Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism: a systematic review of the literature

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Authors' objectives
The objective was to assess the accuracy of the aldosterone-renin ratio (ARR) as a screening test for the presence of primary aldosteronism in patients with presumed essential hypertension.

Searching
MEDLINE, EMBASE and Current Contents were searched from January 1966 to October 2001; the search terms were reported. The reference lists of the papers obtained were checked, and any papers or reports held on file by one of the authors were searched. In addition, experts in the field were contacted. There were no language restrictions.

Study selection

Study designs of evaluations included in the review
Prospective studies were eligible for the review. All of the included studies were prospective studies; the majority were cohort studies and one study appeared to be a case-control study.

Specific interventions included in the review
Studies that used the ARR as a screening test were eligible for inclusion. The included studies used different ARR cut-off values for the presence of primary aldosteronism. These ranged from 200 to 2,774 pmol/L per ng/mL per hour. One study reported diagnostic accuracy results for six different cut-off values of 200, 250, 300, 400, 500 and 1,000 pmol/L per ng/mL per hour. The tests were conducted while the patients were supine, seated or upright.

Reference standard test against which the new test was compared
The reference standard test used was not specified as part of the inclusion criteria. The reference tests used in the included studies were: an aldosterone suppression test with salt loading alone or with fludrocortisone; an aldosterone suppression test with salt loading, or captopril stimulation; and fludrocortisone alone. Cut-off values for the reference standard tests were not reported, while information on the reference test used was not available in some studies.

Participants included in the review
The inclusion criteria specified that patients could have or not have hypokalemia; come from the general population or a hypertension referral clinic; be treated or not be treated with antihypertensive medications; or be following their regular diet or a sodium-restricted/controlled diet. Most of the included studies contained patients following their usual diets and taking no medication, or with medication stopped for a short time (3 days to 4 weeks). Nine of the 16 studies were conducted in patients referred to or receiving care in a hypertension clinic; the rest were from primary care, volunteers or a population-based sample. The proportion of patients with confirmed Conn's adenomas ranged from 3.4 to 100%.

Outcomes assessed in the review
No inclusion criteria were specified for the outcomes. The sensitivity, specificity, numbers of true and false positives, numbers of true and false negatives and likelihood ratios (LRs), at different cut-off values, were extracted from the studies. Where possible, the review authors calculated the sensitivity, specificity and LRs from the original results. The outcomes presented in the review were sensitivity, specificity, positive LR and positive predictive value.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the studies was assessed using the following criteria: independent blinded comparison of the ARR result
with the reference standard result; appropriate disease prevalence in the patient population; the ARR result did not influence the decision to perform the reference standard test; and the study was described in sufficient detail to allow it to be replicated. Two reviewers independently assessed study quality. Agreement between the reviewers was assessed using a weighted kappa analysis.

**Data extraction**
Data were extracted using a standard form to capture relevant details of study design, population and test characteristics. The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**

How were the studies combined?
The study results were not combined using statistical methods, owing to differences in population selection, ARR cut-off values, conditions of testing, choice of the reference standard and the completeness of the results reported. The results were presented in a narrative synthesis.

How were differences between studies investigated?
Differences between the studies were assessed narratively. No formal statistical analysis for assessing heterogeneity was undertaken.

**Results of the review**
Sixteen studies with a total of 3,136 patients with ARR measurements were included in the review (555 patients received confirmatory testing).

The included studies were generally of a poor quality: none satisfied all four quality criteria and only one satisfied three. The reference standard results were not assessed independently and blindly to the ARR results in any of the studies. In addition, in all but one study, not all of the patients with an ARR result received the reference standard test. The agreement between the reviewers for the quality assessment was good (weighted kappa statistic 0.85).

Only one study assessed the screening ability of ARR to detect primary aldosteronism of any cause. This reported a sensitivity of 58.6%, a specificity of 66.6%, and a positive LR of 1.8 for an ARR cut-off value of 1,387 pmol/L per ng/mL per hour. For this cut-off value plus a serum aldosterone level greater than 444 pmol/L, the sensitivity was 44.8%, the specificity was 99.9% and the positive LR was 448.

Two studies assessed the ability of ARR to detect primary aldosteronism caused by an adenoma. One reported a sensitivity of 100%, a specificity ranging from 96.5 to 98.1%, and a positive LR ranging from 28.5 to 52. The other study presented results for a range of ARR cut-off values, for its ability to detect aldosteronism caused by Conn's adenoma. As the ARR cut-off value increased, the sensitivity decreased and the specificity increased. The highest sensitivity (98%) and lowest specificity (87%) occurred at the lowest ARR cut-off (200 pmol/L per ng/mL per hour), while the lowest sensitivity (64%) and the highest specificity (99%) occurred at the highest ARR cut-off (1,000 pmol/L per ng/mL per hour). The positive LRs ranged from 7.5 (at the 200 cut-off) to 64 (at the 1,000 cut-off).

**Authors' conclusions**
It was not possible to obtain valid estimates of the test characteristics of the ARR when used as a screening test in patients with presumed essential hypertension.

**CRD commentary**
This review had a clear research question, with broad inclusion criteria that seemed appropriate given the potential application of the test. The search was adequate and did not have any language restrictions, and the authors consulted experts in the field to locate other published and unpublished data. Two reviewers independently performed the quality assessment, which helps prevent bias, and a thorough discussion of study quality, using criteria appropriate to diagnostic
accuracy studies, was presented. Details of the study settings and some clinical patient details were presented, but there was no information on age, gender or co-morbidity.

The authors described differences between the studies with respect to populations, ARR cut-off values, and reference standard tests and testing conditions, and subsequently did not pool any results. In all but one of the studies less than half of the patients also received the reference standard test, and all but two of the studies failed to give the reference test to patients who were negative on the ARR. In addition, the assessors of the reference test were not blinded to the ARR result. These are major sources of bias, which means that any diagnostic accuracy results will be unreliable: the authors addressed this in their discussion. Given the poor methodological quality of the studies, and the fact that many of them did not provide any accuracy results, the authors' conclusions are appropriate.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that more high-quality data on disease prevalence, morbidity and mortality are needed. Further research on the yield and cost-effectiveness of alternative screening strategies is also required.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.