Adrenalectomy Is Comparable With Medical Treatment for Reduction of Left Ventricular Mass in Primary Aldosteronism: Meta-Analysis of Long-Term Studies

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BACKGROUND
Primary aldosteronism (PA) is associated with an increase in left ventricular (LV) mass beyond the amount needed to compensate the hypertension-related workload. Available evidence suggests effectiveness of surgical treatment of PA in decreasing LV mass, whereas data on medical treatment are controversial. We have conducted a meta-analysis of long-term follow-up studies on surgical and medical treatment of PA to compare the effects of treatments on LV mass.

METHODS
Medline and Cochrane searches were performed including the following words: hyperaldosteronism, left ventricular mass, mineralocorticoid receptor antagonists, surgery, adrenalectomy, and follow-up studies. Studies published within 2013 focusing on cardiac effects of treatment and follow-up longer than 6 months were selected. Data extraction was performed independently by 2 authors.

RESULTS
Of 61 retrieved articles, 4 were included in the analysis. These studies enrolled 355 patients with PA who had an average follow-up of 4.0 years after unilateral adrenalectomy (n = 178) or treatment with mineralocorticoid receptor antagonists (n = 177). Despite greater effect of surgery over medical treatment in reducing blood pressure, meta-analysis of the selected studies demonstrated no significant difference in LV mass change between patients with PA who were treated with mineralocorticoid receptor antagonists or adrenalectomy (standard mean difference = 0.130; 95% confidence interval = −0.085 to 0.345; P = 0.24; P = 0%).

CONCLUSIONS
Available evidence indicates that reduction of LV mass is not different in PA patients treated with adrenalectomy or mineralocorticoid receptor antagonists.

Keywords: adrenalectomy; blood pressure; hyperaldosteronism; hypertension; left ventricular hypertrophy; left ventricular mass; mineralocorticoid receptor antagonists.

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Primary aldosteronism (PA) is an endocrine disorder associated with high blood pressure and suppressed plasma renin in which excess circulating aldosterone is caused by an adrenal adenoma (APA) or bilateral adrenal hyperplasia (IHA) and is not suppressible by volume expansion. Recent evidence indicates a greater frequency of PA among hypertensive patients than the previously accepted prevalence of approximately 1%.1,2 This might result from more effective identification of this condition due to widespread use of the plasma aldosterone-to-renin ratio as a screening test.3 Structural and functional changes of the heart are consequences of all hypertensive states and have also been detected in patients with PA along with additional subclinical cardiovascular endpoints.2

Left ventricular (LV) hypertrophy is a strong independent risk factor for major cardiac events and mortality,4 and anti-hypertensive treatments that induce regression of LV hypertrophy decrease the rate of events and improve survival independent from blood pressure reduction.5,6 Many cross-sectional echocardiographic evaluations have demonstrated excess LV mass and more frequent LV hypertrophy in patients with PA as compared with patients with essential hypertension that were matched for age, sex, anthropometric indices, and disease severity and duration.7-13 Moreover, excess LV hypertrophy might contribute to the greater risk of cardiovascular events that has been reported in patients with PA as compared with patients with essential hypertension.14-18

Current guidelines19 indicate use of unilateral adrenalectomy or mineralocorticoid receptor (MR) antagonists for treatment of PA with or without lateralized aldosterone secretion, respectively. Because of the relevance of LV hypertrophy on cardiovascular outcome of PA patients, it is important to know the effects of these treatments on LV mass. Many follow-up echocardiographic studies have been conducted in PA patients treated with either adrenalectomy or MR antagonists.9,12,20-23 Whereas adrenalectomy was almost consistently found to rapidly decrease LV mass, effects of treatment with MR antagonists were more controversial. Among other factors, differences in findings might be related to duration of follow-up, and some studies have...
suggested that reduction of LV mass requires longer time in medically treated vs. surgically treated patients. Therefore, the aim of this study was to conduct a meta-analysis of the available studies with long-term follow-up of PA patients treated with either surgery or medical treatment to compare the effects of these treatments on LV mass.

METHODS

Study design, data extraction, and endpoint

Study design followed the PRISMA indications for systematic reviews and meta-analyses. Relevant studies published until October 2013 were identified from MEDLINE and the Cochrane Library Central Register of Controlled Trials using a combined free text and the following MeSH search strategy: (Hyperaldosteronism) AND (Left Ventricular Mass OR Mineralocorticoid Receptor Antagonists OR Surgery OR Adrenalectomy OR Follow-up Studies), limited to human studies. The search was not restricted to any language. Two authors (L.M. and G.C.) independently screened the titles and abstracts to identify potentially eligible studies. Full-text articles were examined independently by the same authors to determine whether they met the inclusion criteria: (i) prospective studies focused on hyperaldosteronism; (ii) use of confirmatory test in diagnosis of PA; (iii) inclusion of patients with both APA and IHA; (iv) studies with both surgical and medical treatment of PA; (v) LV mass index included as an outcome variable of treatment; and (vi) echocardiographic follow-up >6 months. Extracted data were assembled using data extraction forms to collect study characteristics and results. We also extracted information on the enrollment criteria of the study participants, baseline characteristics, and outcomes. Discrepancies were rechecked and resolved by consensus discussion with the other authors. A flow diagram of the study selection is summarized in Figure 1. The primary endpoint of this analysis was a LV mass change that occurred in at least 6 months of follow-up. In all studies, the echocardiographic measurements were performed according to the American Society of Echocardiography recommendations.

Statistical analysis

Data are presented as means ± SEMs. The treatment-induced change in LV mass was the primary endpoint of the meta-analysis, and we calculated the change in LV mass within each treatment arm of each study as the percentage of change from baseline. All studies were analyzed only for the comparison between PA patients treated with MR antagonists or surgery and are shown in a forest plot reporting the standardized mean difference (SMD) for each study with both APA and IHA; (iv) studies with both surgical and medical treatment of PA; (v) LV mass index included as an outcome variable of treatment; and (vi) echocardiographic follow-up >6 months. Extracted data were assembled using data extraction forms to collect study characteristics and results. We also extracted information on the enrollment criteria of the study participants, baseline characteristics, and outcomes. Discrepancies were rechecked and resolved by consensus discussion with the other authors. A flow diagram of the study selection is summarized in Figure 1. The primary endpoint of this analysis was a LV mass change that occurred in at least 6 months of follow-up. In all studies, the echocardiographic measurements were performed according to the American Society of Echocardiography recommendations.

RESULTS

Search results and group description

The literature search identified 2,655 articles for eligibility and identified 61 potentially relevant studies, 4 of which met our inclusion criteria for final meta-analysis (Figure 1) and are summarized in Table 1. These 4 studies included a total of 355 patients with PA, 172 (48%) of whom had IHA and 183 (52%) of whom had APA. One hundred seventy-eight patients with APA were treated with adrenalectomy (5 patients with APA did not have adrenalectomy because of bilateral adenoma or refusal of surgery), and the remaining 177 patients received MR antagonists. In these patients, spironolactone was started at a dose that ranged 50–100 mg/day and titrated up to 200–300 mg/day. Patients who did not reach the blood pressure target (<140/90 mm Hg in all studies) after adrenalectomy or treatment with the maximum tolerated doses of MR antagonists were treated with additional antihypertensive drugs.
Table 1. Descriptive summary of the patients’ characteristics in the studies included in the analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Catena et al.(^9)</th>
<th>Rossi et al.(^\text{10})</th>
<th>Giacchetti et al.(^\text{11})</th>
<th>Bernini et al.(^\text{12})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
<td>2007</td>
<td>2013</td>
<td>2007</td>
<td>2012</td>
</tr>
<tr>
<td>Mean/median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>follow-up, y(^a)</td>
<td>6.4</td>
<td>3</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>IHA/APA</td>
<td>MTx (n = 30)</td>
<td>STx (n = 24)</td>
<td>MTx (n = 70)</td>
<td>MTx (n = 36)</td>
</tr>
<tr>
<td></td>
<td>25/29</td>
<td>70/110</td>
<td>36/25</td>
<td>41/19</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>52</td>
<td>54</td>
<td>NR</td>
<td>51</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>9/21</td>
<td>7/17</td>
<td>NR</td>
<td>12/24</td>
</tr>
<tr>
<td>Mean BMI, kg/m(^2)</td>
<td>28.4</td>
<td>28.7</td>
<td>27.5</td>
<td>25.9(^\ast)</td>
</tr>
<tr>
<td>Baseline SBP/DBP, mm Hg</td>
<td>166/103</td>
<td>167/103</td>
<td>165/101</td>
<td>164/100</td>
</tr>
<tr>
<td>Change in SBP/DBP, mm Hg</td>
<td>−30/−20</td>
<td>−33/−21</td>
<td>−32/−18</td>
<td>−27/−17</td>
</tr>
<tr>
<td>Baseline LVMI, g/m(^2), g/m(^3)</td>
<td>52 ± 2</td>
<td>53 ± 2</td>
<td>50 ± 1</td>
<td>53 ± 1</td>
</tr>
<tr>
<td>End-of-study LVMI, g/m(^2), g/m(^3)</td>
<td>44 ± 2</td>
<td>43 ± 2</td>
<td>47 ± 1</td>
<td>49 ± 1</td>
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<tr>
<td>Baseline LVH, %</td>
<td>30</td>
<td>38</td>
<td>49</td>
<td>61(^\ast)</td>
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<tr>
<td>End of study LVH, %</td>
<td>7</td>
<td>8</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Baseline RWT</td>
<td>0.42</td>
<td>0.42</td>
<td>0.46</td>
<td>0.48</td>
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<tr>
<td>End-of-study RWT</td>
<td>0.40</td>
<td>0.40</td>
<td>0.49</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SEM or as median. Comparisons between continuously distributed variables were done by the Student t test and comparisons between percentages were done by \(^\chi^2\) test.

Abbreviations: APA, aldosterone-producing adenoma; BMI, body mass index; DBP, diastolic blood pressure; IHA, idiopathic hyperaldosteronism; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MTx, medical therapy; NR, not reported; PA, primary aldosteronism; RWT, relative wall thickness; SBP, systolic blood pressure; STx, surgical therapy.

\(^{a}\)Mean is given for all except Rossi et al., for which median is given.

\(^{\ast}\)P < 0.05 vs MTx group.

Average pretreatment blood pressure levels (161/100 mm Hg vs. 162/102 mm Hg, respectively) and mean number of antihypertensive drugs taken (2.1 vs. 2.1, respectively) were comparable in PA patients that underwent medical or surgical treatment. Also, average pretreatment plasma aldosterone levels (41.3 ng/dl vs. 41.9 ng/dl, respectively) and prevalence of LV hypertrophy (55.8% vs. 52.2%, respectively) were comparable in PA patients that were treated with surgery or MR antagonists. LV mass was normalized by body surface area (m\(^2\))\(^\dagger\) in 1 study and by height (m\(^2\))\(^\dagger\) in 3 studies.\(^9,10,12\)

In the latter studies, pretreatment values of LV mass index were comparable in the groups of PA patients that were treated with surgery (54.5 ± 1.9 g/m\(^2\)) or MR antagonists (55.5 ± 1.9 g/m\(^2\)).

Outcome analysis

The average duration of echocardiographic follow-up after treatment of PA was 4 years (range = 2.7\(^\dagger\) to 6.4\(^\dagger\)). Average decrease in blood pressure at the end of follow-up as compared with baseline was greater in PA patients treated with adrenalectomy than in those treated with MR antagonists (systolic blood pressure: −28 ± 3 mm Hg vs. −23 ± 3 mm Hg, respectively; diastolic blood pressure: −19 ± 2 mm Hg vs. −13 ± 2 mm Hg, respectively). The number of antihypertensive drugs taken by patients at the end of the study was unchanged in PA patients who were treated with MR antagonists (2.1 vs. 2.1), whereas in those treated with surgery this number was decreased (2.1 vs. 1.0). Hypertension cure was obtained in 44% of PA patients treated with surgery, whereas it was highly variable (from 37% to 0%) in those medically treated. Both medical (−7.1% ± 4.8%) and surgical (−12.5% ± 5.1%) treatment reduced LV mass index, whereas no significant changes were observed in relative wall thickness with both treatments (Table 1). Patients with APA treated with MR blockers (n = 5) did not differ in any variable from those who had adrenalectomy, and their number was too small to permit comparison of outcomes within this group.

Meta-analysis

Meta-analysis of the selected studies demonstrated no significant difference in LV mass change between patients with PA who were treated with adrenalectomy or medical treatment with MR antagonists. In the fixed-effects model, the percentage change of LV mass index between treatment groups was not significant (SMD = 0.130; 95% CI = −0.085 to 0.345; P = 0.24; I\(^2\) = 0.0%) (Figure 2). No significant heterogeneity was detected among the studies included in the analysis for the primary endpoint, and visual inspection of funnel plots suggested no evidence of publication bias (Figure 3).
Primary aldosteronism and cardiac mass

**DISCUSSION**

LV hypertrophy is frequently found in PA and might contribute to the risk of cardiovascular events in these patients. Occurrence of inappropriate LV mass is reported in patients with PA even in the absence of LV hypertrophy as defined by current criteria, suggesting that inappropriately elevated aldosterone levels increase LV mass beyond the amount needed to compensate the hemodynamic load due to increased blood pressure. Regression of LV hypertrophy is associated with improved cardiovascular outcome in hypertension, and therefore understanding the effects of different treatments on LV mass is of major relevance. This meta-analysis has been conducted to compare the long-term effects of medical treatment with MR antagonists or unilateral adrenalectomy on LV mass of patients with PA. Although the design included a large number of candidate studies, only 4 that were appropriately designed and included evaluation of echocardiography with long-term follow-up could be selected for meta-analysis. Findings indicate that both medical and surgical treatment decrease LV mass, showing no significant difference between treatments in an average follow-up of 4.0 years.

Hypertension may persist after adequate treatment of PA, and less than half of patients treated with either surgery or MR antagonists have their blood pressure normalized without the use of additional antihypertensive agents. This might be explained by either coexistence of essential hypertension concurring with PA in approximately 30%–40% of the patients or hypertension-related renal or vascular damage due to long-standing plasma aldosterone increase. Previous studies identified older age of patients, longer
duration of disease, heavier antihypertensive therapy, and decreased renal function at diagnosis as factors associated with persistence of hypertension after correction of PA.27–31 Recent studies suggest also the possibility that autoantibodies to the angiotensin II type I receptor might contribute to residual hypertension in patients treated for PA.32,33 Our analysis confirms the efficacy of both adrenalectomy and MR antagonists in reducing blood pressure in PA, although the effects of surgical treatment were more prominent. Also, in agreement with the majority of the previous studies conducted both in the short- and long-term on the effects of treatment of PA, cure of hypertension was obtained in 44% of patients treated with surgery, whereas results of medical treatment were much more variable. This might be due to relevant differences in the doses of MR blockers that were used in these studies and frequency of persistence on this drug due to their sex-related side effects, but this possibility could not be ascertained because of lack of information in the original articles. Better efficacy on blood pressure of surgical over medical treatment is also reflected by significant reduction in the number of antihypertensive drugs taken by patients with PA treated with surgery, changes that in this analysis were not found in patients treated medically.

Although initial observations on PA reported a low prevalence of cardiovascular complications,34 subsequent studies clearly indicated a striking increase in the relative risk of stroke, myocardial infarction, and atrial fibrillation in these patients as compared with appropriately matched controls with essential hypertension.14–18 In these studies, prevalence of cardiovascular events was comparable in PA patients with tumoral and idiopathic disease, showing that both subtypes are at increased risk. Also, treatment of PA with either unilateral adrenalectomy or MR antagonists significantly decreased the cardiovascular risk.15 Hypertension-related cardiovascular events are preceded by subclinical cardiovascular changes, including an increased LV mass that in cross-sectional studies has been reported to be significantly greater in patients with PA than in patients with other types of hypertensive diseases.7–13 Longitudinal evaluations of the cardiac effects of treatment of PA were initially confined to short-term studies, conducted in patients with APA after adrenalectomy. Subsequent studies have investigated the effects of both medical and surgical treatment on cardiac structure and function in the long term, reporting inconsistent results, mostly related to the effects of MR antagonists. Only 1 of the studies included in this analysis7 reported significant effects of medical treatment of PA on LV mass, although these effects required a longer time to occur than those of surgery. Two studies10,11 reported decrease of LV mass both in surgically and in medically treated PA patients, but changes were statistically significant only in the former group. The last study12 did not find any change in LV mass of patients treated with MR antagonists. Our meta-analysis indicates that the effects of these treatments are not significantly different.

There is substantial evidence suggesting that the decrease in LV mass obtained with surgical and medical treatment of PA is only partially explained by decrease of blood pressure, supporting the contention that aldosterone independently contributes to LV hypertrophy. It has also been reported that pretreatment MR activation levels are independent predictors of LV mass changes after either surgical or medical treatment.35,36 Human cardiomyocytes express MR,37 and aldosterone is a likely contributor to myocardial hypertrophy through mechanisms that result from stimulation of fibroblast proliferation and collagen synthesis, activation of inflammatory cells, and interaction with peptides such as angiotensin, endothelin, and bradykinin.38,39 Interruption of these MR-mediated mechanisms might explain why, in the long term, treatment of PA with MR blockers has comparable effects to the removal of an aldosterone-secreting adenoma in decreasing LV mass. Demonstration that cardiovascular outcomes do not differ significantly between patients with PA who are treated with surgery or MR blockers once again raises the reasonable question of whether the efforts required to distinguish unilateral from bilateral forms of aldosterone overproduction are justifiable and whether surgery should be performed in all APA patients.23,26,40

In this study, all previous investigations that compared prospectively and in the long term the effects of medical and surgical treatment of PA on LV mass were identified from major biomedical literature databases and systematically and independently reviewed. Despite consideration of a large number of candidate studies, only 4 responded to the requisite of inclusion of patients with both APA and IHA that was needed to compare the effects of surgical and medical treatment of PA and had long post-treatment echocardiographic follow-up. Sensitivity analysis was performed on the selected studies with no evidence of heterogeneity among them. However, in addition to the generic limitations of summary data-based meta-analyses, other limitations of this study need to be highlighted. First, although pooling of data in a meta-analysis provides significant increase of the statistical power, this could be limited by the small number of studies that were retrieved from the literature. Second, in all selected studies allocation of PA patients to either surgical or medical treatment depended upon evidence or not of an aldosterone-producing adenoma, and therefore the type of treatment was not randomized. Third, the doses of MR antagonists that were used throughout the study in IHA patients were not reported in the original articles, and therefore the relationships between these doses and reduction of LV mass could not be analyzed. Similarly, lack of detailed information on additional antihypertensive drugs that were used during follow-up in patients treated with surgery or MR blockers did not permit analysis of their relevance on blood pressure response and echocardiographic outcome. This analysis would have been particularly relevant for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers due to recent observations suggesting the possibility that autoantibodies to the angiotensin II type I receptor might contribute to residual hypertension in patients treated for PA.32,33 Finally, there was limited information on internal variability of the echocardiographic measurements reported in the studies included in the meta-analysis.

In conclusion, this meta-analysis of prospective cohort studies has examined the long-term effects of adrenalectomy or treatment with MR antagonists on patients with PA and suggests that surgery is associated with a better chance of cure of hypertension and lesser need of additional
antihypertensive drugs than medical treatment. Meta-analysis comparing cardiac effects of surgical and medical therapy, however, demonstrates a reduction of LV mass that is not different between the 2 treatments. Evidence that cardiovascular outcomes of surgical or medical treatment of PA do not differ significantly might induce physicians to reconsider the need for surgery in all APA patients under a different light. Further research with an adequately designed and powered trial in patients with APA will be needed to examine the efficacy of surgical and medical therapy on cardiovascular complications and to examine the safety and cost of these approaches in these patients.

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


