## Subtyping of Primary Aldosteronism in the AVIS-2 Study: Assessment of Selectivity and Lateralization

### SUPPLEMENTAL MATERIAL

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# **Expanded methods; AVIS2 data collection form; Supplemental tables: 10**, **Supplemental figures: 5**.

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### **EXPANDED METHODS**

The AVIS-2 study was an observational multi-center study conceived in 2012 with the aim of creating a large database of individual adrenal vein sampling (AVS) studies performed worldwide. The original protocol was registered at clinicaltrials.gov (NCT01234220) and thereafter amended to reach the target recruitment number of 1500 patients PA patients submitted to AVS in the last 15 years (2000-2015).

#### Center selection criteria

Eligible centers were identified from those that had published in English on primary aldosteronism (PA) and/or AVS in the last decade following the PICO strategy (P, population = adults with PA; I, intervention = AVS; C, comparator = simultaneous AVS vs. sequential catheterization technique, use of cosyntropin testing vs. non-stimulated condition, use of bilaterally vs. unilaterally selective AVS results, use of absolute hormonal data vs. selectivity and lateralization indices; and O, outcome = the ways AVS was performed and interpreted, adrenal vein rupture) (24). Suitable studies were identified by computer-assisted database searches (PubMed database, U.S. National Library of Medicine) using the key words: aldosterone, primary aldosteronism (PA), endocrine hypertension, adrenal vein sampling, and the Boolean operator "AND"; scanning of reference lists; hand-searching of relevant journals; correspondence with authors of relevant reports and meeting presentations; and consultation with experts in the field.

All procedures were carried out according to the Helsinki Declaration. The protocol of the study was approved by the Ethics Committee of both the coordinating center and the participating centers.

#### Inclusion/exclusion criteria

After identification of the eligible centers the inclusion criteria were: a) age  $\geq$  18 years; b) center's agreement to participate in the data collection; c) approval of the Ethics Committee. The only exclusion criteria were unwillingness of the lead investigator to participate in the study and/or lack of local Ethics Committee's approval.

#### Data collection and harmonization

To warrant privacy protection data anonymization was systematically exploited in an *ad hoc* web-based platform (<u>https://fm.dmcs.unipd.it</u>) and a predefined form (reported below), which was created for on-line data collection. High quality of the data was ensured by using appropriate filters to prevent input of values that were not biologically plausible and/or were in wrong unit of measures. Data were securely stored in a protected server at the coordinating center, which had full access to the dataset; each local lead investigator had access with username and password to the his/her center's database.

## Data collection form for AVIS2 (1)

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	$\bigcirc$	Sam	pling				PROTOCOL IS	AVAILAE PRE	BLE AT: register.clinicaltrials.gov	
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International Study		Study (	AVIS)							
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		Race		] → F	ield ontion	s: Cau	casian/∆fr	ican/l	Hispanic/Asian	
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		DBP [		j	Diastolic Bloc	od Pressu	e (mmHg)			
		Heart Rate [		]	bpm					
	Resist	ant Hypertension	•	] → F	ield option	s: Yes,	/No			
↓ Field options: Yes/No										
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		Bota Blockers			for dose, pleas	se refer to	DDD (defined dail	y dose) ta	ab: i.e. amlodipine 10 mg = 2 DDD	
		Deta Diockeis			propranolol	0,16 g	losartan valsartan	50 mg		
	_	CCH			metoprolol bisoprolol	150 mg	irbesartan candesartan	150 mg 8 mg		
	Ň	ACE-			nebivolol amlodipine	5 mg 5 mg	telmisartan olmesartan	40 mg 20 mg		
	Yes	ARB Vasodilators			felodipine nicardipine	5 mg 90 mg	aliskiren hydrochlorothiazide	150 mg 50 mg		
	ns:	(Minoxidil,Hydralazine	e)		nifedipine lacidipine	30 mg 4 mg	chlortalidone indapamide	25 mg 2,5 mg		
	ptio	(clonidine, metildopa)			manidipine barnidipine	10 mg 10 mg	metolazone furosemide	5 mg 40 mg		
	lo p	Renin Inhibitors	s 🔽 🔻		lercanidipine diltiazem	10 mg 240 mg	amiloride minoxidil	10 mg 20 mg		
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		PACb (ng/dL)			riora option		5,, , (	, u., ,	(pinel) () (pinel) (iii)	
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## Data collection form for AVIS2 (2)

BASELINE AVS DATA	NOTE: please use comma "," for separating decimals	
	Unit ALDO AVS baseline	$\rightarrow$ Field options: (pg/ml) / (nd/dl) / (pmol/l) / (pmol/ml)
ALDOSTERONE	•	please note: pg/ml = ng/l
ALDOIVCb		Aldosterone in inferior vena cava baseline
ALDOIVCb pg/ml		
RightALDOb		Aldosterone in right adrenal vein baseline
RightALDOb pg/ml		
LeftALDOb		Aldosterone in left adrenal vein baseline
LeftALDOb pg/ml		
	Unit CORTISOL AVS baseline	
ORTISOL	•	ightarrow Field options: (ng/dl) / (nmol/l) / (microg/dl) / (umol/l) / (ng/ml)
IVCCb		Cortisol in inferior vena cava baseline
CORTIVCb ng/m	l I	
RightCb		Cortisol in right adrenal vein baseline
RightCORTb ng/ml		
LeftCD		Cortisol in left adrenal vein baseline
5		
STIMULATED AVS DATA	NOTE: please use comma "," for separating decimals	
	Unit ALDO AVS post stimulated	
	*	$\rightarrow$ Field options: (pg/ml) / (nd/dl) / (pmol/l) / (pmol/ml)
ALDOIVCpost		Aldosterone in inferior vena cava post-stimulation
ALDOIVCpost pg/ml		
RightALDOpost		Aldosterone in right adrenal vein post-stimulation
		Aldesteens is to be advect with each standards
LeftALDOpost pg/ml		Audosterone in ten aurenan vein post-sumulation
Ur	it CORTISOL AVS post stimulated	
CORTISOL	•	Field options: (ng/dl) / (nmol/l) / (microg/dl) / (umol/l) / (ng/ml)
	<b>`</b>	
CortIVCpost		Cortisol in inferior vena cava post-stimulation
RightCortpost		Cortisol in right adrenal vein post-stimulation
RightCortpost ng/ml		
LeftCortpost		Cortisol in left adrenal vein post-stimulation
LeftCortpost ng/ml		
Rupture of adre	nal vein 🔹	→ Field options: Yes/No
MAGING DATA		

		↓ Field options: Yes/No						
СТ	CT right adrenal node	if yes indicate the maximum size of node in the field below						
		CT right adrenal node size mm						
	CT left adrenal node	if yes indicate the size of node in the field below						
		CT left adrenal node size						
MR		mm						
	MR right adrenal node	✓ If yes indicate the size of node in the field below						
		MR right adrenal node size						
	MR left adrenal node	if yes indicate the size of node in the field below						
		MR left adrenal node size mm						

## Data collection form for AVIS2 (3)

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		Date of follow u	p		bilateral adenoma / bilateral adenoma with hyperplasia/ adenoma with					
	Hyst	ological Diagnosi	s	•	satellite adrenocorti	cal nodu	iles/ hyperplasia	/ bilateral		
		Treatment			→ Field options: ph	with my	eioiipoma/ inde	eterminate		
		ineachient :		•	adrenalectomy/bilat	Field options: pharmacological/left adrenalectomy/right     adrenalectomy/bilateral adrenalectomy				
Discordant	tCT	or MR and AVS ?		•	→ Field options: Yes	/No				
	Hypertension cured ?			•	BP< 140/90 mmHg with	out therapy	$\rightarrow$ Field option	ns: Yes/No		
Blood Pressure controlled ?				•	BP< 140/90 mmHg with	therapy	ightarrow Field option	ns: Yes/No		
Follow	Follow-up Pharmacological treatment			•	If Yes please fill und	er	$\rightarrow$ Field option	ns: Yes/No		
				חסס	Please complete the foll	owing fields w	ith the tipe of pharmacolog	ical drugs administration;		
		Beta Block	ers 🔹		Farmaco DDD	Farmaco	DDD	ipine to mg = 2 000		
					propranolol 0,16 g atenolol 75 mg	losartan valsartan	50 mg 80 mg			
	9				metoprolol 150 mg bisoprolol 10 mg	irbesartan candesartan	150 mg 8 mg			
	s/	AC			nebivolol 5 mg amlodipine 5 mg	telmisartan olmesartan	40 mg 20 mg			
		A Vasodila			felodipine 5 mg nicardipine 90 mg	aliskiren hydrochlorothi	150 mg iazide 50 mg			
	Suc	(Minoxidil,Hydrala	zine)		nifedipine 30 mg lacidipine 4 mg	chlortalidone indapamide	25 mg 2,5 mg			
	bti	antiadrenei	gic 🔽		manidipine 10 mg barnidipine 10 mg	metolazone furosemide	5 mg 40 mg			
	o p	Renin Inhibit	ors 🔹		lercanidipine 10 mg diltiazem 240 mg	amiloride	10 mg			
	<u>e</u>	diure	ics T		verapamil 240 mg	nitroprussiate,	Na 50 mg			
	$\rightarrow$	Amilo	ide T		enalapril 10 mg	methildopa	1g			
					perindopril 4 mg	prazosin	5 mg			
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		N			tosinopril 15 mg zofenopril 30 mg	K canrenoate	50 mg 0,4 g			
					http://www.whoo	c.no/atc_c	dd_index			
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#### Summary List of the collected variables

- Demography (sex 1 =M 2=F, weight, BMI, race, etc.);
- AVS date (MM/DD/YYYY);
- Birth date (MM/DD/YYYY);
- Calculated age at AVS = AVS date (MM/DD/YYYY)- Birth date (MM/DD/YYYY) in years;
- Systolic and diastolic blood pressure values (mmHg) at the time of AVS;
- Ongoing medical therapy at the time of AVS;
- Biochemical profile at baseline (sK<sup>+</sup>, plasma aldosterone concentration (PAC); plasma renin activity (PRA).
- AVS protocol (bilaterally simultaneous/sequential; stimulated/unstimulated).
- PAC and plasma cortisol concentration (PCC) in each adrenal vein and in the inferior vena cava blood;
- Concordance/discordance between imaging and AVS results.
- Treatment modality: right/left/bilateral laparoscopic adrenalectomy; medical treatment.
- Blood pressure outcome at 6-months defined as reported in Supplemental Table 2.
- Persistence /correction of hypokalemia at follow-up.
- Serum K<sup>+</sup>, PAC and PRA at follow-up.
- Complications: adrenal vein rupture.
- Diagnosis (unilateral aldosterone-producing adenoma (APA); bilateral APA, unilateral adrenal hyperplasia; bilateral adrenal hyperplasia.

The conclusive diagnosis of unilateral PA required demonstration of biochemical cure at follow-up.

Supplemental table 1: Pre-specified definitions of the BP outcome. The PASO criteria, which were proposed afterward based on expert consensus are also reported for comparison.

			PASO CRITERIA*	
Cure		normotension (BP < 140/90 mmHg) without any	Complete	
		antihypertensive agents.	clinical	
			success	
Improvement	Marked	normotension on the same or reduced number of medications and BP similar to baseline but with a marked decrease (> 2 drugs) of medications.	<b>Partial</b> clinical success	
	Mild	a fall of systolic and/or diastolic $BP > 10\%$ , but without achievement of normotension with the same or reduced therapy.		
No improvement		no fall of systolic and/or diastolic BP and/or need for	Absent	
		increased number and/or dose of antihypertensive	clinical	
		medications.	success	

BP = Blood Pressure; \*PASO consensus from *Williams TA, Lancet Diabetes Endocrinol 2017; 5(9):689-699*, for comparison

Center ID	Number of AVS	Years	Technique	Pharm. Stimulation	Selectivity criteria	Lateralisation criteria	
#14	6	2009-2011	Sequential	Unstimulated	SI unstim. > 3.0	LI unstim. > 4.0	
#18	9	2010-2015	Sequential	Cos.	SI Cos. > 3.0	LI Cos. > 4.0	
#2	11	2007-2009	Bil. sim.	Unstimulated	SI unstim. > 2.0	LI unstim. > 2.0	
#19	15	2012-2015	Sequential	Unstimulated	SI unstim. > 3.0	LI unstim. > 2.0	
#4	17	2005-2012	Sequential	Unstimulated	SI unstim. > 1.36	LI unstim. > 3.0	
#7	27	2000-2009	Sequential	Unstimulated / Cos.	SI unstim. > 2.0 SI Cos. >3.0	LI unstim. > 4.0 LI Cos. > 4.0	
#1	39	2010-2015	Sequential	Unstimulated / Cos.	SI unstim. > 2.0 SI Cos. >3.0	LI unstim. > 3.0 LI Cos. > 4.0	
#5	39	2008-2012	Sequential	Unstimulated	SI unstim. > 2.0	LI unstim. > 3.0	
#13	45	2000-2010	Bil. sim.	Unstimulated / Cos.	SI unstim. > 1.36 SI Cos. > 5.0	LI unstim. > 2.0 LI Cos. > 2.0	
#15	63	2000-2011	Bil. sim.	Unstimulated / Cos.	SI Cos. > 5.0	LI Cos. > 2.0.6	
#3	79	2005-2011	Bil. sim.	Unstimulated / Cos.	SI unstim. > 3.0 SI Cos. > 3.0	LI unstim. > 3.0 LI Cos. > 3.0	
#12	98	2005-2015	Sequential	Cos.	SI Cos. > 5.0	LI Cos. > 3.0.5.0	
#17	101	2004-2015	Sequential	Cos.	SI Cos. > 5.0	LI Cos. > 4.0	
#9	107	2005-2011	Sequential	Cos.	SI Cos. > 2.0 (< 2010) SI Cos. > 3.0 (> 2010)	LI Cos. > 3.0 (< 2010) LI Cos. > 4.0 (> 2010)	
#6	115	2006-2014	Sequential	Unstimulated / Cos.	SI Cos. > 5.0	LI Cos. > 2.0.6	
#11	143	2000-2013	Sequential	Unstimulated	SI unstim. > 2.0	LI unstim. > 2.0	
#8	144	2008-2013	Sequential	Unstimulated	SI unstim. $> 2.0$	LI unstim. > 4.0	
#16	196	2000-2015	Bil. sim.	Unstimulated / Cos.	SI unstim. > 2.0	LI unstim. > 2.0	
#10	371	2000-2015	Sequential (< 2009) Bil. sim. (> 2009)	Unstimulated	SI unstim. > 2.0	LI unstim. > 5.0	

Supplemental Table 2. Number of AVS included, technique, protocol and diagnostic criteria in use at participating centers.

Bil. Sim. = Bilateral simultaneous AVS; Cos. = Cosyntropin; LI= lateralization index; SI= selectivity index;

Variable	Value
Age (years)	$50.8 \pm 10.8$
Sex (M/F), n (%)	985 (60.6)/ 640 (39.4)
Ethnicity (%)	
Caucasians	75.2
Asians	20.7
Africans	3.6
Hispanics	0.6
Body Mass Index (Kg/m <sup>2</sup> )	$28.4 \pm 5.3$
Systolic BP (mmHg)	$152 \pm 20$
Diastolic BP (mmHg)	$92 \pm 13$
Heart rate (beats/min)	$73 \pm 12$
Anti-hypertensive treatment (n. of drugs)	2.26 (0-8)
Serum K <sup>+</sup> (mmol/L)	$3.6 \pm 0.5$
Hypokalemia (%)	41.4
PRA (ng/mL/h)	0.30 (0.20 – 0.57)
PAC (ng/dL)	24.8 (15.4 - 33.6)
PAC (pmol/L, Système International)	688 (428 - 933)
ARR (ng/dL)/(ng/mL/h)	65.5 (36.3 – 118.8)
ARR (pmol/L/ng/mL/h, Système	1818 (1008 - 3298)
International)	
Imaging (Single node/bilateral nodes/normal	61.5/8.4/30.1
adrenals, %; n = 1470)	

Supplemental Table 3: Baseline demographic, clinical and biochemical features of the 1625 PA patients.

Mean ± SD, or median and IQ range (PRA, PAC and ARR) or mean and range (n. of drugs). Abbreviations: PRA: plasma renin activity; PAC: plasma aldosterone concentration; ARR: aldosterone/renin ratio.

SI	Unstimulated	p for comparison with the	p for comparison with the most used post-	Cosyntropin
cut-off	(n=1274)	Cosyntropin-stimulated value	Cosyntropin-stimulated value (SI $\geq$ 5.0)	(n=742)
Right				
1.1	1129 (88.6%)	ns	$2 \times 10^{-3}$	674 (90.8%)
1.4	1056 (82.9%)*	$4 \times 10^{-3}$	ns	651 (87.7%)*
2.0	951 (74.6%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	641 (86.4%)*
3.0	779 (61.1%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	631 (85.0%)*
4.0	692 (54.3%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	627 (84.5%)
5.0	618 (48.5%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	621 (83.7%)*
Left				
1.1	1228 (96.4%)	0.004	ns	735 (99.1%)
1.4	1187 (93.2%)*	< 0.001	ns	734 (98.9%)
2.0	1057 (83.0%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	729 (98.2%)*
3.0	876 (68.8%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	723 (97.4%)*
4.0	774 (60.8%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	715 (96.4%)*
5.0	698 (54.8%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	706 (95.1%)*
Bilatera	1			
1.1	1099 (86.3%)	1 x 10 <sup>-2</sup>	$3 \times 10^{-3}$	669 (90.2%)
1.4	1007 (79.0%)*	$= 10^{-3}$	ns	646 (87.1%)*
2.0	857 (67.3%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	636 (85.7%)*
3.0	667 (52.4%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	624 (84.1%)*
4.0	570 (44.7%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	615 (82.9%)*
5.0	489 (38.4%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	603 (81.3%)*

Supplemental Table 4: Rate of selective AVS studies under unstimulated and cosy	ntropi	oin-stimul	lated	conditions
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Number and rate of successful AVS studies by different selectivity index (SI) cutoffs.

Grey shaded cells identify the cutoff values recommended by current guidelines/experts' consensus; the other values are those identified in the AVIS-1 study. The SI value cutoff of 1.4 was identified in this study by the Youden index analysis (see text for explanation and Figure 3;  $SI_{unstimulated} = 1.4$ ). In each column \* indicates that use of the higher cut-off implies a statistically significant fall of AVS studies judged to be successful at the p<0.05 alpha value, as compared

In each column \* indicates that use of the higher cut-off implies a statistically significant fall of AVS studies judged to be successful at the p<0.05 alpha value, as compared to the immediately lower cutoff value.

SI	Unstimulated	p for comparison with the	Unstimulated	p for comparison with the	p for comparison with the	Cosyntropin-
cutoff	no IRCA	Unstimulated IRCA	IRCA	Cosyntropin-stimulated value	most used post-Cosyntropin-	stimulated
	(n=1096)		(n=178)		stimulated value (SI $\geq$ 5.0)	(C; n=742)
Right						
1.1	962 (87.8%)	0.020	167 (93.8%)	ns	< 10 <sup>-3</sup>	674 (90.8%)
1.4	896 (81.8%)	$=8 \times 10^{-3}$	160 (89.9%)	ns	=0.038	651 (87.7%)*
2.0	798 (72.8%)*	< 10 <sup>-3</sup>	153 (86.0%)*	ns	ns	641 (86.4%)*
3.0	647 (59.0%)*	< 10 <sup>-3</sup>	132 (74.2%)*	0.001	$=3x10^{-3}$	631 (85.0%)*
4.0	576 (52.6%)*	=10-3	116 (65.2%)*	< 0.001	< 10 <sup>-3</sup>	627 (84.5%)
5.0	516 (47.1%)*	0.012	102 (57.3%)*	< 0.001	< 10 <sup>-3</sup>	621 (83.7%)*
Left						
1.1	1053 (96.1%)	ns	175 (98.3%)	ns	ns	735 (99.1%)
1.4	1015 (92.6%)	=0.050	172 (96.6%)	0.026	ns	734 (98.9%)
2.0	893 (81.5%)*	< 10 <sup>-3</sup>	164 (92.1%)*	< 0.001	ns	729 (98.2%)*
3.0	726 (66.2%)*	< 10 <sup>-3</sup>	150 (84.3%)*	< 0.001	< 10 <sup>-3</sup>	723 (97.4%)*
4.0	639 (58.3%)*	< 10 <sup>-3</sup>	135 (75.8%)*	< 0.001	< 10 <sup>-3</sup>	715 (96.4%)*
5.0	582 (53.1%)*	$=3x10^{-3}$	116 (65.2%)*	< 0.001	< 10 <sup>-3</sup>	706 (95.1%)*
Bilateral						
1.1	935 (85.3%)	=0.015	164 (92.1%)	ns	< 10 <sup>-3</sup>	669 (90.2%)
1.4	851 (77.6%)	2x10 <sup>-3</sup>	156 (87.6%)	ns	=0.047	646 (87.1%)*
2.0	713 (65.1%)*	< 10 <sup>-3</sup>	144 (80.9%)*	ns	ns	636 (85.7%)*
3.0	549 (50.1%)*	< 10 <sup>-3</sup>	118 (66.3%)*	< 0.001	< 10 <sup>-3</sup>	624 (84.1%)*
4.0	472 (43.1%)*	$=3x10^{-3}$	98 (55.1%)*	< 0.001	< 10 <sup>-3</sup>	615 (82.9%)*
5.0	412 (37.6%)*	ns	77 (43.3%)*	< 0.001	< 10 <sup>-3</sup>	603 (81.3%)*

Supplemental Table 5: Rate of selective unstimulated AVS studies performed with or without use of the intraprocedural rapid cortisol assay (IRCA) and comparison with Cosyntropin stimulation.

Number and rate of successful AVS studies according to different selectivity index (SI) cutoff values. Cosyntropin data are shown for comparison. The grey shaded listed SI values are those recommended by current guidelines/consensus papers; the other are those identified in the AVIS-1 study. The SI value cutoff of 1.4 was identified in this study by the Youden index analysis (see text for explanation and Figure 3;  $SI_{unstimulated} = 1.4$ ).

As in Supplemental Table 5, in each column \* indicates that use of the higher cut-off implies a statistically significant fall of AVS studies judged to be successful at the p<0.05 alpha value as compared to the immediately lower cutoff value.

## Supplemental Table 6: Criterion values and coordinates of the ROC curve of unstimulated SI in the identification of Selectivity of AVS.

20.29         100.0         000         100         90.5         >	Criteri on	Sensi tivity	Speci ficity	+LR	-LR	+PV	-PV	Criteri on	Sensi tivity	Speci ficity	+LR	-LR	+PV	-PV
0-021         99.86         1.00         1.00         90.5         0.00         >2.296         61.05         71.62         21.58         93.48         93.68         1.65           0.041         99.72         1.20         1.01         0.01         90.7         50.06         59.04         74.32         2.37         0.53         95.8         16.6           0.061         99.72         1.216         1.14         0.03         91.5         81.8         >3.05         60.20         75.68         2.47         0.53         95.9         16.6           0.065         99.43         13.51         1.15         0.062         91.6         67.7         2.306         59.27         76.88         2.47         0.53         95.9         16.6           0.07         99.01         14.86         1.16         0.087         91.7         61.1         >40.7         91.75         3.02         0.65.0         3.02         0.43.83         70.73         2.40         0.46         95.8         14.0           0.076         98.87         1.75.7         1.20         0.060         92.1         65.6         94.0         1.48         94.0         1.48         94.0         1.48         94.0	≥0.29	100.0	0.00	1.00		90.5		>2.76	64.87	71.62	2.29	0.49	95.6	17.6
>0.44         99.86         1.35         1.01         0.10         90.6         50.0           >0.64         99.72         2.70         1.02         0.10         90.7         50.0           >0.63         99.43         1.16         1.14         0.03         91.5         81.8           >0.65         99.43         1.35         1.15         0.042         91.6         61.6           >0.066         99.29         1.351         1.15         0.052         91.6         61.7           >0.07         99.01         1.86         1.16         0.067         91.7         61.1           >0.07         99.01         1.757         1.20         0.056         92.0         65.0           >0.76         98.87         1.757         1.20         0.056         92.0         65.0           >0.768         98.16         2.568         1.32         0.077         92.6         57.6           >0.88         98.16         2.568         1.32         0.077         92.6         57.6           >0.88         98.16         2.568         1.32         0.077         92.6         57.6           >0.88         98.16         2.568         1.32	>0.29	99.86	0.00	1.00		90.5	0.0	>2.96	61.05	71.62	2.15	0.54	95.4	16.2
>0.44         99.72         2.70         1.02         0.10         90.7         50.0           >0.63         99.43         12.16         1.14         0.03         91.5         81.8           >0.66         99.43         13.51         1.15         0.042         91.6         71.4           >0.66         99.29         13.51         1.15         0.052         91.6         66.7           >0.70         99.15         14.86         1.16         0.067         91.7         64.7           >0.72         99.01         14.85         1.16         0.067         91.7         64.7           >0.76         98.87         17.57         1.20         0.065         92.0         65.0           >0.82         98.30         18.92         1.20         0.065         92.0         65.0           >0.84         98.30         18.92         1.20         0.000         92.1         63.6           >0.84         98.02         2.703         1.34         0.073         92.6         57.6           >0.85         98.02         2.703         1.34         0.073         92.8         58.8           >1.03         67.4         5.83         0.097	>0.41	99.86	1.35	1.01	0.10	90.6	50.0	>2.97	60.91	74.32	2.37	0.53	95.8	16.6
0-0.61         99.72         12.16         1.14         0.03         91.5         81.8         >3.06         60.20         75.68         2.47         63.3         95.9         16.6           >0.065         99.43         13.51         1.15         0.042         16.5         >3.08         59.77         77.03         2.17         0.65         95.4         1.15           0.076         99.11         1.486         1.16         0.077         91.7         61.1           0.072         99.01         1.757         1.20         0.056         92.0         61.9           >0.074         98.87         1.857         1.20         0.056         92.0         61.9           >0.078         98.87         1.852         1.20         0.056         92.0         61.9           >0.048         98.80         2.433         0.470         79.73         2.30         0.64         95.8         1.44           0.83         93.6         1.22         0.060         92.0         53.8         >8.87         1.04         8.8         9.36         1.07           0.84         98.30         2.432         0.470         79.73         2.33         1.64         0.44	>0.44	99.72	2.70	1.02	0.10	90.7	50.0	>3.02	60.20	74.32	2.34	0.54	95.7	16.4
0-0.63         99.43         12.16         1.13         0.047         91.5         69.2         75.8         2.66         0.53         95.9         16.5           0.066         99.29         13.51         1.15         0.032         91.6         6.7         >         30.8         59.77         77.03         2.60         0.52         96.1         16.7           0.07         99.01         14.86         1.16         0.057         91.7         64.7         >         40.7         49.72         78.38         2.30         0.64         95.6         139           0.074         99.01         17.57         1.20         0.065         92.0         61.9         >         4.41         47.03         77.03         2.40         0.64         95.6         139           0.078         98.87         1.757         1.20         0.005         92.0         53.8         >         4.44         47.03         81.08         2.40         6.65         6.06         13.8           0.085         98.02         2.56         1.32         0.077         92.6         57.6         >         9.81         82.43         1.60         0.87         93.9         1.07           0.0	>0.61	99.72	12.16	1.14	0.023	91.5	81.8	>3.05	60.20	75.68	2.47	0.53	95.9	16.6
0-066         99.43         13.51         1.15         0.042         91.6         64.7           >0.06         99.29         13.51         1.15         0.052         91.6         64.7           >0.07         99.01         14.86         1.16         0.057         91.7         64.17           >0.76         98.87         17.57         1.20         0.065         92.0         65.0           >0.76         98.87         18.92         1.21         0.006         92.0         65.0           >0.78         98.87         18.92         1.21         0.006         92.0         63.6           >0.84         98.30         18.92         1.21         0.007         92.6         59.4           >0.85         98.16         25.68         1.32         0.072         92.6         59.4           >0.87         92.08         1.34         0.073         92.8         8.8         2.904         81.48         0.87         93.6         1.07           >0.88         92.04         81.48         1.04         0.88         94.5         1.07           >0.807         97.33         1.34         0.079         92.8         5.38         -11.7         2.92.8	>0.63	99.43	12.16	1.13	0.047	91.5	69.2	>3.06	59.92	75.68	2.46	0.53	95.9	16.5
0-06         99.29         13.51         1.15         0.052         91.6         44.05         49.86         77.03         2.17         0.64         93.0           0.07.2         99.01         1.75.7         1.20         0.056         92.0         65.0         >4.20         49.72         78.38         2.27         0.66         95.5         13.6           0.07.6         98.87         1.75.7         1.20         0.056         92.0         61.9         >4.44         47.03         97.37         2.32         0.66         95.7         13.6           0.07.8         98.70         1.22         0.060         92.1         63.6         >4.44         47.03         81.08         2.49         0.65         96.0         13.8           0.085         98.16         2.56.8         1.32         0.077         92.6         57.4         >9.51         2.81.9         83.78         1.74         0.66         94.0         10.9           0.086         98.02         2.56.8         1.32         0.077         92.6         57.6         >>1.18         2.94.8         83.78         1.74         0.60         88.4         9.09         9.01         1.05         9.01         1.05         9.01 <td>&gt;0.65</td> <td>99.43</td> <td>13.51</td> <td>1.15</td> <td>0.042</td> <td>91.6</td> <td>71.4</td> <td>&gt;3.08</td> <td>59.77</td> <td>77.03</td> <td>2.60</td> <td>0.52</td> <td>96.1</td> <td>16.7</td>	>0.65	99.43	13.51	1.15	0.042	91.6	71.4	>3.08	59.77	77.03	2.60	0.52	96.1	16.7
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	>0.66	99.29	13.51	1.15	0.052	91.6	66.7	>4.05	49.86	77.03	2.17	0.65	95.4	13.9
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	>0.7	99.15	14.86	1.16	0.057	91.7	64.7	>4.07	49.72	78.38	2.30	0.64	95.6	14.0
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.72	99.01	14.86	1.16	0.067	91.7	61.1	>4.2	49.15	78.38	2.27	0.65	95.6	13.9
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	>0.74	99.01	17.57	1.20	0.056	92.0	65.0	>4.21	48.73	79.73	2.40	0.64	95.8	14.0
>0.78         98.87         18.92         1.22         0.060         92.1         63.6           >0.82         98.30         18.92         1.21         0.000         92.0         53.8           >0.84         98.30         24.32         1.30         0.070         92.5         60.0         88.8         29.04         81.08         2.49         0.65         96.0         13.8           >0.85         98.16         25.68         1.32         0.077         92.6         57.6         >39.3         28.19         82.43         1.60         0.87         93.9         10.7           >0.86         94.02         27.03         1.34         0.073         92.8         58.8         >3.75         >5.11         83.78         1.74         0.86         94.3         10.0           >0.93         97.45         28.38         1.36         0.090         92.8         53.8         >12.41         22.95         86.49         1.70         0.89         94.2         10.6           >1.03         96.88         45.95         1.79         0.070         94.2         60.7         >12.41         22.95         86.49         1.70         0.89         94.2         10.6         >12.41	>0.76	98.87	17.57	1.20	0.065	92.0	61.9	>4.44	47.03	79.73	2.32	0.66	95.7	13.6
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.78	98.87	18.92	1.22	0.060	92.1	63.6	>4.46	47.03	81.08	2.49	0.65	96.0	13.8
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.82	98.30	18.92	1.21	0.090	92.0	53.8	>8.8	29.04	81.08	1.53	0.88	93.6	10.7
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.84	98.30	24.32	1.30	0.070	92.5	60.0	>8.87	29.04	82.43	1.65	0.86	94.0	10.9
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.85	98.16	25.68	1.32	0.072	92.6	59.4	>9.39	28.19	82.43	1.60	0.87	93.9	10.7
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.86	98.02	25.68	1.32	0.077	92.6	57.6	>9.51	28.19	83.78	1.74	0.86	94.3	10.9
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.87	98.02	27.03	1.34	0.073	92.8	58.8	>11.7	23.94	83.78	1.48	0.91	93.4	10.4
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.89	97.73	27.03	1.34	0.084	92.7	55.6	>11.8	23.94	85.14	1.61	0.89	93.9	10.5
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.93	97.45	28.38	1.36	0.090	92.8	53.8	>12.41	22.95	85.14	1.54	0.91	93.6	10.4
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>0.94	97.31	28.38	1.36	0.095	92.8	52.5	>12.49	22.95	86.49	1.70	0.89	94.2	10.5
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>1.02	97.31	43.24	1.71	0.062	94.2	62.7	>12.91	22.24	86.49	1.65	0.90	94.0	10.4
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>1.03	96.88	44.59	1.75	0.070	94.3	60.0	>12.98	22.10	87.84	1.82	0.89	94.5	10.6
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>1.04	96.88	45.95	1.79	0.068	94.5	60.7	>17.14	16.01	87.84	1.32	0.96	92.6	9.9
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>1.06	96.74	45.95	1.79	0.071	94.5	59.6	>17.34	16.01	89.19	1.48	0.94	93.4	10.0
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>1.07	96.46	47.30	1.83	0.075	94.6	58.3	>20.21	13.31	89.19	1.23	0.97	92.2	9.7
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	>1.1	96.46	52.70	2.04	0.067	95.1	60.9	>20.45	13.31	90.54	1.41	0.96	93.1	9.9
>1.1695.4754.05 $2.08$ $0.084$ 95.255.6 $>30.9$ $6.94$ $91.89$ $0.86$ $1.01$ $89.1$ $9.4$ $>1.17$ 95.4756.76 $2.21$ $0.080$ 95.556.8 $>32.61$ $6.37$ $91.89$ $0.79$ $1.02$ $88.2$ $9.3$ $>1.23$ 94.7658.11 $2.26$ $0.090$ 95.653.8 $>32.67$ $6.37$ $93.24$ $0.94$ $1.00$ $90.0$ $9.5$ $>1.23$ 94.7659.46 $2.34$ $0.088$ $95.7$ 54.3 $>35.6$ $5.81$ $93.24$ $0.86$ $1.01$ $89.1$ $9.4$ $>1.25$ 94.7659.46 $2.27$ $0.13$ $95.6$ $44.4$ $>35.6$ $5.81$ $94.59$ $1.07$ $1.00$ $91.1$ $9.5$ $>1.39$ $92.21$ $60.81$ $2.35$ $0.13$ $95.7$ $45.0$ $>37.28$ $5.24$ $94.59$ $0.97$ $1.00$ $90.0$ $9.5$ $>1.62$ $88.39$ $63.51$ $2.42$ $0.18$ $95.9$ $35.4$ $>36.63$ $1.31$ $95.9$ $32.67$ $6.37$ $92.4$ $9.99$ $92.5$ $9.6$ $>1.63$ $88.39$ $62.16$ $2.34$ $0.19$ $95.7$ $35.9$ $>44.14$ $3.82$ $97.30$ $1.42$ $0.99$ $93.1$ $9.6$ $>1.92$ $81.16$ $64.86$ $2.31$ $0.29$ $95.7$ $26.5$ $75.54$ $0.85$ $10.00$ $0.99$ $100$ $9.6$ $>1.94$ $81.16$	>1.15	95.75	52.70	2.02	0.081	95.1	56.5	>30.66	6.94	90.54	0.73	1.03	87.5	9.3
>1.1795.4756.762.210.08095.556.8>1.2195.0456.762.200.08795.454.5>1.2394.7658.112.260.09095.653.8>1.2594.7659.462.340.08895.754.3>1.3892.2159.462.270.1395.644.4>1.3992.2160.812.350.1395.745.0>1.492.0762.162.430.1395.945.1>1.6288.3963.512.420.1895.936.4>1.6986.8363.512.420.1895.936.4>1.6986.8363.512.380.2195.833.6>1.786.6964.862.470.2195.933.8>2.2672.6666.222.100.2895.826.9>2.2872.5267.572.240.4195.520.5>2.3471.6767.572.210.4295.520.0>2.27165.7268.922.110.5095.317.4>2.7165.7268.922.110.5995.317.4>2.7165.7268.922.110.4995.517.6>2.7165.7268.922.110.4995.517.6>2.7165.7268.922.110.5995.517.6>2.7165.7268.922.110.599	>1.16	95.47	54.05	2.08	0.084	95.2	55.6	>30.9	6.94	91.89	0.86	1.01	89.1	9.4
>1.1195.0456.762.200.08795.454.5>1.2394.7658.112.260.09095.653.8>1.2594.7659.462.340.08895.754.3>1.2594.7659.462.270.1395.644.4>1.2992.2160.812.350.1395.745.0>1.492.0762.162.430.1395.945.1>1.6288.3963.512.420.1895.936.4>1.6986.8363.512.420.1895.936.4>1.6986.8363.512.380.2195.833.6>1.786.6964.862.470.2195.933.8>1.2281.1664.862.310.2995.726.5>2.2672.6666.222.150.4195.520.0>2.2872.5267.572.240.4195.520.0>2.2371.6768.922.310.4195.720.3>2.7165.7268.922.110.5095.317.4>2.7165.7268.922.110.5095.317.4>2.7165.7268.922.110.5095.317.6	>1 17	95 47	56 76	2.21	0.080	95.5	56.8	>32.61	6 37	91 89	0.79	1.02	88.2	9.3
>1.2394.7658.112.260.09095.653.8>1.2594.7659.462.340.08895.754.3>1.3892.2159.462.270.1395.644.4>1.3992.2160.812.350.1395.745.0>1.492.0762.162.430.1395.945.1>1.6288.3962.162.340.1995.735.9>1.6388.3963.512.420.1895.936.4>1.6986.8363.512.380.2195.833.6>1.7786.6964.862.470.2195.933.8>1.9281.1664.862.310.2995.726.5>2.2672.6666.222.150.4195.420.2>2.2872.5267.572.240.4195.520.5>2.3471.6767.572.210.4295.520.0>2.3571.6768.922.110.5095.317.4>2.7165.7268.922.110.5095.317.4>2.7265.5870.272.210.4995.517.6	>1.21	95.04	56.76	2.20	0.087	95.4	54.5	>32.67	6.37	93.24	0.94	1.00	90.0	9.5
>1.2594.7659.462.340.08895.754.3>1.3892.2159.462.270.1395.644.4>1.3992.2160.812.350.1395.745.0>1.492.0762.162.430.1395.945.1>1.6288.3962.162.340.1995.735.9>1.6388.3963.512.420.1895.936.4>1.6986.8363.512.380.2195.833.6>1.786.6964.862.470.2195.933.8>1.9281.1664.862.310.2995.726.5>2.2672.6666.222.150.4195.520.5>2.3471.6767.572.210.4295.520.0>2.3571.6768.922.310.4195.720.3>2.7165.7268.922.110.5095.317.4	>1.21	94 76	58 11	2.26	0.090	95.6	53.8	>35.3	5.81	93.24	0.86	1.01	89.1	9.4
>1.3892.2159.462.270.1395.644.4>1.3992.2160.812.350.1395.745.0>1.492.0762.162.430.1395.945.1>1.6288.3962.162.340.1995.735.9>1.6388.3963.512.420.1895.936.4>1.6986.8363.512.380.2195.833.6>1.786.6964.862.470.2195.933.8>1.9281.1664.862.310.2995.726.5>1.9481.1666.222.400.2895.826.9>2.2672.6666.222.150.4195.520.5>2.3471.6767.572.210.4295.520.0>2.3571.6768.922.310.4195.720.3>2.7165.7268.922.110.5095.317.4	>1.25	94.76	59.46	2.34	0.088	95.7	54.3	>35.6	5.81	94.59	1.07	1.00	91.1	9.5
>1.39 $92.21$ $60.81$ $2.35$ $0.13$ $95.7$ $45.0$ $>1.4$ $92.07$ $62.16$ $2.43$ $0.13$ $95.9$ $45.1$ $>1.62$ $88.39$ $62.16$ $2.34$ $0.19$ $95.7$ $35.9$ $>1.63$ $88.39$ $63.51$ $2.42$ $0.18$ $95.9$ $36.4$ $>1.69$ $86.83$ $63.51$ $2.42$ $0.18$ $95.9$ $36.4$ $>1.69$ $86.83$ $63.51$ $2.38$ $0.21$ $95.8$ $33.6$ $>1.7$ $86.69$ $64.86$ $2.47$ $0.21$ $95.9$ $33.8$ $>1.92$ $81.16$ $64.86$ $2.31$ $0.29$ $95.7$ $26.5$ $>1.94$ $81.16$ $66.22$ $2.40$ $0.28$ $95.8$ $26.9$ $>2.26$ $72.66$ $66.22$ $2.15$ $0.41$ $95.5$ $20.5$ $>2.34$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1.20	92.21	59.46	2.27	0.13	95.6	44.4	>36.78	5 24	94 59	0.97	1.00	90.2	9.5
>1.092.0762.162.430.1395.945.1>1.6288.3962.162.340.1995.735.9>1.6388.3963.512.420.1895.936.4>1.6986.8363.512.380.2195.833.6>1.786.6964.862.470.2195.933.8>1.9281.1664.862.310.2995.726.5>1.9481.1666.222.400.2895.826.9>2.2672.6666.222.150.4195.520.5>2.3471.6767.572.210.4295.520.5>2.3571.6768.922.310.4195.720.3>2.7165.7268.922.110.5095.317.4>27.265.5870.272.210.4995.517.6	>1.30	92.21	60.81	2 35	0.13	95 7	45.0	>37.28	5 24	95 95	1 29	0.99	92 5	9.6
>1.62 $88.39$ $62.16$ $2.34$ $0.19$ $95.7$ $35.9$ $>1.63$ $88.39$ $63.51$ $2.42$ $0.18$ $95.9$ $36.4$ $>1.69$ $86.83$ $63.51$ $2.38$ $0.21$ $95.8$ $33.6$ $>1.7$ $86.69$ $64.86$ $2.47$ $0.21$ $95.9$ $33.8$ $>1.92$ $81.16$ $64.86$ $2.31$ $0.29$ $95.7$ $26.5$ $>1.94$ $81.16$ $66.22$ $2.40$ $0.28$ $95.8$ $26.9$ $>2.26$ $72.66$ $66.22$ $2.15$ $0.41$ $95.5$ $20.5$ $>2.28$ $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ $>2.34$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1.0	92.07	62.16	2.43	0.13	95.9	45.1	>42.83	3.82	95 95	0.94	1.00	90.0	9.5
>1.62 $0.61.70$ $2.1.7$ $0.61.70$ $2.1.7$ $0.61.70$ $0.1.7$	>1.62	88 39	62.16	2.34	0.19	95 7	35.9	>44 14	3 82	97 30	1 42	0.99	93.1	9.6
1.69 $86.83$ $63.51$ $2.38$ $0.21$ $95.8$ $33.6$ >1.7 $86.69$ $64.86$ $2.47$ $0.21$ $95.9$ $33.8$ >1.92 $81.16$ $64.86$ $2.31$ $0.29$ $95.7$ $26.5$ >1.94 $81.16$ $66.22$ $2.40$ $0.28$ $95.8$ $26.9$ >2.26 $72.66$ $66.22$ $2.15$ $0.41$ $95.4$ $20.2$ >2.28 $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ >2.34 $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ >2.35 $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ >2.71 $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ >2.72 $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1.62	88 39	63 51	2.3	0.18	95.9	36.4	>62.17	1 13	97.30	0.42	1.02	80.0	9.4
>1.7 $86.69$ $64.86$ $2.47$ $0.21$ $95.9$ $33.8$ $>1.92$ $81.16$ $64.86$ $2.31$ $0.29$ $95.7$ $26.5$ $>1.94$ $81.16$ $66.22$ $2.40$ $0.28$ $95.8$ $26.9$ $>2.26$ $72.66$ $66.22$ $2.15$ $0.41$ $95.4$ $20.2$ $>2.28$ $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ $>2.35$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.5$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1.69	86.83	63 51	2.38	0.21	95.8	33.6	>66.33	1.13	98.65	0.84	1.00	88.9	9.5
>1.92 $81.16$ $64.86$ $2.31$ $0.29$ $95.7$ $26.5$ $>1.94$ $81.16$ $66.22$ $2.40$ $0.28$ $95.8$ $26.9$ $>2.26$ $72.66$ $66.22$ $2.15$ $0.41$ $95.4$ $20.2$ $>2.28$ $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ $>2.34$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.5$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1.05	86.69	64 86	2.33	0.21	95.9	33.8	>75.14	0.85	98.65	0.63	1.01	85.7	9.4
1.32 $0.110$ $0.100$ $2.51$ $0.10$ $95.7$ $2.61$ $0.10$ $100.0$ $100.0$ $100$ $100$ $100$ $100$ $>1.94$ $81.16$ $66.22$ $2.40$ $0.28$ $95.8$ $26.9$ $>2.26$ $72.66$ $66.22$ $2.15$ $0.41$ $95.4$ $20.2$ $>2.28$ $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ $>2.34$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1.92	81.16	64.86	2.17	0.29	95.7	26.5	>75.54	0.85	100.0	0.05	0.99	100	9.6
>2.26 $72.66$ $66.22$ $2.15$ $0.41$ $95.4$ $20.2$ $>2.28$ $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ $>2.34$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.77$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$ $>2.77$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>1 94	81 16	66.22	2.51	0.28	95.7	26.9	>397.9	0.00	100.0		1.00	100	95
>2.28 $72.52$ $67.57$ $2.24$ $0.41$ $95.5$ $20.5$ $>2.34$ $71.67$ $67.57$ $2.21$ $0.41$ $95.5$ $20.5$ $>2.35$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>2.26	72.66	66 22	2.40	0.41	95.0 95.4	20.2	7	0.00	100.0		1.00		2.5
2.35 $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $67.57$ $2.21$ $0.42$ $95.5$ $20.0$ $>2.35$ $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ $>2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ $>2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>2.20	72.00	67.57	2.13	0.41	95. <del>-</del> 95.5	20.5	I	.i	i	i	i		
2.35 $71.67$ $68.92$ $2.31$ $0.41$ $95.7$ $20.3$ > $2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ > $2.71$ $65.72$ $68.92$ $2.11$ $0.50$ $95.3$ $17.4$ > $2.72$ $65.58$ $70.27$ $2.21$ $0.49$ $95.5$ $17.6$	>2.20	71.52	67 57	2.27	0.42	95.5	20.0	Abbrevia	tions + I	$\mathbf{R} = \mathbf{n} \mathbf{o} \mathbf{e} \mathbf{i}$	tive lik	elihood	ratio: -	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	>2.54	71.07	68.07	2.21	0.41	05 7	20.0	$LR = ne\sigma$	ative like	elihood r	atio: $+P$	V = nos	sitive	
>2.71 05.12 06.52 2.11 0.30 55.5 17.4 products the set of the s	>2.33	65 72	68 07	2.31	0.50	95.1 05.2	20.5 17.4	predictive	e value: -	PV = nes	gative n	redictiv	e value	
	>2.71	65 58	70.27	2.11	0.49	95.5 95.5	17.6	1	,	- 4	- r			

17.4

>2.75

65.01

70.27

2.19

0.50

95.4

Supplemental Table 7: Rates of identified unilateral PA (Lat. PA) and of unilateral adrenalectomy (Adx) in AVIS-2 by use of different combinations of cutoff values for the Selectivity Index (SI) and the Lateralization Index (LI) under unstimulated and cosyntropin-stimulated conditions.

		Unstimulated (U) (n=1004)							Cosyntropin (C) (n=637)			
		SI ≥ 1.4	p value vs 2.0	SI ≥ 2.0	p value vs 3.0	SI ≥ 3.0	p value vs 1.4	SI ≥ 5.0	$\begin{array}{l} p \text{ value vs} \\ SI_B \geq 1.4 \\ LI_B \geq 2.0 \end{array}$	$\begin{array}{l} p \text{ value vs} \\ SI_B \geq 1.4 \\ LI_B \geq 3.0 \end{array}$	$\begin{array}{l} p \text{ value vs} \\ SI_B \geq 2.0 \\ LI_B \geq 2.0 \end{array}$	
LI ≥ 2.0	Lat. PA	558 (55.6%)	< 10 <sup>-3</sup>	475 (47.3%)	< 10 <sup>-3</sup>	372 (37.1%)	< 10 <sup>-3</sup>	-	-	-	-	
	Unil. Adrx	398 (39.6%)	< 10 <sup>-3</sup>	335 (33.4%)	< 10 <sup>-3</sup>	268 (26.7%)	< 10 <sup>-3</sup>	-	-	-	-	
	Lat. PA	468 (46.6%)*	< 10 <sup>-3</sup>	400 (39.8%)*	< 10 <sup>-3</sup>	315 (31.4%)*	< 10 <sup>-3</sup>	269 (42.2%)	< 10 <sup>-3</sup>	ns	ns	
LI <u>2</u> 3.0	Unil. Adrx	366 (36.5%)*	< 10 <sup>-3</sup>	312 (31.1%)*	< 10 <sup>-3</sup>	248 (24.7%)*	< 10 <sup>-3</sup>	226 (35.5%)	ns	ns	ns	
11540	Lat. PA	407 (40.5%)*	< 10 <sup>-3</sup>	345 (34.4%)*	< 10 <sup>-3</sup>	269 (26.8%)*	< 10 <sup>-3</sup>	233 (36.6%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	ns	
L1 ≥ 4.0	Unil. Adrx	340 (33.9%)*	< 10 <sup>-3</sup>	289 (28.8%)*	< 10 <sup>-3</sup>	229 (22.8%)*	< 10 <sup>-3</sup>	208 (32.7%)*	0.005	ns	ns	
LI ≥ 5.0	Lat. PA	365 (36.4)*	< 10 <sup>-3</sup>	307 (30.6%)*	< 10 <sup>-3</sup>	242 (24.1%)*	< 10 <sup>-3</sup>	207 (32.5%)*	< 10 <sup>-3</sup>	< 10 <sup>-3</sup>	2 x 10 <sup>-3</sup>	
	Unil. Adrx	309 (30.8%)*	< 10 <sup>-3</sup>	260 (25.9%)*	< 10 <sup>-3</sup>	209 (20.8%)*	< 10 <sup>-3</sup>	186 (29.2%)*	< 10 <sup>-3</sup>	2 x 10 <sup>-3</sup>	ns	

\* = lower than previous cut-off, per column (McNemar test).

# Supplemental Table 8: Results of a sensitivity analysis performed by excluding stepwise the contribution of each of the centers that furnished pairwise unstimulated and cosyntropin-stimulated AVS results.

The pairwise comparison of the Lateralization Index (LI) values in the sub-cohort of patients with bilaterally selective AVS on both unstimulated and post-cosyntropin conditions showed consistently lower post-cosyntropin LI values even after exclusion of each center.

	Whole cohort			Unilateral PA			
Lateralization Index	Unstimulated	Post- cosyntropin	р	Unstimulated	Post- cosyntropin	р	
Excluded center#1	3.81 (1.71-19.61)	2.43 (1.40-11.45)	< 10 <sup>-3</sup>	17.01 (3.86-32.99)	9.96 (3.36-20.02)	0.003	
Excluded center#3	3.88 (1.97-21.64)	2.38 (1.37-9.60)	< 10 <sup>-3</sup>	21.07 (3.74-43.92)	7.07 (3.10-19.63)	< 10 <sup>-3</sup>	
Excluded center#6	3.89 (1.60-21.08)	2.70 (1.42-14.02)	10 <sup>-3</sup>	19.17 (5.33-40.02)	10.19 (3.47-24.5)	10-3	
Excluded center#13	3.91 (1.98-20.60)	2.97 (1.42-13.33)	< 10 <sup>-3</sup>	13.98 (3.817-30.18)	10.19 (3.15-20.55)	3 x 10 <sup>-3</sup>	
Excluded center#15	3.79 (1.61-20.35)	2.41 (1.37-9.59)	< 10 <sup>-3</sup>	18.42 (3.86-33.86)	9.96 (3.36-20.02)	< 10 <sup>-3</sup>	
Excluded center#16	3.67 (1.66-18.47)	2.38 (1.37-9.69)	< 10 <sup>-3</sup>	16.19 (4.27-30.18)	9.43 (3.52-18.44)	0.042	

Data presented as median (interquartile range).

Successful AVS studies were defined as an SI  $\geq$  2.0 and  $\geq$  5.0 under unstimulated and post-cosyntropin conditions.

Wilcoxon test was used to assess statistical significance.

Supplemental Table 9: Lateralization, adrenalectomy and blood pressure outcomes according to different sets of diagnostic criteria.

	Unstimulated (n=880)			$X^2$ for	Cosyntropin (n=580)		$X^2$ for all		
Sets of criteria	SI ≥ 1.4 LI ≥ 2.0	$SI \ge 2.0$ $LI \ge 2.0$	$\begin{array}{c} \text{(II $ 000$)}\\ \text{SI} \ge 2.0\\ \text{LI} \ge 3.0 \end{array}$	$SI \ge 3.0$ $LI \ge 2.0$	$SI \ge 3.0$ $LI \ge 3.0$	unstimulated (p)	$SI \ge 5.0$ $LI \ge 3.0$	$SI \ge 5.0$ $LI \ge 4.0$	(p)
<b>Bilaterally selective</b> (% of total)	724 (82.3%)	619 (70.3%)	619 (70.3%)	482 (54.8%)	482 (54.8%)	< 0.001	478 (82.4%)	478 (82.4%)	< 0.001
Unilateral PA (by AVS criteria) (% of total)	508 (57.7%)	437 (49.7%)	369 (41.9%)	340 (38.6%)	289 (32.8%)	< 0.001	246 (42.4%)	214 (36.9%)	< 0.001
Adrenalectomized pts (meeting criteria) (% of total) (% of successful AVS) (% of unilateral PA)	367 (41.7%) (50.7%) (72.2%)	311 (35.3%) (50.2%) (71.2%)	289 (32.8%) (46.7%) (78.3%)	246 (28.0%) (51.0%) (72.4%)	227 (25.8%) (47.1%) (78.5%)	< 0.001 0.409 0.044*	206 (35.5%) (43.1%) (83.7%)	189 (32.6%) (39.5%) (88.3%)	< 0.001 < 0.001 < 0.001*
<b>Cure</b> (% of total – <i>Figure 4 top</i> ) (% of adrenalectomized pts – <i>Figure 4 bottom</i> )	156 (17.7%) (42.5%)	135 (15.3%) (43.4%)	125 (14.2%) (43.3%)	104 (11.8%) (42.3%)	95 (10.8%) (41.9%)	< 0.001 0.9957	84 (14.5%) (40.8%)	75 (12.9%) (39.7%)	< 0.001 0.9854
<b>Improvement</b> (% of total – <i>Figure 4 top</i> ) (% of adrenalectomized pts – <i>Figure 4 bottom</i> )	194 (22.0%) (52.9%)	160 (18.2%) (51.4%)	148 (16.8%) (51.2%)	129 (14.7%) (52.4%)	119 (13.5%) (52.4%)	< 0.001 0.993	112 (19.3%) (54.4%)	106 (18.3%) (56.1%)	< 0.001 0.955
<i>Marked</i> (% of total) (% of adrenalectomized pts)	139 (15.8%) (37.9%)	113 (12.8%) (36.3%)	105 (11.9%) (36.3%)	93 (10.6%) (37.8%)	87 (9.9%) (38.3%)	0.002 0.981	95 (16.4%) (46.1%)	91 (15.7%) (48.1%)	< 0.001 0.042
<i>Mild</i> (% of total) (% of adrenalectomized pts)	55 (6.3%) (15.0%)	47 (5.3%) (15.1%)	43 (4.9%) (14.9%)	36 (4.1%) (14.6%)	32 (3.6%) (14.1%)	0.087 0.998	17 (2.9%) (8.3%)	15 (2.6%) (7.9%)	0.005 0.059
<b>No Improvement</b> (% of total – <i>Figure 4 top</i> ) (% of adrenalectomized pts – <i>Figure 4 bottom</i> )	17 (1.9%) (4.6%)	16 (1.8%) (5.1%)	16 (1.8%) (5.5%)	13 (1.5%) (5.3%)	13 (1.5%) (5.7%)	0.917 0.979	10 (1.7%) (4.9%)	8 (1.4%) (4.2%)	0.971 0.992

Data from patients with available follow up information (n = 880/1004 for unstimulated AVS and n = 580/637 for cosyntropin-stimulated AVS). \* these suggest the higher confidence of physicians in recommending adrenalectomy based on more restrictive criteria or based on cosyntropin use.

				Cosyntropin-stimulated			
		D	iagnostic criterion	SI $\geq$ 5.0 and LI $\geq$ 3.0	$SI \ge 5.0$ and $LI \ge 4.0$		
	4	LI ≥ 2.0	Adrenalectomy /Lateralization (n, %)	17/74 (23%)	27/86 (31%)		
	SI ≥ 1.	LI ≥ 3.0	Adrenalectomy /Lateralization (n, %)	11/43 (26%)	20/53 (38%)		
Unstimulated		LI ≥ 4.0	Adrenalectomy /Lateralization (n, %)	-	16/38 (42%)		
	SI ≥ 2.0	LI ≥ 2.0	Adrenalectomy /Lateralization (n, %)	14/65 (22%)	22/75 (29%)		
		LI≥3.0	Adrenalectomy /Lateralization (n, %)	11/39 (28%)	18/47 (38%)		
		LI ≥ 4.0	Adrenalectomy /Lateralization (n, %)	-	14/32 (44%)		
	SI≥3.0	LI ≥ 2.0	Adrenalectomy /Lateralization (n, %)	9/42 (21%)	15/48 (31%)		
		LI ≥ 3.0	Adrenalectomy /Lateralization (n, %)	7/25 (28%)	12/30 (40%)		
		LI ≥ 4.0	Adrenalectomy /Lateralization (n, %)	-	9/19 (47%)		

Supplemental Table 10: Number and rate of PA patients submitted to adrenalectomy based on evidence of lateralization under unstimulated conditions, who had post-cosyntropin AVS results indicating bilateral disease.

Supplemental figure 1.

Rate of bilateral selectivity at different SI cutoff values on unstimulated conditions (n = 1274) and after cosyntropin- (n = 742) or metoclopramide- (n = 123) stimulation.



Supplemental figure 2.

Frequency distribution of SI before and after cosyntropin stimulation.



Both left and right SI values are plotted. Grey bars: Unstimulated AVS; Black bars: cosyntropin-stimulated. n = 402. X axis: Log(10) scale.

Supplemental figure 3.

Rate of lateralization rate by different diagnostic values (whole cohort).



Lateralization rates in the whole cohort (regardless of availability of data on surgical indication and performance) according to protocol (Unstimulated [n = 1274] vs cosyntropin stimulated [n = 742]), SI cut-off values (1.4, 2.0 and 3.0) and LI cut-off values (2.0-5.0) are shown on top of the bars. Dashed bars = rates of bilateral selectivity, by group, for comparison with lateralization and adrenalectomy rates.

Supplemental figure 4.

Impact of cosyntropin and metoclopramide stimulation on AVS diagnostic indexes.



Paired analysis within subgroups of AVS performed on both unstimulated and cosyntropin- (n = 402; left panels) or metoclopramide- (n = 123; right panels) stimulated conditions. RASI and LI shown for cases with unilateral PA confirmed at follow-up. White bars = unstimulated; grey bars = stimulated. COSYN = cosyntropin, METO = metoclopramide. Median, IQR. \* = p < 0.0