▪ The diagnosis rate is between 0.1 and 1.0 %;
▪ Ignorance among many general practitioners (G.P.s) of its prevalence;
▪ Reluctance of G.P.s to refer candidate patients, given the complexity of current screening and the costs of confirmatory tests, imaging, adrenal venous sampling (in particular), plus or minus surgery.
Possible Remedies for obstacles to current management include
▪ Ignoring the present 4–6 week program pre-screening in most cases;
▪ Reducing the number of candidates for AVS by enhanced imaging using radiotracers, peripheral plasma steroid levels, etc.
These advances represent at best marginal advances in management, which needs radical disruption. Disruption requires empowering general practice, as follows.
▪ GP orders PRA/PRC for all hypertensives;
▪ If renin non-suppressed, start/continue on standard antihypertensives;
▪ If renin is suppressed GP orders 24-hour urinary aldosterone (UA);
▪ If UA is < 6, standard antihypertensives: watch and wait;
▪ If UA is 6–12, possible PA, include MRA with antihypertensives: watch and wait;
▪ If UA is > 12, patient has PA: GP orders plasma [K +];
▪ If older, moderate UA/BP elevation, normokalemic: include low-dose MRA with standard antihypertensives: watch and wait, PRC/PRA after 6 months.
▪ If young, high UA, high BP, hypokalemic, ↓ ↓ renin – refer to expert center.

familiar with the term, it harks back to the days when goods were made in the home, in workshops, ateliers, forges – rather than made in factories and sold in malls. A present day example might be a dozen grandmothers baking an apple pie for the church fair – different apples, plus or minus rhubarb, cinnamon, egg wash, etc. One or two excellent, most not too bad, one or two not up to scratch. This is PA today: one problem is that it is orders of magnitude more demanding that making a superior apple pie.

Prescriptive Measures No: Harmonization Yes

If one is to take three areas of management – screening, confirmation and lateralization – the possible variations are mind-numbing. Possible candidates for primary aldosteronism are screened on the basis of their aldosterone to renin ratio (ARR). It is true that measurement of plasma aldosterone concentration and plasma renin activity have advanced over the past decade; what needs harmonization are the circumstances (on or off anti-hypertensives for 4–6 weeks) of the initial blood draw, the 'cut offs' for a positive ARR (20 or 30), whether the PAC needs to be above a certain value (14/14.5/15/16 ng/dl) to proceed to confirmatory/exclusion testing. One of half a dozen such tests are commonly used – or in some circumstances none; again, the cut-offs vary between centers in terms of the extent of lowering PAC levels needed to be 'positive'. Finally, in terms of lateralization, regular/tailored/super selective adrenal venous catheters; with cosyntropin (bolus, infusion, bolus plus infusion), without, or both; simultaneous or sequential catheterization; variation in selectivity index (SI) and lateralization index (LI); concomitant measurement of bilateral and peripheral cortisol, androstenedione, or metanephrines…put all this together, and you don't get to the grains of rice on the final square of the chessboard – but you are almost half-way there.

Diagnosis: Towards Uniformity in Confirmatory Testing

To date, essentially nothing has been done to simplify screening: a proposal to do so forms part of the 'where to from here' section. There have been three advances in the area of confirmation/exclusion. The first is the emerging consensus that a patient who has clearly florid primary aldosteronism on the basis of their ARR might be spared confirmatory/exclusion testing and proceed directly to imaging. The second is the recent development of the seated saline suppression confirmatory test [24, 25], results of which align very closely with the four day sodium and fludrocortisone suppression test, clearly the most laborious and on occasion termed 'the gold standard'.

The third are the pioneering studies from Athens underscoring the long-neglected role of ACTH as an aldosterone secretagogue [26]. When normotensive volunteers underwent a fludrocortisone suppression test, plus 1 mg dexamethasone at 11:00 PM on the last day (FDST), 97.5 % of the 72 subjects had a PAC less than 74 pm/l, and an ARR of 32 pm/l/mu/l, thus taken as the normal range. When hypertensives underwent the same dexamethasone-enhanced fludrocortisone suppression test, 31 % (56/180) had values for both PAC and ARR above the upper limit of normal. A subsequent study [27] on 113 hypertensives negative on the FDST test divided them into two groups. One (30/113:27 %) proved hyper-responsive (in terms of elevated aldosterone secretion) to ultra-low dose ACTH/treadmill at 80 % capacity, while the other (83/113:73 %) was not different from normotensive controls: cortisol responses were the same for all three groups.

There is Nothing New Under the Sun: An Example

A step back 40 years. In 1980, a group in Cologne published a study [28] in which patients and controls were maintained for 6 days on a 175 mEq sodium intake. Control patients responded with 24 h urinary aldosterone levels of ≤ 6 µg/day. Of 100 'essential' hypertensives 36 showed urinary aldosterone levels above the upper limit of normal. When patients below the 6 µg/day cut-off were treated with spironolactone, their blood pressure on average fell by 9 mmHg: in those above the cut-off it fell by 23 mmHg. The study also included 16 patients with established primary aldosteronism, whose blood pressure on spironolactone fell by 21 mmHg. Taken together, these findings suggest that hyperaldosteronism, whether screened on the basis of hypokalemia or occult, might account for ~45 % of hypertension – a figure very close to that suggested by the two Greek studies [26, 27].

Even in Normotensives…

The necessity of 24 h urinary aldosterone measurement, rather than a single spot plasma aldosterone concentration, was recently elegantly underlined by a study from Boston [29]. In a group of 210 normotensive study subjects, 14 % (29/210) were found to have urinary aldosterone above 12 µg/day, a very generous cut-off given current sodium intake: only 6/29 of these subjects screened positive for primary aldosteronism on the basis of their plasma aldosterone to renin ratio. The obvious inference is that such subjects have primary aldosteronism, presumably engendered by episodic stress causing spikes in ACTH secretion. They may well become hypertensive over time: but hypertension in itself is not a *sine qua non* for primary aldosteronism, as demonstrated by a small but convincing study [30] on young subjects, normotensive despite a definitive diagnosis of familial hypertension type 1.

Parsing Medical Management of Bilateral Hyperaldosteronism

A second recent study from Boston [31] broke new ground in the medical management of bilateral hyperaldosteronism. A number of previous studies had documented the heightened risk profile of primary aldosteronism compared with age-, sex-, and blood pressure-matched essential hypertensives. The first of these [32] from Paris reported extraordinarily elevated levels (4- to 12-fold higher) for stroke, non-fatal myocardial infarct and atrial fibrillation: subsequent studies [33–35] have been less apocalyptic, but reaffirmed lesser but significant differences. The Boston study showed that patients with an APA resected and biochemically cured post-surgery had a risk profile slightly better than that in matched essential hypertensives, perhaps not surprising if some of the 'essential hypertensive' controls had low grade occult primary aldosteronism as previously discussed [29].

The real breakthrough was seen when the bilateral hyperaldosteronism subjects were divided into two groups – those who at 6 months after starting medical therapy had a suppressed (< 1 ng/ml/h) plasma renin activity, and those in whom PRA was > 1 ng/ml/h, that is, no longer suppressed. The former group had a ~three-fold higher risk profile than controls; the latter the same risk profile as controls. There was tellingly no difference in blood pressure between-groups; the renin suppressed group received slightly but significantly lower daily doses of MRA: (spironolactone 43 vs. 50 mg; eplerenone 53 vs 65 mg). The authors suggest increasing spironolactone in patients with suppressed renin: either a modestly lower sodium diet, or adjuvant amiloride/triamterene, might be more effective, given the relatively high non-compliance rate of male patients on spironolactone. The key advance, however, remains: that of measuring plasma renin, activity or concentration, after six months of medical therapy.

Sixty Years After Spironolactone: A Very New Player

The final, very promising advance has been in the development of generation 3 and generation 4 mineralocorticoid receptor antagonists (MRAs). If spironolactone/canrenone/potassium canrenoate represent generation 1, and eplerenone generation 2, then an ideal generation 3 MRA would be nonsteroidal, with affinity for mineralocorticoid receptors (MR) as high or higher than that of spironolactone, specificity for MR as high or higher than that of eplerenone, cheap to make and with a relatively long half-life. A generation 4 MRA is all of the above, plus tubule sparing, to lessen the risk of hyperkalemia: an example of this class, targeted to the heart, is finerenone. Given its apparent tubule sparing, finerenone (and probably the third recently described MRA, aparerenone) is inappropriate as an MRA for primary aldosteronism. What may be appropriate is esaxerenone [36], a generation 3 compound thus and a possible major player in future management of primary aldosteronism.

The Dilemma of Lateralization

These are truly green shoots, and point the way to substantial change in aspects of the management of primary aldosteronism: whether these changes can be widely embedded in practice remains to be determined. There is a justifiable belief that the major impediments to the unwillingness of general practitioners to refer hypertensive patients for assessment of possible primary aldosteronism is the complexity of the screening process and, more importantly, the cost of lateralization by adrenal venous sampling (AVS). Imaging alone – by CT or any other modality - is not an appropriate method of localization except in very rare circumstances (and at the discretion of the physician) – in a patient with florid hyperaldosteronism, very high aldosterone and suppressed renin, under the age of 35, with a single unilateral adenoma and an unremarkable contralateral adrenal [37].

These are rare cases and currently there are various initiatives to increase the number of patients with confirmed primary aldosteronism in whom it would appear relatively safe to forego AVS. A number of studies have used ^{11}C-metomidate, which binds to the key enzyme (CYP11B2) in aldosterone biosynthesis, to localize (or not) the site of aldosterone overproduction [38]. The first problem is the requirement of a cyclotron at the site to generate the very short-lived radiotracer; the second is that the tracer has ~3-fold higher affinity for CYP11B1, the key enzyme in cortisol biosynthesis, entailing three days of suppression of ACTH by dexamethasone

administration. Parallel studies with ^{125}I-metomidate, a much longer lived tracer, are currently in progress. Perhaps the most promising agent for specifically imaging CYP11B2 (aldosterone synthase) is an ^{18}F-derivative of a specific and very high affinity aldosterone synthase inhibitor (CDP-2230) developed by Merck but not taken further into clinical use [39].

A further possible route towards foregoing AVS may lie in measurement of one particular (and unusual) adrenal steroid, or a selection of adrenal steroids in peripheral plasma. As previously noted, *KCNJ5* mutation-bearing APAs appear to be of fasciculata cell type origin, thus expressing CYP11B1 and CYP11B2. Again, as previously noted, 70–85 % of APA in Japan (and China) reflect a *KCNJ5* mutation; on measurement of peripheral levels APA fell into three groups [40] – those with high, low and intermediate levels of circulating 18-oxocortisol. The inference from these studies is probably limited to the high and low 18-oxocortisol groups, as almost certainly having/not having a *KCNJ5* mutation, so that with careful imaging and consideration of the hybrid steroid levels many patients might reasonably forego AVS.

Where Are We Now; An Interim Summary

The molecular drivers of APA have been largely established, with interesting infill questions remaining (gender/ethnicity/?FH-V/?FH-VI). Those for bilateral hyperaldosteronism are less advanced, and the ground breaking Brisbane–Sendai study needs to be repeated, perhaps by a consortium which pools material from their patients who lateralized on AVS but showed no APA on histology.

What has received scant attention is the mechanism(s) underlying the increased cardiovascular risk in primary aldosteronism. It is unthinkingly, and non-physiologically, generally assumed that this is a direct effect of aldosterone on cardiac/renal/vascular mineralocorticoid receptors, which is not the case. In sodium deficiency aldosterone levels rise to those seen in florid primary aldosteronism, with no evidence for cardiovascular damage, and the crucial role of sodium in primary aldosteronism is neglected. This is covered in further detail in one of the sections to follow.

Screening is complicated, cumbersome and dependent on single estimates of plasma aldosterone and renin, and increasingly done without the recommended 4–6 week period off prior medication. Confirmatory testing is increasingly omitted in patients with a high ARR, and has the possibility of being harmonized if the will for acceptance is there. Currently perhaps 1–2 % of PA patients can reasonably progress to surgery without AVS: there are different avenues (tracers, hybrid steroids) being pursued to increase this percentage. Nothing has changed in terms of the public health and policy issues.

Where to from Here?

The Problem

In his brief welcoming introduction to PiPA6 Martin Reincke showed the data from Germany, where only one in a thousand subjects with primary aldosteronism is ever diagnosed and appropriately treated: there is no reason to believe that the figure would be significantly different elsewhere. In 2020, it is hard to imagine any other disorder with such a low rate of recognition: herein lies the problem, and the issue for health policy makers. This is what faces us; 'Where to from Here?' must address as soon as possible, and as best we can, this medically appalling situation. Current interest and current practice perhaps almost inevitably focus on potentially curable primary aldosteronism, that is, APA, with bilateral disease and lifetime medication a less appealing outcome. Most of the occult primary aldosteronism will be bilateral disease: APA are more florid, and when current figure for prevalence are compared across centers, those with straitened cut-offs report 5 %, of which ~3 % are APA and ~2 % BAH; those at the more inclusive end (up to 13 %) report ~3–4 % APA and ~9–10 % BAH. If occult hyperaldosteronism is ~45–50 % of essential hypertension, it is likely that ≥ 90 % will be BAH, the less florid form – less florid, but with a substantially higher risk profile than comparable essential hypertension unless specifically targeted and treated.

Let not the Perfect Drive out the Good

The current guidelines on screening – for 50 % [37] to 100 % [41] of hypertensive patients – present a massive discouragement for general practitioners to whom a hypertensive patient presents. Many general practitioners are not well informed about primary aldosteronism, which in medical school and post-graduate training may fall between three rather than two stools – endocrinology, cardiology, and nephrology. In a very well designed survey of German and Italian general practitioners [42], among their many hundreds of hypertensive patients, 18 % in Germany and 30 % in Italy reported no patients with primary aldosteronism. For Gian Paolo Rossi in Padua, fewer than 20 % of his patients come from referrals, with the majority from his website. What needs to change, and to change radically, is the way that patients are screened for primary aldosterone in the first instance, and that for most patients who screen positive adrenal venous sampling is not the inevitable sequel.

This cuts right across current management, newly involves and recognizes the role of general practice and thus needs to be carefully and sequentially justified. All hypertensives should have blood taken by their GP for a plasma renin assay. If the DRC is above 8, or plasma renin is > 1, the patient is very unlikely to have primary aldosteronism: standard first line antihypertensives, watch and wait. If renin is suppressed, the next step is for the general practitioner to order a 24-hour urinary collection for levels of aldosterone. If the urinary 24-hour aldosterone (UA) is less than six, standard antihypertensives, watch and wait; between 6 and 12 µg, include an MRA with first line antihypertensive medication, watch and wait. If the 24 h UA is > 12 µg, then the patient has primary aldosteronism; GP to order plasma [K^+]. If the patient is young, has the signs of florid primary aldosteronism – very high blood pressure, high UA, hypertension resistant to current therapy, hypokalemia, renin below detection limit – imaging and possibly AVS. If, on the other hand blood pressure and UA are modestly elevated, the patient normokalemic and not young, which would be the majority of cases, include a low dose MRA in therapy, watch and wait, and a second PRC/PRA at 6 months.

Given the many variations between centers in current screening protocols, it is difficult to regard them as perfect: what they have in common is that they are very similar in capturing florid (~3 % of hypertensives) hyperaldosteronism represented by APAs,

but differ in their concern for those with undoubted but less florid primary aldosteronism due to BAH. Whether - when all the numbers are in – primary aldosteronism is 5–13 %, or 45–50 % of hypertensives, current screening covers a minute fraction of affected patients, and has to be radically simplified before even well-informed general practitioners will embrace screening. The objection that the very much simplified protocol as put forward might condemn some APA patients to a lifetime of MRAs is hollow: for every such patient under the current screening protocol perhaps 100 APAs remain suboptimally treated by conventional hypertensives. The occasional APA would certainly be better off with an MRA added…and let not the perfect drive out the good.

One of the objections currently voiced as 'opening the floodgates' in terms of a major increase in patients diagnosed – and thus needing to be treated – is that of costs that no health service, however well informed and forward looking, can possibly afford. This is true for the way we currently address the issue, and attempts to widen the net beyond Martin Reincke's one in a thousand need a coherent policy of minimizing costs while maximizing benefits. The simplified screening test proposed is much less confronting than the current 4–6 weeks of medication withdrawal/substitution, covers episodic aldosterone secretion – currently neglected – and allows the general practitioner either to refer or to initially manage most patients by including low dose mineralocorticoid receptor antagonists with the regime to lower blood pressure, watch and wait. The florid cases, as previously suggested, are very much in the minority, and should be referred to an expert center.

Part of the watching and waiting should include measurement of PRA/PRC at 6 months, to ensure that renin is no longer suppressed. Spironolactone as an MRA has the advantage of being very cheap, and at 25 mg/day its androgen receptor antagonist activity is very rarely an issue in terms of compliance in male patients. If renin remains suppressed, a trial of 50 mg/day in women, and adjuvant amiloride/triamterene in men, should be instituted, and salt intake lowered. The presumption is that the overwhelming majority of the wait and watch patients will have bilateral disease, but that occasionally a patient with unilateral disease will be caught in the net: very suppressed renin, increasing blood pressure/antihypertensive requirements/hypokalemia should then prompt referral to an expert center. If esaxerenone is marketed at a reasonable price – unlike the global price for eplerenone – then it may become the ideal MRA for use in bilateral PA.

What this high-volume management regime dose is to limit AVS – the bottleneck in terms of costs – to a population less than that currently undergoing the procedure as mandated by present guidelines. Imaging by CT or MRI has been repeatedly shown to be inferior to AVS; enhanced imaging/PET scanning agents which bind to aldosterone synthase would appear some distance off, and their cost is substantial. As previously discussed, levels of 18oxo-cortisol plus an adenoma on imaging may be of more assistance in Japan and China than elsewhere, given their very high percentage of KCNJ5 mutations. What will hopefully very substantially reduce lateralization by AVS, and at a fraction of the cost, may be the possibility of multi-steroid fingerprints in peripheral blood samples that distinguish unilateral from bilateral hypersecretion with a high degree of accuracy.

In terms of policy, the situation is stark. If patients with BAH and suppressed renin are at ~3 fold higher risk – despite being treated with an MRA – it is difficult to imagine that with no MRA the risk would be the same, let alone lower. The eventual health costs – for the individual, for society – are substantial, and can be avoided even in the presence of persistent hyperaldosteronism by increased sodium excretion/lowering sodium intake. This is not the place for a detailed cost-benefit analysis – which in any case is beyond the author's capability – except to express confidence that when it is done the case will be irrefutable.

One final thought, for those interested in the pathophysiology of primary aldosteronism. Aldosterone per se is not a cardiovascular risk; high levels in homeostatic mode in response to sodium deficiency are testimony to its innocence; what drives cardiovascular risk is the combination of aldosterone and inappropriate sodium levels. In one sense aldosterone is the prime mover, inasmuch as it retains more sodium via epithelia than would otherwise be the case: in another sense the inappropriately elevated total body sodium is a *sine qua non* for adverse cardiovascular risk, given that in states of sodium deficiency very high aldosterone levels are harmless. What is currently not known is how the two actors combine to produce cardiovascular damage.

One possibility, previously canvassed, [43] is that of the vasoconstrictor action of endogenous ouabain/ouabain-like molecules, released from the adrenal cortex in response to ACTH, angiotensin via AT_2R_1 and *sodium loading*. Such a mechanism is but one possible explanation: it may provide alternate therapeutic modalities; for example, digibindin has been shown to reverse ACTH-induced hypertension in mice [44]. Rather than blaming aldosterone for the elevated risk profile and cardiovascular morbidity, it would be useful if those involved in primary aldosteronism recognized the duality of causation, and worked towards how it is established.

CODA

What is needed is a seismic shift in focus, from the expert center to public health. This is not to denigrate expert centers, which are the *sine qua non* for the management of unilateral hyperaldosteronism: it is just that to date the *sine qua non* has become the *ne plus ultra*. This shift will require us to return the management of the bulk of primary aldosteronism to general practitioners, at minimal cost to cover the extraordinary number of patients who never receive targeted treatment. It is a big ask – disruptive, bridges to cross, bridges to burn – but it is time we got real about how primary aldosteronism is optimally managed. Now is the time to act.

Conflict of Interest

The author declares that he has no conflict of interest.

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