Primary Aldosteronism: Diagnostic Accuracy of the Losartan and Captopril Tests

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BACKGROUND

To assess whether angiotensin-II receptor blockers (ARBs) offer any additional advantage in confirming the diagnosis of primary aldosteronism (PA) and their use in the differentiation of PA subtypes.

METHODS

A prospective, cohort, head-to-head study was conducted between July 2003 and July 2006. A total of 135 patients received captopril and losartan tests to confirm the diagnosis of PA in the TAIPAI (Taiwan Primary Aldosteronism Investigation) intervention.

RESULTS

In total, 71 patients were diagnosed with PA. The area under the receiver-operating characteristic (ROC) curve of the postcaptopril plasma aldosterone concentration (PAC) was significantly less than that of the postlosartan PAC (0.744 vs. 0.829, $P = 0.038$). Using an aldosterone–renin ratio (ARR, ng/dl per ng/ml/h) >35 with a PAC >10 ng/dl, the specificity was 89.1% vs. 93.8% and the sensitivity was 66.2% vs. 84.5 % for the captopril test vs. the losartan test, respectively. With respect to the losartan test, the accuracy was 88.9%, the agreement was good ($k = 0.778$), and there was no disagreement with the McNemar test ($P = 0.118$). Losartan had the advantage of a better negative predictive value to exclude PA when patients were referred with a serum potassium (SK) level <3.8 mmol/l. When a postlosartan ARR >60 was the cutoff value, the positive predictive value was 82% with a negative predictive value of 57% in distinguishing aldosterone-producing adenomas (APAs) from idiopathic hyperaldosteronism (IHA).

CONCLUSIONS

The postlosartan ARR and PAC were shown to have better accuracy for the diagnosis of PA than the captopril test. With a postlosartan ARR >60, APAs can be adequately differentiated from IHA.

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Primary aldosteronism (PA), characterized by an inappropriate production of aldosterone, affects 5–13% of patients with hypertension.[1,2] The use of the aldosterone–renin ratio (ARR, ng/dl per ng/ml/h) as a screening test contributes to the increased diagnostic rate of this disease.[2] As the incidence of PA has increased since the ARR has been used as a screening test,[3,4] the difficulty in establishing a diagnosis of PA may be encountered because of atypical manifestations. There are several tests that have been used to confirm the autonomous secretion of aldosterone. A high-salt diet with administration of flurocortisone to suppress the renin–angiotensin system was believed to be the gold standard test for the diagnosis of PA.[5] However, the test takes a long time and may not be suitable for patients who have cardiovascular disease, which is more prevalent in PA than essential hypertension (EH).[6]

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The most common pharmacologic test for the diagnosis of PA is the administration of captopril to examine whether an abnormal ARR persists. Several studies have demonstrated that the ARR after a single dose of captopril is diagnostic[7–10] and as sensitive as the saline-loading test for the identification of an aldosterone-producing adenoma (APA).[8] For renin–angiotensin system blockade, angiotensin-II receptor blockers (ARBs) may be suitable for the pharmacologic diagnosis of PA. It has been shown that an ARR change after an ARB was greater than that induced by an angiotensin-converting enzyme inhibitor in PA patients.[7] However, there have been no studies clarifying the diagnostic accuracy of ARBs in PA, nor a comparison of the efficacy in the diagnosis of PA between ARBs and angiotensin-converting enzyme inhibitors. In this study, we examined the performance of the losartan test for the diagnosis of PA, and determined whether losartan offered any additional advantage than captopril in confirming the diagnosis of PA and differentiating the subtypes of PA.

METHODS

Patients. Between July 2003 and Jan 2006, 160 hypertensive patients were referred to the hypertension clinic for suspicion of aldosteronism after an initial evaluation and entered into the Taiwan Primary Aldosteronism Investigation (TAIPAI)

database. The initial evaluation included (i) age at onset <35 years, (ii) hypertension that is difficult to control after initiating therapy, (iii) clinical occurrence of a hypertensive crisis, (iv) the presence of hypokalemia or metabolic alkalosis, or a random ARR >30, and (v) evidence of an adrenal incidentaloma and hypertension or hypokalemia. The database was constructed for quality assurance since 2003 in one medical center (National Taiwan University Hospital, Taipei, Taiwan) and its three branch hospitals in different cities (National Taiwan University Hospital Yun-Lin branch, Yun-Lin, southern Taiwan; Far-Eastern Memorial Hospital, Taipei; Tao-Yuan General Hospital, Tao-Yuan, middle Taiwan). All patients with intention to confirm and requiring a suppression test or adrenal venous sampling (AVS) were recruited and the data were prospectively collected.

This prospective head-to-head comparison was approved by the Institutional Review Board (NTUH No. 9461700402). All antihypertensive medications were discontinued for at least 14 days before the study. Diltiazem and/or doxazosin were administered for control of marked high blood pressure, when required.[11] Medications that might interfere with the renin–aldosterone axis, such as steroids, sex hormones, licorice, or nonsteroidal anti-inflammatory drugs, were also withheld. All patients consumed a low-salt diet with 6 g of NaCl daily for at least 3 days during the test period.

Confirmation of PA. A diagnosis of pheochromocytoma was made in two patients, renal artery stenosis was diagnosed in five patients, polycystic kidney disease was diagnosed in one patient, and IgA nephropathy was diagnosed in one patient. Sixteen patients who did not give their informed consent were excluded. The remaining 135 patients received both captopril and losartan tests (**Figure 1**). The two tests were performed on 2 consecutive days. The patients were asked to sit for at least 10 min for the baseline blood samples at 9 AM, and allowed to ambulate moderately until the second sampling. The second blood samplings

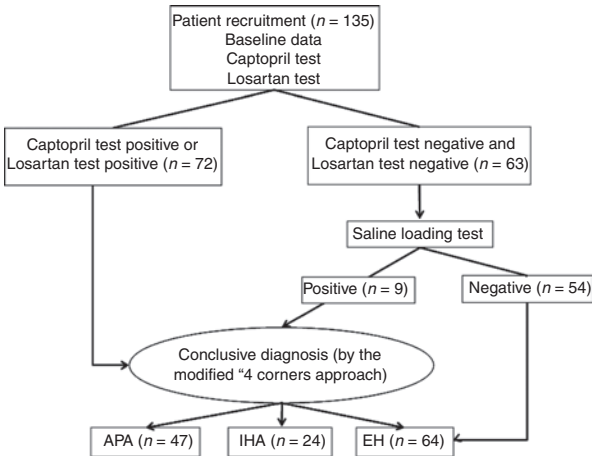

Figure 1 | Flow sheet of the diagnosis of primary aldosteronism. Aldosterone–renin ratio >35 after administration of captopril or losartan indicated a positive result. A plasma aldosterone concentration >10 ng/dl after saline infusion is positive for the test (see text). APA, aldosterone-producing adenoma; EH, essential hypertension; IHA, idiopathic hyperaldosteronism.

were obtained either 1 h after the administration of 50 mg of captopril,[12] or 2 h after the administration of 50 mg of losartan. As previously reported, the time-to-peak plasma concentration of losartan was proportional to the dose and was ~1.5 h with the 50 mg dose.[13] With oral captopril, the time-to-peak was >0.5 h (ref. 14). In this head-to-head comparative study, we set the sampling period at least one half-life of plasma renin activity (PRA) or plasma aldosterone concentration (PAC) because the biological half-life of aldosterone is ~30 min (ref. 15) and the half-life of PRA is ~15 min (ref. 16).

An ARR >35 with a PAC >10 ng/dl (>277 pmol/l) after the administration of captopril or losartan was defined as a positive test for PA. We constructed an ARR >35 because this value had the best sensitivity and specificity to differentiate PA from EH in the TAIPAI database.

Consecutive patients underwent a saline infusion test on a separate day to evaluate the autonomous secretion of aldosterone. Briefly, after at least 1 h in the supine position, 2 l of 0.9% NaCl solution were administrated intravenously from 8:00 to 12:00 AM, and blood samples for PRA and PAC were drawn before and at the end of the saline infusion. Patients in whom the PAC >10 ng/dl after saline infusion were diagnosed with PA.[17]

Imaging studies. A computerized tomographic (CT) scan of the adrenal glands with a nonionic iodinated contrast agent was performed on all patients with PA, with at least 3-mm contiguous slices in the presence of a normal surround. Although there were no strict measurements of normal adrenal size, the CT scan was considered abnormal when any area thicker than 10 mm was detected. A dexamethasone suppression adrenocortical scintigraphy (NP-59, [I-131]6-β-iodomethylnorcholesterol) was performed for those patients without a definite adenoma of the adrenal glands on the adrenal CT scan.[18,19]

Further tests. Bilateral AVS was required if imaging studies were equivocal. A successful venous cannulation was noted if the ratio of the cortisol level of the adrenal vein to the inferior vein cava >3. Lateralization of aldosterone secretion was defined as a difference in the aldosterone/cortisol ratio greater than fourfold between the bilateral adrenal glands.[20]

The concentration of aldosterone was measured by radioimmune assay with commercial kits (Aldosterone Maia Kit; Adaltis Italia, Bologna, Italy), as previously described.[14,21] PRA was measured as the generation of angiotensin-I *in vitro* using a commercially available radioimmune assay kit (Cisbio, Bedford, MA).

Histopathologic studies. All of the operated adenomas were blindly re-evaluated by the same pathologist. The histologic diagnosis of APA was based on well-defined, encapsulated tumors, predominately consisting of foamy clear cells.[22] Adenomas appear as nodules of clear cells in sheets or nests that are sharply demarcated by a pseudocapsule and compress the non-neoplastic uninvolved adrenal gland.[23] Adenomas are differentiated from nodular adrenal hyperplasia by their

solitary and well-circumscribed nature.[21,23] Adrenal glands from hyperplasia are marked by a diffuse hyperplasia of cells resembling those of normal zona glomerulosa with or without macro- or micronodules.

Diagnostic criteria of subtypes of PA. The diagnosis of APA was established when all of the following "modified 4 corners score" criteria were met:[8] (i) evidence of autonomous excess aldosterone production based on an ARR >30, (ii) lateralization of aldosterone secretion at AVS or during dexamethasone suppression adrenocortical scintigraphy, (iii) evidence of an adenoma on CT scan, and (iv) postsaline loading (PAC >10 ng/dl) and/or a pathologically proved adenoma after adrenalectomy and cure of hypertension without antihypertensive agents or improved hypertension, potassium, PAC, and PRA. Idiopathic hyperaldosteronism (IHA) was clarified by the following criteria: (i) evidence of autonomous excess aldosterone production based on an ARR >30, (ii) nonlateralization of aldosterone secretion at AVS or dexamethasone suppression adrenocortical scintigraphy, (iii) evidence of bilateral diffuse enlargement on CT scan, and/or (iv) postsaline loading (PAC >10 ng/dl) and/or evidence of diffuse hyperplasia of cells on pathologic findings. In patients with negative captopril and losartan tests, the prespecified ARR <30 and PAC <25 ng/dl and negative salt-loading test were considered to be diagnostic of EH.

Statistical analysis. The primary objective of the study was to compare the diagnostic accuracy of the losartan test vs. the captopril test for PA. The secondary objective was to compare the acute aldosterone changes by these two drugs. The data were provided as the mean values ± s.d. As the aldosterone and ARR were not normally distributed, a square root transformation of the raw data was used for statistical analyses.[24]

Statistical analyses were performed with SPSS for Windows, version 12.0 (SPSS, Chicago, IL) and MedCalc, version 8.0 (MedCalc Software, Mariaherke, Belgium). A normal distribution was attained by appropriate transformations of skewed variables as aldosterone and ARR. The κ-test was used to compare the levels after administration of captopril vs. losartan, and the MacNemar test was used to evaluate the agreement and repeatability. The aim of the κ-test was to evaluate the reliability assessed by two different methods. The results were expressed as *k* values and were classified according to the scale of Landis and Koch.[25] The aim of the McNemar test was to find out whether one of these two tests under-evaluated or overevaluated the severity. The Bland–Altman plot calculates differences between the post-test PAC and ARR against averages to identify any systemic bias.[26] To test the performance of the test, the post-test PAC was compared using Pearson's correlation coefficient (*r*), and a folded empirical cumulative distribution plot. The *P* value equating significance was <0.05.

RESULTS

Demography of PA patients

Among 135 hypertensive patients (66 women and 69 men; mean age, 47.9 ± 1.5 years), 72 patients had positive captopril or losartan tests (**Figure 1**). Eight patients with losartan- or captopril-positive tests were clarified as EH because they had a negative saline-loading test, and six of the patients had no lateralization by AVS and negative CT findings. Nonetheless, two patients with negative captopril and losartan tests were diagnosed with PA because their baseline ARR was >30 with an upright PAC >10 ng/dl, and had a positive saline-loading test and abnormal imaging findings.

Finally, 71 patients (40 women and 31 men; mean age, 48.8 ± 1.2 years) had the diagnosis of PA, 47 patients were diagnosed with APA, and 24 patients were diagnosed with IHA. All of the EH patients, and 39 of the PA patients (20 IHA and 19 APA) had received the saline infusion test; AVS was performed in 29 patients (3 EH, 16 IHA, and 10 APA). During 39 ± 17 months of follow-up, a unilateral adrenalectomy was performed on 40

Table 1 | Clinical and biochemical characteristics of the study patients

	EH (*n* = 64)	*P* (APA vs. EH)	APA (*n* = 47)	*P* (IHA vs. APA)	IHA (*n* = 24)	*P* (IHA vs. EH)
Gender, male (%)	38 (59.4)	NS	20 (42.6)	NS	11 (45.8)	NS
Age (years)	46.9 ± 12.6	NS	48.8 ± 9.0	NS	48.9 ± 12.5	NS
SBP (mm Hg)	163 ± 20	0.015	153 ± 19	NS	156 ± 20	NS
DBP (mm Hg)	94 ± 13	NS	93 ± 13	NS	96 ± 15	NS
MBP (mm Hg)	115 ± 20	NS	113 ± 14	NS	116 ± 15	NS
BMI (kg/m^2)	26.3 ± 4.3	NS	25.6 ± 4.9	NS	25.7 ± 3.23	NS
Potassium (mmol/l)	4.3 ± 0.6	<0.001	3.4 ± 0.9	0.001	3.7 ± 0.5	0.038
Sodium (mmol/l)	139.5 ± 1.5	NS	139.7 ± 1.8	NS	140.2 ± 2.0	NS
PAC (ng/dl)	21.1 ± 11.0	<0.001	50.5 ± 41.0	0.001	35.7 ± 27.3	NS
PRA (ng/ml/h)	3.84 ± 4.69	<0.001	0.53 ± 0.88	0.005	1.05 ± 1.32	NS
Log ARR	0.99 ± 0.59	<0.001	2.32 ± 0.92	<0.001	1.78 ± 0.68	0.014

Data as the mean values ± s.d.
APA, aldosterone-producing adenoma; ARR, aldosterone–renin ratio (ng/dl per ng/ml/h); BMI, body mass index; DBP, diastolic blood pressure; EH, essential hypertension; IHA, idiopathic hyperaldosteronism; MBP, mean blood pressure; NS, not significant; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.

patients, yielding a pathologic diagnosis of APA in 37 patients and IHA in 3 patients.

The demographics of PA patients and EH patients are shown in Table 1. There were no differences in age, gender, and BMI. EH patients had a higher systolic blood pressure, but a similar diastolic blood pressure compared with the PA patients. The basal levels of serum potassium (SK), PRA, PAC, and ARR were significantly different between the PA and EH patients (all $P < 0.001$). There was no difference in age, gender, BMI, and mean blood pressure between the APA and IHA patients. However, APA patients had higher log ARR and PAC, and lower SK and PRA than IHA patients.

Changes of PAC and ARR by captopril and losartan

In all hypertensive patients, the pretest PACs of the captopril and losartan tests were not different (34.00 ± 3.48 ng/dl vs. 33.78 ± 2.75 ng/dl, $P = 0.942$). However, the postcaptopril PAC was lower than the postlosartan PAC in APA (41.1 ± 5.6 ng/dl vs. 49.8 ± 6.2 ng/dl, $P = 0.026$) and IHA patients (25 ± 4.1 ng/dl vs. 34.9 ± 6.3 ng/dl, $P = 0.025$). In EH patients, there was no difference in the postcaptopril and postlosartan PAC (16.6 ± 1.3 ng/dl vs. 17.3 ± 1.5 ng/dl, $P = 0.701$). There was a significant correlation between the postcaptopril PAC and postlosartan PAC ($r = 0.556$, $P < 0.001$) in all patients, as well as in PA patients ($r = 0.470$, $P < 0.001$). APA patients had a greater postlosartan ARR than IHA patients (2.40 ± 0.12 vs. 1.94 ± 0.16, $P = 0.029$). Nevertheless, the postcaptopril ARR was not different between the APA and IHA patients (2.21 ± 0.13 vs. 2.01± 0.18, $P = 0.398$).

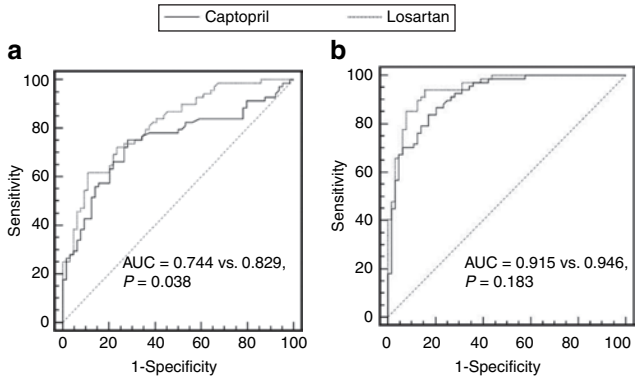

Figure 2 | Receiver-operating characteristic (ROC) curves for the detection of all primary aldosteronism by (**a**) post-test PAC, and (**b**) post-test ARR. ARR, aldosterone–renin ratio; AUC, area under curve; PAC, plasma aldosterone concentration.

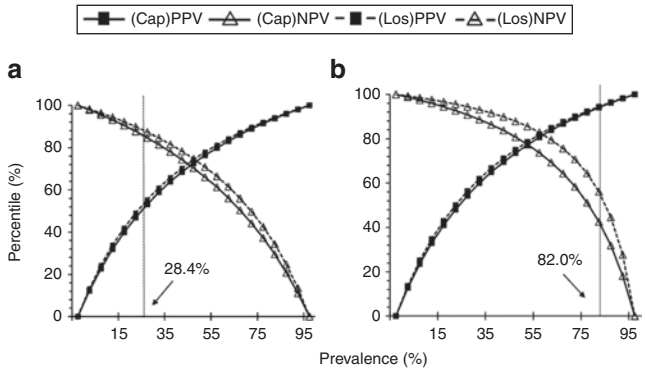

Figure 3 | The plots of predictive values for captopril and losartan tests as a function of APA prevalence. The figures demonstrate the relationship between the prevalence of PA and the diagnostic accuracy of the captopril (Cap) and losartan (Los) tests, when SK >3.8 mmol/l (left panel), or SK <3.8 mmol/l (right panel). The dashed lines represent the prevalence of PA in this study, 28.4 and 82.0% at SK above or below 3.8 mmol/l, respectively. Predictive values were calculated at the sensitivity and specificity corresponding with the values of post-test optimal cutoff of plasma aldosterone concentration. APA, aldosterone-producing adenoma; NPV, negative predictive value; PA, primary aldosteronism; PPV, positive predictive value; SK, serum potassium level.

Table 2 | Diagnostic performance of captopril and losartan tests on ARR in diagnosis of primary aldosteronism

	PA vs. EH ($n = 135$)		APA vs. EH ($n = 111$)		IHA vs. EH ($n = 88$)	
	Captopril	Losartan	Captopril	Losartan	Captopril	Losartan
AUC of ROC curve	0.915	0.946	0.919	0.963	0.904	0.908
P of ROC curve[a]	0.183		0.091		0.927	
Optimal cutoff[b] (ng/dl)	34.6	29.2	23.9	15.8	48.1	32.8
Positive predictive value (%)	87	92.3	82.6	82.1	81.3	77.3
Negative predictive value (%)	74	84.3	87.5	98.2	88.4	89.4
Sensitivity (%)	70.2	84.5	82.6	97.9	61.9	70.8
Specificity (%)	89.1	92.2	87.5	84.4	95.3	92.2
Accuracy (%)	80.2	88.1	81.7	89.6	80.9	87.4
κ (s.e.m.)	0.605 (0.068)	0.703 (0.055)	0.634 (0.067)	0.791 (0.053)	0.621 (0.065)	0.749 (0.057)
McNemar	0.029*	0.210	0.152	0.180	<0.001*	0.143

APA, aldosterone-producing adenoma; ARR, aldosterone–renin ratio (ng/dl per ng/ml/h); AUC, area under curve; EH, essential hypertension; IHA, idiopathic hyperplasia; PA, primary aldosteronism; PAC, plasma aldosterone concentration; ROC, receiver-operating characteristic.
[a]The *P* values related to comparison of the captopril and losartan tests. [b]A positive result using optimal cutoff point.
*$P < 0.05$, statistically significant.

The performance of captopril and losartan tests on patients with PA and EH

With the diagnostic criteria for PA based on an ARR >35 after captopril or losartan, the area under the curve of receiver-operating characteristic (ROC) curve analyzed with the post-test ARR was not different between the captopril and losartan tests (0.915 vs. 0.946, $P = 0.183$; Figure 2). However, the accuracy of the losartan test was higher than that of the captopril test for diagnosis of EH from PA or IHA (Table 2). For the differential diagnosis between EH and PA, the cutoff values of the post-test ARR were 34.6 and 29.2 for the captopril and losartan tests, respectively.

When the ROC curve was analyzed with the post-test PAC to differentiate PA from EH, the area under the curve of postcaptopril PAC was inferior to that of postlosartan PAC (0.744 vs. 0.829, $P = 0.038$; Figure 2), and the between-test difference of accuracy was significant for the differential diagnosis of PA ($P = 0.038$) from EH. In subgroup analysis involving PA vs. EH, APA vs. EH, or IHA vs. EH, the optimal cutoff values of PAC were consistently 16.3 and 23.8 ng/dl for the captopril and losartan tests, respectively.

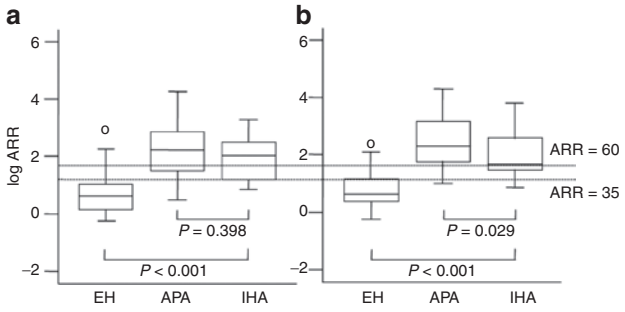

Figure 4 | Comparison of the (**a**) postcaptopril and (**b**) postlosartan ARR (ng/dl per ng/ml/h) in patients with APA to those with IHA and EH. Dashed bars represent ARR = 35, or 60. APA, aldosterone-producing adenoma; ARR, aldosterone–renin ratio; EH, essential hypertension; IHA, idiopathic hyperplasia.

Using an ARR >35 with a PAC >10 ng/dl, the specificity was 89.1% vs. 93.8% and the sensitivity was 66.2% vs. 84.5 % for the captopril test vs. the losartan test, respectively. An accuracy of 77.4% for the diagnosis of PA from EH was achieved with the captopril test, with moderate agreement by the κ-test ($k = 0.545$) and minimal disagreement by the McNemar test ($P = 0.003$). The accuracy of the losartan test was 88.9%, with good agreement ($k = 0.778$) and did not show disagreement in the McNemar test ($P = 0.118$; Table 3).

Effect of SK level on the captopril and losartan tests

The median value of the baseline SK level in the TAIPAI database was 3.8 mmol/l. In this study, 21 PA patients had an SK >3.8 mmol/l (28.4%); there were 61 patients with an SK <3.8 mmol/l, 50 (82.0%) of which were diagnosed of PA (Figure 3).

The negative predictive rates were 84.3 and 89.5% for the captopril and losartan tests, respectively, corresponding with the values of the post-test optimal cutoff of the PAC when the SK >3.8 mmol/l. When the SK <3.8 mmol/l, the losartan test had a higher negative predictive value than the captopril test under a different prevalence of APA (Figure 3).

In the Bland–Altman plot, the differences between the post-test PAC or ARR against the averages showed a random scatter without proportional error (Figure 2). The postlosartan PAC was lower than the postcaptopril PAC with significant systemic biases of −24.2 and −5.9% of ARR, respectively.

Performance of the captopril and losartan tests on patients with APA and IHA

The log ARR after losartan was significantly higher in the APA patients than the IHA patients (Table 1). Nevertheless, the log ARR after captopril was not different between the APA and IHA patients.

The ROC curve was plotted to identify the ideal cutoff value to differentiate patients with APA among all PA patients using the log ARR after losartan. Using an ARR of 60 as a cutoff

Table 3 | The use of the combinative criteria of ARR >35 (ng/dl per ng/ml/h) and a PAC >10 ng/dl (>277 pmol/l) after captopril and losartan in diagnosis of primary aldosteronism

	PA vs. EH ($n = 135$)		APA vs. EH ($n = 111$)		IHA vs. EH ($n = 88$)	
	Captopril	Losartan	Captopril	Losartan	Captopril	Losartan
Positive predictive value[a] (%)	87	93.8	83.3	91.3	63.2	81.2
Negative predictive value (%)	70.4	84.5	82.6	92.3	82.6	91
Sensitivity (%)	66.2	84.5	74.5	89.4	50	75
Specificity (%)	89.1	93.8	89.1	93.8	89.1	93.8
Accuracy (%)	77.4	88.9	82.9	91.9	78.4	88.6
κ (s.e.m.)	0.545 (0.069)	0.778 (0.054)	0.644 (0.074)	0.833 (0.053)	0.418 (0.110)	0.706 (0.086)
McNemar	0.003*	0.118	0.359	>0.999	0.359	0.754

APA, aldosterone-producing adenoma; ARR, aldosterone–renin ratio (ng/dl per ng/ml/h); EH, essential hypertension; IHA, idiopathic hyperplasia; PA, primary aldosteronism; PAC, plasma aldosterone concentration.
[a]A positive result was defined as an ARR >35 (ng/dl per ng/ml/h) and a PAC >10 ng/dl (>277 pmol/l).
*$P < 0.05$, statistically significant.

value, the sensitivity was 74.5%, the specificity was 59.1%, the positive predictive value was 82%, and the negative predictive value was 57% (**Figure 4**).

DISCUSSION

The confirmation test for the diagnosis of PA is based on the discrimination between the normal and autonomous secretion of aldosterone. Administration of captopril has been shown to be a safe and effective test in confirmation of the diagnosis.[7–10] Despite blockade of the renin–angiotensin system, ARBs have rarely been used to confirm the diagnosis of PA. In this study, a single dose of losartan was compared with captopril with respect to the diagnostic accuracy of PA. The correlation between an individual PAC after administration of captopril and losartan was excellent. We demonstrated that both captopril and losartan tests had good positive and negative predictive values, which showed good agreement at confirming the diagnosis of PA. The κ value of the losartan test in the differential diagnosis of EH from APA was >0.8 (**Table 3**), using combinative criteria. The two tests differed from each other with respect to the deviation from the center of zero by the mean difference of −23.5% by the Bland–Altman plot. The losartan test had a superior ROC curve of for the post-test PAC than the captopril test in differentiating PA and APA from EH. In our post hoc subgroup analysis, the optimal cutoff values of the PAC were the same in all the subgroups of both tests, which demonstrates the consistency of our diagnosis.

Regarding the post-test ARR, both tests had similar ROC curves with good positive and negative predictive values (**Table 2**). However, in differentiating PA from EH or IHA from EH, the captopril test had a disagreement in the diagnosis of PA based on the McNemar test, and the κ values of the losartan test were higher than those of captopril test in all differential diagnoses. All these results indicate that the losartan test has a better performance in the diagnosis of PA and its subtypes.

However, the previous study by Giacchetti *et al.*[19] demonstrated that the captopril test was superior to the losartan test in the diagnosis of PA. There are several reasons that may account for the discrepancy between Giacchetti *et al.*[19] results. First, the elapsed time for the second samples was longer in their study, in spite of the same doses administered (2 and 4 h for captopril and losartan, respectively). As previously reported, the time-to-peak plasma concentration of losartan was proportional to the dose and was around 1.5 h with a dose of 50 mg (ref. 13). With oral captopril, the time-to-peak was >0.5 h (ref. 14). The approximate biological half-life of aldosterone and PRA is 30 and 15 min, respectively.[15,16] Therefore, we set the sampling period at least one half-life of PRA or PAC plus the time-to-peak plasma level of the drugs. Second, fewer patients in the Giacchetti *et al.*[19] study, especially the EH group, had taken the losartan test than the captopril test. Third, none of the patients had taken both the captopril and losartan tests.

It may be argued that the postlosartan result may be confounded by a previous captopril effect in our study. Our protocol reflects the common practice in the confirmatory diagnosis of PA, i.e., the captopril test is usually used as a first-line test. Because the half-life of captopril is short, there is little residual effect on the losartan test performed on the subsequent day. Based on the Bland–Altman plot analysis, there are no proportional errors between the two tests, which indicates that the systemic confounding from the previous administration of captopril is limited.

It is not known whether less suppression of PAC by losartan in PA patients contributed to the higher performance of the losartan test in our study. One study showed that treatment with irbesartan, a selective ARB, led to a greater false negative result (ARR <50) in the diagnosis of PA than fosinopril.[7] In that study, the effect of drugs on ARR was observed after 2 months of treatment instead of a single-dose administration. It has been noted that escape of angiotensin-converting enzyme inhibition can occur after long-term treatment,[27] but not for ARBs. Accordingly, PAC may have been less suppressed by fosinopril than by irbesartan in that study, which probably led to the greater false negative result of ARB.

All confirmatory tests for the differential diagnosis of PA stand on angiotensin-II-nonresponsiveness in patients with PA. Therefore, these tests can lead to missing cases that are angiotensin-II responsive.[28] This is also true for the diagnosis of IHA, which is also partially responsive to renin–angiotensin system. A clinical and biochemical overlap may exist between low-renin EH and IHA, which could make it difficult to obtain an unequivocal differentiation between these two conditions.[8] As shown in our study, the discrimination between EH and IHA was not as reliable as that of APA from EH by both tests. A combination of several parameters of a test and/or tests is mandatory to make a diagnosis of PA.[9,29] As shown in our study, the diagnosis for these PA patients may not be confirmed by only one test. The use of the combined criteria of PAC and ARR was suggested by Lyons *et al.*,[9] which gave a satisfactory result in screening for PA.

The median SK in our cohort was 3.8 mmol/l, which is compatible with other cohorts.[8,19] Although an important clue for the diagnosis of PA, hypokalemia is observed in only two-thirds of patients with PA because the ARR has been used as a screening test.[8,19] Usually, the prevalence of PA is >50%, as in our TAIPAI cohort, when the patient's SK <3.8 mmol/l. Our study showed that when patients have an SK <3.8 mmol/l, the losartan test has better accuracy and is more useful to exclude PA than the captopril test.

In this study, the postlosartan ARR >60 provided a good separation and diagnosis of patients with PA from EH, as well as an adequate differentiation of APA and IHA. As a suppression test, losartan is easier to perform than a salt-loading test, and further work should be aimed at determining the performance of losartan and salt-loading tests.

In summary, this study showed that both the captopril and losartan tests have good specificity for excluding PA from EH. The losartan test was superior to the captopril test with better accuracy in the diagnosis of PA using the combined criteria. Using aldosterone, losartan offered an advantage to exclude PA when patients were referred with a potassium <3.8 mg/dl. With

a postlosartan ARR >60, APA was adequately differentiated from IHA. Nevertheless, our finding provides a rationale for devising the losartan test compared with other suppression tests (e.g., salt infusion and fludrocortisones suppression) in the diagnosis of PA.

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