Diagnostic Accuracy of the Aldosterone–to–Active Renin Ratio for Detecting Primary Aldosteronism

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Context: The aldosterone–to–active renin ratio (AARR) is the recommended screening test for primary aldosteronism (PA), but prospective study data on its sensitivity and specificity are sparse.

Objective: To investigate the diagnostic accuracy of the AARR for detecting PA.

Design: Prospective diagnostic accuracy study.

Setting: This study was conducted from February 2009 to August 2015 at the outpatient clinic of the Department of Endocrinology and Diabetology of the Medical University of Graz, Austria.

Participants: Four hundred patients with arterial hypertension who were referred to a tertiary care center for screening for endocrine hypertension.

Intervention: Participants had a determination of the AARR (index test) and a second AARR determination followed by a saline infusion test (SIT) after 2 to 6 weeks. PA was diagnosed in individuals with any AARR $\geq 3.7$ ng/dL/mU/mL [including a plasma aldosterone concentration (PAC) of $\geq 9$ ng/dL] who had a PAC $\geq 10$ ng/dL after the SIT. We did not substantially alter antihypertensive drug intake.

Main Outcome Measures: Primary outcome was the receiver-operating characteristic (ROC) curve of the AARR in diagnosing PA.

Abbreviations: AARR, aldosterone–to–active renin ratio; GECOH, Graz Endocrine Causes of Hypertension; NPV, negative predictive value; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PPV, positive predictive value; ROC, receiver-operating characteristic; SIT, saline infusion test.
Results: A total of 382 participants were eligible for analyses; PA was diagnosed in 18 (4.7%) patients. The area under the ROC curve of the AARR in detecting PA was 0.973 (95% CI, 0.956 to 0.990). Sensitivity and specificity for a positive AARR in diagnosing PA were 100% (95% CI, 81.5% to 100.0%) and 89.6% (95% CI, 86.0% to 92.5%), respectively.

Conclusions: The AARR has good diagnostic accuracy for detecting PA.

Primary aldosteronism (PA) affects approximately 5% to 10% of patients with arterial hypertension and is associated with an excess risk of morbidity and mortality when compared with essential hypertension [1–3]. Therefore, the Endocrine Society clinical practice guideline for the management of PA recommends wide screening for PA in ∼50% of patients with arterial hypertension, including patients with resistant hypertension or hypokalemia [1]. Real-life data, however, show that screening for PA is rarely performed, and PA remains an underdiagnosed and undertreated disease [3].

The recommended screening test for PA is determination of the aldosterone-to-renin ratio because it reflects the degree of aldosterone synthesis that is autonomous with regard to renin [1, 4]. Measuring and interpreting the aldosterone-to-renin ratio is, however, a challenge because several factors affect aldosterone and renin concentrations [5, 6]. Moreover, few prospective studies have evaluated the diagnostic accuracy of the aldosterone-to-renin ratio in detecting PA. Several previous studies in this field were limited by, for example, a missing prespecified statistical analysis plan, restricting confirmatory tests for PA to participants with a positive screening test result (and thus risk of verification bias), or incomplete adherence to guidelines for study reporting [7–16]. In many of those studies, common antihypertensive drugs were discontinued for the purpose of PA diagnostics, an approach that may limit the implementation of such procedures into routine clinical care. Hence, diagnostic accuracy studies on the aldosterone-to-renin ratio in detecting PA are still needed.

Herein we present the results of the prospective Graz Endocrine Causes of Hypertension (GECOH) study, a diagnostic accuracy study with the primary aim of evaluating the sensitivity and specificity of the aldosterone–to–active renin ratio (AARR) in detecting PA [17, 18].

1. Methods

A. Design

The GECOH study is a single-center, prospective diagnostic accuracy study of the AARR in detecting PA. Details of the study design and methods, including sample size calculation and statistical analysis plan, have been published previously, and we adhere to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) statement and the Declaration of Helsinki [17–20]. The Ethics Committee of the Medical University of Graz, Austria, approved the study, and all study participants gave written informed consent.

According to our published study protocol, patients were scheduled to have two determinations of the AARR 2 to 6 weeks apart [17]. A saline infusion test (SIT) in the recumbent position with infusion of 2 L 0.9% saline intravenously over 4 hours was performed on the day of the second AARR determination in the first consecutive 200 study participants; afterward, SIT was exclusively done in participants with a positive (pathologic) AARR [17]. The SIT was chosen as the reference standard test in accordance with published guidelines and because
of our clinical expertise with this test [1]. PA was diagnosed in individuals with any AARR ≥3.7 ng/dL/μU/mL (including a plasma aldosterone concentration (PAC) ≥9 ng/dL) who had a PAC ≥10 ng/dL after the SIT, whereas PA was excluded if results of only one or none of these two tests was positive [21, 22]. The cutoff for the AARR is derived from the Endocrine Society clinical practice guideline for PA; the PAC cutoffs are also based on previous publications that, in terms of the post-SIT PAC, used the same assay as in our study [1, 21–23].

B. Participants

We enrolled 400 patients with arterial hypertension, age ≥18 years, who were routinely referred to our department for screening for endocrine hypertension. Because certain medications have a substantial effect on aldosterone and renin concentrations, and according to the Endocrine Society guideline, we did not include participants who received spironolactone, canrenone, eplerenone, amiloride, and/or triamterene within 4 weeks before study inclusion but did not change intake of first-line antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, angiotensin-2–blockers, thiazides, and calcium antagonists [1, 17]. Therefore, patients taking these latter medications had to withdraw them at least 4 weeks before study inclusion, a common practice for patients routinely referred to our outpatient clinic for screening for endocrine hypertension. Other exclusion criteria were a glomerular filtration rate <30 mL/min/1.73 m², liver failure with Child-Pugh class B or C, severe heart failure with New York Heart Association class 3 or 4, acute coronary syndrome within the last 2 weeks, immunosuppressive therapy, oral glucocorticoid therapy (because glucocorticoids suppress aldosterone), pregnancy, ongoing chemotherapy, and any other disease with an estimated life expectancy <1 year.

Without any specific advertisement, study participants were informed about the study by a conversation and recruited from the outpatient clinic by the principal investigators of the GECOH study (S.P. and A.T.). Therefore, our study population is a convenience sample because participants were enrolled when the principal investigators were on duty in the outpatient clinic and had enough time for this investigation. The entire GECOH study was performed from 3 February 2009 to 10 August 2015 in the outpatient clinic of the Department of Endocrinology and Diabetology at the Medical University of Graz, Austria. Data entry was finished in December 2018.

C. Outcome Measures

The primary outcome measure was the receiver-operating characteristic (ROC) curve for the first AARR (index test) in detecting PA. The secondary outcome measure was the ROC curve for the SIT in detecting PA.

D. Measurements

Details of laboratory measurements and study procedures have been published elsewhere [17, 18]. In brief, all blood samples for this study were obtained after an overnight fast in the morning (8:00 to 11:00 AM) after the patients had been seated for 10 minutes. Participants were advised to avoid smoking and taking their antihypertensive drugs in the morning before the blood collection.

Active renin concentration was measured in EDTA plasma by a Renin III Generation radioimmunoassay (Renin IRMA RIA-4541; DRG Instruments GmbH, Marburg, Germany), which has been calibrated against a World Health Organization standard [24]. Intra-assay and interassay coefficients of variation of this assay are 0.6% to 4.5% and 2.7% to 14.5%, respectively. PAC was measured by radioimmunoassay (Active Aldosterone RIA DSL-8600; Diagnostic Systems Laboratories, Inc., Webster, TX; now distributed by Beckman Coulter, Inc, Brea, CA.) with intra-assay and interassay coefficients of variation of 3.3%, to 4.5% and 5.9% to 9.8%, respectively [21].
E. Data Analysis

Continuous data that followed a normal distribution are shown as means with SDs, and parameters with a skewed distribution are shown as medians with interquartile ranges. Categorical data are presented as percentages. Where appropriate, skewed variables were log(e)-transformed before they were used in parametric analyses. Group differences were calculated by Student \( t \) test, \( \chi^2 \) test, or Fisher exact test, as appropriate. We calculated ROC curves with area under the curve and respective 95% CIs for the first AARR and for the SIT in detecting PA. We also calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios for both tests [25]. A \( P \) value < 0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed by using SPSS software, version 23.0 (IBM Inc., Chicago, IL).

2. Results

The participant flow chart of the GECOH study is shown in Fig. 1. In brief, of ~440 patients who were approached for study inclusion, 400 agreed to participate in the GECOH study. The SIT was performed regardless of AARR values in 167 of the first 200 study participants; 33 of the first 200 study participants declined to undergo the SIT. Afterward, the SIT was exclusively performed in participants with a positive AARR (i.e., AARR \( \geq 3.7 \text{ ng/dL/\mu U/mL} \)), including a PAC \( \geq 9 \text{ ng/dL} \). Because of insufficient funding for this study, a second AARR determination was routinely performed in the first consecutive 268 participants only (resulting in 231 available values) and was thereafter not measured except in participants who had undergone a SIT. In the entire study, two determinations of the AARR with a median (interquartile range) time interval in between of 30 days (22 to 38 days) were available in 241 participants, and the SIT was performed in 181 participants. We excluded 18 participants who declined to undergo further testing to exclude or confirm PA. Therefore, 382 were finally eligible for analyses because they had sufficient data to exclude or confirm the diagnosis of PA with consistently negative (normal) AARR or any positive AARR, plus the result of the SIT. PA was diagnosed in patients with a positive AARR and a positive result of the SIT, whereas PA was excluded if results of only one or none of these two tests was positive. We did not impute for missing data, and no severe adverse events resulted from the index or reference standard test.

Baseline characteristics of all eligible study participants and stratified according to the presence or absence of PA are shown in Table 1. PA was diagnosed in 18 of the 382 participants (4.7%). In addition, two patients were diagnosed with pheochromocytoma on the basis of elevated plasma metanephrines and/or normetanephrines and two were diagnosed with hypercortisolism [26, 27]. Hypercortisolism was diagnosed according to the Endocrine Society guideline (i.e., pathologic result on a 1-mg dexamethasone suppression test plus elevated midnight salivary cortisol concentration); one patient had ACTH-dependent and one had ACTH-independent hypercortisolism [27]. These patients were not excluded from the ROC analyses.

The contingency table for the diagnostic accuracy of a positive AARR at the first study visit (at baseline), and for a positive SIT result (i.e., PAC \( \geq 10 \text{ ng/dL after the SIT} \)) is shown in Table 2. The area under the ROC curve for the AARR at the first study visit in detecting PA was 0.973 (95% CI, 0.956 to 0.990) (Fig. 2). The point on the ROC curve with the minimum distance from the left-upper corner of the unit square was at an AARR of 4.33 ng/dL/\( \mu \text{U/mL} \) with a sensitivity of 100% and a specificity of 91.8% (Fig. 2). The sensitivity, specificity, PPV, NPV, and positive and negative likelihood ratios (with 95% CIs) of a positive AARR in detecting PA were 100% (81.5% to 100.0%), 89.6% (86.0% to 92.5%), 32.1% (26.0% to 39.0%), 100%, 9.58 (7.09 to 12.94), and 0, respectively. The respective area under the ROC curve for the PAC concentration after the SIT was 0.998 (95% CI, 0.994 to 1.000). The sensitivity, specificity, PPV, NPV, and positive and negative likelihood ratios (with 95% CIs) of a positive SIT result for detecting PA were 100% (81.5% to 100.0%), 96.1% (90.6% to 99.3%), 60.8% (45.7% to 74.2%), 81.9% (75.1% to 87.2%), and 0.001 (0.000 to 0.045), respectively.
97.9%), 69.2% (53.4% to 81.6%), 100%, 20.4 (10.4 to 40.1), and 0, respectively. Characteristics of patients without PA who had a positive AARR at the first study visit or a positive SIT result are shown in Table 3. Of note, among participants without PA, the PAC after the SIT (median with interquartile ranges) did not significantly different between those with (n = 38) and without (n = 125) a positive baseline AARR [5.7 (4.6 to 7.4) vs 5.2 (3.8 to 7.0) ng/dL; P = 0.071].

Some of the prespecified secondary outcomes could not be analyzed because we did not have funding to measure PAC by liquid chromatography mass spectrometry or 24-hour urine aldosterone concentrations with subsequent comparisons of the ROC curves using these parameters with the ROC curve of the AARR in detecting PA. Furthermore, we did not compare the ROC curves before (first AARR determination) and after (second AARR
Table 1. Baseline Characteristics of GECOH Study Population

| Variable                              | All Study Participants (n = 382) | No PA (n = 364) | PA (n = 18) | P Valuea |
|----------------------------------------|----------------------------------|-----------------|-------------|----------|
| Age, y                                 | 50.3 ± 14.9                      | 50.3 ± 15.1     | 48.9 ± 9.3  | 0.543    |
| Women, %                               | 56.3                             | 56.6            | 50.0        | 0.582    |
| BMI, kg/m²                              | 28.7 ± 5.7                       | 28.7 ± 5.7      | 28.7 ± 6.1  | 0.984    |
| Systolic blood pressure, mm Hg         | 155 ± 22                         | 154 ± 22        | 177 ± 22    | <0.001   |
| Diastolic blood pressure, mm Hg        | 96 ± 33                          | 96 ± 34         | 107 ± 13    | 0.235    |
| Aldosterone after SIT, ng/dL           | 16.1 (11.9–23.3)                 | 15.7 (11.6–22.0)| 41.6 (25.9–59.8)| <0.001|
| Renin, μU/mL                           | 13.4 (6.6–30.6)                  | 14.9 (7.4–33.0)| 3.2 (2.5–5.8)| <0.001   |
| Baseline AARR, ng/dL/μU/mL             | 1.15 (0.47–2.39)                 | 1.06 (0.45–2.12)| 9.35 (6.24–15.95)| <0.001|
| Second AARR, ng/dL/μU/mL               | 1.47 (0.64–3.17)                 | 1.38 (0.57–2.57)| 10.48 (6.97–13.58)| <0.001|
| Aldosterone after SIT, ng/dL           | 5.6 (4.2–7.9)                    | 5.3 (4.0–7.2)   | 20.7 (14.8–43.0)| <0.001|
| Serum potassium, mmol/L                | 3.9 ± 0.4                        | 3.9 ± 0.4       | 3.1 ± 0.4   | <0.001   |
| Serum potassium < 3.5 mmol/L, %        | 12.3                             | 9.1             | 77.8        | <0.001   |
| Serum sodium, mmol/L                   | 141 ± 2                          | 141 ± 2         | 144 ± 2     | <0.001   |
| Creatinine, mg/dL                      | 0.92 ± 0.51                      | 0.92 ± 0.52     | 0.92 ± 0.23 | 0.989    |
| eGFR-MDRD, mL/min/1.73 m²              | 80.4 ± 18.0                      | 80.4 ± 18.0     | 80.5 ± 18.4 | 0.984    |
| PTH, pg/mL                             | 48.6 ± 20.7                      | 47.2 ± 19.2     | 75.4 ± 31.6 | 0.002    |
| Fasting glucose, mg/dL                 | 90 (84–100)                      | 90 (83–99)      | 90 (86–109) | 0.386    |
| HbA1c, %                               | 36 (33–39)                       | 36 (33–39)      | 34 (34–40)  | 0.926    |
| HDL cholesterol, mg/dL                | 61 ± 19                          | 61 ± 19         | 58 ± 23     | 0.492    |
| LDL cholesterol, mg/dL                | 119 ± 31                         | 119 ± 31        | 113 ± 19    | 0.258    |
| Triglycerides, mg/dL                   | 103 (74–146)                     | 103 (73–146)    | 125 (78–154)| 0.678    |
| C-reactive protein, mg/dL              | 1.8 (1.0–3.9)                    | 1.8 (1.0–3.9)   | 2.8 (1.1–5.3)| 0.299    |
| No. of antihypertensive drugs          | 2 (1–3)                          | 2 (1–3)         | 4 (2–4)     | 0.002    |
| ACE inhibitors, %                      | 34.6                             | 35.2            | 22.2        | 0.318    |
| Angiotensin-2-receptor blockers, %     | 24.9                             | 24.2            | 38.9        | 0.159    |
| Calcium-channel blockers, %            | 35.9                             | 34.1            | 72.2        | 0.001    |
| β-blockers, %                          | 53.7                             | 52.7            | 72.2        | 0.106    |
| Diuretics, %                           | 27.5                             | 27.2            | 33.3        | 0.569    |
| Thiazide diuretics, %                  | 32.7                             | 32.4            | 38.9        | 0.568    |
| Loop diuretics, %                      | 1.8                              | 1.9             | 0            | 1.000    |
| NSAIDs, %                              | 11.5                             | 11.8            | 5.6         | 0.707    |

Continuous data are presented as mean ± SD or as median with interquartile range. Categorical data are presented as percentages.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; eGFR-MDRD, estimated glomerular filtration rate calculated according to the Modification of Diet in Renal Disease criteria; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.

aP value for paired Student t test for continuous variables and for χ² or Fisher exact test for categorical variables comparing patients with PA vs no PA.

determination) discontinuation of β-blockers because the study participants were largely unwilling to alter their antihypertensive treatment; only 10 patients receiving β-blocker therapy stopped this treatment before the second visit. Of note, in all GECOH study participants with two available AARR measurements (n = 241), values at the first measurement did not significantly differ from those at the second measurement [1.58 (0.67 to 3.51) vs 1.54 (0.66 to 3.38) ng/dL/μU/mL; P = 0.685; Spearman correlation coefficient, 0.841; P < 0.001].

Although this was not prespecified in the study protocol, according to previously defined criteria, the six patients in the GECOH study with an aldosterone-producing adenoma who were subsequently treated by unilateral adrenalectomy showed a complete biochemical success; four of these patients had a complete clinical success and two had a partial clinical success (data not shown) [28]. Follow-up data for the remaining 12 patients with PA who were treated with mineralocorticoid receptor–blocker therapy are not reported because there are no clear criteria for medical treatment success of PA; thus, we did not perform a prespecified follow-up of the patients [29].
3. Discussion

This prospective diagnostic accuracy study in hypertensive patients showed that the area under the ROC curve for the AARR at the first study visit in detecting PA was 0.973 (95% CI, 0.956 to 0.990). The SIT also had good diagnostic accuracy, and we found good intraindividual reproducibility of the AARR.

The results from the GECOH study substantially add to the limited knowledge on the diagnostic accuracy of the AARR in detecting PA. Our findings are roughly in line with those of a meta-analysis of 974 patients from nine studies that reported a sensitivity, specificity, and area under the ROC of the AARR in detecting PA of 0.89 (95% CI, 0.84 to 0.93), 0.96 (95% CI, 0.95 to 0.98), and 0.985, respectively [14]. Methodological differences and limitations are, however, inherent in the existing literature on the diagnostic accuracy of the AARR and account for a relatively high heterogeneity [14]. Of note, our AARR cutoff of $3.7 \text{ ng/dL/μU/mL}$ is equivalent to a cutoff of $30 \text{ ng/dL/ng/ml/h}$ and $2.5 \text{ ng/dL/pmol/L/min}$, respectively, for measuring plasma renin activity instead of direct renin concentration [1]. Notably, Vorselaars et al. [10] performed a prospective study in 233 patients with difficult-to-control hypertension who were all referred to a SIT. In that study, the PA prevalence was 6.9% and

| Test Result | No PA | PA | Total |
|-------------|------|----|-------|
| AARR        |      |    |       |
| Positive    | 38   | 18 | 56    |
| Negative    | 326  | 0  | 326   |
| Total       | 364  | 18 | 382   |
| SIT         |      |    |       |
| Positive    | 8    | 18 | 26    |
| Negative    | 155  | 0  | 155   |
| Total       | 163  | 18 | 181   |

Values are numbers of patients. PA was diagnosed in patients with a positive AARR and a positive SIT result, whereas PA was excluded if results of only one or none of these two tests were positive.

Figure 2. ROC curve for the AARR in detecting PA. The point on the ROC curve with the minimum distance from the left-upper corner of the unit square (marked with a circle) was at an AARR of $4.33 \text{ ng/dL/μU/mL}$, with a sensitivity of 100% and a specificity of 91.8%.
the sensitivity, specificity, PPV, and NPV for the aldosterone-to-renin activity ratio in detecting PA were 100%, 86.7%, 35.6%, and 100%, respectively [10]. Despite the use of different laboratory methods, these findings are similar to those from the GECOH study [10]. One major difference between our study and the existing literature is that we performed PA diagnostic testing under ongoing antihypertensive treatment without substantially altering drug intake, except for spironolactone, canrenoate, eplerenone, amiloride, and/or triamterene, which interfere with aldosterone action. We are well aware that several antihypertensive drugs may alter renin concentrations and PAC, but we have shown that AARR measurements performed under standardized conditions (as in the GECOH study) have excellent reproducibility, with very low intraindividual variability [18]. In this context, we found that the second AARR determination did not lead to the diagnosis of any additional PA case that would have been overlooked by just a single AARR determination. We cannot rule out, however, that we missed PA cases because of ongoing drug intake; however, among individuals without PA, the PAC after the SIT did not significantly differ between those with and without a positive baseline AARR. Furthermore, only eight participants with a positive

**Table 3. Characteristics of Participants Without PA Who Had Positive AARR at Baseline or Positive SIT Result**

| Variable                                      | Positive AARR and No PA (n = 38) | Positive SIT Result and No PA (n = 8) |
|-----------------------------------------------|----------------------------------|---------------------------------------|
| Age, y                                        | 58.6 ± 11.6                      | 42.9 ± 13.6                           |
| Women, %                                      | 60.5                             | 25.0                                  |
| BMI, kg/m²                                    | 27.3 ± 4.1                       | 31.1 ± 6.4                            |
| Systolic blood pressure, mm Hg                | 162 ± 25                         | 153 ± 27                              |
| Diastolic blood pressure, mm Hg               | 96 ± 12                          | 95 ± 11                               |
| Aldosterone, ng/dL                            | 19.5 (15.3–24.6)                 | 26.1 (17.4–32.5)                      |
| Renin, µU/mL                                  | 3.4 (2.3–4.2)                    | 17.7 (7.2–41.0)                       |
| Baseline AARR, ng/dL/µU/mL                    | 5.63 (4.53–7.42)                 | 1.42 (0.66–2.59)                      |
| Second AARR, ng/dL/µU/mL                      | 5.59 (3.06–9.23)                 | 1.01 (0.31–2.04)                      |
| Aldosterone after SIT, ng/dL                  | 5.7 (4.6–7.4)                    | 11.2 (10.2–11.9)                      |
| Serum potassium, mmol/L                       | 3.8 ± 0.3                        | 3.8 ± 0.5                             |
| Serum potassium < 3.5 mmol/L, %               | 10.5                             | 25.0                                  |
| Serum sodium, mmol/L                          | 142 ± 2                          | 142 ± 3                               |
| Creatinine, mg/dL                             | 0.93 ± 0.21                      | 0.94 ± 0.16                           |
| GFR-MDRD, ml/min/1.73 m²                      | 73.8 ± 15.7                      | 82.8 ± 14.4                           |
| PTH, pg/mL                                    | 48.2 ± 14.8                      | 50.2 ± 11.4                           |
| Fasting glucose, mg/dL                        | 90 (82–106)                      | 91 (84–104)                           |
| HbA1c, mmol/mol                               | 37 (35–38)                       | 34 (31–47)                            |
| HDL cholesterol, mg/dL                       | 59 ± 13                          | 56 ± 26                               |
| LDL cholesterol, mg/dL                        | 122 ± 30                         | 111 ± 30                              |
| Triglycerides, mg/dL                          | 103 (81–159)                     | 121 (81–165)                          |
| C-reactive protein, mg/dL                     | 1.7 (1.0–3.1)                    | 3.4 (1.3–26.4)                        |
| No. of antihypertensive drugs                 | 3 (1–4)                          | 3 (1–4)                               |
| ACE inhibitors, %                             | 23.7                             | 37.5                                  |
| Angiotensin-2–receptor blockers, %            | 34.2                             | 25.0                                  |
| Calcium-channel blockers, %                   | 52.6                             | 50.0                                  |
| β-blockers, %                                 | 68.4                             | 37.5                                  |
| Diuretics, %                                  | 34.2                             | 62.5                                  |
| Thiazide diuretics, %                         | 39.5                             | 50.0                                  |
| Loop diuretics, %                             | 0                                | 12.5                                  |
| NSAIDs, %                                     | 18.4                             | 0                                     |

Continuous data are presented as mean ± SD or as median with interquartile range. Categorical data are presented as percentages. PA was diagnosed in patients with a positive AARR and a positive SIT result, whereas PA was excluded if results of only one or none of these two tests were positive. Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; GFR-MDRD, glomerular filtration rate calculated according to the Modification of Diet in Renal Disease criteria; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.
SIT result had a negative AARR and thus were not classified as having PA. These participants were, however, likely to have secondary aldosteronism with relatively high renin concentrations and only slightly elevated post-SIT PAC.

Apart from this, it must be acknowledged that diagnostic studies on PA are, in general, prone to verification bias and are limited because there is no gold standard for the confirmation or exclusion of PA, although there are excellent approaches for standardization [29]. This diagnostic challenge may be attributed to the fact that the association of AARR with blood pressure and cardiovascular risk exists on a continuum [30]. In this context, a recent trial has shown that the blood pressure-lowering effects of spironolactone is linearly associated with the prevailing AARR that was measured, as in the GECOH study, under ongoing antihypertensive treatment [31]. Although it may therefore appear arbitrary to choose an AARR cutoff for PA diagnostics, it has to be stressed that correct diagnosis of PA is pivotal due to highly effective treatment of this disease with either unilateral adrenalectomy or mineralocorticoid receptor blocker therapy resulting in significantly improved overall health outcome [32]. Of note, the six patients with an aldosterone-producing adenoma undergoing unilateral adrenalectomy showed excellent responses to treatment; four of these patients reached normotensive blood pressure without the aid of antihypertensive drugs. For clinical practice, the ARR carries important quantitative information—previous research found that increasing ARR values identifies patients with an exponentially increasing probability of carrying an aldosterone-producing adenoma [15].

Our data are limited because we studied a cohort of patients referred to a tertiary care center, and therefore we cannot uncritically generalize our results to other populations. In addition, there are no gold standard criteria for the diagnosis of PA; although we strictly adhered to published criteria in terms of assay cutoffs and guideline-recommended case confirmation by the SIT, we cannot rule out some misclassifications. Moreover we could not (mainly because of a lack of funding) analyze some prespecified secondary outcomes. Furthermore, our participants were not willing to stop β-blocker intake; this suggests that at least in our study setting, but probably also in other populations, it may not be possible to perform AARR measurements without potentially interfering drugs, such as e.g. β-blockers or angiotensin-converting enzyme inhibitors. Therefore, we consider it a main strength of our study that we provide data on the diagnostic accuracy of the AARR under ongoing antihypertensive treatment, an approach that is supported by the Endocrine Society clinical practice guideline for the management of PA [1]. Finally, our results confirm some previously published characteristics of patients with PA, such as the high PTH concentrations [33].

In conclusion, we have documented in the GECOH study that even without significantly altering intake of first-line antihypertensive drug treatment, the AARR has good diagnostic accuracy in detecting PA, as does the SIT. These findings may contribute to a broader implementation of PA diagnostic tests.

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Additional Information

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