META-ANALYSIS

Effect of diuretics on plasma aldosterone and potassium in primary hypertension: A systematic review and meta-analysis

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Aim: By contrast with drugs inhibiting the renin-angiotensin-aldosterone system (RAAS), diuretics stimulate renin release by the kidneys. Although plasma aldosterone (PA) is thought to be mainly regulated by RAAS activity, serum potassium has been shown to be an important factor in animal models and humans. Here we perform a systematic review and meta-analysis of randomised controlled trials (RCT) in hypertension investigating the effects of diuretic therapy on PA and the correlation of change in PA with that of potassium and blood pressure (BP).

Methods: Three databases were searched: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). Titles were first screened by title and abstract for relevance before full-text articles were assessed for eligibility according to a predefined inclusion/exclusion criteria.

Results: A total of 1139 articles were retrieved, of which 42 met the prespecified inclusion/exclusion criteria. The average standardised difference in mean PA was similar for all classes of diuretic: thiazide/thiazide-like 0.299 (95% confidence interval [CI] 0.150, 0.447), loop 0.927 (0.37, 1.49), MRA/potassium-sparing 0.265 (0.173, 0.357) and combination 0.466 (0.137, 0.796), \( Q = 6.33, P = .097 \). In subjects untreated with another antihypertensive, there was a significant relationship between change in PA and change in systolic BP but no relationship with the change in potassium.

Conclusion: In RCTs of diuretic therapy in hypertension, there is an increase in PA with all classes of diuretic and no significant between-class heterogeneity. Change in PA is not related with potassium but correlates with the change in BP in subjects untreated with another antihypertensive medication.

KEYWORDS
aldosterone, blood pressure, hypertension, potassium, renin

1 | INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is a complex neuroendocrine system that regulates salt and water homeostasis and blood pressure (BP) amongst several other actions.\(^1\) Drugs that inhibit the RAAS are a cornerstone in the treatment of hypertension, working at least in part by reducing the formation or blocking the effects of angiotensin II and plasma aldosterone (PA), an independent cardiovascular risk factor promoting cardiovascular and renal inflammation, fibrosis and cardiovascular remodelling.\(^2\)
Compared to RAAS inhibitors, diuretics have a more complex mechanism of action\(^3\) which includes an initial reduction in plasma volume and a sustained decline in peripheral resistance, thereby improving an underlying haemodynamic defect of hypertension.\(^4\)–\(^7\) Under acute and chronic conditions, diuretics induce an increase in plasma renin activity (PRA)\(^8\) but whether diuretics also increases PA has been debated.\(^9\) Apart from the level of activation of the RAAS, potassium,\(^10\)–\(^12\) which is also affected by diuretic treatment, plays an important role in the regulation of PA production and some diuretics (such as mineralocorticoid receptor antagonists) are known to have direct inhibitory action on aldosterone formation.

The objective of the present study was to perform a systematic review and meta-analysis of randomised clinical trials (RCTs) where diuretics were used to treat hypertension and measurements of PA were available before and after diuretic treatment to determine if they lead to a sustained increase in PA and whether this differs according to class of diuretic. Secondary objectives were to establish if there is correlation between difference in PA and that of serum potassium and if the decrease in BP relates to the difference in PA.

2 | METHODS

2.1 | Search strategy

This systematic review and meta-analysis was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,\(^13\) similarly to our previously published review.\(^14\) A systematic literature search was performed on three databases: Ovid MEDLINE (1946 to 16 September 2020), EMBASE (1974 to 16th September 2020) and the Cochrane Central Register of Controlled Trials (CENTRAL) databases (up to 16 September 2020). Studies which were included were trials of diuretics used either as mono- or multitherapy in hypertension, and which examined how they affected plasma aldosterone ±/– renin, serum potassium and blood pressure. The keywords used included “thiazide”, “thiazide-like”, “potassium-sparing”, and “diuretic”. Medical subject headings (MeSH) and non-MeSH terms were used to search the databases for relevant publications. The full search strategy for MEDLINE is provided in the Supporting Information. The review protocol was not registered but the PROSPERO database was searched before starting the review to ensure that a similar review was not ongoing.

2.2 | Study selection and eligibility criteria

Papers were initially screened by title and abstract. Studies were eligible for inclusion if they were an RCT performed in hypertensive human subjects ≥18 years old, examining antihypertensive effects of a thiazide, thiazide-like, loop, mineralocorticoid receptor antagonist (MRA) or potassium-sparing diuretic with a duration of at least 1 week. Studies investigating novel diuretics or “diuretic-like” drugs not currently licensed for clinical use were excluded as were studies in which subjects had pulmonary arterial hypertension or heart failure. We included in the analysis all the diuretic compounds currently licenced in the UK for the treatment of arterial hypertension. We also included drugs which were licenced for hypertension at the time that the original study was conducted. All studies were required to have examined PA with results available before and during diuretic treatment or, in the case of placebo-controlled trials, during treatment with placebo. Studies were eligible if diuretic therapy was added to either no previous therapy or to stable background treatment. The search was limited to the English language only and review articles were disregarded. Titles and abstracts were screened by one author (R.J.M.), and the same author reviewed the full-text articles.

2.3 | Data collection process

Data were extracted independently by one author (R.J.M.) using a standard form. This included author, year of publication, class of diuretic(s) and dose used, protocol (including presence of background therapy and whether placebo controlled), sample size, average age, sex distribution, ethnicity (if available) and prevalence of diabetes (if available). For the outcome measurements, mean (± standard deviation/standard error) of values for BP and aldosterone before and during diuretic (and before and during placebo treatment in placebo-controlled studies) and the difference between values on and before treatment were extracted from the relevant articles. Where available, the differences in renin, serum potassium and systolic blood pressure (SBP) were extracted. If standard deviations were not reported these were calculated from standard errors, \(P\) values or confidence intervals. The duration of diuretic treatment at the time of measurement was also recorded. Where only graphical reports of measurements were available, an estimation from the graph was taken if it was judged to be accurate to within 10%. Units of aldosterone were converted to pmol/L for analysis if other units were used.

2.4 | Quantitative data synthesis and statistical analysis

Meta-analysis was conducted using Comprehensive Meta-Analysis Software Version 3 (Biostat, Englewood, New Jersey, USA).\(^15\) Net changes in PA, renin, potassium and SBP were obtained as the difference from baseline after treatment with either diuretic or placebo. If there was no standard error of the mean change stated, it was estimated from the \(P\) value, number of observations and size of the change. A random-effects model was used to compensate for between-study heterogeneity in terms of demographic inconsistencies and different diuretic doses\(^16\) with calculation of the standardised mean difference in PA and its 95% confidence interval (CI). The standardized mean difference expresses the size of the intervention effect in each study relative to the standard deviation of the measurement (in this case PA). Raw mean differences were calculated...
for plasma potassium, and SBP and standardised differences for PRA. Statistical heterogeneity was assessed using Cochran’s Q test.\textsuperscript{17} \(P < .05\) was considered statistically significant and all tests were two-tailed.

### 2.5 Meta-regression

Random-effects meta-regression was performed using the method of moments to evaluate the association between standardised difference in PA and change in SBP in the overall data and in subjects previously untreated with another antihypertensive. The same method was used to examine the association between change in PA and change in serum potassium.

### 2.6 Publication bias

Potential publication bias was assessed by inspection of Begg’s funnel plot asymmetry and Egger’s asymmetry tests.\textsuperscript{18} We did not perform any risk of bias within individual studies because we were not examining the primary outcome of the studies.

### 3 RESULTS

#### 3.1 Description of studies

The study selection process is detailed in a flow chart as per PRISMA guidelines (Figure 1). The initial MEDLINE search returned 191 results, Embase 384 and Central 564 (1139 in total). After removal of duplicates there were 967 articles of which 769 were excluded based on title and abstract. The remaining 198 full-text articles were assessed for eligibility and 156 were excluded for various reasons (Figure 1). The remaining 42 articles were included in the qualitative synthesis. MRA and potassium-sparing diuretics were grouped together for the analysis as only one study had measurements for a potassium-sparing diuretic (amiloride) with the remainder MRA. The most commonly used diuretic class was the MRA/potassium-sparing class. Classes of

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**FIGURE 1** PRISMA diagram. Flow-chart of included and excluded studies against a predefined search criteria.
TABLE 1  Summary of randomized controlled antihypertensive trials in which plasma aldosterone (PA) was measured before and after treatment with a placebo/diuretic in one or more arms or treatment phases

| Study ID, year          | Diuretic, dose | Study design, sample size | Age (years) | Male (%) | Time measured (weeks) | Aldosterone unit | Aldosterone before | Aldosterone after | Serum K + before | Serum K + after |
|------------------------|----------------|---------------------------|-------------|----------|-----------------------|-----------------|-------------------|-------------------|-----------------|-----------------|
| Hood, 2007             | SPIRO 50-100 mg | Crossover, 51             | 59.5 ± 11.9 | 54       | 10                    | Pmol/L          | 375 (276-438)     | 1116 (893-1339)  | 4 (3.9-4.1)     | 4.5 (4.4-4.6)   |
| Hood, 2007*            | AMIL 20-40 mg   | Crossover, 51             | 59.5 ± 11.9 | 54       | 10                    | Pmol/L          | 375 (276-438)     | 963 (797-1129)   | 4 (3.9-4.1)     | 4.8 (4.6-4.9)   |
| Hood, 2007*            | BENDRO 2.5-5 mg | Crossover, 51             | 59.5 ± 11.9 | 54       | 10                    | Pmol/L          | 375 (276-438)     | 374 (330-419)    | 4 (3.9-4.1)     | 3.6 (3.4-3.8)   |
| Ubaid-Girioli, 2009    | SPIRO 25 mg     | Parallel, 39              | ...         | ...      | 24                    | Ng/mL           | 15.4 ± 8.2        | 19.2 ± 9         | 4.2 ± 0.4       | 4.4 ± 0.5       |
| Ubaid-Girioli, 2009*   | SPIRO 25 mg     | Parallel, 32              | ...         | ...      | 24                    | Ng/mL           | 16.8 ± 5.4        | 22.3 ± 12.6      | 4.1 ± 0.3       | 4.3 ± 0.4       |
| Weinberger, 2002       | E 50 mg         | Parallel, 49              | 70 ± 8      | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.26             | ...              |
| Weinberger, 2002*      | E 100 mg        | Parallel, 43              | 61 ± 8      | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.17             | ...              |
| Weinberger, 2002*      | E 400 mg        | Parallel, 52              | 64 ± 8      | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.2              | ...              |
| Weinberger, 2002*      | E 25 mg BD      | Parallel, 49              | 70 ± 8      | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.21             | ...              |
| Weinberger, 2002*      | E 200 mg BD     | Parallel, 43              | 69 ± 8      | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.20             | ...              |
| Weinberger, 2002*      | SPIRO 50 mg BD  | Parallel, 42              | 75 ± 8      | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.24             | ...              |
| Kams, 2012*            | Placebo         | Parallel, 33              | 56.2 ± 7.7  | 57.6     | 8        | Mean-adjusted changes | Mean-adjusted changes | 4.2              | ...              |
| Kams, 2012*            | Placebo         | Parallel, 33              | 59.8 ± 9.33 | 66.7     | 8        | Mean-adjusted changes | Mean-adjusted changes | ...              | ...              |
| Vasavada, 2003*        | TORS 40 mg or FURO 80 mg | Crossover, 14 | 67 ± 11   | 93       | 3        | Mean-adjusted changes | Mean-adjusted changes | ...              | ...              |
| Matsui, 2010*          | HCTZ 12.5 mg    | Parallel, 104             | 68 ± 9.1    | 40       | 24       | Mean-adjusted changes | Mean-adjusted changes | 46.14 (est. from % change) | ...              |
| Lijnen, 1981           | HCTZ 100 mg     | Parallel, 5               | 37.2 ± 2.7  | 57.1     | 12       | Mean-adjusted changes | Mean-adjusted changes | 5.28 ± 1.48 [SE] | 8.11 ± 1.31     | 4.12 ± 0.15     | 3.44 ± 0.22     |
| Lijnen, 1981*          | TIE 250 mg      | Parallel, 5               | 37.2 ± 2.7  | 57.1     | 12       | Mean-adjusted changes | Mean-adjusted changes | 4.78 ± 1.25     | 5.15 ± 1.2      | 4.07 ± 0.12     | 3.68 ± 0.14     |
| Lijnen, 1981*          | TIE 1000 mg     | Parallel, 4               | 37.2 ± 2.7  | 57.1     | 12       | Mean-adjusted changes | Mean-adjusted changes | 2.72 ± 1.5      | 14.92 ± 1.18    | 4.08 ± 0.12     | 3.23 ± 0.16     |
| Koenig, 1991*          | HCTZ 25 mg      | Crossover, 51             | 68 ± 8      | 20       | 12 & 24   | Mean-adjusted changes | Mean-adjusted changes | 70.4 ± 30.6     | 91.5 ± 42 (3 m), 78.9 ± 31 (6 m) | 4.2 ± 0.4 | 4.5 ± 0.4 (3 m), 4.3 ± 0.4 (6 m) |
| Saruta, 2004           | Placebo         | Parallel, 48              | 54.3 ± 10.55| 68       | 8        | Mean-adjusted changes | Mean-adjusted changes | ...              | ...              |
| Saruta, 2004*          | E50mg           | Parallel, 48              | 54.2 ± 11.3 | 63.3     | 8        | Mean-adjusted changes | Mean-adjusted changes | ...              | ...              |
| Saruta, 2004*          | E100mg          | Parallel, 45              | 52.8 ± 10.02| 69.6     | 8        | Mean-adjusted changes | Mean-adjusted changes | ...              | ...              |
| Study ID, year | Diuretic, dose | Study design, sample size | Age (years) | Male (%) | Time measured (weeks) | Aldosterone unit | Aldosterone before | Aldosterone after | Serum K+ before | Serum K+ after |
|---------------|----------------|--------------------------|------------|---------|----------------------|-----------------|------------------|------------------|----------------|---------------|
| Saruta, 2004* | E200mg         | Parallel, 47             | 52.6 ± 10.76 | 72.9    | 8                    | …               | % change reported | % change reported | …              | …             |
| Chalmers, 1982* | INDA 2.5 mg    | Crossover, 16            | 53 ± 10    | 44      | 8                    | Ng/100 mL       | 8 (placebo)    | 13.8 (INDA)     | 4.4 (placebo) | 3.6 (INDA)    |
| Calhoun, 2011* | E 50 mg BD     | Parallel, 68             | 55.3 ± 9.1 | 59.7    | 8                    | Pmol/L          | 189.7           | 379.8           | …              | …             |
| Calhoun, 2011* | Placebo        | Parallel, 60             | 53.9 ± 8.7 | 66.7    | 8                    | Pmol/L          | 181.7           | 172.3           | …              | …             |
| Svendsen, 1983* | HCTZ - AMIL   | Parallel, 15             | 48.5       | 43      | 12                   | Pmol/L          | 208             | 478.4           | 3.3            | 3.80 (Est from %) |
| Ubaid-Girioli, 2007* | HCTZ 25 mg     | Parallel, 18             | 49.3 ± 7.2 | 46      | 12                   | Ng/dL           | 9.1 ± 2.2       | 14.1 ± 1.4      | …              | …             |
| Ramsay 1981* | SPIRO 25 mg    | Crossover, 14            | 50         | 43      | 4                    | Pmol/L          | 12.02 ± 1.70    | 15.85 ± 2.45    | 3 ± 0.43       | 3.37 ± 0.44    |
| Ramsay 1981* | SPIRO 50 mg    | Crossover, 14            | 50         | 43      | 4                    | Pmol/L          | 12.02 ± 1.70    | 31.62 ± 1.41    | 3 ± 0.43       | 3.52 ± 0.48    |
| Ramsay 1981* | SPIRO 100 mg   | Crossover, 14            | 50         | 43      | 4                    | Pmol/L          | 12.02 ± 1.70    | 34.67 ± 1.32    | 3 ± 0.43       | 3.83 ± 0.43    |
| Ramsay 1981* | SPIRO 200 mg   | Crossover, 14            | 50         | 43      | 4                    | Pmol/L          | 12.02 ± 1.70    | 42.66 ± 1.78    | 3 ± 0.43       | 3.91 ± 0.35    |
| O'Connor, 1980* | HCTZ          | Crossover, 19            | 50.1 ± 2.6 | 100     | 4                    | Pg/mL           | 48.3 ± 8 [SE]   | 98.4 ± 19       | 4.1 ± 0.1      | 3.8 ± 0.1      |
| Ferguson, 1982* | HCTZ 50 mg    | Crossover, 4             | 51         | 66      | 2                    | Ng/dL           | 13.5 (group 1), 21.8 (group 1), 20.8 (group 2) | …             | …             |
| Matthesen, 2012* | AMIL 5 mg BD | Crossover, 23             | 60 (45-70) | 60.9    | 4                   | Pmol/L          | 84 (placebo)    | 303             | …              | …             |
| Matthesen, 2012* | SPIRO 25 mg BD | Crossover, 23           | 60 (45-70) | 60.9    | 4                   | Pmol/L          | 84 (placebo)    | 299             | …              | …             |
| Ni, 2014* | SPIRO 25 mg | Parallel, 40             | 55.7 ± 12.3 | 60    | 12                   | Pg/mL           | 23.8 ± 10.9     | 24.5 ± 11       | 4.1 ± 1.5      | 4.4 ± 0.7      |
| Ni, 2014* | Placebo       | Parallel, 36             | 54.9 ± 14.2 | 58.3    | 12                   | Pg/mL           | 23.4 ± 10.2     | 23.5 ± 9.8      | 3.9 ± 0.9      | 4.1 ± 1.4      |
| Koopmans, 1987* | HCTZ 50 mg OD | Crossover, 9             | 50.5 ± 9.1 | 55.6    | 4                   | Ng/100 mL       | 8.5 ± 4.8       | 11.8 ± 5.2      | 3.8 ± 0.17     | 3.2 ± 0.26     |
| Swaminathan, 2008* | SPIRO 25-50 mg | Crossover, 33           | 62.6       | 66      | 4                   | Pmol/L          | 150.84 ± 83.1 (placebo) | 264.33 ± 107.8 | 4.4 ± 0.3      | 4.8 ± 0.37    |
| Kreeft, 1983* | CLTD 100 mg | Crossover, 19            | 42-66      | 52.6    | 8                   | Ng/L            | 7.8 ± 4.8       | 11.56 ± 10.9    | 4.31 ± 0.4     | 3.35 ± 0.3     |
| Kreeft, 1983* | SPIRO 400 mg | Crossover, 19            | 42-66      | 52.6    | 8                   | Ng/L            | 7.8 ± 4.8       | 14.4 ± 13.3     | 4.31 ± 0.4     | 5 ± 0.6        |
| Jarvis, 2015* | HCTZ 12.5-25 mg | Parallel, 10         | 68 ± 6     | 50      | 24                  | Ng/dL           | 5.4 ± 4.7       | 11.8 ± 10.5*    | …             | …             |
| Yang, 2016* | SPIRO 20-40 mg | Parallel, 15            | 44.7 ± 10.8 | 12    | 12                  | Ng/dL           | 18 ± 5.4        | 8.2 ± 3.3       | 4.3 ± 0.3      | 4.3 ± 0.2      |
| Karashima, 2016* | HCTZ 6.25 mg | Parallel, 22            | 65 ± 1     | 68      | 48                  | Pg/mL           | 87 ± 6 (SEM)    | 83 ± 5          | 4.1 ± 0.1      | 4.1 ± 0.1      |
| Karashima, 2016* | E 50 mg     | Parallel, 23             | 66 ± 2     | 68      | 48                  | Pg/mL           | 85 ± 7          | 103 ± 1*        | 4.2 ± 0.1      | 4.3 ± 0.1      |
| Karashima, 2016* | SPIRO 12.5-100 mg | Parallel, 27         | 56.1 ± 9.9 | 40.7    | 48                  | Pg/mL           | 128 ± 55        | 244 ± 84        | 3.9 ± 0.3      | 4.3 ± 0.3      |
| Karashima, 2016* | EPLER 25-100 mg | Parallel, 27            | 54.9 ± 10.7 | 48.1    | 48                  | Pg/mL           | 140 ± 60        | 184 ± 88        | 3.9 ± 0.3      | 4.2 ± 0.3      |
| Ferrara, 1988* | CLTD 25 mg | Parallel, 16            | 49 ± 8     | 50      | 6                   | Pg/mL           | 222 ± 105       | 320 ± 227       | …             | …             |
| Ferrara, 1988* | Placebo     | Parallel, 16            | 49 ± 8     | 50      | 6                   | Pg/mL           | 327 ± 185       | 356 ± 166       | …             | …             |
| Study ID, year | Diuretic, dose | Study design, sample size | Age (years) | Male (%) | Time measured (weeks) | Aldosterone unit | Aldosterone before | Aldosterone after | Serum K+ before | Serum K+ after |
|---------------|----------------|---------------------------|-------------|----------|----------------------|----------------|-------------------|------------------|----------------|----------------|
| Derosa, 2018  | CAN 50-100 mg  | Parallel, 81              | 53.4 ± 7.2  | 53.4     | 24 & 48              | Pg/dL          | 143.1 ± 22.5      | 121.8 ± 16.5 (6 m), 104.6 ± 13.2 (12 m) | 3.9 ± 0.4 | 4.1 ± 0.6 (6 m), 4.3 ± 0.7 (12 m) |
| Derosa, 2018  | HCTZ 12.5-25 mg| Parallel, 82              | 52.6 ± 6.9  | 48.8     | 24 & 48              | Pg/dL          | 153.8 ± 25.6      | 164.1 ± 27.9 (6 m), 169.4 ± 30.6 (12 m) | 4.1 ± 0.5 | 3.8 ± 0.4 (6 m), 3.5 ± 0.3* (12 m) |
| Henning, 1980 | AMIL + HCTZ    | Crossover, 43              | ...         | 56.4     | 8                    | Pmol/L         | 416               | 1257             | 4.26            | 3.82           |
| Krum, 2002    | Placebo (added to ACE) | Parallel, 60            | 54.7         | 51       | 8                    | Ng/dL          | 6.9               | 6.7              | 4.36            | +0.06 ± 0.04    |
| Krum, 2002    | Placebo (added to ARB) | Parallel, 58            | 55.1         | 40       | 8                    | Ng/dL          | 7.4               | 6.9              | 4.28            | +0.05 ± 0.03    |
| Krum, 2002    | EPLER 50-100 mg (- ACE) | Parallel, 63            | 55.7         | 47       | 8                    | Ng/dL          | 7.1               | 11.8             | 4.32            | +0.14 ± 0.04    |
| Krum, 2002    | EPLER 50-100 mg (+ ARB) | Parallel, 64            | 54.2         | 49       | 8                    | Ng/dL          | 7.8               | 12.4             | 4.31            | +0.20 ± 0.04    |
| Derosa, 2016  | CAN 50 mg      | Parallel, 87              | 57.15 ± 8.91 | 65.5    | 12                   | Pg/dL          | 58.64 ± 54.67     | 77.76 ± 72.14    | 4.25 ± 0.43      | 4.50 ± 0.45     |
| Derosa, 2016  | CAN 100 mg     | Parallel, 88              | 57.75 ± 9.18 | 63.6    | 12                   | Pg/dL          | 68.77 ± 63.19     | 68.50 ± 66.01    | 4.32 ± 0.72      | 4.65 ± 0.40     |
| Belleau, 1982 | HCTZ 50 mg     | Crossover, 18             | 44 (23-58)  | 54.6     | 4                    | Ng/100 mL      | 10.99 ± 5.6       | 10.90 ± 4.84     | ...             | ...            |
| Fouassier, 2020 | SPIRO + FUR + AMIL | Parallel, 73            | 53.7 ± 10.3  | 79       | 12                   | Pmol/L         | 104 (69-152) median + IQR | 270 (177-344) | 3.8 ± 0.4 | 4.3 ± 0.5 |
| Dorrsteijn, 2013 | HCTZ 25 mg    | Crossover, 29            | 60 (55-63)  | 74       | 8                    | Ng/L           | Placebo: 53 (33-74) median IQR | 87              | 4.1 (4-4.5) | 3.82 |
| Parthasarathy, 2011 | SPIRO 75-225 mg | Parallel, 61            | 53.2 ± 10.92 | 73.2    | 4 & 16              | Ng/dL          | 20.1              | 37.7 (4w), 44.1 (16w) | ...             | 3.93 (w4), 3.95 (w16) |
| Parthasarathy, 2011* | E 100-300 mg    | Parallel, 67             | 53.9 ± 10.89 | 62.9    | 4 & 16              | Ng/dL          | 18.6              | 26.4 (4w), 33.3 (16w) | ...             | 3.84 (w4), 3.95 (w6) |
| Solini, 2019* | HCTZ 12.5 mg   | Parallel, 20             | 62 ± 8      | 70       | 4                    | Pg/mL          | 1.44 ± 0.95       | 1.01 ± 0.43      | 4.57 ± 0.35      | 4.47 ± 0.31     |
| Ohta, 2015*   | EPLER 50 mg    | Crossover, 20             | 71 ± 13     | 55       | 12                   | Ng/dL          | 15.4 ± 8.0        | 21.0 ± 11.8      | 4.3 ± 0.5        | 4.8 ± 0.4       |
| Ohta, 2015    | INDA 1 mg      | Crossover, 20             | 71 ± 13     | 55       | 12                   | Ng/dL          | 15.4 ± 8.0        | 20.2 ± 9.3       | 4.3 ± 0.5        | 4.2 ± 0.4       |
| Vaclavik, 2014 | Placebo        | Parallel, 76             | 59.7 ± 9.9  | 63.2     | 8                    | Ng/L           | 117               | 111             | 4.1 ± 0.5        | +0            |
| Vaclavik, 2014 | SPIRO 25 mg    | Parallel, 74             | 60.4 ± 9.5  | 67.6     | 8                    | Ng/L           | 87                | 143             | 4.1 ± 0.5        | +0.4           |
| Kithas, 2010  | HCTZ           | Parallel, 21             | 69 ± 6      | 52.4     | 24                   | Ng/dL          | 106 ± 49          | 157 ± 9         | 3.8 ± 0.4        | 3.8 ± 0.4       |
| Kithas, 2010* | SPIRO         | Parallel, 24             | 70 ± 5      | 58.3     | 24                   | Ng/dL          | 107 ± 51          | 300 ± 37        | 4.1 ± 0.2        | 4.2 ± 0.3       |
Individual diuretics were hydrochlorothiazide, amiloride, indapamide, bendroflumethiazide, chlorthalidone, canrenone, furosemide, spironolactone, eplerenone, tielnic acid and torsemide. Details of individual trials are summarised in Table 1. In those studies where patients were previously treated with another antihypertensive medication before the diuretic was added, an Angiotensin-converting enzyme (ACE) inhibitor/Angiotensin II Receptor Blocker (ARB) was included in over 50%. Plasma renin activity (PRA) was used as this was the most common measure.

### 3.2 Primary outcome meta-analysis: Effect of placebo and diuretic on plasma aldosterone

Placebo had a negligible effect on PA in the present analysis (Figure 2D). The standardized difference in mean PA after placebo was $-0.11$ (95% CI $-0.36$, $0.14$). With diuretic therapy, all diuretic classes led to a significant increase in PA but there was no between-class heterogeneity (Figure 2A). The average standardized difference in mean PA change was: thiazide/thiazide-like $0.299$ ($0.150$, $0.447$), loop $0.927$ ($0.37$, $1.49$), MRA/potassium-sparing $0.265$ ($0.173$, $0.357$) and combination $0.466$ ($0.137$, $0.796$), $Q = 6.33$, $P = .097$. In studies where there was no background antihypertensive use, the average increase in PA was $0.398$ ($0.229$, $0.566$; Figure 2B). There was a similar increase in PA for those in whom diuretic was added to previous antihypertensives: $0.301$ ($0.040$, $0.563$; Figure 2C). After separating MRA from potassium-sparing diuretics, the same homogeneity between classes was found.

### 3.3 Secondary outcomes meta-analysis: Effect of placebo and diuretic on serum potassium, plasma renin activity and blood pressure

Changes in serum potassium were thiazide/thiazide-like $-0.239$ ($-0.40$, $-0.08$) mEq/L, loop $-0.617$ ($-0.98$, $-0.254$) mEq/L, K+ sparing/MRA $0.248$ ($0.152$, $0.344$) mEq/L and combination $0.048$ ($-0.324$, $0.420$) mEq/L, with significant between-class heterogeneity ($Q = 41.5$, $P < .001$; Figure 3). The analysis of PRA and SBP can be found in the Supporting Information. Of the 42 included studies, 26 had differences in SBP, 26 had differences in serum potassium and 23 had differences in PRA both before and after diuretic. All diuretics decreased blood pressure significantly, apart from the loop diuretics, with combination diuretics lowering SBP by the largest amount ($-23.4$ [$-35.56$, $-11.28$] mmHg). In studies where there was no background antihypertensive use, the average decrease in SBP was $-13.46$ ($-18.53$, $-8.39$) mmHg and was similar to those in which diuretic was added to previous antihypertensives: $-14.94$ ($-19.04$, $-10.83$) mmHg.

The overall average increase standardised mean PRA difference was $0.556$ ($0.272$, $0.846$) with a similar trend in both previously untreated subjects and those receiving another antihypertensive medication.
Meta-regression: Relation of change in plasma aldosterone to that of serum potassium after diuretic

Random-effects meta-regression was also used to examine whether the change in PA was associated with changes in serum potassium and we found there was no relationship (coefficient $0.09$, $95\%$ CI $0.32$, $0.15$, $P = 0.466$; Figure 4A) with similar findings in studies where the participants were on no background therapy (coefficient $0.14$, $95\%$ CI $0.36$, $0.07$, $P = 0.186$; Figure 4B).

Meta-regression: Relation of change in SBP to change in plasma aldosterone

Random-effects meta-regression was performed to examine whether change in SBP was associated with change in PA. In the overall population, changes in SBP were independent of changes in PA (coefficient $-0.005$, $95\%$ CI $-0.019$, $0.008$, $P = 0.44$; Figure 5A). However, in studies where the participants were not on background treatment with another antihypertensive, there was a significant relationship between the change in SBP and change in PA (coefficient $-0.02$, $95\%$ CI $-0.034$, $-0.01$, $P < 0.001$; Figure 5B).

Publication bias

The funnel plot of standard error vs effect size was asymmetric and suggestive of potential publication bias. Presence of publication bias was also suggested by Egger’s linear regression ($P = 0.001$). After adjustment of effect size for potential publication bias using the “trim and fill” correction, 14 potentially missing studies on the left side of the funnel plot were imputed, leading to a corrected overall effect size that was slightly but not significantly less than the initial estimate ($0.21$ $95\%$ CI $0.17$-$0.26$; Figure 6).
DISCUSSION

As far as we are aware, this is the first study to systematically review the effect of diuretic therapy on PA and the relationship of change in PA with that of serum potassium and BP in hypertensive individuals. The abstract of this manuscript was submitted and presented at the British and Irish Hypertension Society Annual Scientific Meeting. Diuretics have been used in treatment of hypertension for more than 50 years, both as monotherapy and in combination with other anti-hypertensive agents. They are safe, effective, well tolerated and considered as first line pharmacological agents in specific populations. However, the short- and long-term mechanisms of action of the various classes of diuretics has been debated. Chronic diuretic treatment leads to an increase in PRA suggesting activation of the RAAS. Whether the raised PRA is accompanied by an increase in PA and if this relates to specific classes of diuretics and/or concomitant change of serum potassium is unknown.

The main finding of the present meta-analysis is that diuretics lead to an increase in PA that does not differ significantly between classes of diuretic, but which is significantly associated with change in SBP in previously untreated subjects. In the studies where PRA was also measured before and after treatment, a raise in PRA occurred (a finding in line with a previously published systematic review), demonstrating activation of the RAAS, which is likely to be the driver of the increased PA.

Whether activation of the RAAS could be harmful has been debated. The RAAS is a complex system in which angiotensin II acts through two main receptor subtypes, the AT1 and AT2 receptors. All classic physiological effects of angiotensin II, such as vasoconstriction, aldosterone production and water retention, are largely mediated by the AT1 receptor which promotes hypertension, endothelial

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dysfunction, vascular remodelling and end organ damage. On the other hand, the AT2 receptor elicits antithrombotic, anti-inflammatory and natriuretic effects. Thus, the activation of the RAAS could have complex actions according to the balance of the activation between the AT1 and AT2 receptors which counteract each other in their biological actions on the cardiovascular system. However, the increase in PA is thought to have a number of adverse actions, including renal inflammation, fibrosis and cardiovascular remodelling.

Whilst there is evidence that PRA is helpful in selecting patients who will benefit from diuretic therapy, the potential use of change in PRA in guiding dose-titration and selecting class of diuretic remains speculative and was not confirmed by a recently published systematic review. PA is another potential biomarker that could be used to guide treatment. In our analysis the change in SBP related to that of PA. Failure of PA to rise after initiation of a diuretic could therefore be used to assess adherence to diuretic therapy and to guide dose adjustment, although this is speculative and would require testing in prospective studies. It could be also speculated that the use of a concomitant medication might play a role in limiting the rise in PA, which in turn could have a beneficial effect per se since that aldosterone may cause cardiac remodelling without affecting arterial pressure.

Apart from the RAAS, the other major factor regulating aldosterone secretion is potassium. In humans and in experimental animals, alterations in potassium balance as well as acute increments in serum potassium can stimulate aldosterone production. For example, in

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**FIGURE 4** Meta-regression plot of the association between mean changes in PA with diuretic therapy and the change in serum potassium (mEq/L) in (A) overall and (B) previously untreated with another antihypertensive. Std diff, standardised difference

![Meta-regression plot](image-url)

1973
**FIGURE 5** Meta-regression plot of the association between mean changes in PA with diuretic therapy and the change in SBP in (A) overall and (B) previously untreated with another antihypertensive. SBP, systolic blood pressure; Std diff, standardised difference

**FIGURE 6** Funnel plot displaying publication bias in the studies reporting the impact of diuretic therapy on PA change. Open diamond represents observed effect size; closed diamond represents imputed effect size. Std diff, standardised difference
normal subjects, infusion of 10 mEq of potassium produces a 25% increase in plasma aldosterone. Changes in dietary potassium intake for as little as 24 hours can also substantially modify the secretion of aldosterone from the adrenal glands induced by acute potassium administration: high dietary potassium intake enhances aldosterone secretion, while low potassium intake reduces it. Our results suggest that variation of serum concentration of potassium per se has a limited effect in regulating PA. However, there are suggestions that this mechanism could be relevant in specific populations.

Finally, the subanalysis investigating MRA showed similar effects of these agents on PA compared to other diuretic classes. It has been reported that similarly to other RAAS inhibitors, after an initial suppression/blockade of aldosterone, the PA level often returns to normal or even rises above pre-treatment levels.

This review is subject to several limitations. We were unable to stratify results by ethnicity (and difference in RAAS activity between ethnic groups have been described) because the majority of studies were performed in Caucasians and in many studies ethnicity was not reported. Studies in specific ethnic groups will be required to determine if effects of diuretics on PA differ according to ethnicity. The use of background therapy in some studies and a variable dose in others prevent a useful estimate of the effect size relating to a standard dose of diuretic. The duration of studies was relatively short and very few studies were performed with loop diuretics (which are not commonly used in hypertension). The MRA/potassium sparing group was mostly composed of spironolactone, which in many trials was used at high dose unrepresentative of its current use in primary hypertension. Finally, the present study is limited by the lack of availability of some full-text articles.

In conclusion, this systematic review and meta-analysis demonstrates that diuretic therapy in hypertension leads to an increase in PA which does not differ between classes of diuretics. The use of drugs that might antagonise the effects of this rise in PA or the combination of other diuretics with RAAS inhibitors is a rational means to prevent the adverse effects of this rise in PA, but whether such a treatment strategy leads to BP-independent effects remains to be tested.

### 4.1  
**Nomenclature of targets and ligands**

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

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### COMPETING INTERESTS

The authors have no conflict of interest to declare.

### CONTRIBUTORS

All authors developed the study concept and designed the research. R.J.M. conducted the electronic searches, study selection and extraction. R.J.M. and L.F. performed data analysis, and B.F. helped to interpret the results. R.J.M., L.F. and P.J.C. wrote the majority of the manuscript. All authors read and approved the final version of the manuscript.

### DISCLOSURES

None.

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