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Title page

Title

Comparative effectiveness of 4th line anti-hypertensive agents in resistant hypertension; A systematic review and meta-analysis

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Three Appendices (two tables and one figure)

Abstract

Aim

We assessed the effectiveness of 4th line mineralocorticoid receptor antagonists in comparison to other 4th line anti-hypertensive agents in resistant hypertension.

Methods and Results

We systematically searched Medline, EMBASE and the Cochrane library from database inception until January 2016. We included randomised and non-randomised studies that compared mineralocorticoid receptor antagonists to other 4th line anti-hypertensive agents in patients with resistant hypertension. The outcome was change in systolic blood pressure, measured in the office, at home or by ambulatory blood pressure monitoring. Secondary outcomes were changes in serum potassium and occurrence of hyperkalaemia. We used random effects models and assessed statistical heterogeneity using the I^2 test and corresponding 95% confidence intervals.

From 2,506 records, 5 studies met our inclusion criteria with 755 included patients. Two studies were randomised and three were non-randomised. Comparative fourth line agents included bisoprolol, doxazosin, furosemide and additional blockade of the renin angiotensin-aldosterone system. Using data from randomised studies, mineralocorticoid receptor antagonists reduced blood pressure by 7.4mmHg (95% CI 3.2 – 11.6) more than the active comparator. When limited to non-randomised studies, mineralocorticoid receptor antagonists reduced blood pressure by 11.9mmHg (95% CI 9.3 – 14.4) more than the active comparator.

Conclusion

On the basis of this meta-analysis, mineralocorticoid receptor antagonists reduce blood pressure more effectively than other 4th line agents in resistant hypertension. Effectiveness stratified by ethnicity and comorbidities, in addition to information on clinical outcomes such as myocardial infarction and stroke now needs to be determined.

Keywords

Resistant hypertension, blood pressure, mineralocorticoid receptor antagonists, spironolactone, comparative effectiveness research, meta-analysis.

1 Introduction

2
3 Hypertension is a leading cause of mortality worldwide. It occurs in 1 out of 4 people
4 and is responsible for 9.4 million deaths annually.^{1,2} Of those affected, approximately 14%
5 are said to have resistant hypertension (RH)³, defined as blood pressure (BP) that remains
6 $\geq 140/90$ mmHg despite being treated with maximum doses, or best tolerated doses, of three or
7 more antihypertensive agents, one of which should be a diuretic.⁴ The prevalence of RH is
8 equally distributed between men and women, but is more common in older people (mean age
9 60yrs).³ Those with diabetes and chronic kidney disease (CKD), along with those who are
10 obese, are over-represented in the RH population.⁵ Patients with RH generally have a poorer
11 prognosis than those whose hypertension is controlled, with a 50% increased risk of a
12 cardiovascular event.⁶

13 The pathophysiology of RH remains poorly understood. Once adherence and white
14 coat hypertension have been ruled out, over activation of the renin-angiotension-aldosterone
15 system (RAAS), over activation of the sympathetic nervous system, sodium retention leading
16 to volume expansion and/or vascular stiffening have all been suggested as potential
17 pathological mechanisms.⁷⁻¹⁰ Given the mixed pathologies and a historical dearth of evidence
18 for the treatment of RH¹¹, current clinical guidance from international sources is slightly
19 discordant. For example, NICE guidelines in the UK suggest the use of either spironolactone
20 (a mineralocorticoid receptor antagonist (MRA) with potassium sparing diuretic activity), or
21 increasing the dose of the thiazide diuretic in the case of high serum potassium as potential
22 4th line options on top of an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin
23 receptor blocker (ARB), a calcium channel blocker, and a diuretic.⁴ The European Society of
24 Hypertension/European Society of Cardiology guidelines refer to the use of fourth-line MRA,
25 amiloride or an alpha-blocker.¹² In the USA, both the American Heart Association and the
26 Eighth Joint National Committee guidance specify adding a beta-blocker or a MRA as fourth-

27 line agents and/or seeking specialist advice.^{13, 14} Despite these disparities, the general
28 message from all is to enhance diuretic treatment.^{4, 12-14}

29 Two recent systematic reviews have pointed to the effectiveness of MRAs versus
30 placebo in lowering BP in those with RH.^{15, 16} While this is important evidence, it would now
31 be useful to establish how MRAs compare to other potential 4th line agents.

32 Hence, we assessed the effectiveness, in terms of systolic BP reductions, of MRAs in
33 comparison to alternative 4th line anti-hypertensive agents in patients with RH.

34

35 **Methods**

36

37 *Data sources and searches*

38 We searched Medline, Embase and the Cochrane Library from inception up to January 2016
39 with no language restriction. The search terms used in Medline were ‘resistant hypertension’
40 AND "Hypertension/drug therapy"[Mesh] AND "Antihypertensive Agents"
41 [Pharmacological Action]; we constructed analogous searches in the other databases. We
42 searched Clinicaltrials.gov for ongoing or completed trials of anti-hypertensive agents in RH.
43 We also searched the reference lists of included articles and recent clinical guidelines. Where
44 relevant abstracts were found without corresponding full papers, we contacted study authors
45 for full text papers. If a full text paper did not exist at that time, the record was excluded. We
46 also contacted study authors to clarify any questions on their reported results.

47 *Study selection*

48 *Definition of RH*

49 We included studies that defined RH as systolic BP ≥ 140 mmHg despite being on ≥ 3 anti-
50 hypertensive agents.

51 *Study types*

52 Full texts of both randomised studies and non-randomised studies were eligible for inclusion.
53 Letters, editorials and opinion pieces were excluded.

54 *Intervention and comparator*

55 The intervention was the addition of an MRA. The comparator was the addition of an
56 alternative fourth-line anti-hypertensive agent. There was no restriction on agent, dose,
57 duration of treatment or length of follow up. Studies that examined drugs that are not
58 available on the market or not currently being tested in phase 2 or phase 3 trials were
59 excluded.

60 *Outcome*

61 The outcome was change in systolic BP in the intervention group relative to the comparator
62 group. We used systolic BP, as opposed to both systolic and diastolic BP for two reasons.
63 First, because systolic hypertension is much more common in populations aged >50yrs than
64 diastolic BP.¹⁷ Second, because systolic hypertension contributes more to the global
65 cardiovascular disease burden than diastolic hypertension.¹⁷ There were no restrictions on
66 how BP was measured; office, home or ambulatory blood pressure monitoring (ABPM)
67 measurements were all included. In studies where more than one type of measurement was
68 reported, ABPM was the preferred outcome for inclusion in the meta-analysis. Secondary
69 outcomes included mean changes in serum potassium and the number of cases of
70 hyperkalaemia in each treatment group.

71 *Data extraction and quality assessment*

72 SJS carried out the searches. After exclusion of duplicates and irrelevant titles and abstracts,
73 four study authors (SJS, AR, RM and KM) independently assessed full texts for eligibility,
74 and carried out data extraction and quality assessment in duplicate. Any differences of
75 opinion were discussed and a third reviewer was available to arbitrate any issues that
76 remained unresolved. We used a standardised data extraction form to collect information for
77 each study on: the definition of RH used, including whether due consideration was given to
78 white coat hypertension, adherence and secondary causes of hypertension; the type of study
79 design and analysis used; and details on population characteristics for example, number of
80 people included, mean age, proportion of females, mean body mass index (BMI), proportion
81 of diabetic patients and mean estimated Glomerular Filtration Rate (eGFR). We extracted
82 detailed data on baseline systolic BP, systolic BP at the end of follow up and change in
83 systolic BP between the treatment arms for each study along with information on how BP

84 was measured. We collected adverse event data specifically for mean changes in serum
85 potassium and hyperkalaemia.

86 We assessed the quality of included studies using a modified Downs and Black checklist,
87 which can be used for randomised studies and non-randomised studies.¹⁸ This checklist
88 assesses quality across four domains: internal validity (bias and confounding), external
89 validity and general quality of study reporting. Included studies were scored out of a potential
90 21 points across these four domains.

91 *Data synthesis and statistical analysis*

92 We used the difference in mean reductions in systolic BP between treatment arms and the
93 standard error in DerSimonian-Laird random effects models. Statistical heterogeneity was
94 assessed using the I^2 test and corresponding 95% confidence intervals estimated using the
95 formula proposed by Higgins and Thompson.¹⁹ An I^2 threshold of >60% indicated substantial
96 heterogeneity. We analysed randomised and non-randomised studies separately. We did not
97 formally test for the presence of publication bias due to the small number of included
98 studies.²⁰ Rather, we visually inspected the funnel plot. Secondary outcomes were
99 qualitatively assessed.

100 *Sensitivity analyses*

101 Three methods of measuring BP were reported in the included studies; 1) office BP, 2) home
102 BP and 3) ABPM. We conducted sensitivity analyses to assess whether combining different
103 types of BP measurements in a meta-analysis gave substantially different result. We ran all
104 analyses in Revman Version 5.3.²¹ We referred to Preferred Reporting Items for Systematic
105 Reviews and Meta-Analyses (PRISMA) guidelines for reporting (*Supplementary Information*
106 *I*).²²

107 Results

108 From 2506 citations, after exclusion of duplicates and irrelevant titles, 22 full texts were
109 assessed for eligibility. Seventeen of these were excluded (**Figure 1**). Thus, five articles were
110 included in the review.^{8, 23-26}

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125 **Insert Figure 1**

126 **Gap in text maintained above to preserve order of referencing**

127

128 This included 755 patients with a mean age of 62 years and 30% female. Diabetes was highly
129 prevalent at 45.6%, while eGFR was 83.9 ml/min, likely due to exclusion of patients with
130 chronic kidney disease in some studies.^{8, 23, 25, 26} Mean BMI was 30.7 kg/m² (**Table 1**).

131

132 **Insert Table 1**

133

134 Of the included studies, two were randomised controlled trials^{26 23} and three were non-
135 randomised^{24, 25 8} The intervention was spironolactone in all studies. The comparator drugs
136 included doxazosin, bisoprolol, furosemide and additional RAAS blockade (**Table 2**).

137 **Insert Table 2**

138 There was substantial heterogeneity across the included studies in terms of how RH was
139 defined and identified. Four studies referred to adherence to medication regimen before
140 including patients as RH cases, but the reported detail on how this was examined was
141 variable.^{8, 24-26} Bobrie *et al.* referred to adherence measurement during the study by pill count,
142 but the threshold for adherence was not reported.²³ The results of on treatment adherence
143 assessment by urinalysis in the PATHWAY-2 trial is yet to be published.²⁶ One study did not
144 clearly define the BP thresholds used to define RH⁸ and two studies did not define how long a
145 patient should be on 3 or more anti-hypertensive agents before being defined as having RH.^{8,}
146 ²⁵

147 Two studies measured the outcome, systolic BP, both in the office and with ABPM
148 monitoring^{8, 23}, one study each used office and ABPM monitoring respectively^{24, 25} and one
149 study used home monitoring and office measurements.²⁶ Follow up ranged from eight weeks
150 to six months.

151 Non-randomised studies were of much lower quality than randomised studies (**Table 3**).
152 They achieved lower scorings on internal validity due to baseline characteristics being non-
153 comparable, statistical tests that did not account for confounding, not accounting for losses to
154 follow up, not being adequately powered and not tracking adherence to the intervention or
155 comparator drug.

156 **Insert Table 3**

157 **Results of meta-analysis**

158 We included two studies, including a total of 502 patients, in a meta-analysis of randomised
159 studies. Using a random effects model, the overall pooled estimate for reduction of systolic
160 BP by MRAs was 7.4mmHg (95% CI 3.2 – 11.6) more than the active comparator (**Figure**
161 **2a**). Heterogeneity was measured as $I^2 = 76\%$ (95% CI 0 – 95.5). There was one ABPM
162 measurement in this analysis²³ and one home measurement.²⁶

163

164 **Insert Figure 2A and 2B**

165

166 We included three studies, including a total of 253 patients, in a meta-analysis of non-
167 randomised studies. Using a random effects model, the overall reduction in systolic BP was
168 11.9mmHg (95% CI 9.3 – 14.4) more in spironolactone users than the active comparator
169 (**Figure 2b**). Heterogeneity was measured as $I^2 = 0\%$ (95% CI 0 - 40). There were two
170 ABPM measurements^{8, 25} in this analysis and one office measurement.²⁴

171

172 **Sensitivity analyses**173 *Office measurements in non-randomised studies*

174 In the main analysis using randomised and non-randomised studies, ABPM measurements
175 were included where reported. In a sensitivity analysis, we included office BP, where
176 reported, to assess the influence of measurement types on pooled results. For randomised
177 studies, this analysis included two office BP measurements as opposed to one ABPM
178 measurement²³ and one home measurement in main analysis.²⁶ Using a random effects
179 model, the overall effect measure estimated that spironolactone reduced systolic BP by
180 7.3mmHg (95% CI 0.9 – 13.8) more than the active comparator (**Figure 3a**). Heterogeneity
181 was measured as $I^2 = 87\%$ (95% CI 24.8 -97.8). For non-randomised studies, the sensitivity
182 analysis included two office BP measures^{8, 24} and one ABPM measurement.²⁵ Using a

183 random effects model, the overall effect measure estimated that spironolactone reduced
184 systolic BP by -13.4mmHg (95% CI 8.4 – 18.3) more than the active comparator (**Figure**
185 **3b**). Heterogeneity was measured as $I^2 = 66\%$ (95% CI 0 – 94).

186 **Insert Figure 3**

187

188 Changes in serum potassium and hyperkalaemia

189 All five included studies reported changes in serum potassium or cases of hyperkalaemia.^{8, 23-}

190 ²⁶ From **Table 4**, there were 12 cases of hyperkalaemia in 424 patients treated with MRAs, in
191 comparison to 0 events in 471 patients treated with another fourth-line agent. Mean serum
192 potassium values increased to a greater extent in patients treated with MRAs than patients
193 treated with another fourth-line agent (**Table 4**).

194

195 **Insert Table 4**

196

197 Publication bias

198 There was some visual evidence of asymmetry in the funnel plot, suggesting a small study
199 bias (*Supplementary Information 3*).

200 Conclusions

201 This meta-analysis, encompassing five separate studies and 755 patients, found that when
202 MRAs were compared with another fourth-line agent or strategy in the treatment of RH,
203 MRAs achieved larger reductions in systolic BP, in the order of 7 to 12mmHg.

204 Three previous reviews have indicated the effectiveness of MRAs versus placebo, in
205 addition to its' safety.^{15, 16, 44} The reduction in systolic BP achieved by MRAs in previous
206 reviews averaged at approximately 20mmHg. This is roughly double the reduction in BP
207 shown in our review. This difference was not unexpected considering we included studies
208 with an active comparator only, whereas previous reviews included studies where placebo
209 was the comparator group. Whether this magnitude of reduction in systolic BP will translate
210 to a decrease in cardiovascular outcomes in patients with RH remains to be examined. It
211 might be reasonably expected that clinical relevance is likely given recent evidence that, in a
212 general hypertensive population, a 10mmHg reduction in systolic BP was associated with an
213 approximate 20% reduction in risk of cardiovascular and coronary heart disease events, and
214 an approximate 30% reduction in risk of stroke and heart failure.⁴⁵

215 Our sensitivity analysis for randomised studies demonstrated little difference in the
216 magnitude of reductions gained in systolic BP when measured using office measurements
217 *versus* home or ABPM measurements. The randomised nature of these studies likely
218 preserved the relative difference between treatment arms. In contrast, when the majority of
219 non-randomised studies reported office BP rather than the majority reporting ABPM
220 measurements larger reductions in systolic BP were found (-13.8mmHg versus -11.9mmHg).
221 Although the difference in these findings was not significant, the trend towards greater
222 reductions *via* office measurements is in line with current knowledge on the contribution of
223 white coat hypertension in RH, and indeed in hypertension more broadly.^{46, 47} This finding

224 also points to the importance of home BP or ABPM monitoring in detecting BP levels that
225 are ultimately predictive of clinical events and mortality.⁴⁸

226 In all studies, where reported, the average increase in serum potassium was larger in the
227 MRA group compared with other 4th line agents. The magnitude of mean changes appeared
228 to be larger in non-randomised studies than randomised studies. Similar findings were
229 reported in a recent systematic review whereby the increase in serum potassium, found in
230 non-randomised studies, was 0.46mmol/L higher than in placebo treated patients.¹⁶ However,
231 in randomised studies, the mean change between the groups was 0.15mmol/L, and this was
232 non-significant.¹⁶ A second review, encompassing a meta-analysis of mixed randomised and
233 non-randomised studies, showed an increase of 0.33mmol/L (95% CI, 0.27-0.39) in serum
234 potassium in users of MRAs.¹⁵

235 Our review also points to an increased number of hyperkalaemia-related events in patients
236 treated with MRAs in comparison to patients treated with other 4th line agents. The
237 systematic review authored by Dahal et al. reports an event rate of 46/1000 for hyperkalaemia
238 in patients treated with MRAs in comparison to placebo, but this was solely in non-
239 randomised studies and the same finding of increased risk was not found in randomised
240 studies.¹⁶ The difference in biochemical parameters reported by randomised and non-
241 randomised studies may reflect differences in how patients are monitored in different study
242 settings. For example, in clinical trials frequent follow up visits allow opportunity to identify
243 changes in serum potassium before advancement to hyperkalaemia. In contrast, non-
244 randomised studies are often conducted in routine care and reflect the true
245 frequency/infrequency of laboratory testing, and thus the real world safety implications of
246 treatments for patients.⁴⁹ Discordant findings between randomised and non-randomised
247 studies aside, the risk of hyperkalaemia related events, especially in people using both and

248 ACEI/ARB and spironolactone, remains a worry and frequent lab monitoring is
249 recommended.⁵⁰

250 Our review provides evidence that on average, MRAs are more efficient in lowering
251 systolic BP than other potential fourth-line agents such as bisoprolol, doxazosin and
252 additional RAAS blockade. This may be explained by the main pathophysiology associated
253 with RH; volume expansion secondary to salt sensitivity/retention.¹⁰

254 MRAs' antagonism of aldosterone at the distal tubule, resulting in the removal of sodium
255 in exchange for potassium thus increasing diuresis, reduces the problem of volume
256 expansion.⁵¹ While the use of an ACEI or an ARB should block the production of
257 aldosterone at an earlier stage in the RAAS, a phenomenon referred to as "aldosterone
258 synthesis escape" requires direct blockade of aldosterone at the mineralocorticoid receptor to
259 ensure lowering of blood pressure, thus providing a functional and productive role for
260 spironolactone on top of other anti-hypertensive agents.⁵²

261 While other pathophysiologies can be implicated in RH, such as over-activation of the
262 sympathetic nervous system¹⁰, the success of MRAs in RH may be due to volume expansion
263 being the most prevalent mechanism underpinning the disease. A second reason for the
264 benefit of MRAs above other 4th line agents is that, in addition to its' action at the distal
265 tubule, there is evidence to suggest that MRAs also work on the vasculature reducing BP by
266 other mechanisms. For example, spironolactone has been found to increase vascular
267 compliance in rats⁵², inhibit vasoconstriction in the arterioles⁵³ and eplerenone has been
268 found to improve endothelial function and inhibit Rho-associated kinases, which are involved
269 in the contracture of vascular smooth muscle cells.⁵⁴

270 We observed several important sources of heterogeneity between the studies included in
271 the review, for example; study authors rarely discussed how long their included populations

272 were on ≥ 3 anti-hypertensive agents before being classified as RH. Not all studies sought to
273 exclude white coat hypertension, nor did all studies examine insufficient adherence to anti-
274 hypertensive medication regimens during the study. This points to a requirement for a more
275 stringent application of a standardised definition of resistant hypertension to avoid mixed
276 samples of patients, leading to results that do not apply to the actual RH population. We
277 noted some evidence of publication bias in the funnel plots. This was likely associated with
278 poor methodological quality in the included non-randomised studies.⁵⁵

279 Our review has multiple strengths. First, we used a comprehensive search strategy
280 yielding more than 2,500 records that we screened for inclusion. Second, we carried out study
281 selection and data abstraction in duplicate to enhance the reliability of our findings. Third,
282 this review provides a quantitative estimate of the effectiveness of MRA in comparison to
283 other antihypertensive agents that could be used as fourth-line agents in RH, improving on
284 other reviews that examined placebo as the comparison group.^{15 16, 44} Information on
285 comparative effectiveness is constructive in that MRAs will not suit every patient with RH,
286 for example in patients where a drug-drug interaction is expected or adverse events such as
287 hyperkalaemia could reasonably occur.⁵⁶ In such cases, information on the effectiveness of
288 alternative pharmacologic options is required.

289 Our review is limited in that it we did not assess individual level patient data. This would
290 have allowed comprehensive subgroup analyses according to sex, age, diabetes status and
291 renal function. The number of included studies in each meta-analysis was low. While more
292 studies would have been preferable, it was still appropriate to carry out a meta-analysis. This
293 was for reasons of transparency in the processes employed to reach a summary conclusion,
294 and also because combining the results of studies added information beyond what was held in
295 each individual study.⁵⁷ A small number of included studies meant it was also challenging to
296 accurately assess between-study heterogeneity. We attempted to ameliorate this limitation by

297 presenting 95% confidence intervals around the point estimate for I^2 value.^{58,19} A further
298 limitation is that the included studies were of varying quality. Non-randomised studies, in
299 particular, often include an amount of confounding by indication, and the studies included in
300 this review mostly used methodology not designed to address this, for example simple
301 statistical analyses such as t-tests or Wilcoxon tests. Nonetheless, a meta-analysis of these
302 studies was useful for the reasons of transparency and combining information as mentioned
303 above.⁵⁷ In addition, for a topic area where not many trials exist, it seems efficient to use all
304 available evidence, with due appreciation for its' limitations. The non-randomised studies we
305 included found a similar overall effect to the randomised studies in this review suggesting
306 confounding may not have been strong in this instance. This is likely to arise if the choice
307 between different drugs is not driven by strong evidence and could indicate a perception of
308 equipoise in many cases. It therefore appears that observational data may be of further use for
309 investigating the comparative effects of different drug choices for RH. However, our nuanced
310 summary of deficits noted in the literature should be addressed in future studies.

311 While quantitative estimates of the benefits of MRAs in reducing BP in RH are now
312 available, it would be helpful to stratify these changes in BP by patient characteristics such as
313 ethnicity, and co-morbidities such as diabetes and renal function.^{15, 59} Future meta-analyses
314 might endeavour to stratify by different classes of comparator agents, e.g., beta-blockers,
315 diuretics and alpha-blockers to enable a more nuanced understanding of the comparative
316 effectiveness of MRA. It is now important that an assessment of effects on clinical outcomes
317 such as stroke and myocardial infarction is conducted. A rough calculation using information
318 on outcome parameters from the SPRINT trial indicates that an RCT of approximately 15,000
319 patients with 2 years follow up would be required to detect a 20% difference in
320 cardiovascular outcomes for RH patients on spironolactone versus other 4th line agents.⁶⁰ The
321 practical challenges of recruiting this number could be sidestepped by conducting a well-

322 designed and appropriately powered observational study. From the data presented in this
323 study, it appears that observational studies can detect similar effect sizes to randomised trials
324 in studies of RH, and thus, if designed appropriately offer a useful and practical way forward.

325

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333

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336

337 [Conflicts of Interest](#)

338 There are no conflicts of interest to report.

339

340 [Authorship](#)

341 SJS contributed to the conception or design of the work. SJS, ID, LT, RM, KM, AR and LS
342 contributed to the acquisition, analysis, or interpretation of data for the work. SJS drafted the
343 manuscript. ID, LT, RM, KM, AR and LS critically revised the manuscript. All gave final
344 approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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[update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia](#) 2016.

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Figures

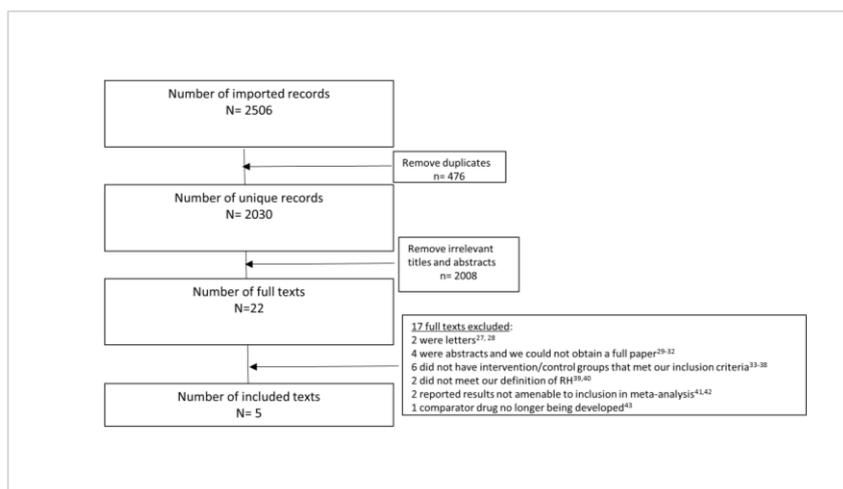


Figure 1: Flowchart of results

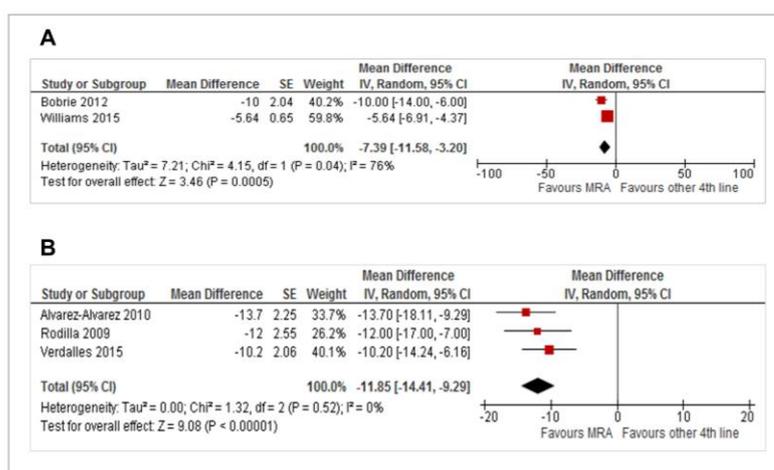


Figure 2A (upper panel): Meta-analysis of changes in systolic BP for randomised studies.

Figure 2B (lower panel): Meta-analysis of changes in systolic BP for non-randomised studies

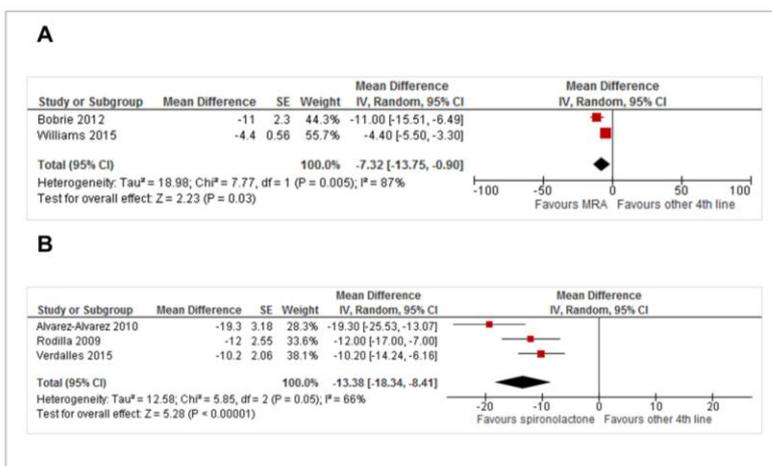


Figure 3: Meta-analysis of changes in systolic BP for non-randomised studies, using office BP measurements where reported

Tables

Table 1: Description of participants in included studies

	n	Mean Age	% Female	% Diabetes	Mean eGFR	% Smoking	Mean BMI	Mean no. of drugs	Baseline systolic BP	Outcome measurement 1	Outcome measurement 2
Randomised studies											
Bobrie 2012 ²³	167	55.87	24.51	19.96	83.44 [^]	51.91	28.36	3.00	146.00	24 hr ABPM	Office BP
Williams 2015 ²⁶	335	61.40	31.00	41.00	91.00 [#]	7.80	NR	NR	147.60	Home BP	Office BP
Non-randomised studies											
Alvarez-Alvarez 2010 ⁸	42	66.85	50	NR	83.08 [~]	10.3	31.79	4.10	141.00	24 hr ABPM	Office BP
Rodilla 2009 ²⁴	181	65.49	29.00	76.09	76.09 [^]	9.41	32.45	NR	165.43	Office BP	Office BP
Verdalles 2015 ²⁵	30	66.30	30.00	56.70	55.85 [*]	NR	31.35	3.80	162.80	24 hr ABPM	NR
Total	755	61.65	30.1	45.64	83.92	18.51	30.68	3.29	151.76	~	~

eGFR – estimated Glomerular Filtration Rate, ABPM – Ambulatory Blood Pressure Monitoring, BMI – Body Mass Index, BP –Blood Pressure

[^]GFR calculated with MDRD equation, [#]GFR calculated with unknown method, ^{*}GFR calculated with CKD EPI equation [~]Creatinine Clearance given

NR- not reported

Table 2: Description of included studies

Study	Study Design	Location	n	Intervention	Comparator	Assessment of	Assessment of	Assessment	Follow up
						white coat hypertension	adherence prior to inclusion	of adherence during trial	
Randomised studies									
Bobrie 2012 ²³	RCT	France	165	Nephron blockade: spironolactone 25mg, followed by furosemide 20mg/day, titrated to 40mg/day, followed by addition of amiloride.	Block of RAS: ramipril 5mg/day, titrated to ramipril 10mg/day, followed by bisoprolol 5mg/day titrated to bisoprolol 10mg/day	Yes	No details	Yes - pill counts	12 weeks
Williams 2015 ²⁶	RCT	UK	335	Spironolactone (25mg-50mg)	Bisoprolol (5 – 10mg) or doxazosin (4-8mg)	Yes	Yes - pill counts and directly observed therapy	Urinalysis	12 weeks
Non-randomised studies									
Alvarez-Alvarez 2010 ⁸	Prospective crossover	Spain	39	Spironolactone 25mg increased to 50mg	Addition of ACEI/ARB	Yes	No details	No details	12 weeks
Rodilla 2009 ²⁴	Cohort study	Spain	181	Spironolactone 14mg (average)	Doxazosin 4mg (average)	Yes	Yes, but no details how	No details	3 months for spironolactone and 6 months for doxazosin
Verdalles 2015 ²⁵	Cohort study	Spain	30	Spironolactone 25mg	Furosemide 40mg	Yes	Yes, but no details how	No details	6 months

RCT – randomised controlled study, RAS – renin-angiotensin system, RH – resistant hypertension, ABPM- ambulatory blood pressure monitoring. ACE – angiotensin converting enzyme, ACEI/ARB - angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Table 3: Description of quality of included studies

	Internal Validity - Bias	Internal Validity - Confounding	External Validity	Adverse event reporting
Randomised studies				
Bobrie 2012 ²³	6.5/8	6/10	2/2	1/1
Williams 2015 ²⁶	8/8	8/10	1/2	1/1
Non-randomised studies				
Alvarez-Alvarez 2010 ⁸	5/8	4/10	0/2	1/1
Rodilla 2009 ²⁴	3/8	3/10	0/2	1/1
Verdalles 2015 ²⁵	5/8	4/10	0/2	1/1

Notes: A detailed scoring sheet along with description of quality assessment form is included in **Supplementary Information 2**.

Table 4: Number of cases of hyperkalaemia and mean changes in serum potassium in patients treated with spironolactone and other 4th line agents

	Spironolactone		Other 4 th line agents	
	Cases of hyperkalaemia	Mean change in serum potassium (SE)	Cases of hyperkalaemia	Mean change in serum potassium (SE)
<i>Bobrie 2012</i> ²³	3/85	0.30 (0.80)	0/82	0.00 (0.13)
<i>Williams 2015</i> ²⁶	6/285	0.42*	0/335	0.15 [^] */0.08 [#] *
<i>Subtotal events for randomised studies</i>	9/370	~	0/417	~
<i>Alvarez-Alvarez 2010</i> ⁸	1/39	0.53 (0.09)	0/39	0.09 (0.08)
<i>Rodilla 2009</i> ²⁴	NR	0.41 (0.05)	NR	0.11 (0.08)
<i>Verdalles 2015</i> ²⁵	2/15	NR	0/15	NR
<i>Subtotal events for non-randomised studies</i>	3/54	~	0/54	~
<i>Total events</i>	12/424	~	0/471	~

Notes: NR = not reported. Verdalles reported two cases of “mild” hyperkalaemia defined as serum potassium 5.0-5.5mmol/L. *

*Variance for serum potassium changes not reported. [^]Bisoprolol as comparator. [#]Doxazosin as comparator.

Supplementary Information 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3+4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No, attempted to register at PROSPERO however, our work had begun so our protocol could not be included in PROSPERO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5+6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5+6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5+6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5+6

MRAs versus other 4th line agents in RH

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6+7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 and page 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 and page 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2 and page 10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2 and 3.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2, and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 3 and page 14.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 3 and Table 3, also pages 13 and 14.
DISCUSSION			

MRAs versus other 4th line agents in RH

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pg 18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pg 18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Pg 19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplementary Information 2

Quality Assessment

Table S2: A detailed scoring across quality indicators as assessed using a modified Downs and Black quality assessment tool

Question #	Internal Validity - Bias								Internal Validity - Confounding										External Validity		Misc - study quality	Total	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	21	
Alvarez-Alvarez	0	0	1	1	1	1	0	1	1	1	1	0	0	0	1	0	0	0	0	0	0	1	10
Bobrie	0	1	1	1	1	1	0.5	1	1	0	1	1	1	1	0	1	0	0	1	1	1	1	15.5
Rodilla	0	0	1	0	0	1	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	6
Verdalles	0	0	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	0	0	0	0	1	10
Williams	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	1	1	18

Supplementary Information 3

Publication bias

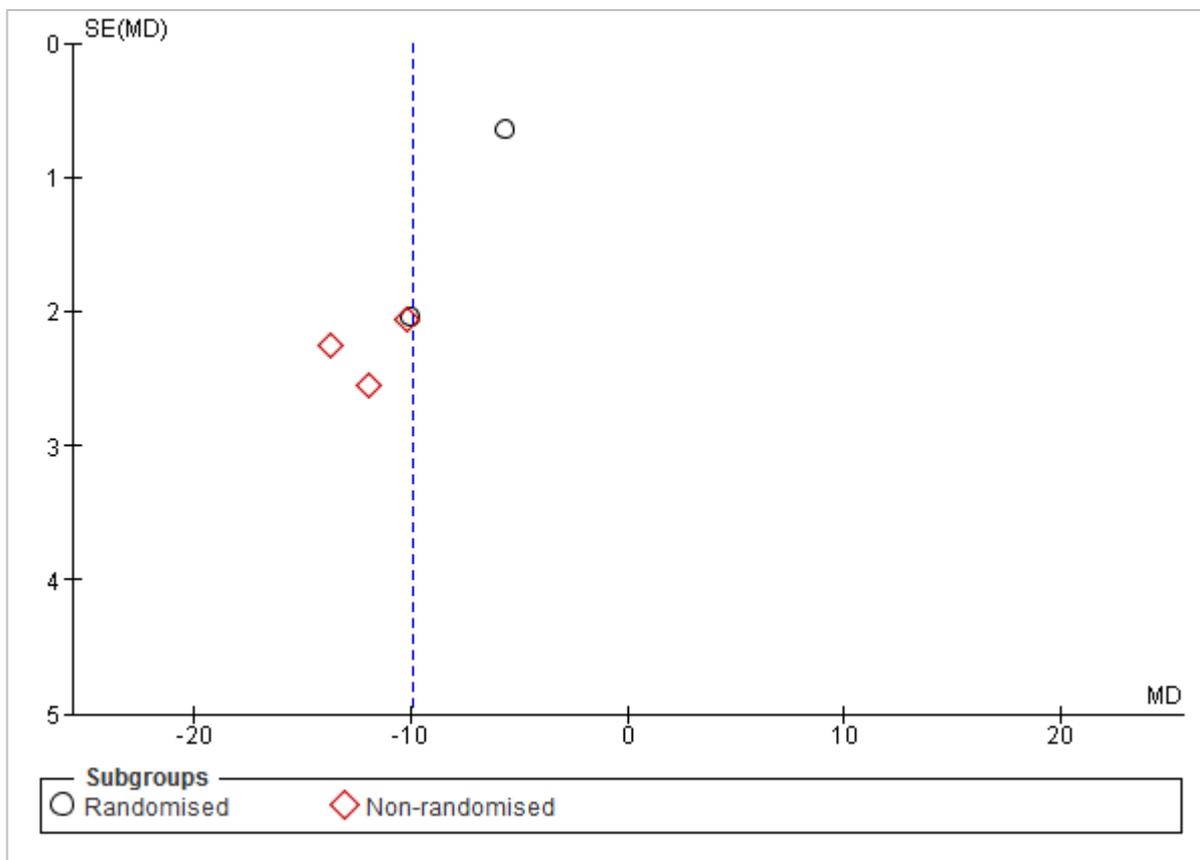


Figure S1: A funnel plot demonstrating the direction and size of effects in Randomised Studies and non-Randomised Studies.

- Largest study (Williams, n=335) is at the top of the graph, with a smaller effect size than the mean estimated effect.
- Note, all the NRS lie to the left of the mean effect estimate. This indicates that the effect of MRA is more beneficial in NRS than in RS.
- The likelihood of publication bias is small for two reasons.
 - First, the most commonly used MRA, spironolactone, is an off-patent medicine and investigators would have little financial incentive to not publish negative results. Second, the small study effects are likely due to poor methodological quality. Asymmetry in the graph is caused by the distribution of NRS. The methodological quality of all the NRS was quite low, as recorded in quality assessment forms.