Blood Pressure-Lowering Efficacy of Spironolactone in Patients with Resistant Hypertension: A Meta-analysis

Mithi Kalayaan Zamora, M.D.*; Jeremiah Vallente, M.D.*; Raymond Oliva, M.D.**

Abstract

Introduction: Resistant hypertension (RH) is defined as a blood pressure (BP) reading that remains above goal despite concurrent use of three optimally dosed anti-hypertensives of different classes, including a diuretic. Spironolactone, a mineralocorticoid receptor antagonist, has shown significant benefit in reduction of BP in recent trials and is used empirically as an add-on therapy for RH. The researchers' objective is to evaluate the BP-lowering efficacy of spironolactone in patients with resistant hypertension.

Methods: A meta-analysis was performed on randomized controlled trials (RCTs) comparing office or home BP reduction using spironolactone with placebo or an alternative drug regimen on top of standard-triple drug therapy among patients with RH. The study was conducted in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results: Five RCTs were included comprising a total of 662 patients. Three of these studies were found to have low risk of bias while two had unclear risk of bias. Compared to placebo, the addition of spironolactone significantly decreased office systolic BP (weighted mean difference (WMD)= -16.33, 95% confidence interval (CI)=-24.68 to -7.97, *P*=0.0001) and office diastolic BP (WMD=-6.12, 95% CI= -9.35 to -2.89, *P*=0.0002). Compared to an alternative drug regimen, additional spironolactone resulted in a significantly greater reduction in office systolic BP (WMD=-4.58mmHg, 95% CI=-7.19, -1.97, *P*= 0.0006) and home systolic BP (WMD= -4.33, 95% CI= 5.55, -3.12, *P*< 0.00001); while the addition of spironolactone had no significant difference compared to an alternative drug regimen in reducing office diastolic BP (WMD=-3.35, 95% CI=-12.08 to +5.38, *P*=0.45) and home diastolic BP (WMD= 0.00, 95 % CI=-0.73 to 0.73, *P*=1.0).

Conclusion: Spironolactone, when added to triple-drug anti-hypertensive therapy, showed significant reduction of systolic office and home BP. It should be considered as the add-on medication of choice for BP reduction in patients with RH.

Keywords: resistant hypertension, anti-hypertensive, spironolactone, blood pressure

Introduction

Hypertension is the most common chronic disease in both developed and developing countries and is a major public health concern affecting almost one-third of adults.[1] There are approximately 972 million hypertensive people worldwide with an estimated 60% increase in the number of adults with hypertension globally by 2025.[1] Hypertension and levels of blood pressure has shown to have a linear relationship with stroke and cardiovascular disease with cardiovascular mortality risk doubling for every 20 mmHg increase in systolic blood pressure.[1,2]

Resistant hypertension (RH) is a growing problem among primary care physicians and specialists with increasing incidence and prevalence as the population becomes elderly and heavier.[3] Drug-resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes, of which one is a diuretic and all three agents are used in optimal doses.[3] At present, in patients with truly resistant hypertension,[3] recommendations for pharmacological management has been empiric with thiazide diuretics considered as one of the initial agents.[3,4] The other two agents usually included are calcium channel blockers and angiotensin-converting enzyme inhibitors for cardiovascular protection.[4]

Spironolactone is a mineralocorticoid receptor antagonist with proven benefit in reducing morbidity and mortality among patients with heart failure[5] and in lowering blood pressure among hypertensive patients

** Resident-in-Training, Department of Medicine, Philippine General Hospital, Manila Philippines*
*** Consultant, Section of Hypertension, Department of Medicine, Philippine General Hospital, Manila Philippines*

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Corresponding author: Mithi Kalayaan Zamora, MD, Philippine General Hospital, Manila, Philippines
Email:mithikalayaanzamora@gmail.com

with or without hyperaldosteronism.[6-14] A number of small uncontrolled trials have also demonstrated the benefit of adding spironolactone as a fourth line therapy in patients with difficult to control blood preassure (BP).[15-18]

A recent meta-analysis[19] has shown significant systolic and diastolic BP reduction with spironolactone as an add-on therapy to triple-drug anti-hypertensive regimen on both ambulatory and office BP. However, home BP reduction was excluded as an endpoint in the study. A recent large scale double-blind, placebo controlled, crossover randomized trial[22] demonstrated spironolactone as the most effective add-on to standard triple-drug therapy and measured home BP reduction as one of its outcome. Hence, to provide a more definite evidence of the BP lowering efficacy of spironolactone, we made a meta-analysis of all available RCTs to evaluate the BP-lowering efficacy of additional spironolactone versus placebo or another anti-hypertensive medication on both home and office blood pressures in patients with resistant hypertension.

Methods

The study was conducted in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All studies were identified and aggregated from a pool of available data and did not necessitate ethics approval. All references and authors were acknowledged and identified properly.

Search strategy and study selection

The COCHRANE Library and PubMed were searched for available published articles. Unpublished and ongoing studies were sought by searching ClinicalTrials.gov and the website of pharmaceutical companies. The following search terms were used: spironolactone, mineralocorticoid receptor antagonist, resistant hypertension, refractory hypertension. The reference lists of retrieved trials were scanned for potentially relevant articles.

Eligibility criteria

Studies were eligible for inclusion if they met the following criteria:

1. randomized controlled trial as study design;
2. population of patients with age of 18 years or older; with resistant hypertension defined as SBP ≥140 mmHg or DBP ≥90 mmHg despite treatment with three anti-hypertensive medications, including a diuretic;
3. studied spironolactone as add-on medication to a triple-drug therapy, in comparison to placebo or an alternative drug regimen; and
4. with relevant outcome of change or reduction in office or home blood pressure.

Data extraction and quality assessment

After duplicate studies were removed and articles were screened based on the inclusion criteria, two authors reviewed the eligible full-text articles independently. Eligibility of each study was determined by consensus and divergences were resolved via discussion.

The cochrane data extraction template was used for data extraction of the following: characteristics of the studies (first author, year of publication, study design, definition of RH), patient characteristics, number of patients enrolled/ sample size, inclusion and exclusion criteria for patients of each study, interventions (spironolactone versus placebo or an alternative drug regimen) including the dose and duration of intervention, and outcomes (mean changes from baseline of blood pressure measurements). Results from multiple arm studies comparing different types of alternative anti-hypertensive medications versus spironolactone were pooled under a single intervention (alternative drug regimen).

Results

Study selection

Search of the electronic database and records from other sources yielded a total of 266 trials. Upon screening, nine RCTs were found to be potentially eligible. However, two trials were still ongoing and one was not retrievable. A total of six full-text articles were reviewed. Of these, five studies [20-24] were ultimately included for the meta-analysis.

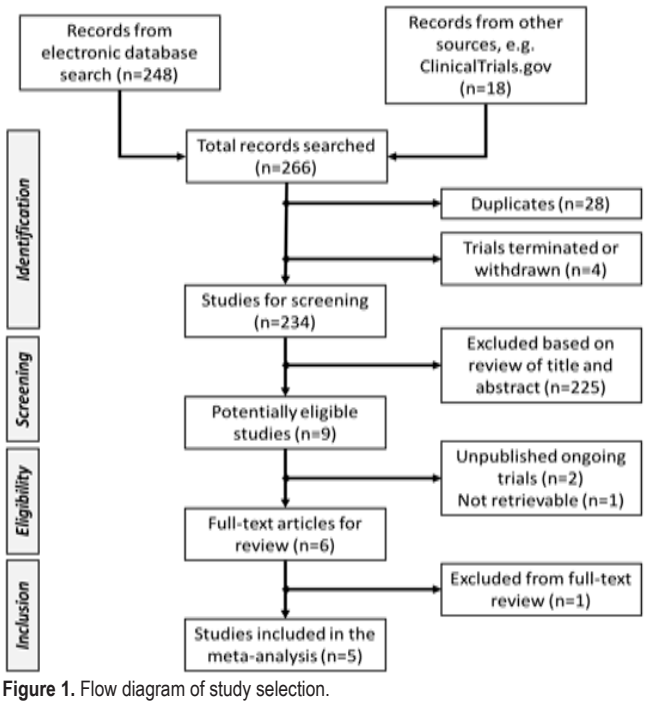

Figure 1. Flow diagram of study selection.

Table I. Assessment of risk of bias

Study	Sequence generation	Allocation concealment	Blinding			Incomplete outcome	Selective outcome reporting	Over-all risk of bias
			Participant	Personnel	Outcome assessor			
Abolghasmi 2011[20]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Oxlund 2013[21]	Low	Low	Low	Low	Unclear	Low	Low	Low
Vaclavik 2014 (ASPIRANT-EXT)[22]	Low	Low	Low	Low	Low	Low	Low	Low
Williams 2015 (PATHWAY-2)[23]	Low	Low	Low	Low	Low	Low	Low	Low
Djoumessi 2016[24]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

Table II. Characteristics of included studies

Study	Sample size	Mean age (SD)	Diabetic patients (%)	Interventions	Efficacy outcomes	Duration, weeks	Definition of resistant hypertension
Abolghasmi 2011[20]	41	49.5 (11.5)	-	Spironolactone Placebo	Office BP	12	Uncontrolled hypertension at ≥2 clinic visits, in spite of the use of ≥3 antihypertensive medications at pharmacologically effective doses, including a diuretic, an ACE-I and CCB
Oxlund 2013[21]	119	63.4 (7.0)	119 (100%)	Spironolactone Placebo	Daytime ABP Nighttime ABP 24-H ABP Office BP	16	Mean ambulatory SBP ≥130 and/or DBP at ≥80mmHg during daytime in spite of treatment with ≥3 antihypertensive drugs including a diuretic and an ACE-I or ARB in appropriate dosages
Vaclavik 2014 (ASPIRANT-EXT)[22]	150	60.0 (9.7)	57 (38%)	Spironolactone Placebo	Daytime ABP Nighttime ABP 24-H ABP Office BP	8	Office SBP >140 or DBP >90mmHg despite being treated with ≥3 antihypertensive drugs, including a diuretic
Williams 2015 (PATHWAY-2)[23]	335	61.4 (9.6)	46 (14%)	Spironolactone Placebo Doxazosin Bisoprolol	Home BP Office BP	12	Seated clinic SBP ≥140mmHg (or 135mmHg for patients with diabetes) and home SBP ≥130mmHg, despite treatment for ≥3 months with maximally tolerated doses of three drugs (ACE-I or ARB, a CCB, and diuretic
Djoumessi 2016[24]	17	62.9 (8.2)	17 (100%)	Spironolactone Atenolol Candesartan Alpha methyldopa	Home BP Office BP	4	Office BP ≥140/90mmHg and self BP measurement (SBPM) ≥130/80 mmHg under ≥3 antihypertensive drugs at optimal dosages for ≥2 months, including a diuretic

Abbreviations: SD, standard deviation; ABP, ambulatory blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24-H, 24-hour; ACE-I, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; CCB, calcium channel blocker.

One study[26] was excluded because it included patients who were either oliguric or anuric, and were not on diuretics which is in contrary to the definition of resistant hypertension that was previously set by the investigators. The process of study selection is outlined in Figure 1.

Study characteristics

All included studies were RCTs published from 2011– 2016 involving a total of 662 patients. Four[21-24] of the five studies explicitly mentioned the inclusion of diabetic patients as part of their samples; one[24] of the studies included only diabetic patients. The fifth study[20] did not mention whether diabetic patients were included in the sample. All studies had a similar definition of resistant hypertension and included comparison of the effect of spironolactone versus either placebo or an alternative drug regimen on blood pressure reduction. One[23] study compared spironolactone with both placebo and alternative drug regimen; one[24] compared spironolactone and alternative drug regimen only; the other three[20-22] compared spironolactone with placebo only. Three[21-23] of these studies were found to have low risk of bias while two[20-24] had unclear risk of bias. The summary of risk of bias assessment is shown in Table I while the characteristics of the five included trials[20-24] are summarized in Table II.

Efficacy outcomes

All the five eligible studies in this meta-analysis included the change in office BP as outcome; only two of the five included home BP as outcome.

Four studies[20-23] compared spironolactone with placebo in terms of the reduction of office BP. Pooled analysis of these studies showed that, compared to placebo, the addition of spironolactone to standard triple-drug therapy resulted in significantly greater reduction in the office systolic BP (WMD= -16.33, 95% CI= -24.68 to -7.97, *P*= 0.0001) and office diastolic BP (WMD= -6.12, 95% CI= -9.35 to -2.89, *P*= 0.0002) in patients with resistant hypertension (Figure 2). However, substantial

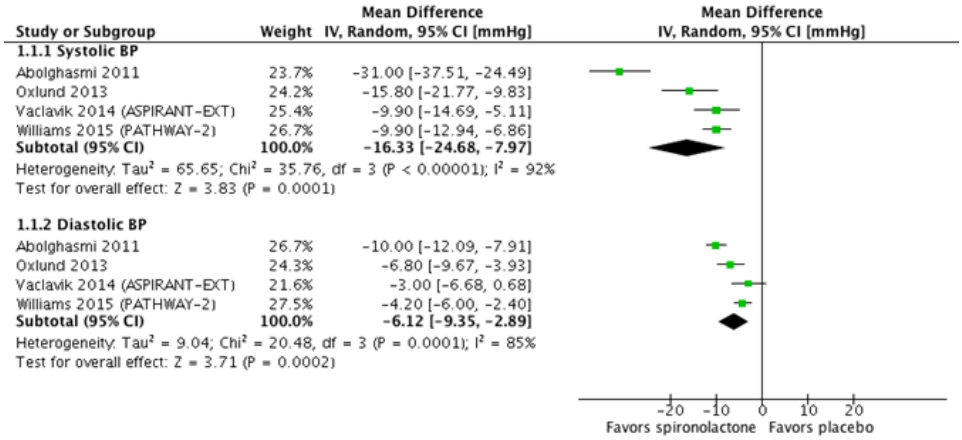

Figure 2. Effect of spironolactone versus placebo on office blood pressure. BP, blood pressure.

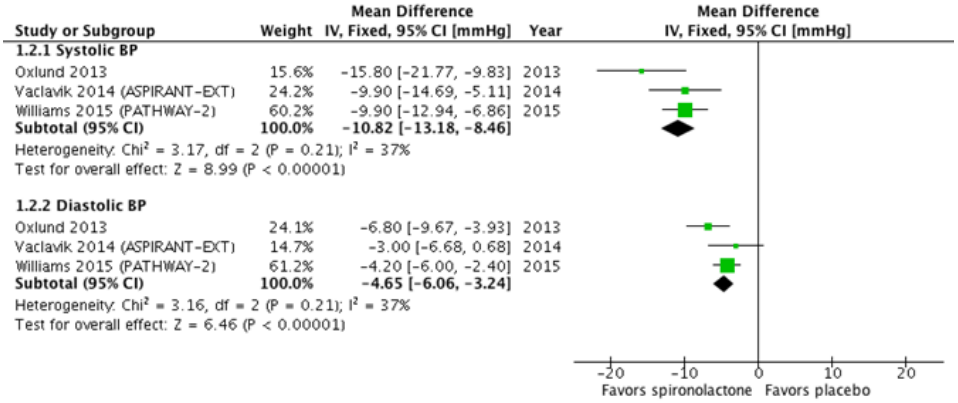

Figure 3. Effect of spironolactone versus placebo on office blood pressure, with the exclusion of one study: Abolghasmi 2011.

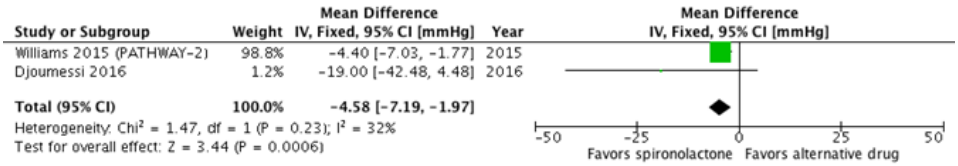

Figure 4. Effect of spironolactone versus alternative drug regimen on office systolic blood pressure

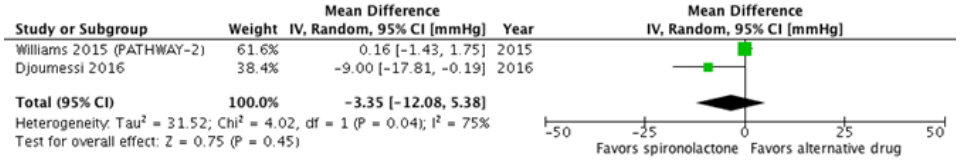

Figure 5. Effect of spironolactone versus alternative drug regimen on office diastolic blood pressure

heterogeneity was observed for both office systolic BP (I^2= 92%) and diastolic BP (I^2= 85%), hence the random effects model was used for the analysis of these outcomes.

The substantial heterogeneity may be partly due to one[20] of the studies which did not report enough details regarding its study design, rendering it to have unclear risk of bias. Pooled analysis with the exclusion of this study (Figure 3) showed not only a significantly greater reduction in both office systolic BP (WMD= -10.82, 95% CI= -13.18 to -8.46, *P*< 0.00001) and office diastolic BP (WMD= -4.65, 95% CI= -6.06 to -3.24, *P*< 0.00001) in favor of spironolactone over placebo, but also a decrease in heterogeneity for both office systolic (I^2= 37%) and diastolic BP (I^2= 37%).

Two studies[23-24] compared spironolactone and an alternative drug regimen in office BP reduction. One[23] of them, however, reported separate results for two intervention groups, each received one of two different alternative antihypertensive drugs. These two intervention groups were combined into a single intervention group of alternative drug regimen. Pooled analysis of these two studies showed that when added to standard triple-drug therapy in patients with resistant hypertension, spironolactone decreased

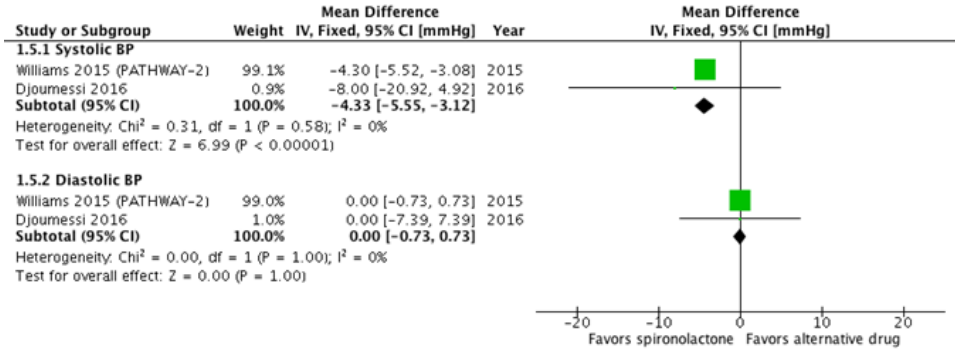

Figure 6. Effect of spironolactone versus alternative drug regimen on home/self-monitored blood pressure.

office systolic BP by 4.58 mmHg more (95% CI= -7.19, -1.97, *P*= 0.0006, I^2= 32%) than alternative drug regimen (Figure 4). However, the effect on the reduction of office diastolic BP by the addition of spironolactone was not significantly different from that of the addition of an alternative drug regimen (WMD= -3.35, 95% CI= -12.08 to +5.38, *P*= 0.45). The comparison also showed substantial heterogeneity (I^2= 75%), therefore, the random effects model for analysis was used (Figure 5).

Only two[23-24] of the five eligible studies included change in home or self-monitored BP. One[23] study compared spironolactone with both placebo and two different alternative drugs in terms of effect in home BP reduction; the other[24] compared it only to alternative drug regimen. Therefore, pooled analysis was only done for the comparison between spironolactone and alternative drug regimen (Figure 6) and the two intervention groups from one[23] of the studies were again combined into a single group for the outcome with alternative drug regimen. Spironolactone decreased the home systolic BP by 4.33 mmHg more than alternative drug regimen (95% CI= -5.55, -3.12, *P*< 0.00001, I^2= 0%). On another hand, the effect of the addition of spironolactone on decreasing the home diastolic BP was not significantly greater than that of the addition of an alternative drug regimen (WMD= 0.00, 95 % CI= -0.73 to 0.73, *P*= 1.0, I^2= 0%).

Discussion

Based on the results, spironolactone versus placebo or an alternative anti-hypertensive provided a more substantial reduction in office systolic and diastolic, and home systolic BP. The results were similar to the conclusion of a recently published meta-analysis[19] showing significant systolic and diastolic BP reduction with spironolactone (as add-on therapy) on both ambulatory and office BP.

Resistant hypertension carries with it a high burden of target organ damage, carrying a poor prognosis due to prolonged periods of uncontrolled hypertension.[25] Evidence suggest that hyperaldosteronism is an important underlying mechanism in resistant hypertension. This is supported by studies evaluating aldosterone antagonists in resistant hypertension.[29-31] This study aimed to evaluate the effect of spironolactone, a mineralocorticoid receptor antagonist, on systolic and diastolic office and home blood pressure versus placebo or another anti-hypertensive medication.

Four randomized control studies included a comparison of spironolactone versus placebo and two randomized control studies[23-24] versus an alternative drug regimen on office systolic and diastolic BP[20-23] while two randomized control studies[23-24] included a comparison of spironolactone versus an alternative drug regimen on home BP.

The results of the meta-analysis show significant reduction in systolic and diastolic BP of patients on spironolactone versus placebo. However, substantial heterogeneity was present in the analysis of randomized control trials for office BP. With the removal of one study found to have potentially low quality, heterogeneity was decreased to low to moderate. Although heterogeneity was decreased with the removal of one study, the low to moderate heterogeneity can be accounted for by confounding factors including but not limited to placebo effect, white coat hypertension, insufficient adherence, selection bias and concomitant comorbidities (i.e. diabetes mellitus, hyperaldosteronism) of the population group in the studies included.

In the comparison of office systolic and diastolic BP of patients on spironolactone versus an alternative drug regimen, results are consistently favorable for spironolactone in systolic BP. However diastolic BP reduction was not significant with substantial heterogeneity which can be attributed to clinical heterogeneity due to the variability in the outcomes of the trials included with the trial with the bigger population straddling the line of no effect.

Two studies included home BP as an endpoint to measure efficacy of spironolactone versus another anti-hypertensive medication. While there was significant BP reduction in the systolic BP of patients on spironolactone versus another anti-hypertensive, fall in the respective diastolic values was not significant. This result however, is also

limited in power by the inclusion of only two studies with the effect size being estimated significantly by the larger study. The previously done meta-analysis[19] compared spironolactone with a control which included and did not separate placebo from another anti-hypertensive medication. In this study, a separate comparison of spironolactone versus placebo and versus another anti-hypertensive medication was done to avoid attributing the effect of placebo to an alternative anti-hypertensive and vice versa. In addition, this study included home systolic and diastolic blood pressure reduction which was excluded in the previously published meta-analysis and included more recent randomized control trials following the inclusion criteria set by the authors.

Although spironolactone has been empirically used as the fourth line therapy (Grade C recommendation),[28] no existing guidelines have recommended spironolactone as the standard add-on to resistant hypertension. However, existing small uncontrolled studies and large scale trials,[20-24] including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[27] consistently resulted in significant reduction in systolic BP in patients with resistant hypertension which is similar to the result of this study.

Given the accordance of the results of the meta-analysis with existing available data, there were several limitations to the meta-analysis that should be highlighted and considered. First, the meta-analysis included RCTs with small sample sizes, increasing the risk of bias. Second, the dose, duration and baseline BP of the included trials were not standardized which may lead to confounding bias. Third, the heterogeneity of the population included in the trials may have had an impact on the reduction of systolic and diastolic BP, and may make the results less generalizable. Fourth, the treatment exposure of studies included is short and cannot provide data on the long term prognostic outcomes, cardiovascular and renal morbidity and mortality. And finally, two of the included studies have uncertain risk for bias due to incomplete reporting of methods.

Conclusion

In conclusion, spironolactone when combined with a triple-drug therapy significantly decreases office and home BP in patients with resistant hypertension. Compared to the addition of alternative anti-hypertensive medications, the addition of spironolactone to a triple-drug therapy appears superior in decreasing both office and home systolic BP of these patients.

These findings support the potential use of spironolactone as the add-on anti-hypertensive medication of choice for patients with resistant hypertension.

Nonetheless, to demonstrate the long-term sustained blood pressure-lowering efficacy, as well as to determine the long-term safety profile and impact of spironolactone on other clinically relevant outcomes for patients with resistant hypertension (e.g. cardiovascular morbidity and mortality), high-quality studies especially RCTs with long follow-up periods are warranted.

With stronger evidence of its efficacy, the investigators recommend spironolactone to be considered as the standard add-on in patients with resistant hypertension taking into consideration the limitations set forth by this study.

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