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Diagnosis of primary aldosteronism in the hypertension specialist centers in Italy: a national survey

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1 **Diagnosis of primary aldosteronism in the hypertension**
2 **specialist centers in Italy. A national Survey.**

3 *Running title: diagnosis of primary aldosteronism among hypertension specialist centers*

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34 **Abstract**

35 Primary aldosteronism (PA) is the most common endocrine cause of resistant hypertension.
36 Individuals with PA are at increased cardiovascular risk, and an appropriate management
37 and treatment would ideally reduce such risk. Screening and diagnosis of PA requires specific
38 diagnostic test, it is considered as a time- and cost-consuming and, as a result, it is
39 underperformed in clinical practice. An online survey reviewing available diagnostic
40 procedures, laboratory testing and clinical protocols for screening and confirmation of PA
41 diagnosis was conducted among clinical lead of Excellence centers of the Italian
42 Hypertension Society.

43 A total of 102 questionnaires were sent and 62 centers participated to the survey. The
44 assessment of the plasma renin (plasma renin activity/direct renin concentration) and
45 plasma aldosterone concentration (PAC) were available among all centers. Captopril
46 challenge test (CCT) and saline infusion test (SIT) were available in the 60% and 61% of
47 centers, respectively. Fludrocortisone suppression test was available in the 32% of the units.
48 Adrenal vein sampling was accessible at the 32% of the centers. We found discrepancies in
49 cut-off levels of aldosterone-to-renin ratio (ARR), and PAC after SIT. Other discrepancies
50 involved the duration of the wash-out period before ARR testing, and dosage of captopril
51 administered during CCT.

52 In conclusion, although all centers are sufficiently equipped to perform PA screening, often
53 patients should be referred to other centers to confirm the diagnosis of PA. A greater
54 uniformity across centers to define precise cut-offs for screening and confirmatory testing
55 for the diagnosis of PA would be of utility.

56

57 **Summary table**

58

59 *What is known about topic*

60 1. Screening and diagnosis of primary aldosteronism is usually underperformed by
61 general practitioners, because of excessive time consumption, technical difficulties,
62 and potential harm related to some procedures.

63 2. The evaluation of primary aldosteronism performed among Hypertension Reference
64 Centers would ideally ensure an optimal allocation of resources, in view of the fact
65 that most of the centers are equipped with dedicated medical staff and appropriate
66 diagnostic techniques.

67

68 *What this study adds*

69 1. The present research demonstrated that, among Italian Excellence and Reference
70 Centers, there is large availability of screening and confirmation test for the diagnosis
71 of primary aldosteronism.

72 2. However, we found a rather heterogeneous behavior across Centers in terms of
73 methodologies, protocols and cut-off values related to diagnostic work-up for PA,
74 suggesting that a greater uniformity across centers to confirm/exclude PA is highly
75 desirable.

76 3. Finally, some technically-demanding and costly procedures, such as lateralization
77 procedures requiring adrenal venous sampling and genetic testing, are available in
78 only a small minority of the centers, suggesting the need to create a national network
79 to facilitate the access to these procedures.

80

81 **Introduction**

82 Arterial hypertension, defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood
83 pressure (DBP) ≥ 90 mmHg, is a major public health concern [1]. Despite increased
84 awareness, the estimated rate of annual cardiovascular (CV) and all-cause deaths associated
85 with arterial hypertension is on the rise [2]. This finding could be, in part, attributable to the
86 increased burden of resistant hypertension (RH), defined as the failure of anti-hypertensive
87 drug treatment with at least 3 drugs to obtain adequate BP control [3]. RH is frequently
88 sustained by the presence of secondary causes, which require specific diagnostic testing
89 and management.

90 Primary aldosteronism (PA), defined as the autonomous overproduction of aldosterone,
91 inappropriate for sodium status, is the most common endocrine cause of arterial
92 hypertension. Recent studies have described the true prevalence of PA to vary between 5%
93 and 10% of all cases of arterial hypertension [4-6], with even higher rates of prevalence
94 among subjects with RH [7]. As compared with individuals with essential hypertension,
95 subjects with PA display higher rates of target organ damage [8-12] and CV events for
96 similar BP values [13-17]. Therefore, the prompt diagnosis of PA and the identification of its
97 subtypes is of outmost importance, not only to address affected patients to the appropriate
98 management, but also to potentially revert this risk excess [15-17].

99 The Endocrine Society Clinical Practice Guideline recommends case detection of PA in certain
100 patient subgroups with: BP $> 150/100$ mmHg or RH, hypertension and spontaneous or
101 diuretic-induced hypokalemia, hypertension and adrenal incidentaloma, hypertension and
102 obstructive sleep apnoea, hypertension and a family history of early onset hypertension or
103 cerebrovascular accident at a young age, and all hypertensive first-degree relatives of
104 patients with PA [18]. These would cover nearly 50% of all hypertensive subjects. However,
105 screening and diagnosing PA, in particular in the general practitioner setting, is often
106 considered as time-consuming, cumbersome, and in some cases potentially harmful (e.g.
107 due to wash-out of some anti-hypertensive drugs, salt-loading protocols and invasive

108 examinations). As a result, screening and diagnosis of PA by general practitioners is often
109 largely underperformed [19].

110 The Italian Hypertension Society (Società Italiana dell'Ipertensione Arteriosa, SIIA)
111 promotes a network of Italian Excellence and Reference Centers for the diagnosis and
112 treatment of arterial hypertension, where hypertensive patients are usually referred by
113 general practitioners for a second-level assessment. This network ensures an optimal
114 allocation of health resources for an accurate diagnosis of PA. In fact, most of the centers
115 do have availability of dedicated medical staff, advanced diagnostic techniques and the
116 expertise to perform a comprehensive assessment of secondary forms of hypertension [20].

117 The current article presents the results of a National survey conducted among SIIA Italian
118 Hypertension Centers, with the aim of reviewing the current available diagnostic procedures,
119 laboratory testing and clinical protocols for screening and diagnosis of PA.

120

121

122 **Methods**

123 The survey was conducted between August and November 2016. An online questionnaire,
124 drafted by the Young Investigator Group of the SIIA under the supervision of the SIIA
125 Executive Committee, was sent to the clinical lead of Reference and Excellence centers of
126 the SIIA. Those who gave explicit consent to participate, received a link with the electronic
127 form, and were invited to fill the online questionnaire anonymously. The questionnaire was
128 easy to fill in and the average time to complete it was around 15 minutes. The questionnaire
129 included 12 items exploring the availability and accessibility of technologies, methodologies
130 and related procedures, usually adopted to screen and confirm the diagnosis of PA in
131 hypertensive outpatients (first wave). Non-responders were invited to participate two more
132 times with repeated online invitations. Those who did not respond to any of the three
133 invitations were excluded from the study. Reasons for not responding were not assessed.

134 In brief: the questionnaire included three questions to understand the list of laboratory
135 exams, functional test and instrumental settings available within each center. Question 4
136 and 5 evaluated some aspects related to the methodology for PA screening. Two questions
137 investigated the diagnostic cut-off values adopted by each center for the aldosterone-to-
138 renin ratio (ARR) and plasma aldosterone levels after intravenous saline infusion test (SIT).
139 Question 8 explored the drug dosage commonly used in captopril challenge test (CCT).
140 Question 9 investigated the instrumental diagnostic for the evaluation of the morphology of
141 the adrenal gland. Finally, questions 10 to 12 were related to the screening for obstructive
142 sleep apnea syndrome (OSAS) in subjects with PA, the use of ABPM as a tool for the
143 diagnosis of secondary hypertension, and the accessibility of each single center to genetic
144 testing facilities. To better elucidate some aspects of the questionnaire, responders were
145 subsequently invited to provide further details by filling a further list of brief questions
146 (second wave) related to: details of drug withdrawal before screening test for PA, indications
147 to fludrocortisone suppression test (FST) and dexamethasone suppression test, body
148 position during SIT, availability at the center and success rate of adrenal vein sampling
149 (AVS).

150

151

152 **Results**

153 The questionnaire was sent to 102 Hypertension Centers, and a total of 62 fully-filled
154 questionnaires were collected, both including the first and second wave, giving an overall
155 response rate of 61%. Responders were well distributed among the three Italian macro-
156 regions (North n=30, 48%; Centre n=15, 24%, and South n=17, 28%).

157 Table 1 reported a list of the main diagnostic test and procedures for PA screening and
158 diagnosis, and the number of excellence and reference centers where each test is available,
159 divided by macro-regions. The assessment of the plasma renin activity (PRA) or direct renin
160 concentration (DRC) plus plasma aldosterone concentration (PAC) was available among all
161 centers (100%). Second-level functional tests to confirm/exclude the suspect of PA are

162 available in the 82% of the units (at least one available test in 51 out of 62 centers).
163 Specifically, CCT and SIT are technically available at the 60% and 61% of centers,
164 respectively, whereas the fludrocortisone suppression test (FST) is available at the 32% of
165 the units. This test is routinely performed only in the 20% of these units (n=4), whereas in
166 the majority of the cases (55%) the test is performed only in the presence of contrasting
167 results from other confirmatory tests. In five units, although technically available, the test
168 is usually not performed.

169 Dedicated staff and diagnostic resources to perform selective catheterization of adrenal
170 veins (AVS) were available at 20 centers (32%, North=10, Center=6, South=4). However,
171 only in half of the cases (n=10) the test is performed at the center, whereas in the remaining
172 cases (n=10), although the procedure is technically available, the patients is usually referred
173 to another center. Interestingly, in 5 centers (8%), the surgical treatment of lateralized PA
174 is based only upon laboratory and imaging results. The overall approximate success rate in
175 those centers where the procedure is usually performed (n=10) is >80% in 8 out of 10
176 centers, 60-70% in 1 center, and below 60% in the remaining center.

177 We found that in more than half of the centers (N=34, 55%), ARR was calculated by
178 considering PRA, whereas in 27 units (45%) through the assessment of direct renin
179 concentration (DRC). The evaluation of 24-h sodium and potassium urinary concentrations
180 was systematically requested to all subjects screened for PA only by 27 centers (44%) whilst
181 in the majority of the units (56%, n=35), this exam was performed only in selected cases.
182 The discontinuation from drugs interfering with the renin-angiotensin-aldosterone system
183 (e.g. β -blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, with the exception
184 of alpha-blockers and calcium channel blockers) before plasma renin assay is variably
185 performed among units, being always performed in rather 2/3 of the centers (n=40, 65%);
186 in other cases, drugs with minor effects on the RAA system are maintained and results are
187 interpreted by taking into account the effects of concomitant treatment on PRA/DRC and
188 PAC levels (n=18, 29%). In 6% of the cases (n=4) the wash-out of interfering drugs is

189 usually not performed. The average duration of wash-out period is rather variable among
190 units, being ≥ 15 days for 44 centers (71%), 3-4 days for 23% of the units (n=14).

191 The cut-off value of ARR suggesting the presence of PA was set at 30 (with PAC in ng/dL
192 and PRA in ng/mL/h) / 2.7 (with PAC in ng/dL and DRC in mU/L) in 56% of the centers
193 (n=35), at 40/4.9 in the 40% (n=25), and at 20/2.4 in only 4% of centers (n=2, Figure 1).

194 The diagnostic cut-off level of serum aldosterone adopted to confirm the diagnosis of PA
195 after SIT also showed heterogeneity among centers: it was 10 ng/dL in 47% of centers, 7.5
196 ng/dL in 24% of centers, and 5 ng/dL in 29% of the centers (Figure 2). Another discrepancy
197 between centers is related to body position during SIT test: in 15 centers (39%) it is
198 performed in seated position, whereas in 23 centers (61%) in supine position. Also drug
199 dosage administered for CCT was relatively variable among centers: 50 mg was the dosage
200 adopted in the 77% of the centers, while the remaining 23% performed the test after
201 administering 25 mg.

202 With regards to imaging testing, CT-scan was the preferred test for 97% of the centers,
203 whereas the remaining 3% considered magnetic resonance (MR) as the first imaging test to
204 be performed after the confirmation of PA diagnosis. In subjects with PA, in the presence
205 of adrenal nodule evaluated by imaging test, a dexamethasone overnight suppression test
206 is always performed among 39% of the centers, performed only in the presence of large
207 adrenal nodules (>1 cm) in 28% of the centers, and not routinely performed at the 33% of
208 the centers unless a specific clinical suspicion of hypercortisolism is present.

209 The evaluation of characteristics of circadian BP profile through automated blood pressure
210 monitoring (ABPM) was requested by the vast majority of centers (90%). Conversely,
211 screening for features of obstructive sleep apnea syndrome (OSAS) through validated
212 questionnaires (e.g. Epworth Sleepiness Scale) in subjects screened for PA was habitually
213 performed only by 29% of the centers. Genetic testing for familial forms of PA (long PCR
214 for the chimeric *CYP11B1/CYP11B2* gene and sequencing of the *KCNJ5* gene) [18] are
215 available in a small minority of the centres (27%).

216

217 **Discussion**

218 The current article presents state-of-the-art results of laboratory and instrumental
219 procedures and resources to perform a diagnosis of PA across Italian Hypertension
220 Excellence and Reference centers endorsed by the SIIA. The two main findings of this survey
221 are that there is large availability, among Italian centers, of laboratory and instrumental
222 resources for screening and confirmation test for the diagnosis of PA. Conversely, some
223 selected and cost-demanding procedures, which usually require dedicated staff and specific
224 facilities, are available only in a limited proportion of the centers. The second evidence of
225 the present survey is a rather heterogeneous behavior across centers in terms of
226 methodologies and protocols related to diagnostic work-up for PA.

227 According to guidelines, the diagnosis of PA is a three step process, comprising screening
228 test, confirmatory testing and subtype diagnosis. Each of these steps could be variably
229 affected by sub-optimal sensitivities and specificities, depending on a number of factors such
230 as the characteristics of the population and the choice of cut-off points. A missed diagnosis
231 of PA would result in an inappropriate exposure to increased CV risk, since PA is associated
232 with a worse CV prognosis as compared to essential hypertension [Monticone S., 2018].
233 Moreover, insufficient detection and treatment of lateralized PA may be associated with a
234 residual increased risk for cardiovascular events and mortality [Hundemer GL, 2018].

235 Additionally, several studies pointed towards a reduced quality of life (QOL) in patients
236 affected by PA compared with the general population [Veelema MS, JCEM 2018; Ahmed AH,
237 JCEM 2011]. Specific PA treatment has been shown to improve QOL, with the unilateral
238 adrenalectomy being more effective than MR antagonists [Veelema MS, JCEM 2018; Ahmed
239 AH, JCEM 2011], underscoring once again the importance of diagnosing unilateral PA.

240 The most reliable means to screen for PA is the ARR, which can be calculated using both
241 the PRA and DRC in the denominator [18]. PRA has been traditionally measured by Radio-
242 Immuno-Assay, however DRC measurement with chemiluminescence assays (currently
243 adopted in the 45% of the centers), which are fully automatized and do not produce
244 radioactive waste, is progressively replacing the traditional PRA in the evaluation of patients

245 affected by arterial hypertension. Several studies showed that PRA and DRC display an
246 overall good correlation, that becomes weaker for PRA values < 1 ng/mL/h, (Burrello J.,
247 2016; Dorrian C.A., 2010). The ES guideline [Funder JW, 2016] proposes a conversion factor
248 of PRA (ng/mL/h) to DRC (mU/L) of 8.2. Applying this factor, an ARR of 30 (calculated with
249 PRA measured in ng/mL/h) corresponds to an AARR (aldosterone to active renin ratio) of
250 3.7 (calculated with the DRC measured in mU/L). However, three independent studies
251 showed that the optimal sensitivity and specificity for the AARR are reached with significantly
252 lower cut-offs (Burrello J., 2016; Rossi G.P., 2016; Manolopoulou J., 2015). According to
253 these data, the use of a conversion factor between PRA and DRC should be discouraged
254 and distinct cut-offs should be adopted for the ARR and the AARR. Several factors, including
255 age, gender, time of day, serum K^+ levels and, most importantly, antihypertensive
256 medications, may affect ARR and should be taken into account [Funder JW, 2016].
257 According to ES guideline, it is mandatory to withdraw the most interfering medications,
258 including K^+ sparing and K^+ wasting diuretics while the ARR can be confidently interpreted
259 under the relatively noninterfering medications. Significant heterogeneity is expected for
260 this step, reflecting clinicians' preferences, the severity of hypertension and patients'
261 comorbidities. The practice of drug discontinuation (with the exception of alpha-blockers
262 and calcium channel blockers), despite potentially associated with side effects [Fischer E,
263 *Rev Endocr Metab Disorder 2011*], carries the lowest risk of false positive or false negative
264 results and it is therefore the most frequently adopted strategy across the SIIA centers.
265 Notably, the guidelines do not establish a precise cut-off for the ARR, which ideally should
266 be tailored by each center according to the type of assay used and the Na^+ intake of the
267 population. The choice of a low cut-off to define a positive screening test (e.g. 20 with PAC
268 in ng/dL and PRA in ng/mL/h or 2.4 with PAC in ng/dL and direct renin concentration in
269 mU/L), as it is performed at the 4% of the centres, if on one hand maximizes sensitivity, on
270 the other hand results in a high rate of false positives, thereby reducing the specificity and
271 increasing time and costs associated with the performance of a confirmatory test.

272 Giving the high rate of false positive results of the ARR (57% in the PATO study), a
273 confirmatory testing should always be performed to avoid patients with low renin essential
274 hypertension to undergo costly and invasive diagnostic procedures such as adrenal CT
275 scanning and AVS [18]. According to some authors [22], the FST is regarded as the gold-
276 standard test to definitively confirm or exclude PA diagnosis. However, it is costly and time
277 consuming, and often requires the patient to be hospitalized for four days. For these reasons
278 nowadays the SIT and the CCT, which represent valid alternatives to the cumbersome FST
279 [23], are the most widely used ones. As expected, our results follow this trend, with the FST
280 being available only in approximately 1/3 of the centres. Surprisingly, also the possibility
281 of performing a relatively simple confirmatory test is available only in 60% of the units in
282 the case of SIT, and in 61% of the units in the case of CCT, indicating that a significant
283 proportion of patients has to be referred to another centre. There is not an optimal protocol
284 to perform the CCT test and two different doses (25 mg or 50 mg) of captopril can be
285 administered. According to this survey, 50 mg is more frequently used dosage (in 77% of
286 centres), but there is not enough evidence to prefer one protocol over the other. According
287 to historical pharmacological studies, the main pharmacokinetic parameters after the
288 administration of 25 mg or 50 mg of captopril were not significantly different (except for the
289 area-under-the-curve standardized in relation to 1 mg of the dose) [24]: it is therefore
290 conceivable that the administration of 25 mg or 50 mg of captopril will not significantly affect
291 the performance of the test.

292 As for the screening test, also for the SIT and the CCT test there is not general agreement
293 on the best cut-off to define complete aldosterone suppression and definitively exclude PA
294 diagnosis. While post SIT infusion PAC >10 ng/dL are generally deemed to be diagnostic of
295 PA and a concentration <5 ng/dL indicative of a normal aldosterone suppression, values
296 between 5 and 10 ng/dL represent a grey zone. We observed a wide heterogeneity across
297 centres with respect to the cut-off chosen to define normal suppression after SIT: the
298 answers were in fact almost equally distributed among the three options (5 ng/dL, 7.5 ng/dL
299 and 10 ng/dL). Choosing a cut-off of 10 ng/dL maximizes the specificity and reduces the
300 number of patients that have to be addresses to lateralization procedures; however, in a

301 recent study it has been shown that 29% of the patients with a post SIT PAC <5 ng/dL had
302 a lateralized aldosterone production and were successfully cured by unilateral
303 adrenalectomy [25]. The results of this study, methodologically sound and using strict
304 criteria to define lateralized AVS, challenge the performance and the validity of SIT in
305 definitively confirming or excluding PA diagnosis [25]. Therefore, some authors claim that
306 prospective studies are warranted to establish if AVS indication should be extended to all
307 patients with a positive screening test, in order to offer curative surgery to a greater number
308 of PA patients (Cornu E., Hypertension 2016).

309 After confirming the diagnosis, subtype testing should be performed in all PA patients who
310 are candidate and desire surgical treatment by unilateral adrenalectomy. Subtype diagnosis
311 comprises adrenal CT scanning (to rule out an aldosterone producing adrenal carcinoma)
312 and the AVS to distinguish between unilateral and bilateral disease [18]. Despite significant
313 advances in the optimization of the AVS procedure, with several issues having been
314 addressed (Monticone S., Lancet DE 2015), it remains a poorly standardized procedure across
315 centers (Kempers; Rossi). Different studies showed that adrenal imaging alone is not
316 sensitive neither specific enough to define the source of aldosterone overproduction [26],
317 notwithstanding the controversial SPARTACUS trial failed in demonstrating a superiority of
318 AVS-based treatment over adrenal CT-scanning (Dekkers T., Lancet DE 2016; Beuschlein F,
319 HMR 2017) in intensity of antihypertensive medication or clinical benefit. However, it must
320 be acknowledged that the study was underpowered and the selected selection criteria did
321 not allow to generalize the results to the overall PA population (Beuschlein F, HMR 2017).

322 Whereas all hypertension centres should be encouraged to set up their own protocol and
323 perform one or more confirmatory tests (which are safe and very often uncomplicated
324 procedures) the "centralization" of AVS performance in few referral centers may be
325 supported by the fact that an expert and dedicated radiologist is a key factor for increasing
326 the successful cannulation of adrenal veins [Buffolo F., IJMS 2017] and a higher rate of
327 adrenal vein rupture was observed in centres where a low number of procedures is
328 performed [27]; by contrast this complication is rarely observed in centres with long

329 experience and high number of procedure per year [28]. In our cohort good AVS
330 performance is achieved in the majority of the hypertension units; in centers with a low
331 success rate, ACTH(1-24) infusion and measurement of serum cortisol during the procedure
332 should be considered as useful strategies to improve successful cannulation of adrenal veins
333 [Buffolo F., IJMS 2017].

334 A centralized approach would also be effective to improve the diagnosis of genetic forms of
335 PA, such as familial hyperaldosteronism [29,30]. In fact, we observed that genetic testing
336 is available only in a small minority of the hypertension specialist centers, suggesting that
337 genetic forms of hyperaldosteronism could be currently underdiagnosed.

338 We acknowledge that our results should be viewed in the lights of some limitations. Even
339 whether the online survey could be conceived as a faster way of collecting data and
340 increasing the response rate as compared to paper-and-pencil methods, some inherent
341 disadvantages such as the absence of an interviewer, possible cooperator problems and
342 potential dishonesty could negatively impact on results. In our survey we proposed
343 anonymity to responders to reduce part of these limitations. As a consequence, those who
344 did not respond to the survey could not be better characterized.

345 In conclusion, a greater uniformity across centres to confirm/exclude PA is highly desirable,
346 in order to guarantee the consistency of a diagnosis across the country. Creating a national
347 consensus to define precise cut-offs for screening and confirmatory testing would be of
348 great utility, in particular for those centres with low experience in the clinical management
349 of patients with PA. However, this still could be largely hampered by the great heterogeneity
350 of the assays used for aldosterone measurement, as mentioned previously. The promotion
351 a national network between Italian hypertension specialist centers endorsed by the SIIA, in
352 order to improve the awareness and spread the knowledge on PA screening and diagnosis,
353 would be desirable also to facilitate the access to technically-demanding or costly
354 procedures.

355

356 **Conflict of interest**

357 None of the authors has financial or other conflicts of interest that might have biased the
358 work.

359

360

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487 **Figure legends**

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489 Figure 1: cut-off value of aldosterone-to-renin ratio adopted by centers, suggesting the
490 presence of PA. Reported values are related to ARR calculated from plasma aldosterone

491 concentration (ng/mL) and plasma renin activity (ng/mL/h)/ plasma aldosterone
492 concentration (ng/mL) and direct renin concentration (mU/L)

493

494 Figure 2: cut-off value of aldosterone-to-renin ratio adopted by centers, suggesting the
495 presence of PA. Reported values are calculated from plasma renin activity, and
496 correspond to 2.4, 3.7 and 4.9 ng/dL/mU/L if direct renin concentration is assessed

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499 **Tables**

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502

503 **Table 1:** number of centers (and %) with availability of the related test and procedure
 504 for screening and diagnosis of PA, divided by macro-regions

	Total (n=62)	North (n=30)	Centre (n=15)	South (n=17)
Plasma renin activity	50 (81)	22 (73)	13 (87)	15 (88)
Direct renin concentration	35 (56)	18 (60)	9 (60)	8 (47)
Plasma aldosterone	62 (100)	30 (100)	15 (100)	17 (100)
Urinary aldosterone	46 (74)	23 (77)	11 (73)	12 (71)
Saline loading test	37 (60)	18 (60)	9 (60)	10 (59)
Captopril challenge test	38 (61)	19 (63)	10 (67)	9 (53)
Fludrocortisone suppression test	20 (32)	11 (37)	4 (27)	5 (29)
Adrenal vein sampling	20 (32)	10 (33)	6 (40)	4 (27)

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