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REVIEW PAPER

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The effect of medication on the aldosterone-to-renin ratio. A critical review of the literature

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Abstract

The aldosterone-to-renin ratio (ARR) is a common screening test for primary aldosteronism in hypertensives. However, patients often use medications that could confound the ARR and, thereby, reduce the interpretability of the test. Since it is not always feasible to stop such medication, several drugs that are supposedly neutral with respect to the ARR have been recommended as alternative treatment. The objective of the present review is to explore whether sufficient evidence exists to justify the recommendations. To this end, we performed a systematic PubMed and Cochrane literature search regarding medications that may influence the ARR. Our review revealed that many commonly prescribed antihypertensives seem to have significant effects on renin, aldosterone, and resulting ARR values. However, the magnitude of these effects is poorly quantifiable with the present level of research. We conclude that several medications can affect the ARR. Not taking this into account could lead to misinterpretation of the ARR. Therefore, standardization of the medications used during ARR measurement is advisable for a reliable and accurate interpretation. Further research is needed to ascertain how to best optimize these medications.

1 | INTRODUCTION

The aldosterone-to-renin ratio (ARR) is a widely used screening test for primary aldosteronism (PA). However, there are various confounding factors, including medication, that may influence the levels of renin and/or aldosterone and consequently the ARR. While withdrawal of antihypertensive treatment prior to screening is advisable, this is not always practical or safe. When it is not possible to interrupt treatment, medications with a neutral, or at least a negligible effect on the ARR are required for bridging the diagnostic period.

Current guidelines recommend the use of non-dihydropyridine calcium channel blockers, alpha-adrenoceptor blocking drugs, and the vasodilator hydralazine as noninterfering medications, as these drugs allegedly do not influence the results of ARR testing.[1,2] Although several investigators have reported the effect of these medications on average levels of renin and aldosterone in groups of patients, the calculation of the magnitude of effect on the ARR cannot be inferred by simply dividing the mean values of the entire study population. Thus, drawing conclusions about whether or not the individual ARR is modified by such medication is not a sound approach.

The objective of the present review is to identify medications that do and do not impact the ARR on the basis of robust evidence. Addressing the effects of these medications could help researchers and clinical practitioners in choosing a safe drug to use in severe hypertensives in whom temporary treatment withdrawal is not an option, while not significantly hampering the interpretations of the ARR.

2 | METHODS

In accordance with the PRISM recommendations for the reporting of systematic reviews of diagnostic tests, we performed a literature search on PubMed and the Cochrane database based on a combination of MeSH and free terms to find articles discussing the ARR in the context of pharmaceutical preparations. To this end, we used the search string: (((((((((("Hyperaldosteronism"[Mesh]) OR Conn Syndrome) OR Conn's Syndrome) OR Aldosteronism) OR Hyperaldosteronism)) AND (("Renin"[Mesh]) OR "Aldosterone"[Mesh])) AND ((("Pharmaceutical Preparations"[Mesh]) OR "Antihypertensive Agents"[Mesh])))). Our search encompassed all articles published until 8 April 2020. Finally, cross-references of relevant literature were included.

Our literature search retrieved 191 potential articles to include in the study. Papers that were not published in English (n = 26) were excluded. After reading the abstracts, another 102 articles were rejected because they did not contain information relevant to the present analysis. The remaining 63 articles were read in full and considered eligible if they (a) had a clearly described and reproducible method for the determination of renin and aldosterone, (b) only studied hypertensive patients with or without PA, and (c) the ARR for all individual participants (as opposed to using population means) was calculated at baseline and at follow-up. Finally, articles determined by two of the authors (RMA, GPV) to have low relevance for the present research question were excluded. These include animal studies, cardiovascular-related usage of the ARR, articles focusing on PA confirmatory tests without baseline ARR values, case studies, and articles with the detection of genetic variations as their primary aim. (Figure 1).

Studies accepted for this review were independently screened by two of the authors (RMA, GPV), who applied the selection criteria and reviewed the full-text versions. In the event of disagreement with regard to their selection, said articles were discussed among the aforementioned authors in order to obtain consensus. In the event that consensus between the two authors was not obtained, a third author (P.L) was decisive. Ultimately, only 9 papers could be selected for our analysis.

Based on our scrutiny of the available data, we divided the drugs into those with an effect on the autonomic nervous system, those which interfere with the renin–angiotensin system, calcium channel blockers, vasodilators, and diuretic agents.

As part of our search, we also retrieved three studies that did not fulfill all of our selection criteria because they had been performed in normotensives rather than hypertensives. For the sake of completeness, the results from these studies will be mentioned as well.

Finally, we scored each paper with respect to the reliability of the existing evidence. The latter was weighed as strong when there were more than 40 participants for the medication being studied and no major uncontrolled confounding factors, as moderate with less than 40 participants and /or minor confounding factors that was not controlled for and as weak with 10 or less participants and/or significant confounders that was not controlled for.

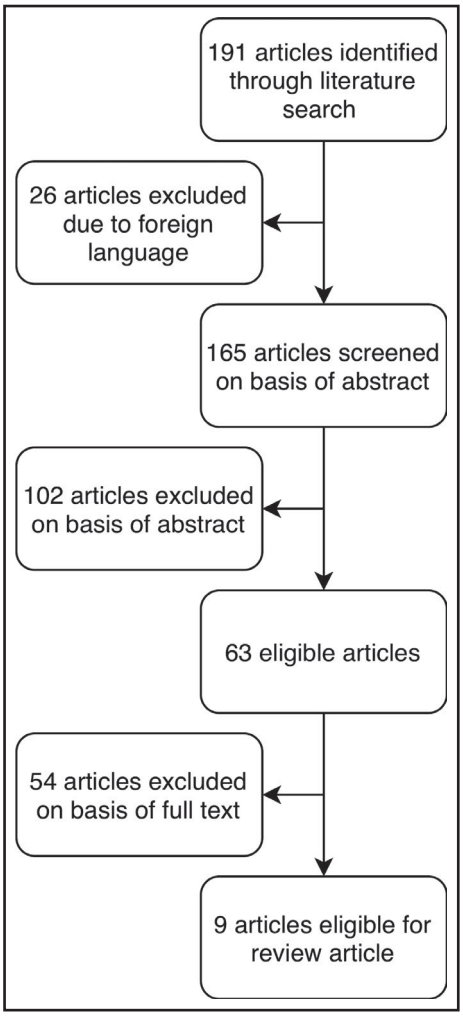

FIGURE 1 Flow chart indicating the selection of papers

3 | RESULTS

A summary of our findings is presented in Table 1.

3.1 | Drugs with an effect on the autonomic nervous system

3.1.1 | Beta-blockers

With regard to beta-blockers, some relevant information is available for atenolol only. The effect of treatment with this drug was assessed in the study by Mulatero et al.[3] These investigators measured the ARR (using PRA) in a group of 2160 patients who had been referred for evaluation of their hypertension and in whom all previous drug therapy could be safely withheld for 1 month. A total of 230 patients exhibited an ARR above 50 and were, therefore, suspected of having PA. These individuals were subsequently randomized to treatment with either atenolol (n = 51), amlodipine (n = 55), doxazosin (n = 55), or fosinopril (n = 52). Later on, a fifth group of 17

TABLE 1 Summary of the effects of various medications on aldosterone, renin, and their ratio

Reference	Population characteristics	*N*	Intervention	Aldosterone	Renin	Baseline ARR	Follow-up ARR	Reliability of evidence
Drugs with an effect on the autonomic nervous system								
12	Normotensive males	20	Moxonidine (0.4 mg/day)	Unchanged	Unchanged (PRA and DRC)	73 (36-218)	84 (32-192)	Moderate
4	Hypertensives with type II diabetes, taking beta-blockers and ≥ 1 additional antihypertensive	19	Beta-blocker cessation	↑	↑*	No numerical values stated.	↓*	Weak
5	Hypertensives using beta-blockers at baseline in addition to multiple other drugs with elevated ARR at baseline	10	Beta-blocker cessation	Not stated	Not stated	112 (61-228)	51 (13-152)*	Weak
3	Suspected PA patients	51	Atenolol (100 mg/day)	↓*	↓*	179.1 ± 138.3	249.4 ± 152.9*	Moderate
		55	Doxazosin (8 mg/day)	↓*	Unchanged	142.0 ± 86.9	132.7 ± 86.9*	Moderate
11	Normotensive males	21	Atenolol (50 mg/day)	↓*	↓* (PRA and DRC)	61 (30-73)	78 (49-125)*	Moderate
Drugs which interfere with the renin–angiotensin system								
3	Suspected PA patients	52	Fosinopril (20 mg/day)	↓*	↑*	176.2 ± 92	121.7 ± 65.2*	Moderate
		17	Irbesartan 300 mg/day	↓*	↑*	167.2 ± 87	104.5 ± 84.7*	Weak
6	Drug naïve essential hypertensives	17	Ramipril 10 mg/day	↓*	↑*		−46.6 ± 61.8*	Weak
		18	Telmisartan 80 mg/day	↓*	↑*		−59.5 ± 40.6*	Weak
Calcium channel blockers								
3	Suspected PA patients	55	Amlodipine 10 mg/day	↓*	↑*	173.9 ± 113.4	134.5 ± 86.2*	Moderate
6	Drug naïve essential hypertensives	22	Amlodipine 10 mg/day	↑*	↑*	134.3 ± 72.8	−22.2 ± 44.1*	Moderate
7	Hypertensive men and women	10	Nifedipine 60 mg/day	↑*	↑*	716 ± 833	305 ± 315*	Weak
	Normotensive men and women	10		↑*	↑*	435 ± 454	182 ± 107*	Weak
8	Hypertensive patients on amlodipine at baseline	10	Azelnidipine 16 mg/day	↓	↓*	56.7 ± 20.5	65.9 ± 14.3	Weak
	Hypertensive patients on manidipine at baseline	10		↓*	↓*	14.4 ± 1.8	28.4 ± 5.1*	Weak
	Hypertensive patients on nifedipine at baseline	10		↓*	↓*	17.0 ± 2.4	26.7 ± 3.6*	Weak
	Hypertensive patients, drug naïve at baseline	10		↑	↑	54.8 ± 18.7	63.3 ± 18.3	Weak
Diuretics and mineralocorticoid receptor antagonists								
5	Hypertensives using amiloride at baseline in addition to multiple other drugs	15	Amiloride cessation	↓*	↓*	28 (2-86)	34 (2-186)	Weak
9	Therapy Resistent Low-Renin hypertensives on multiple antihypertensives	38	Amiloride (2.5 mg/day, HCT 25-50 mg/day)	↑*	↑*	23 (3-107)	11 (1-50)*	Weak
10	PA patients (unilateral *n* = 32, bilateral *n* = 10)	42	Canrenone 100 mg/day	Unchanged	Unchanged	No numerical values stated	Unchanged	Strong

Note: Unless otherwise stated, PRA used. Brackets indicate 95% confidence intervals, ± indicates standard deviation. For interpretation of the reliability of the evidence, see text.

*$p < .05$.

patients taking irbesartan was added. After 2 months of treatment with atenolol in a dose of 100 mg per day, aldosterone and renin values had fallen significantly, while the resulting ARR was significantly elevated as compared to baseline measurements. As there was no placebo control group in this study, the observed changes could still, at least in part, be due to spontaneous changes in hormonal levels.

In two other studies in patients taking multiple antihypertensives who had beta- blocker usage (not further specified) suspended, the resulting ARR fell significantly compared to baseline.[4,5] However, due to the nature of these studies such as only partial cessation of antihypertensive agents[5] and small population size,[4] the quality of the evidence presented is not comprehensive enough to gauge to what extent the change in ARR was the result of beta-blocker cessation.

3.1.2 | Alpha-blockers

With respect to the recommended drugs prazosin and terazosin, we found no studies that measured the ARR in individual patients before and during treatment with either of these two drugs. Only a single study looking at alpha-blockers met our criteria, namely the doxazosin treatment arm in the trial of Mulatero et al[3] mentioned above. In the 55 patients, who received doxazosin in a dose of 8 mg per day, aldosterone values were significantly lower after 8 weeks, while no significant change in PRA occurred. Although the resulting ARR was significantly lower when compared with baseline measurements, the lack of a control group again precludes drawing firm conclusions.

3.1.3 | Centrally acting agents

Although moxonidine has occasionally been recommended as a drug with minimal effects on the ARR,[2] there are no studies in hypertensive patients where this has been tested. The same is true for other centrally acting antihypertensives.

3.2 | Drugs which interfere with the renin–angiotensin system

As part of the study by Mulatero et al,[3] 52 patients with suspected PA were placed on the ACE inhibitor fosinopril (20 mg daily) and 17 on the ARB irbesartan. After 8 weeks of treatment, aldosterone levels had fallen significantly in both groups while renin levels had risen. This resulted in the expected effect of a statistically significant decrease in the ARR as compared to baseline values.

A similar effect was noted by Lamarre-Cliche and coworkers who randomized 57 hypertensive patients to treatment for 8 weeks with either telmisartan (n = 18), amlodipine (n = 22), or ramipril (n = 17). All patients had been taken off previous antihypertensive medication and had been treated with placebo for 4 weeks. Both in the ramipril and the telmisartan group, the ARR fell significantly due to a rise in renin and a decline in aldosterone levels.[6] Once more, no data on a concurrent placebo-treated group are available.

3.3 | Calcium channel blockers

3.3.1 | Non-dihydropyridines

Our search yielded no studies that investigated the effects of slow-release verapamil or diltiazem, the only two clinically available non-dihydropyridine calcium channel blockers on the ARR in individual patients.

3.3.2 | Dihydropyridines

The group of dihydropyridines has been studied more extensively in terms of their influence on the ARR. For instance, Fiad and coworkers found in 10 hypertensive men and women who were off their antihypertensive medication for 2 weeks that treatment with 60 mg of nifedipine GITS for 8 days led to a significant rise in aldosterone and renin levels but a significant decline in the ARR.[7] However, this study too lacked a placebo control group.

In a novel study design by Kondo et al,[8] 40 hypertensive patients were broken down into 4 groups of 10 patients each: those using amlodipine at baseline, those using manidipine, those using nifedipine, and those who were drug naïve. They then had their previous medication stopped and replaced with azelnidipine over a 4-week period. In the drug naïve group, no significant changes in aldosterone, renin or ARR occurred, suggesting that azelnidipine had a negligible effect on the renin–angiotensin–aldosterone system (RAAS). However, in both the manidipine and nifedipine cessation groups, aldosterone and renin values were significantly lower, with the resulting ARR's being significantly elevated in both these groups. In the amlodipine cessation group, renin was significantly reduced. Although the resulting ARR tended to be elevated, this was not statistically significant.

In the study by Mulatero et al,[3] referred to above, 55 patients with suspected PA were placed on amlodipine for an 8-week period. In this group, aldosterone values fell significantly while renin values were significantly elevated. This had the consequent effect of a significantly reduced ARR when compared with baseline values. This result was echoed by the Canadian study of Lamarre-Cliche[6] in which 22 hypertensives were placed on amlodipine over a 4-week period. In these patients, both aldosterone and renin were elevated by treatment but to such extents that the resulting ARR dropped significantly.

3.4 | Vasodilator drugs

Of the direct vasodilators, only hydralazine is sometimes used as monotherapy in hypertension. While this drug belongs to the

recommended agents for bridging the diagnostic period,[1,2] it appears that there are no studies that have looked specifically into its effects of the ARR in individual hypertensive patients. Neither have such studies been performed with other direct vasodilators such as minoxidil.

3.5 | Diuretics

3.5.1 | Thiazides/amiloride

In two studies, the effect of amiloride was assessed. In one of these,[9] therapy-resistant low-renin hypertensives using multiple antihypertensive medications were placed on amiloride and hydrochlorothiazide. In this group, aldosterone and renin both significantly rose, but the resulting ARR was significantly reduced. In the other study,[5] hypertensives using amiloride at baseline in addition to multiple other drugs had their amiloride usage stopped for a period of 4 weeks. In this group, aldosterone and renin significantly fell, but the resulting ARR did not significantly change from baseline.

3.5.2 | Mineralocorticoid receptor blockers

Recently, Rossi et al[10] studied the effect of canrenone, which is a Mineralocorticoid receptor (MR) antagonist and the main active metabolite of spironolactone, in patients with confirmed PA who had been scheduled to undergo either surgical or medical treatment. Participants received 100 mg/day of canrenone over the course of a 1-month period. In both groups, renin, aldosterone, and the ARR were not significantly affected by the antagonist.

3.6 | Studies in normotensives

Only a few papers have addressed the effect of antihypertensive agents on the ARR in normotensives. For instance, in a small but strictly controlled study on normotensive male volunteers, Ahmed et al[11] found that 4 weeks of treatment with the beta-blocker atenolol (25 mg daily for the first week, 50 mg daily thereafter) caused significant falls in aldosterone and renin values and a statistically significant rise in the ARR. Notably, PRA fell more rapidly than DRC, indicating that also the assay technique could impact ARR values in those using atenolol.

The same group also assessed the effect of the centrally acting agent moxonidine on the ARR.[12] In that particular study, the investigators administered moxonidine over a 6-week period to twenty normotensive male volunteers. At the end of this period, neither aldosterone nor renin values had changed from baseline measurements, and the resulting post-therapeutic ARR had not significantly changed either. This was true, irrespective of whether PRA or DRC was used to assess renin levels.

Finally, in the study by Fiad and coworkers, already referred to above, the effect of treatment with nifedipine for 2 weeks was also evaluated in 10 normotensive men and women.[7] As was the case in the hypertensives, aldosterone, and renin rose in the normotensives while ARR significantly fell.

4 | DISCUSSION

In this review, we have scrutinized the effects of a variety of medications on the ARR. From our analysis, it appears that all major antihypertensive drug classes can affect the ARR result. This is unfortunate because the test has become increasingly important in the screening for PA. Recent guidelines and consensus statements stipulate that, whenever bridging therapy is required in patients in whom antihypertensive treatment cannot be stopped, one should use drugs with no or a minimal effect on the ARR. In this regard, the alpha-blocking agents prazosin, doxazosin, and terazosin, the centrally acting drug moxonidine, the non-dihydropyridine verapamil (slow-release), and the vasodilator hydralazine are recommended.[1,2] However, there is virtually no evidence to substantiate this recommendation. Indeed, no studies have assessed the effects of prazosin, terazosin, moxonidine, verapamil and hydralazine on the pre- and post-treatment ARR in individual hypertensive patients. Inasmuch as information is available for doxazosin, this is still not very conclusive either. The one study that met our inclusion criteria lacked a placebo control group. Any inferences about the effect of doxazosin should, therefore, be viewed upon with caution. Admittedly, there is a small placebo-controlled study (n = 17) which did find that renin, aldosterone, and changes in the ARR were not affected by doxazosin.[13] However, in that particular study no individual calculations of the ARR were presented, thus the true effect of the alpha-blocker remains uncertain.

Based on the limited research, it would appear that azelnidipine is the only antihypertensive agent that does not significantly affect the ARR. This could potentially indicate that this drug should be the antihypertensive of choice when ceasing other antihypertensive usage prior to PA screening. However, we should bear in mind that even for azelnidipine the evidence is not very strong. The suggestion that this drug is neutral with respect to the ARR results is, unfortunately, based on a sample of only 10 patients who did not have any previous treatment. When patients had already been treated with other drugs, which is a situation that much better reflects ordinary clinical practice, azelnidipine was not so neutral anymore.[8]

Canrenone also appears to be a valid option to use based on its negligible effect on the ARR in participants with confirmed PA. This is important, as due to the mechanism of action of this drug, false negatives are potentially a realistic concern.

Although one can find many papers in the literature that examined the effects of antihypertensive drugs on the renin–angiotensin system, none of these qualified for our analysis, either because it was not possible to assess per-patient changes in the ARR or because studies were not performed in hypertensives people,[11,12,14,15] the target population of the test.

The only specific medication to cause a significant rise in ARR was atenolol, which is the sole beta-blocker that has been studied in a thorough manner. Notably, PRA fell more rapidly than DRC, indicating that also the assay technique could impact ARR values in those using atenolol.

Significant decreases in the ARR were noted for nifedipine, amlodipine, ramipril, fosinopril, telmisartan, and irbesartan while amiloride had conflicting results regarding its effect. It should be noted that in none of these studies a placebo-group was included which makes it difficult to draw solid conclusions regarding the effects of these drugs. Nevertheless, the recommendation to stop these treatments is probably justified.

Interestingly, there appears to be tentative evidence that hormone replacement therapy and some SSRI's could potentially influence the ARR.[16,17] While this information comes from normotensive people, many patients with hypertension may take these medications as well. This makes it worthwhile to study in hypertensives the effects of these drugs as well as those of others used for comorbid conditions.

In this review, our criteria for inclusion were fairly strict. We required aldosterone, renin as well as the calculation of the ARR to be given at baseline and after drug intervention/cessation. In addition, we only included studies which were performed in hypertensive participants. While there is a somewhat larger body of research available with less rigorous study designs (for example, no baseline measurements or no ARR calculations), we felt that this research is not comprehensive enough to draw clear conclusions. Such research has the potential to hint at a possible effect of a given drug, but knowing the established mean of per-participant ARR values, neither the magnitude nor the veracity of the effect can be determined in a clinically significant manner.

Clinically, our review demonstrates the necessity for clinicians to be mindful of the choice of drugs being used (or suspended) by their patients prior to screening, as well as being conscious of the effects of these drugs when interpreting the ARR. This includes being aware of drugs which at first glance would not appear to be a cause for concern. It is also important to point out that our findings are in contrast to the Endocrine Society Guidelines, which state that the ARR in many cases can be confidently interpreted despite the effect of medication with the exception of mineralocorticoid receptor blockers. As we have shown here, many drugs, including those without a direct mechanism of action on the RAAS, could potentially have a significant effect on the ARR. It is an important finding that little to no strong evidence exists for many widely used antihypertensives such as non-dihydropyridine Calcium channel blockers (CCB's). This is especially concerning since these medications are commonly used during PA screening on the assumption that they minimally affect the RAAS. In this regard, it is important to remember that the activity and the effects of the renin–angiotensin system, in particular in relation to aldosterone release, is dependent upon a variety of factors such as volume status and the degree of sympathetic stimulation. In addition, at least part of the action of angiotensin II involves calcium influx through those channels that are targeted by calcium channel blockers. As a consequence of these and other regulatory mechanisms, the effects of most antihypertensive agents, notably with respect to the ARR, are unlikely to be absolutely straightforward.

In conclusion, a wide variety of drugs may influence the ARR. There is a clear and pressing need for more high-quality prospective trials looking into the effects of antihypertensive agents on the ARR and these trials should look at both essential hypertensive and PA participants separately. While there are shortcomings in the usage of the ARR as a screening test under non-standardized conditions, the high prevalence and the generally good prognosis warrant the importance of screening all eligible patients with minimal confounding by medication.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of this study as well as data acquisition and analysis. RMA and GPV drafted the manuscript. AAK and PWdL were involved in data acquisition, interpretation of data, and revision of the manuscript. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

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