

Role of Adrenal Vein Sampling in Guiding Surgical Decision in Primary Aldosteronism

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Key words

adrenal vein sampling, primary aldosteronism, ACTH stimulation, adrenalectomy, contralateral basal suppression

received 20.12.2022

revised 24.04.2023

accepted 01.06.2023

Bibliography

Exp Clin Endocrinol Diabetes 2023; 131: 418–434

DOI 10.1055/a-2106-4663

ISSN 0947-7349

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ABSTRACT

Adrenal vein sampling (AVS) is recommended for subtyping primary aldosteronism (PA) to identify lateralized or bilateral sources of aldosterone excess, allowing for better decision-making in regard to medical or surgical management on a case-by-case basis. To date, no consensus exists on protocols to be used during AVS, especially concerning sampling techniques, the timing of sampling, and whether or not to use adrenocorticotropic hormone (ACTH) stimulation. Interpretation criteria for selectivity, lateralization, and contralateral suppression vary from one expert center to another, with some favoring strict cut-offs to others being more permissive. Clinical and biochemical post-operative outcomes can also be influenced by AVS criteria utilized to indicate surgical therapy.

In this review, we reanalyze studies on AVS highlighting the recent pathological findings of frequent micronodular hyperplasia adjacent to a dominant aldosteronoma (APA) overlapping with bilateral idiopathic hyperaldosteronism (IHA) etiologies, as opposed to the less frequent unilateral single aldosteronoma. The variable expression of melanocortin type 2 receptors in the nodules and hyperplasia may explain the frequent discordance in lateralization ratios between unstimulated and ACTH-stimulated samples. We conclude that aldosterone values collected during simultaneous bilateral sampling, both at baseline and post-ACTH stimulation, are required to adequately evaluate selectivity, lateralization, and contralateral suppression during AVS, to better identify all patients with PA that can benefit from a surgical indication. Recommended cut-offs for each ratio are also presented.

Introduction

Early case detection and adequate therapeutic management of primary aldosteronism (PA) are crucial to reducing the associated increased risk of metabolic and cardiovascular complications of PA [1–3]. In a classic dichotomous manner, PA was believed to be mostly secondary, in almost equal proportions, to either unilateral

single aldosterone-producing adenomas (or aldosteronomas) (APA) or bilateral idiopathic hyperaldosteronism (IHA) [1, 4, 5]. Adrenal vein sampling (AVS) has been performed to distinguish between both etiologies and recommending surgical therapy in unilateral APA or medical therapy in bilateral IHA [4]. Patient preferences, comorbidities, and co-secretion of cortisol also affect the final therapeutic decision. To date, AVS remains the gold-standard localization test for adequate subtyping of PA and tailoring of therapeutic management [4, 6, 7]. In one systematic review, compared

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► **Table 1** Different AVS protocols and interpretations, according to National Societies and cited expert centers.

Expert Authority	AVS Procedure	Success Criteria	Unilateral PA Diagnosis
International and national endocrine societies			
European Society of Hypertension (2020)	Unstimulated or continuous ACTH infusion	Unstimulated SI ≥ 2	Unstimulated LR ≥ 2 [4]
		ACTH-stimulated SI ≥ 5	ACTH-stimulated LR ≥ 4
Endocrine Society (2016)	Unstimulated (sequential or simultaneous), continuous ACTH infusion, or ACTH bolus	Unstimulated SI ≥ 2	Unstimulated LR ≥ 2
		ACTH-stimulated SI ≥ 5	ACTH-stimulated LR ≥ 4
French Society of Endocrinology (2016)	Unstimulated, simultaneous	Unstimulated SI ≥ 2	Unstimulated LR ≥ 4
Japan Society of Endocrinology (2009)	ACTH bolus	ACTH-stimulated SI ≥ 5	ACTH-stimulated LR ≥ 2.6 , or aldosterone concentration > 1400 ng/dL on one side
AACE (2006)	Continuous ACTH infusion	ACTH-stimulated SI ≥ 10	ACTH-stimulated LR ≥ 3
Expert centers*			
Munich and Paris	Unstimulated	Unstimulated SI ≥ 2	ACTH-stimulated LR ≥ 4
Torino	Unstimulated and continuous ACTH infusion	Unstimulated SI $\geq 2-3$ [47]	LR ≥ 4 or ≥ 3 and CLS ≤ 1
Brisbane	Unstimulated	Unstimulated SI ≥ 3	LR ≥ 2.5 and CLS ≤ 1
Rochester	Continuous ACTH infusion	ACTH-stimulated SI ≥ 5	ACTH-stimulated LR ≥ 4
Sendai	ACTH bolus	ACTH-stimulated SI ≥ 5	ACTH-stimulated LR ≥ 2.6
Yokohama City	ACTH bolus and continuous infusion	AV[Cortisol] > 200 mcg/dL	Ipsilateral AV[PAC] > 1400 ng/dL
Abbreviations: AV: adrenal vein; AVS: adrenal vein sampling; Ipsilateral AV: ipsilateral adrenal vein; LR: lateralization ratio; PA: primary aldosteronism; PAC: plasma aldosterone concentration; SI: selectivity index.; *Adapted from reviews by Williams and Reincke [100] and Reincke et al. [5].			

to AVS, conventional imaging led to an incorrect diagnosis in 37.8% of PA patients [8], with similar discordance rates in other studies [9–11]. Additionally, recent studies have shown that, even in younger patients in which AVS could potentially be avoided [4, 6], imaging alone cannot undoubtedly confirm lateralized PA [12–14]. Thus, AVS remains indispensable for a correct diagnosis, regardless of age, when the patient is able and accepts an adrenalectomy if a lateralized source of aldosterone excess is demonstrated. The main limitation of AVS resides in the successful cannulation of the right adrenal vein (RAV) because it is smaller and shorter compared to the left adrenal vein (LAV), and it drains directly into the inferior vena cava (IVC). It can also share a common trunk with a hepatic accessory vein in 8–12%, thus diluting the cortisol concentration and decreasing the selectivity index (SI) [15, 16]. Therefore, AVS should be done by an experienced interventional radiologist in referral centers to increase rates of successful RAV cannulation and limit procedure-related complications. Additionally, no standardized protocol has been agreed upon, and protocols vary from one center to another, especially regarding the sampling procedure, the use of adrenocorticotrophic hormone (ACTH) stimulation, and their interpretation criteria, including expert consensus opinions on the conduct of AVS (► **Table 1**) [5, 17, 18].

Although the use of ACTH stimulation improves the SI [18], its influence on the lateralization ratio (LR) is still somewhat controversial in the literature [18–21], leading several centers, particularly in Europe, to abandon ACTH stimulation and adopt only unstimulated values for interpretation of lateralization. In this review, we will discuss the different techniques of AVS, the numerous interpretation criteria, and the clinical and biochemical outcomes of AVS-guided surgery.

Classical dichotomy between uniform phenotypes of aldosteronoma and idiopathic hyperaldosteronism revisited

a. Overlap between histological subtypes based on positive CYP11B2 immunohistochemistry (IHC)

The traditional classification of PA into either APA or unilateral/bilateral IHA was challenged and revamped into a modern classification based on both morphology and functionality, determined by CYP11B2 IHC. The recent development of monoclonal antibodies targeting CYP11B2 [22] allowed for a better understanding of the pathophysiological mechanisms governing PA. In fact, areas within the adrenal cortex, known as aldosterone-producing micronodules (previously aldosterone-producing cell clusters), express CYP11B2 and can produce aldosterone in excess without being necessarily restricted to a well-defined radiologically detected nodule or hyperplasia [23–25]. Such micronodules are often found adjacent to a dominant APA in resected adrenals based on lateralized AVS, which had suggested that a unique APA would be found [26]. The modern classification suggested by the international HISTALDO consensus includes, in addition to classical APA, non-classical PA histology including either multiple aldosterone-producing nodules, aldosterone-producing micronodules, or rarely, diffuse hyperplasia of *zona glomerulosa* [5, 25]. Accordingly, bilateral PA is explained by multiple aldosterone-producing micronodules/nodules harboring somatic driver mutations, most frequently *CACNA1D* mutations [14, 25, 27–29]. However, it can be presumed that micronodules found adjacent to an APA can also be present in the contralateral adrenal, further explaining the persistence of PA after adrenalectomy and highlighting the role of CYP11B2 IHC in the post-operative follow-up of patients [25, 30, 31].

b. Variable expression of melanocortin type 2 receptors (MC2R) in primary aldosteronism

ACTH stimulatory effects on AVS results vary greatly in part due to the variable expression of ACTH receptors, or MC2R, in APAs and PA micronodules compared to normal *zona glomerulosa* [32]. It has been shown that while APAs with ATPase somatic mutations demonstrate a high MC2R expression, those with *KCNJ5* mutations tend to be poor in MC2R [1]. In the former case, this results in an increased ipsilateral aldosterone secretion, and in the latter, a relatively higher aldosterone secretion from the surrounding (and contralateral) cortex following ACTH stimulation [1]. Independently of the underlying driving somatic mutations, other authors have noted in contrast, that only a minority of florid PA cases overexpress MC2R, while about two-thirds under-expressed it [20]. Thus, the MC2R expression variability impacts ACTH-stimulated LR and can contribute to discordance between unstimulated and ACTH-stimulated LR, as will be discussed in a further section.

c. AVS without adrenocorticotropic hormone stimulation

Several centers discontinued the use of ACTH stimulation during AVS following initial reports of discordant lateralization between unstimulated values and ACTH-stimulated values [33] and only collected unstimulated samples for cortisol and aldosterone measurements. The most recent studies on AVS without ACTH stimulation and their essential conclusions are summarized in ► **Table 2**. The 2014 expert consensus statement on the use of AVS for subtyping PA [17] recommended that unstimulated AVS be performed in the morning to minimize false-negatives caused by the diurnal variations of aldosterone secondary to endogenous diurnal rhythm of ACTH [34]. Moreover, the selectivity and lateralization indices are influenced by the transitory stress reaction at the beginning of the procedure. The increase in cortisol in both adrenal veins at the start of AVS would generate different ratios between samples taken 15 min apart, with higher values on the first samples [35, 36]. Even in the absence of a stress reaction, aldosterone levels are highly variable and not persistently elevated during AVS. In fact, Yozamp et al. [37] recently showed that unstimulated triplicate measurements of aldosterone had a mean percent difference of 57% and 73% in the left and right adrenal veins, respectively. This resulted in discordant lateralization in 17% of patients, mostly from lateralized to bilateral PA, when using only one of the three unstimulated samples for aldosterone-to-cortisol (A/C) ratio calculation [37].

Additionally, peripheral aldosterone values were also found to fluctuate importantly, often reaching normal values in a high proportion of patients during AVS, without hypokalemia, but potential fluctuations in ACTH, posture, or other aberrant regulators of aldosterone secretion may be implicated [32, 37, 38]. These findings led to recommending the collection of at least 2 or 3 unstimulated samples during the AVS procedure to overcome the variability of aldosterone.

The question of whether simultaneous or sequential sampling achieves better results in unstimulated AVS is rather controversial. In fact, a large retrospective study, including 188 patients undergoing simultaneous bilateral AVS and simulated sequential AVS, did not report significant differences in both selectivity and lateralization indices between the two procedures [39], confirming the

results of a previous smaller study [40]. However, two prospective studies from the same group [35, 36] reported better accuracy for the diagnosis of lateralized PA with simultaneous bilateral sampling and discouraged sequential sampling unless samples can be successfully drawn from both adrenal veins within 15 min at most. The discordance between these studies might be due to the differences in the timing of samples, where Almarzooqi et al. suggested a maximal delay of 5 min between sampling of both sides in sequential AVS, after which possible inaccurate ratios might derive [39]. In inexperienced hands, this time interval could be difficult to achieve, rendering sequential AVS longer and less accurate.

As discussed earlier, successful cannulation of both adrenal veins is required to accurately interpret AVS results. This is measured by calculating the SI, which is the ratio of the serum cortisol concentration in the adrenal vein (AV) to that in the IVC. No approved cut-off exists for SI interpretation, and each center uses its own criteria, with variations from 1.1 to a more stringent SI of 3 for unstimulated ratios (► **Table 2**). When using a strict cut-off of 5 compared to 1.1, the rate of unsuccessful cannulation increased from 4% to 45% [41]. This is concordant with a previous study demonstrating that while a permissive SI cut-off increased the rate of successful cannulation from 34 to 91%, an SI of < 2.75 had poor diagnostic reproducibility and could lead to incorrect PA subtyping [42]. In contrast, Mailhot et al. reported no difference in specificity between cut-offs 2 and 3 for unstimulated SI, and no false positives were found with either (i. e., 100% specificity), but sensitivity increased from 50.4% to 70.8% with a more permissive cut-off of 2 [43].

The LR, the ratio of A/C on the dominant side to A/C on the contralateral side, is also subject to different criteria (► **Table 2**). The basal or unstimulated LR varies between 2 and 4 depending on the center where AVS is performed. Monticone et al. [18] recommended an LR > 4 for the diagnosis of lateralized PA and < 3 for bilateral PA, for both stimulated and unstimulated ratios, while an unstimulated LR of > 2 for lateralized PA was suggested by others [21, 44]. In the case of intermediate LR (= 3–4), patient-related clinical and biochemical characteristics should be used to achieve a final decision regarding treatment [18]. Additionally, El Ghorayeb et al. [21], concluded that unstimulated LR plays a major role in the treatment decision and suggested that when unstimulated and stimulated LR were discordant, as is the case in up to 28% of patients, unilateral adrenalectomy could still be considered even when ACTH-stimulated LR was < 4 but unstimulated LR was ≥ 2. Recently, an unstimulated LR > 4 was found to be significantly associated with complete clinical (*OR* 4.30, 95% *CI* 1.18–15.68) and biochemical success (*OR* 7.55, 95% *CI* 1.28–44.47) [45]. Nonetheless, some cases of lateralized PA that would benefit from surgery could be missed when choosing a higher LR cut-off.

One other important limitation of unstimulated AVS is that presence of a quiescent phase of aldosterone secretion in some lateralized cases of PA leads to a missed diagnosis, and lateralization can only be revealed after ACTH administration (see later section).

AVS with sampling performed only under adrenocorticotropic hormone perfusion

The theoretical benefits of ACTH administration during AVS include increased identification of successful AV cannulations due to improved SI, reduced fluctuations in aldosterone and cortisol secre-

► **Table. 2** Studies on AVS performed without ACTH stimulation.

Study	Country	Patients' Selection	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions
Benoit et al., 2022 [53]	France	188	Sequential or bilateral simultaneous	≥ 2	≥ 4	N/A	Adequate cannulation in 82.3%
		2018–2020 prospective					Lateralization in 38 patients (24.6%)
		Concordance between lateralization and CT in 35.4%					
		Cure in 83.3% of patients with radical treatment					
		Clinical recovery higher in women (88.9 vs. 38.9%; <i>p</i> 0.0153)					
Huang et al., 2020 [45]	Taiwan	54	Sequential	≥ 2	≥ 2	A/C non dominant side < A/C peripheral vein	Complete clinical success in 57.4% (PASO criteria)
		2011–2016 retrospective					Complete biochemical success in 80.8% (of 52 evaluated)
		LR > 4: significantly associated with complete clinical success (OR 4.30, 95% CI 1.18–15.68) and biochemical success (OR 7.55, 95% CI 1.28–44.47)					
		Contralateral suppression: an independent predictor of complete biochemical success only					
Aono et al., 2019 [10]	Japan	362	Bilateral simultaneous	> 2	≥ 2	< 1	No nodules on CT: 88% successful AVS and 36% lateralized
		2005–2016 retrospective					Bilateral nodules on CT: 100% successful AVS and 17% lateralized
		Unilateral nodules on CT: 85% successful AVS and 41% ipsilateral PA					
		Concordance rate between CT and AVS: 53%					
		Bilateral nodules on CT + lateralized disease on AVS (<i>n</i> = 17) had a complete biochemical success rate < unilateral nodules on CT + ipsilateral disease on AVS (<i>n</i> = 30) (41% vs. 80%, <i>p</i> 0.01)					
Rossitto et al., 2018 [36]	Italy	138	Bilateral simultaneous and simulated sequential R->L and L->R	≥ 2	≥ 2	N/A	Simultaneous is superior to sequential AVS for APA diagnosis
		2007–2015 prospective					Of 37 patients who lateralized on AVS: 100% had a biochemical cure
Pedersen et al., 2016 [101]	Denmark	50	Sequential	N/A	N/A	N/A	Lateralized PA: 39/50 patients
		1992–2006 retrospective					28% with lateralized PA on AVS had normal imaging
Citton et al., 2015 [102]	Italy	128	Bilateral simultaneous	> 1.1	> 2	N/A	56 patients underwent AVS-guided unilateral adrenalectomy
		1990–2013 retrospective					The combination of AVS/scintigraphy and CT/MRI reduced the failure rate from 10.6 to 1.4%
		PPV of scintigraphy for the biochemical cure: 93%					
		PPV of AVS 100%					
		Recurrence of PA in 3.7%					
Haase et al., 2014 [103]	Germany	4	Sequential	≥ 2	≥ 4	N/A	Four patients had AVS under MR antagonist: all four had persistent suppressed renin despite MR antagonists and lateralized PA and underwent adrenalectomy
		2008–2014 retrospective					6 months after surgery: all patients showed remission of PA

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► **Table 2** Continued.

Study	Country	Patients' Selection	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions	
Wolley et al., 2013 [104]	Australia	1439	Sequential	≥ 3	A/C _{one side} ≥ 2-fold peripheral ratio	A/C _{one side} ≤ P _{peripheral} ratio	1200 satisfactory AVS	
		1978–2012 retrospective	Samples drawn at t-15 and t0 min				37 (2.5%) had adequate samples but bilateral A/C ≤ A/C _{peripheral}	
							22/37 had repeat AVS with 18 diagnostic AVS	
							9/22 had concordant imaging and 10/22 had lateralized disease	
Seccia et al., 2012 [35]	Italy	34	Bilateral simultaneous and Simulated sequential	≥ 1.10–2	N/A	N/A	Simultaneous > sequential for AVS selectivity	
		prospective					All 34 patients had an APA and a PAC decrease, PRA increase, normalization of the ARR and K + plasma levels post adrenalectomy	
Vonend et al., 2011 [41]	Germany	200	Sequential	≥ 2	≥ 3	N/A	Bilaterally selective: 30.5% (retrospective); 61.3% (prospective)	
		1990–2007 retrospective phase						Bilaterally nonselective: 16.5% (retrospective); 8.5% (prospective)
		106					2008–2009 prospective phase	The rate of unsuccessful bilateral cannulation rose from 4% to 45% with a stringent cut-off of 5.0 compared to 1.1.
								178 patients (retrospective) also had cross-sectional imaging: the agreement between AVS and imaging was 27%
<p>A/C: Aldosterone/Cortisol; ACTH: adrenocorticotropic hormone; APA: Aldosterone-producing adenoma; ARR: Aldosterone-to-renin ratio; AVS: Adrenal vein sampling; CLS: Contralateral suppression; CT: Computed tomography; L: Left; LR: Lateralization ratio; MR: Mineralocorticoid receptor; MRI: Magnetic resonance imaging; N/A: Not available; OR: odds ratio; PA: Primary aldosteronism; PAC: Plasma aldosterone concentration; PASO: Primary Aldosteronism Surgical Outcome; PPV: Positive predictive value; PRA: Plasma renin activity; R: Right; SI: Selectivity index.</p>								

tion (especially if non-simultaneous sampling), identification of aldosterone source when secretion is in a quiescent phase basally, and possibly increased aldosterone secretion and LR from an APA [46, 47]. ACTH is also necessary for patients with contrast media allergy who are premedicated with glucocorticoids, as well as for patients undergoing AVS at times other than in the early morning [18, 48].

► **Table 3** summarizes the most recent studies on AVS with ACTH administration, their protocols, and their main conclusions. Protocols of ACTH administration during AVS vary between centers. Notably, only one of the recent studies in ► **Table 3a**, mentioned simultaneous bilateral sampling for post-ACTH infusion only measurements [49], while Dekkers et al. [50] performed sequential AVS, and the other two studies did not specify their sampling technique [9, 51]. Whenever ACTH stimulation is used, Monticone et al. recommended that continuous perfusion be favored because the ACTH bolus might excessively stimulate aldosterone release from the contralateral adrenal gland [18]. All four studies in ► **Table 3a** performed AVS under ACTH infusion at a rate of 50 mcg/h. However, only one compared ACTH bolus (250 mcg) and ACTH infusion (50 mcg/h) and reported a higher SI in the RAV in the bolus subgroup [49]. No other differences in terms of cannulation success, LR, or surgical outcomes were demonstrated between the two sub-

groups [49]. While the SI cut-offs varied between 3 and 5 (post-ACTH), they tended to be closer to 3 in most recent studies [49, 50]. The cut-off for ACTH-stimulated LR, in studies only using post-ACTH infusion samples, also differed from center to center, with ratios from 3 to 4. The latter had the best sensitivity and specificity for lateralized disease, according to the study by Young et al., which was one of the first studies attempting to prospectively determine the optimal ACTH-stimulated LR [51]. ACTH-stimulated LR was higher on average in cured adrenalectomized PA patients than in those with residual post-operative disease and was concordant with surgical pathology results in all cases [9]. Although the prospective SPARTACUS trial challenged the importance of AVS in the management of PA, finding no significant difference in clinical or biochemical outcomes between patients managed according to either computed tomography (CT) scan or post-ACTH infusion AVS results, the latter demonstrated a trend in favor of reducing biochemical failure among patients who had AVS-guided adrenalectomy [50]. However, several limitations should be mentioned regarding the SPARTACUS trial. First, it mostly included florid and severe cases of PA, which could have reduced the odds of cure or significant improvement following surgical management in both groups. Second, the number of patients in each subgroup (n = 46) may have been insufficient to detect a significant difference between the two

groups when one possibly exists. In addition, it cannot be excluded that the management of patients in the CT subgroup with normal or bilaterally enlarged adrenals may have been different if AVS were used. Finally, the authors should have concluded that AVS performed under ACTH infusion may not be superior to CT scan only, but this study did not compare other techniques of AVS with adrenal imaging. Regardless of the criteria used to interpret sampling, AVS-guided surgery led to significantly more hypertension cures compared with non-AVS-guided (40.0% compared to 30.5%; $p=0.027$) in a large multicenter analysis of 1625 cases [52]. Women were more likely to be cured following adrenalectomy [52, 53].

AVS performed with both basal and post-adrenocorticotrophic hormone sampling

The majority of AVS studies presented in ► **Table 3b, c** are from centers performing AVS under basal (without stimulation) and post-ACTH stimulation conditions, mostly using a simultaneous bilateral sampling technique. An intravenous (IV) bolus of 250 mcg of ACTH was the most common administration method (► **Table 3b**), but some centers used either smaller bolus doses, a continuous infusion, or a sequence of bolus followed by continuous infusion (see details in ► **Table 3c**). Most studies used an unstimulated SI ratio of 2 or 3 and a stimulated ratio between 3 and 5. Few, such as Seccia et al., used less stringent criteria [54]. The SI consistently increases after ACTH stimulation [20, 21]. As demonstrated by Deinum et al. in their debate article on ACTH use in AVS, the rate of successful AV cannulation is increased by 20 to 30% after ACTH stimulation, and this is directly due to the manifest increase in adrenal cortisol secretion [55]. In other words, depending on the stringency of unstimulated SI criteria, a significant percentage of unstimulated AVS procedures are inappropriately concluded as non-selective; thus, these patients would not benefit from further AVS interpretation.

Meanwhile, the effect of ACTH on LR is variable in the literature, with possibly a general tendency to a decreased LR following ACTH administration compared to baseline [19, 54, 56–58]. One study, however, found a tendency to increased ACTH-stimulated LR [59]. Similarly, many studies examined the discordance rate of LR between individual unstimulated and ACTH-stimulated samplings. This discordance varies greatly between studies, from around 9% [59, 60] up to 41% [61]. In their review of the last 12 studies, Yozamp et al. estimated the discordance in lateralization to be around 26% [56]. In many cases, the discordance was driven by a loss of lateralization following ACTH administration (i. e., lateralized-to-bilateral) [11, 19, 21, 47, 54, 56–58, 61, 62]. However, a large retrospective cohort of 222 patients demonstrated roughly equal proportions of patients with increasing (27%), decreasing (33%), and stable LR (40%) following ACTH stimulation [62]. This variability in discordant AVS results might be explained by the variable individual under- or upregulation of MC2R in APA and adjacent hyperplastic micronodular adrenal tissue, itself driven by certain somatic mutations, as discussed above [1, 55, 62]. Indeed, the presence of an *ATP1A1* or an *ATP2B3* somatic mutation in adrenalectomized glands was associated with an increasing ACTH-stimulated LR, while the presence of a *KNCJ5* mutation was associated with a decreasing LR [62]. The latter would lead to relatively more aldosterone secretion from the contralateral gland following ACTH administration, thus

revealing the bilateral nature of the disease (albeit possibly asymmetrical) [32]. However, some patients with true lateralized PA may be missed if ACTH stimulation were to be discarded. As shown by El Ghorayeb et al., 5% of patients with bilateral PA, according to unstimulated LR (cut-off of 2), had lateralized PA after ACTH (LR cut-off of 4) [21]. While up to 91% of discordant LR results were driven by a lateralized to the bilateral pattern (depending on the stringency of LR cut-offs), 2.35% lateralized only after ACTH stimulation [56]. Another study (not shown in ► **Table 3**) found a high percentage of patients (18.8%), with lateralized PA, based exclusively on ACTH-stimulated LR, compared to 22% based on baseline ratios (LR > 4) [63]. Moreover, Shibayama et al. demonstrated that ACTH stimulation reduced rates of apparent bilateral aldosterone suppression (see ► **Table 3c**) [64]. These cases underline the importance of interpreting AVS according to both unstimulated and ACTH-stimulated samples. In addition, it clearly suggests that performing AVS only under ACTH perfusion may deprive 25–30% of patients with basal lateralization (appearing as bilateral during ACTH infusion) from possible beneficial surgical therapy.

Biochemical and clinical outcomes post adrenalectomy were studied by some groups and are included in ► **Table 3**. Overall, a strong majority of patients chosen to undergo adrenalectomy succeeded in achieving a complete biochemical cure. In the study by Desrochers et al., 83% and 4% of the total cohort had, respectively, complete and partial biochemical success at 12 months post-operatively [65]. On the other hand, only 29% and 67% had complete and partial clinical success, respectively [65]. This discrepancy between biochemical and clinical success, and between complete and partial clinical success, is consistent across all studies of the post-Primary Aldosteronism Surgical Outcome (PASO) criteria era [11, 19, 56, 58, 59, 61, 64–67]. This trend is difficult to extrapolate to studies with post-operative outcomes of the pre-PASO era, as the criteria for PA cure varied from one study to another. Interestingly, patients with a lateralized-to-bilateral AVS pattern had less favorable post-operative clinical and biochemical outcomes (57.5% and 79.5%, respectively) than patients who maintained a lateralized pattern after ACTH injection (72.6% and 94.3%, respectively) [61]. In the lateralized-to-bilateral subgroup of patients, a higher unstimulated LR was predictive of better surgical outcomes [61]. Chee et al. also reported complete biochemical success in 3 out of 7 patients with discordant LRs (lateralized-to-bilateral pattern) who underwent adrenalectomy. Even though all 7 patients had other characteristics suggestive of lateralized disease (a unilateral adenoma on CT scan or hypokalemia), and all had a CLS index < 1, the only significant difference was an ACTH-stimulated LR of > 2 in the 3 patients with biochemical success [57].

Contralateral adrenal suppression

Contralateral aldosterone suppression (CLS) has been extensively studied by several groups [21, 65, 68–72] and found to be helpful in ascertaining aldosterone lateralization [69–72], especially in cases where the LR is lower than 4 [69], as it is expected that a single APA would suppress renin and consequently suppress aldosterone in the contralateral adrenal gland. Although some authors did not report better outcomes when CLS is present [68, 73], in particular for patients with clear lateralization on AVS [68], others found that it can predict surgical outcomes [21, 65, 69, 72].

▶ **Table 3** Studies on AVS performed with ACTH stimulation.

3a. ACTH-stimulated only									
Study	Country	Patients' Selection	ACTH	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions	
Hu et al., 2021 [49]	China	174	250 mcg bolus (n = 80) or continuous infusion 50 mcg/h (n = 94)	Simultaneous bilateral	> 3	> 4 or > 3-4 if CLS present	A/C nondominant side < A/C IVC	Comparable number of patients with LR < 3, 3-4, > 4 between the bolus and infusion groups. Post-adrenalectomy, the rate of complete biochemical remission was not significantly different between the bolus (97.7%) and infusion groups (100%, p0.454).	
		2016–2021 retrospective							
Dekkers et al., 2016 [50]	Netherlands, Poland	184	Continuous infusion 50 mcg/h	Sequential	≥ 3.0	≥ 4.0	≤ 1.0	At 1 year F/U: No difference between CT-guided and AVS-guided treatment regarding the number of antihypertensive medications, biochemical and clinical outcomes (non-PASO criteria).	
		2010–2013 RCT							
Lim et al., 2014 [9]	USA	263 (213 had AVS)	Continuous infusion 50 mcg/h	N/A	> 5	> 4	A/C nondominant < A/C IVC	44.9% discordance between AVS and CT In lateralized PA: 100% concordance rate between AVS and the surgical side. ACTH-stimulated LR in cured PA (14.8, 95%CI 7.4-26.3) is higher than ACTH-stimulated LR in non-cured PA (5.5, 95% CI 3.2-7.4, p0.02).	
		1993–2011 retrospective							
Young et al., 2004 [51]	USA	203	Continuous infusion 50 mcg/h	N/A	> 5	Study outcome	N/A	LR > 4.0: sensitivity 95.2%, and specificity 100% for lateralized PA. Based on CT alone: 21.7% missed lateralization, 24.7% unnecessary adrenalectomy.	
		1990–2003 prospective							
3b. Unstimulated and ACTH-stimulated (bolus) samplings.									
Study	Country	Patients' Selection	ACTH	Simultaneous OR Sequential	SI	LR	CLS	Essential Conclusions	
Yozamp et al., 2021 [56]	USA	340	Bolus of ACTH (250 mcg)	Simultaneous bilateral	≥ 3	Unstimulated ≥ 2 ACTH-stimulated ≥ 4	N/A	90% of patients with concordant unstimulated and ACTH-stimulated AVS underwent unilateral adrenalectomy: – clinical success: 61% partial, 24% complete – biochemical success: 6% partial, 92% complete	
		2005–2019 retrospective							
Desrochers et al., 2020 [65]	Canada	192 (Montréal)	Bolus of ACTH (250 mcg)	Simultaneous bilateral Calgary: bolus + infusion	ACTH-stimulated > 5	Unstimulated > 2 ACTH-stimulated > 4 (Montréal) or > 3 (Calgary)	A _{CL} /A _P : < 1.0 A _{CL} /A _P : < 1.5	A _{CL} /A _P of 2.15 and 6.15 had the best sensitivity and specificity for clinical and biochemical cures at 1 year, respectively.	
		2009–2018							
		138 (Calgary)							
2005–2018 retrospective									

► Table 3 Continued

3b. Unstimulated and ACTH-stimulated (bolus) samplings.								
Study	Country	Patients' Selection	ACTH	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions
Yatabe et al., 2020 [19]	Japan	185	Bolus of ACTH (250 mcg)	Sequential	Unstimulated ≥ 2	Unstimulated ≥ 2	< 1.0	Stimulated LR ≥ 2.6 had a better clinical outcome.
		2000–2015 retrospective						
Rositto et al., 2018 [20]	Italy	53	Bolus of ACTH (250 mcg)	Simultaneous bilateral	SI = primary outcome	Unstimulated > 2.0	Secondary outcome	26.5% discordance between unstimulated and ACTH-stimulated LR.
		2000–2016 retrospective						
Durivage et al., 2017 [84]	Canada	197 (with repeat AVS in 11 patients)	Bolus of ACTH (250 mcg)	Simultaneous bilateral	ACTH-stimulated ≥ 5	Unstimulated ≥ 2	N/A	ACTH facilitates ascertainment of selectivity but lessens LR. 62% of patients had HTN cure post adrenalectomy.
		1989–2015 retrospective						
El Chorayeb et al., 2016 [21]	Canada	175	Bolus of ACTH (250 mcg)	Simultaneous bilateral	ACTH-stimulated > 5	Unstimulated > 2	Primary outcome	CLS of 1.44: highest specificity and sensitivity.
		1989–2014 retrospective						
Wolley et al., 2016 [60]	Australia	47	Bolus of ACTH (250 mcg)	Sequential	Unstimulated ≥ 3	ACTH-stimulated ≥ 2	≤ 1	28% discordance between unstimulated and ACTH-stimulated LR (lateralized to bilateral PA after ACTH).
		prospective and retrospective						
Rossi et al., 2006 [33]	Italy	24 prospective	Bolus of ACTH (250 mcg)	Simultaneous bilateral	> 1.1	> 2	N/A	13/15 underwent unilateral adrenalectomy: 5 had a biochemical cure. ACTH increased aldosterone secretion from the contralateral adrenal but not from APA and does not improve diagnostic accuracy for APA.

▶ Table 3 Continued

3c. Mixed ACTH protocols									
Study	Country	Patients' Selection	ACTH	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions	
Kometani et al., 2022 [85]	Japan	4057 enrolled	159: Unstimulated	N/A	Unstimulated > 2	Unstimulated > 2	N/A	Real-time intraoperative cortisol measurements increase the success rate of unstimulated AVS and ACTH-stimulated AVS.	
		2006–2018 retrospective	473: ACTH 2396: both 250 mcg bolus or continuous infusion or bolus + infusion		ACTH-stimulated > 5	ACTH-stimulated > 4		No effect on subtype diagnosis.	
Sung et al., 2020 [59]	USA	76	Pre and post-250 mcg bolus of ACTH + infusion (0.25 mg in 250 mL NS)	Simultaneous bilateral	≥ 2	> 2 and > 4 (outcome)	N/A	ACTH stimulation increased SI.	
		1984–2009 retrospective				Mean ACTH-stimulated LR > unstimulated LR.			
Kobayashi et al., 2020 [61]	Japan	1834 (314 adrenalectomy)	Pre and post-ACTH	Sequential	Unstimulated ≥ 2	Unstimulated ≥ 2	A/C nondominant < A/C NC	When LR > 4 was used: 9.2% of patients who did not lateralize with ACTH stimulation, lateralized without ACTH.	
		2006–2018	Bolus or continuous infusion or bolus + infusion		ACTH-stimulated ≥ 5	ACTH-stimulated ≥ 4		76/76: had adrenalectomy: all had a biochemical cure, 34% complete success and 66% partial success (PASO criteria).	
Chee et al., 2020 [57]	Australia	201	Pre and post-250 mcg bolus of ACTH + infusion (50 mcg/h)	Sequential	Unstimulated > 2	Unstimulated > 3	< 1	40.6% had discordant LR: 37.9% from lateralized to bilateral, 2% from bilateral to lateralized, and 0.6% from lateralized to contralateral lateralized	
		(102 pre- and post-ACTH successful AVS)			ACTH-stimulated > 3	ACTH-stimulated > 4		22% of those who underwent adrenalectomy had discordant unstimulated and ACTH-stimulated LR: mostly driven by lateralized to bilateral PA post-ACTH.	
Wannachalee et al., 2020 [11]	USA	234	Pre and post-125 mcg bolus of ACTH + infusion (75–125 mcg/h)	Simultaneous bilateral	Unstimulated > 2	Unstimulated and/or ACTH-stimulated ≥ 4	< 1	Basal CLS = 0.40 was significantly associated with clinical and biochemical success post-surgery; ACTH-stimulated CLS = 0.81 was not.	
		2009–2019 retrospective			ACTH-stimulated > 5	ACTH-stimulated > 5		ACTH stimulation decreased lateralization: 70% with unstimulated to 52% with ACTH-stimulated.	
								62% concordance between AVS and cross-sectional imaging, highest in unilateral lesions on both.	
								89% of patients had a clinical benefit and 83% biochemical cure (PASO criteria).	

▶ **Table 3** Continued

3c. Mixed ACTH protocols									
Study	Country	Patients' Selection	ACTH	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions	
Wannachalee et al., 2019 [62]	USA	222	Pre and post-125 mcg bolus of ACTH + infusion (75-125 mcg/h)	Simultaneous bilateral	Unstimulated > 2	Unstimulated and/or ACTH-stimulated ≥ 4	< 1	24 % discordance between unstimulated and ACTH-stimulated LR (lateralized to the bilateral pattern)	
		2009-2018 retrospective			ACTH-stimulated > 5				LR increased after ACTH stimulation in 27 %, decreased in 33 %, and remained stable in 40 %.
Takeda et al., 2019 [58]	Japan	2197	Pre and post-bolus of ACTH, or continuous infusion, or bolus + infusion	24 centers: sequential 4 centers: Simultaneous bilateral	Unstimulated ≥ 2	Unstimulated ≥ 2 ACTH-stimulated ≥ 4	N/A	ATP1A1 and ATP2B3 mutations associated with ascending LR. KCNJ5 associated with descending LR. ACTH improved the success rate (67 to 89 %) but decreased LR (62 to 28 %). The method of ACTH administration did not affect SI or LR. Clinical success: absent in 33 %. Biochemical success: absent in 15 %. ACTH did not influence clinical and biochemical outcomes.	
		2006-2016 retrospective			ACTH-stimulated ≥ 5				Apparent bilateral aldosterone suppression (ABAS) is the outcome.
Shibayama et al., 2018 [64]	Japan	1689	Pre and post-ACTH	23 centers: Simultaneous bilateral	Unstimulated > 2	Unstimulated > 4	N/A	- prevalence of ABAS post-ACTH (7.6 %) lower than unstimulated ABAS (18.0 %, <i>p</i> 0.007). - 20/45 patients with some degree of ABAS had an adrenalectomy.	
		2006-2016 retrospective	18 centers: 250 mcg bolus	4 centers: sequential	ACTH-stimulated > 5	ACTH-stimulated > 4			- 15/20 with available outcome data post-op: complete clinical success in 5 (33.3 %), partial clinical success in 8 (53.3 %), and absent clinical success in 2 (13.3 %).
			8 centers: 200 or 250 mcg bolus + infusion 1 center: infusion						- 13/20 with available biochemical data post-op: complete biochemical success in 12 (92.3 %).
Kline et al., 2013 [105]	Canada	32	Pre and post-infusion of ACTH 250 mcg over 15 minutes	Simultaneous bilateral	Unstimulated > 3	Unstimulated > 3	N/A	Post ACTH SI is preferred for confirmation of successful AVS.	
		2005-2011 retrospective			ACTH-stimulated > 3	ACTH-stimulated > 3			Post adrenalectomy: hypokalemia resolved in all patients who had pre-operative hypokalemia; ARR normalized in 19 patients; 34 % had normotension.
Monticone et al., 2012 [106]	Italy, Japan	76	Pre and post-ACTH	Japan: Simultaneous bilateral	Unstimulated > 3	Unstimulated strict > 4 permissive > 2	< 1	The diagnosis did not change: - in 88 % of patients before and after ACTH infusion - in 78 % of patients before and after ACTH IV bolus.	
		prospective	Japan: bolus 250 mcg Italy: continuous infusion	Italy: N/A	ACTH-stimulated strict > 4 intermediate > 2	Discordance was more driven by the switch from lateralized PA to bilateral PA post-ACTH. When permissive criteria were used: concordance between unstimulated and stimulated diagnoses was reduced from 13 % to 26 % according to ACTH infusion protocol.			

▶ Table 3 Continued

3c. Mixed ACTH protocols								
Study	Country	Patients' Selection	ACTH	Simultaneous or Sequential	SI	LR	CLS	Essential Conclusions
Webb et al., 2012 [107]	USA	108	Pre and post-250 mcg bolus of ACTH + infusion (250 mcg in 250 mL NS)	Simultaneous bilateral	Unstimulated > 1.1-3	Unstimulated > 1-4	N/A	ACTH-stimulated LR criterium of >4 was the most accurate in diagnosing lateralization.
		1991–2010 retrospective				ACTH-stimulated > 4 or > 10		
Mathur et al., 2010 [108]	USA	114	Pre and post-250 mcg bolus of ACTH + infusion (250 mcg in 250 mL NS)	Simultaneous bilateral	> 2	≥ 4	< 1.0	19.3% of patients had discordant AVS and CT results.
		Timeline N/A retrospective						ACTH-stimulated LR was more accurate for lateralization.
Seccia et al., 2009 [54]	Italy	67	Pre and post-ACTH: High dose (HD) bolus; 250 mcg (n = 47) Intermediate dose (ID): 100 mcg + infusion 50 µg/h (n = 14) Very low dose (VLD) 250 pg + infusion 0.5 pg/min (n = 6).	Simultaneous bilateral	≥ 1.1	≥ 2	N/A	HD and ID improved the selectivity of AVS but influenced lateralization.
		2001–2007 prospective						Lateralization was on the wrong side in 3.0% and 12.5% with HD and ID, respectively.
								HD group misdiagnosed APA as idiopathic hyperaldosteronism in 19.4% more cases than based on unstimulated AVS. All 35 patients who underwent adrenalectomy had complete biochemical success, and hypertension was cured in 33% (non-PASO criteria).

A: aldosterone concentration; A/C: Aldosterone/Cortisol; A₁/A₂: aldosterone in contralateral adrenal vein/aldosterone in peripheral vein; (A/C)_{CL}/(A/C)_P: aldosterone/cortisol in contralateral adrenal vein/aldosterone/cortisol in peripheral vein); ACTH: adrenocorticotropic hormone; ABAS: Apparent bilateral aldosterone suppression; APA: Aldosterone-producing adenoma; ARR: Aldosterone-to-renin ratio; AVS: Adrenal vein sampling; CLS: Contralateral suppression; CT: Computed tomography; F/U: follow-up; HD: high dose; HTN: Hypertension; ID: intermediate dose; IVC: inferior vena cava; LR: Lateralization ratio; N/A: Not available; NS: normal saline; PA: Primary aldosteronism; PASO: Primary Aldosteronism Surgical Outcome; post-op: post-operatively; SI: Selectivity index; VLD: very low dose.

However, in most studies, CLS was calculated by dividing A/C in the non-dominant AV by the A/C ratio in the IVC and was considered suppressed if the ratio was < 1 , some at baseline and some after ACTH stimulation. Yet, when we examined aldosterone concentrations in the contralateral AV in our lateralized cases, it became evident that aldosterone concentrations were higher than in peripheral veins, on average 2.4 times that of IVC levels [21]. We reasoned that there was no rationale for correcting aldosterone with cortisol concentrations in the IVC. In fact, to estimate LR, aldosterone is divided by cortisol to correct for the variable blood flow and dilution in each AV, while no such correction is required when examining the concentration of aldosterone in the IVC. We believe it is also inappropriate to estimate CLS under ACTH stimulation as one is searching for a suppressed status. Despite all of this, Monticone et al. had previously reported that 82% of lateralized PA patients had CLS using A/C corrected ratios and, surprisingly, a higher percentage with ACTH stimulation compared to baseline (90% and 77%, respectively) [68]. The authors did not report a change in post-operative outcomes in terms of blood pressure reduction nor a reduction in clinical and biochemical response to adrenalectomy when CLS was absent, more so when the LR was > 4 [68].

When using the unstimulated ratio of aldosterone ($A_{\text{contralateral (CL)}}$ / $A_{\text{peripheral (P)}}$), with a cut-off of 1, the prevalence of CLS in PA was reduced from 45 to 6%, as compared to $(A/C)_{\text{CL}}/(A/C)_{\text{P}}$ [65]. Another previous study also demonstrated a reduction from 77% to 30% in basal CLS with a cut-off of 1.5 when using corrected and absolute ratios, respectively [21]. Therefore, true CLS is rare in PA and when absent, patients responded less to adrenalectomy [21, 45, 65, 74]. A basal CLS of < 2.15 was associated with the best clinical outcomes at 12 months following adrenalectomy [65]. While these studies encourage clinicians to factor in CLS in their decision-making, some authors consider it not required to decide when to offer surgery because as much as 32% of IHA had a CLS ratio < 1 [51, 75]. It is, however, important to mention that CLS was calculated with corrected rather than absolute ratios in the Young et al. study [51], which in fact, overestimates CLS [21], thus explaining their high percentage of CLS in IHA.

The rarity of true CLS in PA supports the hypothesis that bilateral, asymmetrical aldosterone production is frequent in PA and precludes the occurrence of hypotension and hyperkalemia in the immediate post-operative period. Therefore, CLS, as generally estimated by A/C ratios in most studies, does not consistently predict outcomes after adrenalectomy, and long-term follow-up should be implemented to detect cases of residual PA secondary to the asymmetrical bilateral source of aldosterone excess instead of relying solely on AVS, in general, to predict recurrence or persistence after surgery [1, 68, 73, 76].

Other methods for performing and interpreting AVS

Super selective AVS or segmental AVS (sAVS) is performed in some specialized centers in Japan by sampling adrenal tributary veins to detect possible heterogeneity in aldosterone production within the adrenal glands and possibly offer partial unilateral adrenalectomy to some patients with bilateral PA [77–79]. sAVS had a success rate of 98% and was able to successfully detect distal APAs and differentiate between bilateral PA secondary to either APAs/nodules or diffuse hyperplasia, thus allowing for good biochemical and clinical outcomes post-adrenalectomy in the former group

[77, 78, 80]. In one recent study, sAVS detected a unilateral elevation in aldosterone in 85% of APA with a positive predictive value (PPV) of 97.1% for APA, compared to conventional central AVS, which only detected 73%, based on an ACTH-stimulated LR of > 4 [81]. This method could also be used in specific groups of patients with associated subclinical cortisol co-secretion [82]. However, it is more difficult and time-consuming, especially in inexperienced hands. Conventional AVS can also present with some difficulties, especially regarding RAV cannulation. If unsuccessful, AVS results could still be interpreted using the ratio of $(A/C)_{\text{LAV}}$ to $(A/C)_{\text{IVC}}$. When ≥ 5.5 , it depicts left adrenal disease and ≤ 0.5 right adrenal disease, with a sensitivity of 77% and specificity of 100% [83]. However, values between 0.5 and 5.5 cannot reliably differentiate between lateralized and bilateral disease [83]. Considering the frequent multiplicity of micronodules in addition to the dominant aldosterone-secreting one, it appears that a total adrenalectomy would be more logical than a selective adrenalectomy for long-term remission of PA, but this will require longer-term prospective studies. Another method allowing for successful interpretation of AVS when RAV cannulation has failed, is the multinomial regression modeling of peripheral and LAV samplings, which was able to successfully detect lateralization of PA with a 95% specificity and obviated the need for a repeat AVS [84] (► **Table 3b**).

Intraprocedural cortisol measurement during AVS is another method suggested for improving selectivity, in particular for unstimulated samples [85]. In addition, steroid profiling using liquid chromatography with tandem mass spectrometry (LC-MS/MS) for 15 different adrenal steroids during AVS reported higher AV to peripheral vein ratios, both before and after ACTH stimulation, compared to that for cortisol, with the exceptions of DHEAS, cortisone, and 18-hydroxycortisol [86]. This may be beneficial to use in place of cortisol in patients with significant cortisol co-secretion, but extensive data on this issue are still scarce, and modest cortisol co-secretion has little impact on interpretation [87, 88]. While there is some evidence that high cortisol co-secretion can increase the non-ACTH-stimulated LR contralateral to it and misclassify some cases as bilateral [88], another study suggests that the LR is not significantly influenced by cortisol co-secretion when performed only under ACTH perfusion [87]. Recently, LC-MS/MS was shown to be superior to immunoassays for lateralization diagnosis, particularly for ACTH-stimulated samples where the discordance between the two methods was higher [89]. The steroids measured by LC-MS/MS could potentially be used for aldosterone correction and assessment of selectivity instead of cortisol. In fact, as much as 43 to 73% of failed AVS based on SI using cortisol concentrations can be salvaged by using 17- α -hydroxyprogesterone or androstenedione for correction, respectively [90]. Specifically, androstenedione conceded more successful AVS because the SI was 16-fold higher than with cortisol [90]. Metanephrines were also extensively studied as an alternative to cortisol for selectivity assessment and were found to be better than cortisol in detecting successful cannulation in the unstimulated state [91–93]. Both androstenedione and metanephrines were superior to cortisol and increased the rate of successful AVS by 14 and 15%, respectively, without any gender differences and without influencing the LR [94]. However, androstenedione, and possibly 17- α -hydroxyprogesterone, also respond to the stress reaction occurring at the beginning of AVS, leading to higher SI immediately after cannulation compared to 15 min later; similar to what is seen with cor-

► **Table 4** Recommended therapy based on LR cut-offs during AVS.

We recommend unilateral adrenalectomy in patients with:
<ul style="list-style-type: none"> ▪ Unstimulated LR ≥ 2 and ACTH-stimulated LR ≥ 4 ▪ Unstimulated LR $> 3-4$, despite ACTH-stimulated LR < 4 ▪ Unstimulated quiescent LR < 2, with ACTH-stimulated LR ≥ 4 (rare) ▪ Asymmetrical bilateral severe PA with unstimulated LR > 3 ▪ Bilateral PA with clinical cortisol co-secretion (PBMAH)
We recommend medical therapy with mineralocorticoid receptor antagonists if:
<ul style="list-style-type: none"> ▪ Unstimulated LR < 2 and ACTH-stimulated LR < 4
AVS: adrenal vein sampling; ACTH: adrenocorticotropin hormone; LR: lateralization ratio; PA: primary aldosteronism; PBMAH: primary bilateral macronodular adrenal hyperplasia.

tisol, thus a possible limitation for their use in AVS without ACTH stimulation [94]. An even higher percentage of missed AVS with cortisol was recently found (36.6%) compared to free metanephrine, with an SI cut-off suggested at 10 for free metanephrines [93]. Finally, although epinephrine measurement in AV > 364 pg/mL predicts successful AVS, there is a wide variability in what is considered to be normal values for the adrenal veins, with a significant difference between the RAV and LAV, thus probably limiting its use in AVS [95, 96]. Without any prospective studies comparing outcomes when using these newer parameters for aldosterone correction in AVS to standard cortisol measurements, it is difficult to recommend their wider use in clinical practice.

Conclusion

In our opinion, AVS, when performed in expert centers, is indispensable in most patients eligible for surgery for treatment guidance in PA. Similarly, to several other groups, we identified that both unstimulated and stimulated measurements are required for adequate interpretation of AVS results. ACTH stimulation increases the selectivity of AVS, therefore increasing the opportunity to detect lateralized or strongly asymmetrical PA. Lateralized PA could be quiescent at baseline and be identified only after ACTH stimulation because of a high MC2R expression and distribution in adrenal dominant nodule(s) [1]. However, relying exclusively on ACTH-stimulated results may miss lateralized PA because LR tends to be lower after ACTH, thus depriving these patients of beneficial adrenalectomy. Contralateral suppression should be examined using direct aldosterone ratios.

To conclude, we recommend adrenalectomy in PA patients presenting with one of the following scenarios (see ► **Table 4**): 1) both an unstimulated LR of ≥ 2 and an ACTH-stimulated LR of ≥ 4 ; 2) an unstimulated LR > 3 but < 4 , despite an ACTH-stimulated LR < 4 ; 3) an unstimulated LR < 2 and an ACTH-stimulated LR ≥ 4 (a rare occurrence, as discussed above); 4) an unstimulated LR > 3 in the case of severe, bilateral asymmetrical PA; and 5) presence of bilateral PA with clinically significant cortisol co-secretion, such as in the case of primary bilateral macronodular adrenal hyperplasia (PBMAH). If clinically significant hypercortisolism and low morning ACTH levels are documented, we recommend removing the gland with the dominant source of cortisol excess, to treat Cushing's syndrome first and foremost, as residual aldosterone excess can be treated

► **Table 5** Practical recommendations for performing and interpreting AVS:

<ul style="list-style-type: none"> ▪ Bilateral simultaneous unstimulated and ACTH-stimulated sampling with 2-3 samples is preferable, the average of which should be used for ratio calculation (due to the variability of aldosterone secretion). ▪ Both unstimulated and ACTH-stimulated aldosterone ratios are required for the adequate diagnosis of lateralized PA (See rationale below). ▪ Direct basal (unstimulated) ratio of (A) in the non-dominant adrenal vein to (A) in the IVC should replace the A/C ratio and be considered to estimate the risk of residual micronodular PA in the remaining adrenal after unilateral adrenalectomy (in addition to CYP11B2 IHC on resected adrenal tissue).
Following adrenalectomy using the pre-operative basal contralateral suppression ratio A non-dominant AV / A IVC:
<ul style="list-style-type: none"> ▪ < 1: close monitoring for potential post-operative transient hyperkalemia. ▪ > 2: long-term surveillance for PA relapse from residual PA. ▪ > 5 and surgery for asymmetrical bilateral disease: perform ARR and confirmation test for residual PA during follow-up. MR antagonist indication.
The rationale for using both unstimulated and stimulated ratios; 1. AVS performed exclusively under ACTH perfusion can miss ~25% of patients with lateralized PA and deprive them of potentially curative surgery.; 2. AVS performed with unstimulated samples only reduces adequate selectivity rate and can miss quiescent lateralized APA in the basal state.; Abbreviations: A: aldosterone; A/C: aldosterone/cortisol; APA: aldosterone-producing adenoma; ARR: aldosterone to renin ratio; AVS: adrenal vein sampling, CYP11B2: aldosterone synthase; IHC: immunohistochemistry; IVC: inferior vena cava; MR: mineralocorticoid receptor; PA: primary aldosteronism.

with a mineralocorticoid receptor antagonist; in case of PBMAH with combined Cushing's syndrome and primary aldosteronism, removing the largest adrenal on abdominal CT scan is recommended [97]. If the cortisol co-secretion is mild, removing the gland overproducing aldosterone, according to AVS results, is recommended, while being aware of its impact on AVS interpretation itself [87, 88] and on post-surgical management [5]. We, along with other groups, advocate for unilateral adrenalectomy (UA) in some cases of severe PA with documented asymmetrical bilateral aldosterone source on AVS in light of the recent findings on clear clinical and biochemical benefits in patients with bilateral PA who underwent UA with or without partial contralateral adrenalectomy [98, 99].

Finally, considering that complete basal CLS is rare, we recommend that patients with a pre-operative basal CLS index < 1 be closely monitored after adrenalectomy for potential immediate post-operative hyperkalemia. On the other hand, patients with a basal CLS > 2.15 benefit from long-term surveillance to assess potential residual PA and relapse from remaining, recurrent, or emerging aldosterone-producing micronodules [65]. In the case of a pre-operative basal CLS > 5 , we would suggest repeating the aldosterone-to-renin ratio along with a confirmation test for residual PA during post-operative follow-up and anticipate potential need for mineralocorticoid receptor antagonist treatment (see ► **Table 5**).

Disclosure statement

The authors have no conflict of interest related to this article to disclose. This review was based on an invited symposium presentation on the same topic by AL during the Seventh Conference on Progress in Primary Aldosteronism (PIPA-7), Munich, Germany, October 14, 2022.

Authors contributions

N.Y., S.L., and A.L. conducted the review of the literature and N.Y. and SL contributed equally to writing the first draft of the manuscript. A.L. conceived the objectives and plan of this report. I.B., E.T., and A.L. critically revised the article. All authors approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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