Hypertension Research (2019) 42:817–824
https://doi.org/10.1038/s41440-019-0244-4

ARTICLE

JSH2019 Systematic Review Series: Clinical Questions in the Management of Hypertension

Systematic review of the clinical outcomes of mineralocorticoid receptor antagonist treatment versus adrenalectomy in patients with primary aldosteronism

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Received: 22 December 2018 / Revised: 18 February 2019 / Accepted: 20 February 2019 / Published online: 5 April 2019

Abstract

Primary aldosteronism (PA) is the most common cause of secondary hypertension. The aim of this study was to review the clinical outcomes after mineralocorticoid receptor (MR) antagonist treatment versus adrenalectomy treatment in patients with PA. Relevant medical literature from PubMed, the Cochrane Library, and the ICHUSHI database from 1985 to August 2017 was reviewed. Data extraction was performed independently by three authors. The incidence of cerebrovascular or cardiovascular disease, the improvement of left ventricular hypertrophy or hypokalemia, the severity of hypertension, the incidence of renal dysfunction, and the reduction in the number of oral antihypertensive agents were set as the clinical outcomes. Of the 302 articles selected, 16 were included in the final analysis. Regarding the two therapeutic strategies, no difference in the reduced incidence of cerebrovascular or cardiovascular disease, the prevalence of left ventricular hypertrophy or hypokalemia, or the severity of hypertension, as well as an increase in the incidence of renal dysfunction was observed. Regarding the decrease in the number of oral antihypertensive agents, more agents were reduced in patients who underwent adrenalectomy. Available evidence indicated that the clinical outcomes were not different in PA patients treated with MR antagonist or adrenalectomy, except for a reduction in the number of antihypertensive agents.

Keywords Adrenalectomy · JSH 2019 guidelines · Mineralocorticoid receptor antagonist · Primary aldosteronism

Introduction

Primary aldosteronism (PA) is a typical form of secondary hypertension accounting for 5–15% of patients with hypertension [1]. It is characterized by autonomous aldosterone secretion and low plasma renin activity (PRA); hypokalemia is observed only in typical cases [2]. PA is a common disease that often causes organ dysfunction; therefore, early diagnosis and treatment of this disease are important. PA is often associated with cardiovascular complications such as cerebrovascular disease, ischemic heart disease, arrhythmia (e.g., atrial fibrillation), and peripheral arterial disease [3, 4]. The complication rate in patients with PA is 3–5 times higher than in those with essential hypertension [5–9]. Patients with hypertension, particularly those at a high risk of developing PA, are actively screened by plasma aldosterone concentration and plasma renin activity. Many of PA patients have refractory hypertension that cannot be controlled even with a combination of three types of antihypertensive agents including diuretics. Based on the results of confirmatory testing and localization, these patients undergo either a curative operation or receive drug treatment with a mineralocorticoid receptor (MR) antagonist (spironolactone or eplerenone).

The treatment option for PA is dependent on whether it is the unilateral or bilateral lesion subtype. Prognosis

Supplementary information The online version of this article (https://doi.org/10.1038/s41440-019-0244-4) contains supplementary material, which is available to authorized users.

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should be assessed separately in terms of biochemical cure, including the resolution of hyperaldosteronemia and hypokalemia, and clinical cure, such as the resolution of hypertension [10]. The unilateral lesion subtype (typically an aldosterone-producing adenoma [APA]), requires a unilateral adrenalecotmy to be performed and the bilateral adrenal hyperplasia subtype (idiopathic hyperaldosteronism [IHA]) requires drug treatment. For the unilateral PA, laparoscopic adrenalectomy is the first-choice treatment, which can offer a postoperative biochemical cure. In patients who refuse or are not candidates for surgery and in those with bilateral lesions, MR antagonists are used to treat hypertension and hypokalemia. Although the differences in the clinical outcomes between surgical and drug treatments are unknown, there are some reports that surgical treatment is associated with a lower all-cause rate of mortality and a better prognosis of atrial fibrillation [11, 12].

To elucidate the outcomes of the surgical versus MR antagonist treatment of patients with PA, we performed a systematic review of the literature.

Methods

Search strategy

The protocol for this review was prospectively developed detailing the specific objectives, the criteria for study selection, the approach to assess the study quality, the outcomes, and the statistical methods as recommended by the PRISMA statement [13]. A systematic search was performed using the PubMed, Cochran, and ICHUSHI (the Japan Medical Abstracts Society databases) electronic databases. The search was limited to articles published after 1985 in English and to studies in humans in reference to an previous report [14]. The search strategy is described in Supplemental File 1. The last search was performed on 24 Aug 2017. In addition, the reference lists of all retrieved articles were manually reviewed. Three independent authors (M.S., T.M., and Y. Y.) screened the titles and abstracts to identify potentially eligible studies. Full text articles were examined independently by the same authors to determine the inclusion articles.

Randomized controlled trial (RCT), prospective cohort study, and retrospective cohort study which compared the operative treatment with the medical therapy in PA patients were included in this analysis. Moreover, to be included in the analysis, a study had to provide values (means with standard deviation) of at least one of the following variables: left ventricular (LV) mass, serum potassium, systolic blood pressure (SBP), glomerular filtration ratio (GFR), and the number of oral antihypertensive agents. Studies that reported the incidence of cardiovascular events were also included. Three authors independently performed the data extraction. Discrepancies were rechecked and resolved by consensus discussion with the other authors.

Outcome

Outcomes of interest were (1) cardiovascular events: a composite of fatal or non- fatal myocardial infarction, fatal or non-fatal stroke, sudden death, hospitalization due to heart failure or angina, (2) left ventricular mass: echocardiographic measurements according to the American Society of Echocardiography recommendations [15], (3) systolic blood pressure, (4) serum potassium level, (5) renal function assessed by GFR, and (6) number of antihypertensive agents.

Statistical analysis and bias risk assessment

The statistical analysis was carried out using Review Manager (Version 5.3, The Cochrane Collaboration, Oxford, UK). For each trial, differences between the cases and controls were expressed as the mean difference (MD) with the pertinent 95% confidence interval (CI) for continuous variables, and as the risk ratio with the pertinent 95% CI for dichotomous variables. Summary estimates of MD or risk ratios were obtained using random effects model. The overall effect was tested using Z scores and the significance was set at $P < 0.05$. Statistical heterogeneity between studies was assessed with the χ^2 Cochran's Q test and with the I^2 statistic, which measures the inconsistency across the study results and describes the proportion of total variation in the study estimates due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [16].

The risk of publication bias was evaluated by creating a funnel plot where the pseudo–95% CIs define the limits within which, in the absence of a publication bias, individual studies should cluster symmetrically around the standard mean difference (SMD) of the overall estimated treatment effect. Further statistical tests for funnel plot asymmetry were not conducted given the limited specificity and power of these tests when <10 studies are included in the primary meta-analysis [17]. Three reviewers independently assessed the risk of bias using the modified Cochrane risk of bias instrument. We resolved disagreements between reviewers in the data extraction and assessments of risk of bias or quality of evidence by discussion and, if needed, by third party adjudication.

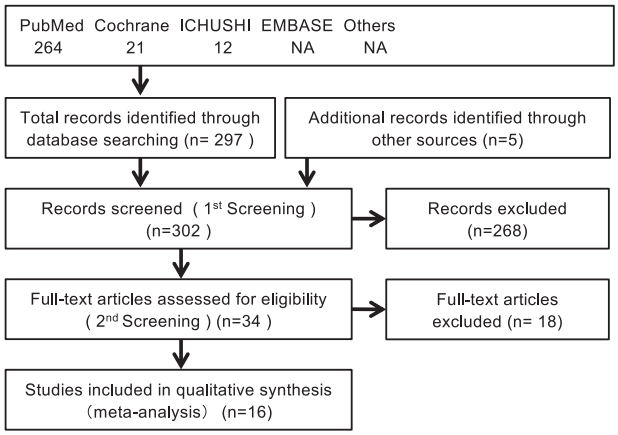

Fig. 1 Study selection flow diagram

Results

Search results

After excluding duplicate results, the search retrieved 302 articles. There were no RCTs in the searched articles. Of these studies, 268 were excluded because they were off the topic after scanning the title and/or the abstract, or they lacked data of interest. Therefore, 16 articles were included in the final analysis (Fig. 1) [3, 4, 11, 18–30]. The prevalence of cardiovascular events was evaluated in four studies [3, 4, 11, 18]. Thirteen studies [18–30] compared adrenalectomy with MR antagonist treatment, of which, four studies compared data on the LV mass [19–22], eight reported on the SBP [19, 21, 23–28], five on serum potassium [18, 21, 23, 27, 28], three on GFR [23, 26, 29], and three on the number of antihypertensive drugs [21, 27, 30]. The risk of bias is summarized in Supplementary Table 1. Quality assessment showed that performance bias owing to wide variations in definitions of biochemical diagnosis of PA, heterogeneity in investigations and treatment protocol was the main causes of potential bias.

Cardiovascular events

Of the 16 retrieved articles, four were included in the analysis of cardiovascular events [3, 4, 11, 18]. A meta-analysis of the selected studies demonstrated no significant difference in the risk of cardiovascular events between patients with PA who were treated with a MR antagonist or an adrenalectomy (risk ratio = 1.15; 95% CI = 0.58–2.27; P = 0.69; I^2 = 52%; Fig. 2a). High heterogeneity was detected among the studies including analysis for cardiovascular events; however, a visual inspection of the funnel plots suggested no evidence of publication bias (Fig. 3a).

Reduction of left ventricular mass

Of the 16 retrieved articles, four were included in the analysis of the LV mass [19–22]. These studies included a total of 326 patients with PA who had received MR antagonist treatment (n = 152) or an adrenalectomy (n = 174). The average end-of-study LV mass index was comparable in PA patients who underwent MR antagonist or surgical treatment (49.2 g/m$^{2.7}$ vs. 47.9 g/m$^{2.7}$). The meta-analysis of the selected studies demonstrated no significant difference in change in the LV mass between patients with PA who were treated with MR antagonist or adrenalectomy (MD = 2.83; 95% CI = −2.45–8.10; P = 0.29; I^2 = 74%; Fig. 2b). There was a significant heterogeneity among the studies included in the analysis for LV mass (I^2 = 74%, P = 0.010). Visual inspection of the funnel plots suggested no evidence of publication bias (Fig. 3b).

Systolic blood pressure

Eight of the 16 retrieved articles were included in the SBP analysis [19, 21, 23–28]. These studies included total of 903 patients with PA who had received MR antagonist treatment (n = 410) or an adrenalectomy (n = 493). The end-of-study average SBP was comparable in PA patients who underwent MR antagonist or surgical treatment (134.8 mmHg vs. 133.5 mmHg). Adrenalectomy and MR antagonist treatment had equivalent outcomes in five studies [19, 23, 24, 27, 28]; however, two studies reported a more favorable outcome after adrenalectomy [21, 26] and one reported a better outcome after MR antagonist treatment [25]. The meta-analysis of the selected studies demonstrated no significant difference in the SBP in patients with PA who were treated with MR antagonist or adrenalectomy (MD = 1.88; 95% CI = −1.39–5.16; P = 0.26; I^2 = 50%; Fig. 2c). Significant moderate heterogeneity was detected among the studies included in the analysis for SBP (I^2 = 50%, P = 0.05); however, a visual inspection of the funnel plots suggested no evidence of publication bias (Fig. 3c).

Hypokalemia

Five studies were included in the hypokalemia analysis [18, 21, 23, 27, 28]. These studies included a total of 499 patients with PA who had received MR antagonist treatment (n = 224) or an adrenalectomy (n = 275). The average end-of-study serum potassium levels was comparable in PA patients that underwent MR antagonist or surgical treatment (4.18 mEq/L vs. 4.25 mEq/L). The meta-analysis of the selected studies demonstrated no significant difference in the serum potassium levels in patients with PA who were treated with MR antagonist or adrenalectomy (MD = −0.09; 95% CI = −0.25–0.88; P = 0.31; I^2 = 77%;

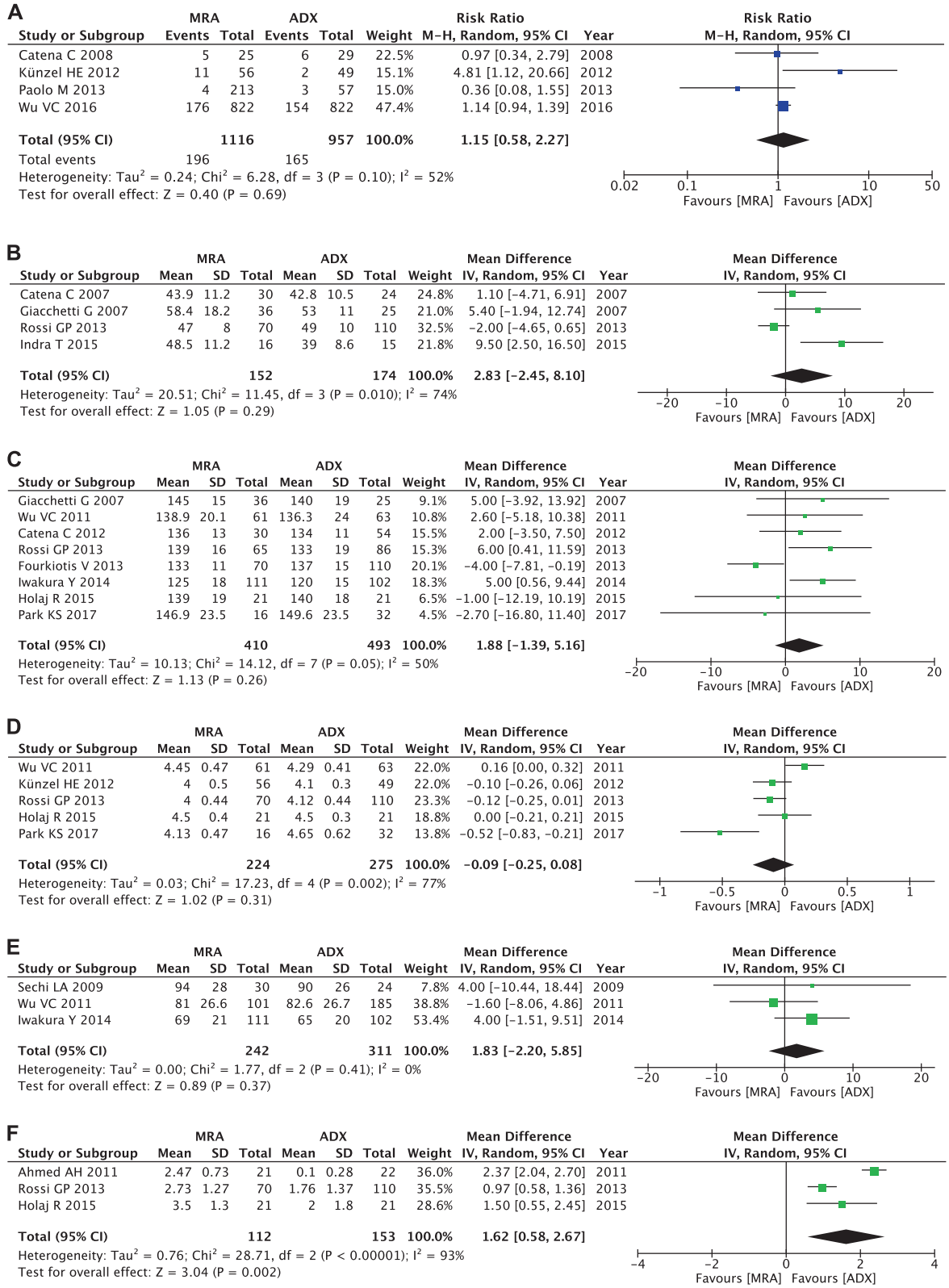

Fig. 2 Forest plot for each outcome. Forest plot of the effects of mineralocorticoid receptor (MR) antagonist treatment vs. adrenalectomy treatment of primary aldosteronism (PA) on cardiovascular events (**a**), left ventricular (LV) mass (**b**), systolic blood pressure (SBP) (**c**), hypokalemia (**d**), renal function (**e**), and number of antihypertensive agents (**f**). Central squares of each horizontal line represent the mean difference (MD) for each study. Lines indicate the range of the 95% confidence interval (CI). The vertical line at a MD of 0 is the line of no difference between treatments

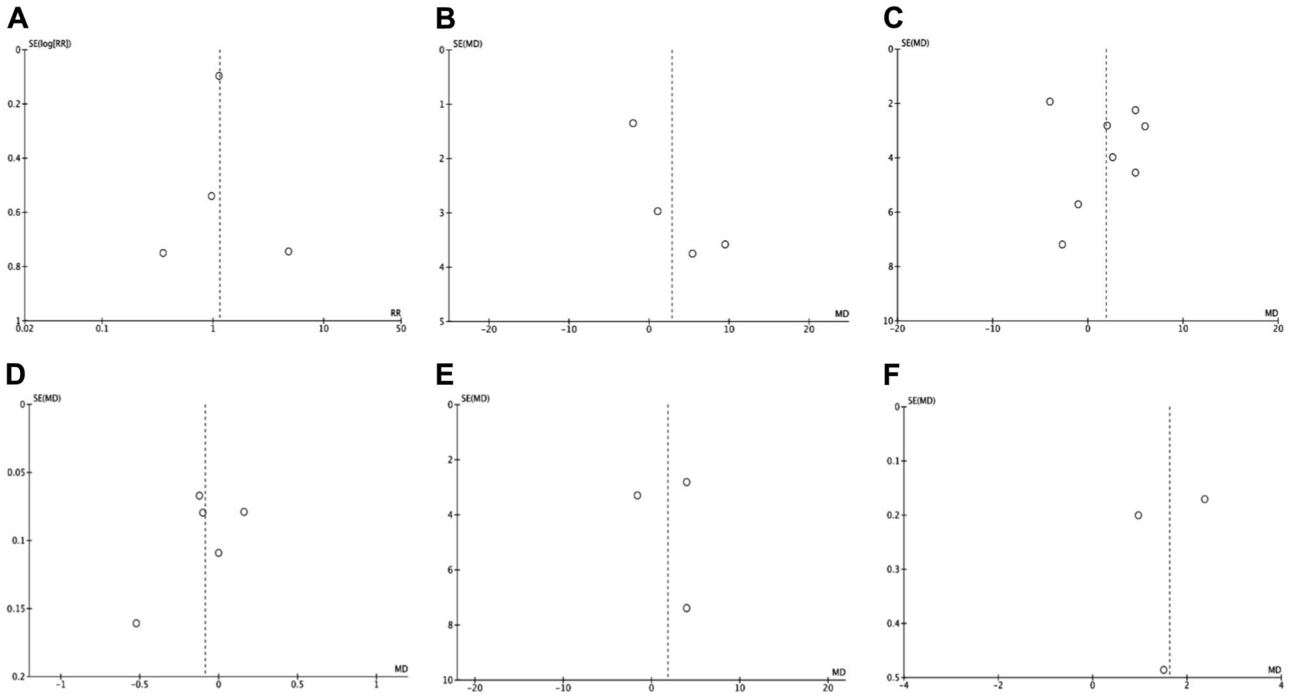

Fig. 3 Funnel plot for each outcome. Funnel plot of the effects of mineralocorticoid receptor (MR) antagonist treatment vs. adrenalectomy treatment of primary aldosteronism on cardiovascular events (**a**), left ventricular (LV) mass (**b**), systolic blood pressure (SBP) (**c**), hypokalemia (**d**), renal function (**e**), and number of antihypertensive agents (**f**). Funnel plots are constructed to evaluate possible publication bias. The vertical line indicates the standardized mean difference (SMD) of the overall estimated treatment effect. The black circles indicate the treatment effects of each study

Fig. 2d). No difference between the two therapeutic strategies was observed with respect to the decreased prevalence of hypokalemia. There was high significant heterogeneity between the enrolled studies for serum potassium ($I^2 = 77\%$, $P = 0.002$); however, a visual inspection of the funnel plots suggested no evidence of publication bias (Fig. 3d).

Renal function

Three studies were included in the renal function analysis [23, 26, 29], which included a total of 553 patients with PA who had received either MR antagonist treatment ($n = 242$) or an adrenalectomy ($n = 311$). The average end-of-study GFR was comparable in PA patients that underwent MR antagonist or surgical treatment (77.1 ml/min/1.73 m^2 vs. 77.4 ml/min/1.73 m^2). The meta-analysis of the selected studies demonstrated no significant difference in the GFR in patients with PA who were treated with MR antagonist or adrenalectomy (MD = 1.83; 95% CI = −2.20–5.85; $P = 0.37$; $I^2 = 0\%$; Fig. 2e). No difference between the two therapeutic strategies was observed with respect to the increased incidence of renal dysfunction. No significant heterogeneity was detected among the studies included in the analysis for GFR ($I^2 = 0\%$, $P = 0.41$), and a visual inspection of the funnel plots suggested no evidence of publication bias (Fig. 3e).

Number of antihypertensive agents

Three studies were included in the analysis of the number of antihypertensive agents [21, 27, 30]. These studies enrolled a total of 265 patients with PA who had received an adrenalectomy ($n = 153$) or MR antagonist treatment ($n = 112$). The average number of antihypertensive drugs taken was significantly lower in PA patients who underwent surgical treatment than in those who underwent MR antagonist treatment (2.83 vs. 1.55), as determined by the meta-analysis (MD = 1.62; 95% CI = 0.58–2.67; $P < 0.00001$; $I^2 = 93\%$; Fig. 2f). Adrenalectomy was associated with the use of fewer antihypertensive agents after surgery compared with MR antagonist treatment. There was a significantly high heterogeneity between the studies included in the analysis for the number of antihypertensive medications ($I^2 = 93\%$, $P < 0.00001$); however, a visual inspection of the funnel plots suggested no evidence of publication bias (Fig. 3f).

Discussion

In this study, we systematically reviewed the treatment of PA with specific reference to the outcomes after surgical versus drug treatment. To compare MR antagonist therapy

with adrenalectomy, the following items were assessed: decreases in the incidence of cerebrovascular and cardiovascular diseases, the prevalence of LV hypertrophy and hypokalemia, the severity of hypertension, the number of oral antihypertensive agents, and an increase in the incidence of renal dysfunction. Assessment of all-cause mortality was not possible because of the small number of recorded deaths and the lack of studies that could be compared. One report showed that surgical treatment is associated with a lower all-cause rate of mortality [11]. No differences between the two therapeutic strategies were observed with respect to the decreased incidence of cerebrovascular or cardiovascular diseases (risk ratio = 1.15; 95% CI = 0.58–2.27), decreased prevalence of LV hypertrophy (MD = 2.83; 95% CI = −2.45–8.10), decreased severity of hypertension (MD = 1.88; 95% CI = −1.39–5.16), decreased prevalence of hypokalemia (MD = −0.09; 95% CI = −0.25–0.08), or the increased incidence of renal dysfunction (MD = 1.83; 95% CI = −2.20–5.85). Regarding the decrease in the number of oral antihypertensive agents, significantly more agents were able to be discontinued in patients undergoing adrenalectomy (MD = 1.62; 95% CI = 0.58–2.67). The two therapeutic strategies were found to have comparable effects on the outcomes of PA treatment, except the reduction in the number of oral antihypertensive agents, due to the limited evidence available.

PA is classified into two disease subtypes: APA and IHA. Generally, aldosterone production is higher in patients with APA than in those with IHA, and is associated with high blood pressure, coexistence with hypokalemia, and a high incidence of cerebrovascular and cardiovascular events. In addition, APA is clinically cured by surgery in ~45% of cases, whereas oral drug treatment is usually still needed for life. Therapeutic strategies vary depending on the disease subtype. In principle, the established therapeutic strategies are unilateral adrenalectomy of the affected side for APA and MR antagonist therapy for IHA, which are recommended by the clinical practice guidelines of PA [31–33]. Even in patients with APA, a limited number do not undergo adrenalectomy, including those with a poor general condition who are unsuitable for surgery and those who request not to undergo surgery. This meta-analysis did not reveal any studies comparing adrenalectomy and MR antagonist therapy separately for APA and IHA. It should be noted that the results of this study are derived from a combined review of articles on APA treated with adrenalectomy and IHA treated with MR antagonists. Comparisons between surgically and MR antagonist treated patients with PA should, therefore, be interpreted with caution.

As described above, therapeutic strategies for PA have already been established according to the disease subtypes; therefore, future clinical studies comparing the therapeutic strategies by disease type would be difficult to conduct. In this meta-analysis, which compared patients undergoing adrenalectomy for APA with those treated with MR antagonists for IHA, no differences were observed between these patients except for a reduction in the number of oral drugs used. However, there are also reports showing that both all-cause mortality and the incidence of cerebrovascular and cardiovascular diseases were lower in surgically treated patients than in non-surgically treated patients [11]. Furthermore, a recent prospective study showed that the incidence of atrial fibrillation was comparable between surgically treated patients with APA and patients with essential hypertension; however, it was reported to be higher in those treated with oral drugs for IHA than those with essential hypertension [12]. Therefore, adrenalectomy should be actively considered for the treatment of APA. In addition, it has been reported that when MR antagonist therapy is administered at doses adjusted to resolve suppression of PRA, the cardiovascular prognosis does not significantly differ between PA and essential hypertension [34]. It is also reported that, when PRA is suppressed, the cardiovascular prognosis is poorer in PA than in essential hypertension patients; therefore, it is important to administer MR antagonists at a dosage based on blood pressure, serum potassium, and PRA [34].

Treatment recommendations are hampered by the lack of systematic reporting of the clearly defined outcomes and randomized controlled trials. Clinical practice guidelines, which have been published in Japan, the United States, and France [31, 33, 35], indicated that adrenalectomy of the affected side is recommended for the unilateral lesion subtype because normalization of the excess aldosterone and a reversal of hypertension can be expected. Surgical treatment improves the quality of life, is cost-effective, and curative with normalization of the aldosterone and renin levels [14]. On the other hand, in patients with the bilateral lesion subtype and those who refuse or are not candidates for surgery, the first-choice treatment is drug treatment with an MR antagonist, which should be administered for life. Drug treatment has been demonstrated to be comparable to surgical treatment with respect to the cardiovascular risk associated with essential hypertension when blood pressure and serum potassium concentrations are well controlled and when doses of MR antagonists are adjusted to maintain PRA (≥1 ng/mL/h) [34]. A suggested algorithm for the diagnosis and treatment of PA has been compiled based on consensus documents and guidelines, together with the results of the present study.

In conclusion, this meta-analysis of cohort studies examined the effects of treatment with MR antagonists or adrenalectomy on patients with PA. The results indicate that surgery is associated with a reduced need for additional antihypertensive drugs than MR antagonist treatment.

Further research with an adequately designed and powered trial in patients with APA is needed to examine the efficacy of surgical and MR antagonist therapy on cardiovascular complications and to examine the safety and cost of these approaches in APA patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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