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Cardiovascular events and all-cause mortality in surgically or medically treated primary aldosteronism: A Meta-analysis

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Abstract

Objectives: To compare the effect of surgical or medical treatment on the risk of cardiovascular diseases (CVD) and all-cause mortality in patients with established primary aldosteronism (PA).

Methods: We searched PUBMED, MEDLINE and Cochrane Library for the meta-analysis. We included patients who were diagnosed with PA following guideline-supported protocols and received surgery or mineralocorticoid receptor antagonist (MRA)-based medical treatment, and age-sex matched patients with treated essential hypertension (EH). Primary endpoints were CVD incidence and all-cause mortality.

Results: Compared with EH, patients with treated PA had a higher risk of CVD [odds ratio (OR) 1.79; 95% confidence interval (CI) 1.39–2.31]. This elevated risk was only observed in patients with medically treated PA [OR 2.11; 95%CI 1.88–2.38] but not in those with surgically treated PA. The risk of all-cause mortality was significantly lower in patients with treated PA [OR 0.86; 95% CI 0.77–0.95] compared to EH. The reduced risk was only observed in patients with surgically treated PA [OR 0.47; 95% CI 0.34–0.66], but not in those with medically treated PA.

Conclusions: Patients with medically treated PA have a higher risk of CVD compared to patients with EH. Surgical treatment of PA reduces the risk of CVD and all-cause mortality in patients with PA.

Keywords

Primary aldosteronism, cardiovascular diseases, all-cause mortality, adrenal surgery, mineralocorticoid receptor antagonist

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Introduction

Primary aldosteronism (PA), the most common form of secondary hypertension, is a disease characterised by autonomous aldosterone secretion from adrenocortical lesions and feedback inhibition of the renin-angiotensin system.[1] The aldosterone excess leads to a higher risk of cardiovascular damage and worse prognosis compared to patients with essential hypertension (EH).[2] Targeted treatment with lifelong mineralocorticoid receptor antagonist (MRA) or unilateral adrenalectomy are the expert consensus recommendations for PA management. Considering that aldosterone blockade and ameliorated hypertension are often achieved after surgery or MRA treatment, it was thought that cardiovascular outcomes may also be improved by these treatments.

Based on previous studies, however, whether the risk of cardiovascular diseases (CVD) and all-cause mortality

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could be reduced by surgery or MRA remains controversial. On the one hand, it was reported that compared to patients with matched EH, the risk of CVD and all-cause mortality in surgically treated PA is significantly decreased.[3] However, this effect was not observed in another population.[4] On the other hand, the risk of CVD and all-cause mortality in medically treated PA was shown to be higher than patients with EH,[5] but this difference was not observed in other studies.[6,7]

In the past few years, there has been an increasing number of high-quality studies comparing the risk of CVD and mortality in patients with EH and surgically or medically treated PA. We included all of these longitudinal studies in a meta-analysis to better define the effect of surgical versus medical treatment on the incidence of CVD and all-cause mortality in patients with PA compared to those with treated EH.

Methods

Search strategy and selection criteria

We searched PUBMED, MEDLINE and Cochrane Library for relevant articles using a combination of the following terms: (hyperaldosteronism) OR (Primary hyperaldosteronism) OR (Primary aldosteronism) OR (Aldosteronism) OR (Conn Syndrom) and ((myocardial infarction) OR (atrial fibrillation) OR (heart failure) OR (percutaneous transluminal coronary angioplasty) OR (stroke) OR (leg pain on exertion) OR (claudication) OR (mortality)) up to July 31, 2020, with no start date restriction. Both prospective and retrospective studies were included. Two reviewers independently assessed the eligibility of all abstracts. We considered studies eligible for inclusion if they met the following criteria: patients who were clearly diagnosed as PA and received surgery or MRA treatment; age-sex matched patients with treated EH were recruited as a control group; all subjects were followed up for more than 5 years.

We excluded studies if one of the following conditions existed: data was repeatedly published (only the most recent publication data was used); absence of EH patients; PA diagnosis was not based on the US Endocrine Society guidelines[1,8] or the Japan Endocrine Society guidelines;[9] absence of follow-up data.

The primary outcomes included CVD incidence and all-cause mortality. Incidence of CVD was defined as the development of any of these following diseases: coronary artery disease (including myocardial infarction and stable or unstable angina requiring cardiac revascularisation), atrial fibrillation (including paroxysmal, persistent, long-standing persistent or permanent, shown by electrocardiogram), heart failure, stroke (including ischaemic or haemorrhagic), or death due to CVD. The all-cause mortality was any cause of death.

The main comparison of primary outcomes was based on all of the patients with treated PA and EH. Subgroup analyses compared patients with surgically treated PA to those with EH, medically treated PA to EH and surgically treated PA to medically treated PA.

Data extraction and quality assessment

Two unmasked independent reviewers (Y.J. and J.B.H) separately extracted the basic information (authors, journal, year of publication, sample size, follow-up years for each group), baseline features and the number of end-point events. For each study, the method of matching (statistically or clinically driven) was appraised.

The study quality was assessed by the Newcastle-Ottawa Scale,[10,11] which consisted the following items: representativeness of the PA cohort (1 point), selection of the EH cohort (1 point), ascertainment of therapy (1 point), demonstration that outcome of interest was not present at start of study (1 point), comparability of cases and controls on the basis of the design or analysis (2 points), assessment of outcome (1 point), was follow-up long enough for outcomes to occur (1 point), adequacy of follow up of the cohort (1 point). A point of less than 5 indicated relative poor quality. Two authors (Y.J. and J.B.H) allotted the point scores independently. The report was conformed following the Preferred Reporting Items for the Quality of Reporting of Meta-Analyses (PRISMA) checklist.[12]

Data analysis and synthesis

We used Review Manager (RevMan, version 5.3) to calculate the summary estimates and computed risk estimates with 95% CI. We identified statistical heterogeneity using the Cochran Q,[13] with I^2 values of less than 25% representing mild statistical inconsistency, 25%–75% representing moderate statistical inconsistency and >75% representing extensive statistical inconsistency.[14] The results were confirmed by random effects model with generic inverse-variance weighting if the I^2 value is greater than 50%,[15,16] otherwise by the Mantel-Haenszel fixed-effect model to avoid small studies being overly weighted.[17,18] Publication bias was examined by funnel plots and Egger's tests.[19] Stata 12.0 was used for the analysis while Open-meta analysist was used to merge single variables with a random effect model.[20]

Results

Characteristics of included studies

We identified 1480 publications through our search and evaluated them for eligibility at title or abstract level. Of the 72 full-text articles assessed, 35 were excluded due to lack of follow-up data, 17 for duplicate reports, 7 for lack of

appropriate control group and 5 because the PA diagnosis was not in agreement with guidelines (Figure 1). There were eight studies included in the final analysis,[3–7,21–23] with details summarised in Table 1. Among them, the study from Kunzel et al.[22] did not recruit subjects with EH, but compared surgically and medically treated PA patients. Studies from Wu et al.[3] and Chen et al.[21] were based on the same TAIPAI cohort but their endpoints were different. The two studies, Kunzel et al.[22] and Chen et al.[21] were only used for subgroup analyses while the other six studies were used for whole and subgroup analyses. Clinical and biochemical characteristics of the included patients have been summarised (Supplemental Table S2).

The quality of the included studies was assessed independently by two authors (Y.J. and J.B.H). All studies had a Newcastle-Ottawa Scale score of 5 or more. Specific parameters of matching between PA and EH have been described (Supplemental Table S3) and no publication bias was found (Supplemental Figure S1).

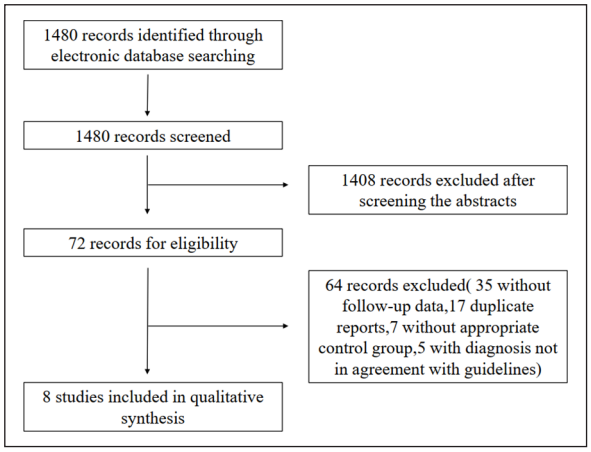

Figure 1. Flow chart of literature search and study selection.

CVD in treated PA versus EH

A total of six studies including 3905 patients with PA and 53,733 patients with EH were identified. The risk of CVD in patients with treated PA was significantly higher (odds ratio [OR] 1.79; 95% CI 1.39–2.31; $p < 0.001$) than the matched EH cohort. In subgroup analyses, the risk of CVD in patients with medically treated PA was 2-fold higher than those with matched EH (OR 2.11; 95% CI 1.88–2.38; $p < 0.001$), while no statistically significant difference in CVD risk was observed between patients with surgically treated PA and EH (OR 1.51; 95% CI 0.66–3.42; $p = 0.33$) (Figure 2). Furthermore, patients with medically treated PA showed a 1.75-fold higher risk of CVD than surgically treated PA patients (OR 1.75; 95% CI 1.07–2.86; $p = 0.33$) (Figure 3).

Table 1. Characteristics of the studies meeting the inclusion criteria.

	Country	Study period	Study type	Sample size (PA vs EH)		Duration of follow-up (years)	Main outcome variables	BAH/MRA	ADX (*n*)	NOS score
Catena et al.[6]	Italy	1994–2001	Prospective, matched	54	108	7.4	CVD, stroke, arrhythmias, claudication	25/30	24	5
Rossi et al.[4]	Italy	2000–2005	Prospective, not matched	107	894	11.8	AF	66/66	41	6
Hundemer et al.[5]	America	1991–2016	Prospective, matched	602	41853	7.0 vs 8.8	CVD, AF, DM, mortality	Not provided	Not provided	9
Reinck et al.[7]	Germany	1994–2010	Retrospective, matched	300	600	10	Cardiovascular disease mortality	Not provided	157	7
Mulatero et al.[23]	Italy	1992–2009	Retrospective, matched	270	810	12	CVD, stroke, arrhythmias, HF	213/213	67	8
Wu et al.[3]	Taiwan	1999–2007	Prospective, matched	2367	9468	5.2	MACE, DM, all-cause mortality	Not provided	Not provided	6
Kunzel et al.[22§]	Germany	2008–2010	Prospective, matched	105	/	4.3 vs 5.4	CVD, DM	56/56	49	6
Chen et al.[21†]	Taiwan	1999–2007	Prospective, matched	2699	10796	5.2	All-cause mortality, ESRD	1938/2042	657	6

PA: primary aldosteronism; EH: essential hypertension; APA: aldosterone-producing adenoma; BAH: bilateral adrenal hyperplasia; MRA: mineralocorticoid receptor antagonists; ADX: adrenalectomy; CVD: cardiovascular events; AF: atrial fibrillation; DM: diabetes mellitus; HF: heart failure; ESRD: end-stage renal disease; MACE: major adverse cardiac events.

§In this study, patients were followed-up for 5 years; however, at the end of the study the authors reported only the comparison between patients treated with ADX(49) versus MRA(56) and not with patients with essential hypertension.

†In this study, patients were from the same cohort with this one, but different from main outcome.

A final diagnosis of APA was considered proven, providing that all the following conditions were satisfied: (1) histologic demonstration of adenoma, (2) nor-Malization of hypokalaemia if present, (3) cure or improvement of hypertension and (4) normalisation of ARR and suppressibility of aldosterone levels less than 5 ng/dL under saline load.

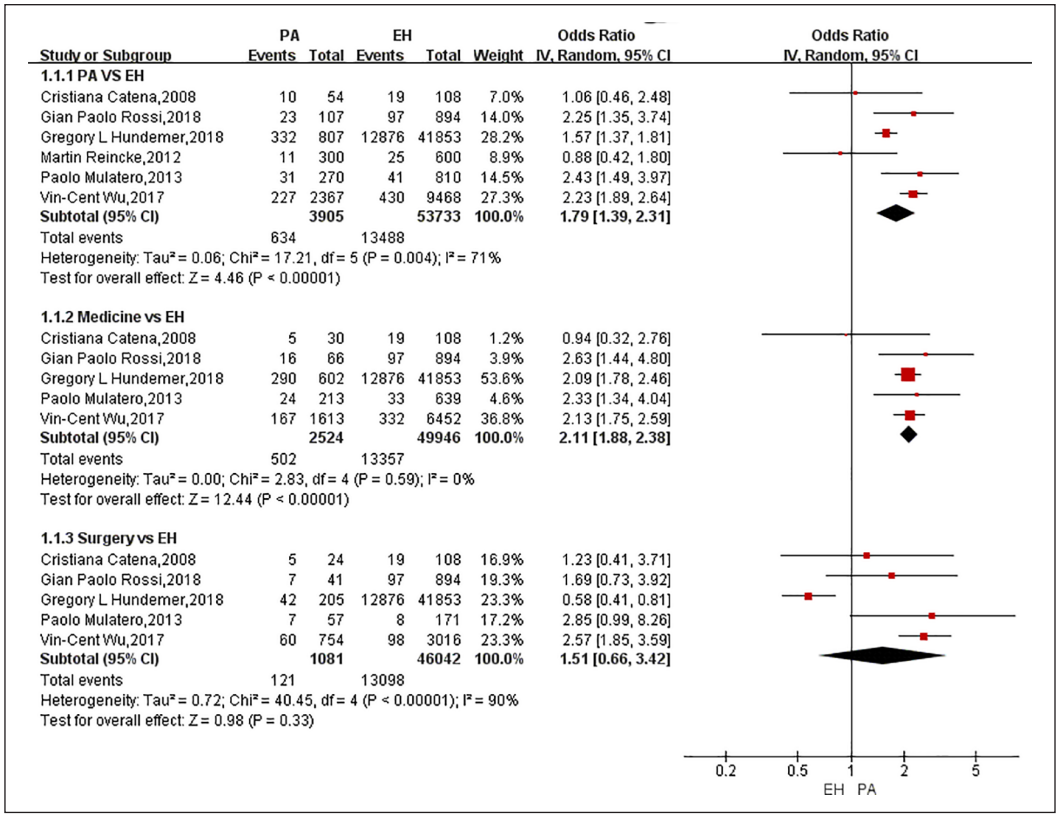

Figure 2. Cardiovascular events in treated patients with primary aldosteronism (include surgery group and medical therapy group) versus essential hypertension.
Forest plot of the OR of cardiovascular events in treated patients with primary aldosteronism and essential hypertension. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95%CI); boxes, the weight of individual studies in the pooled analysis. Central squares of each horizontal line represent the OR for each study. Horizontal lines indicate the range of the 95%CI and the vertical line indicates an OR of 1.0 (which indicates no differences in the OR between the groups).
OR: odds ratio.

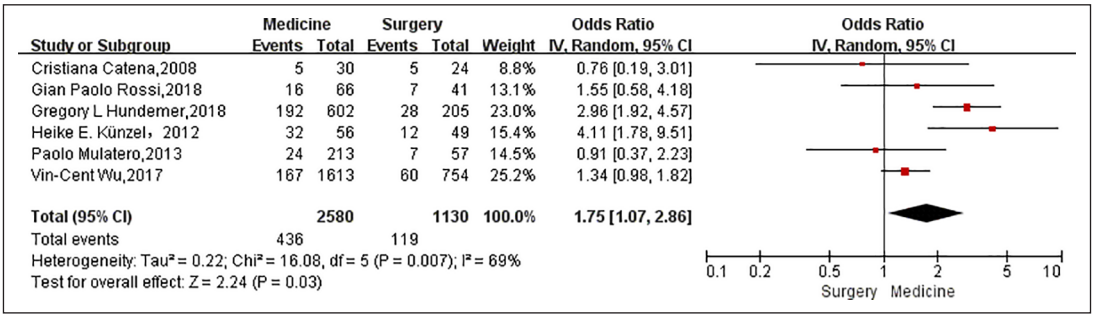

Figure 3. Cardiovascular events in patients treated with surgery and medical therapy.
Forest plot of the OR of coronary artery disease in patients treated with medical therapy versus surgery. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95%CI); boxes, the weight of individual studies in the pooled analysis. Central squares of each horizontal line represent the OR for each study. Horizontal lines indicate the range of the 95%CI and the vertical line indicates an OR of 1.0 (which indicates no differences in the OR between the groups).
OR: odds ratio.

All-cause mortality in treated PA versus EH

Four studies including 3708 patients with PA and 54,143 patients with EH were identified. Compared to patients with matched EH, the risk of all-cause mortality in patients with treated PA was significantly lower (OR 0.86; 95% CI 0.77–0.95; $p = 0.004$). The lower risk of all-cause mortality was only observed in the surgically treated PA group when compared to the EH cohort in a subgroup analysis (OR 0.47; 95% CI 0.34–0.66; $p < 0.001$). In contrast, there was no significant difference in the risk of all-cause mortality between patients with medically treated PA and EH (OR

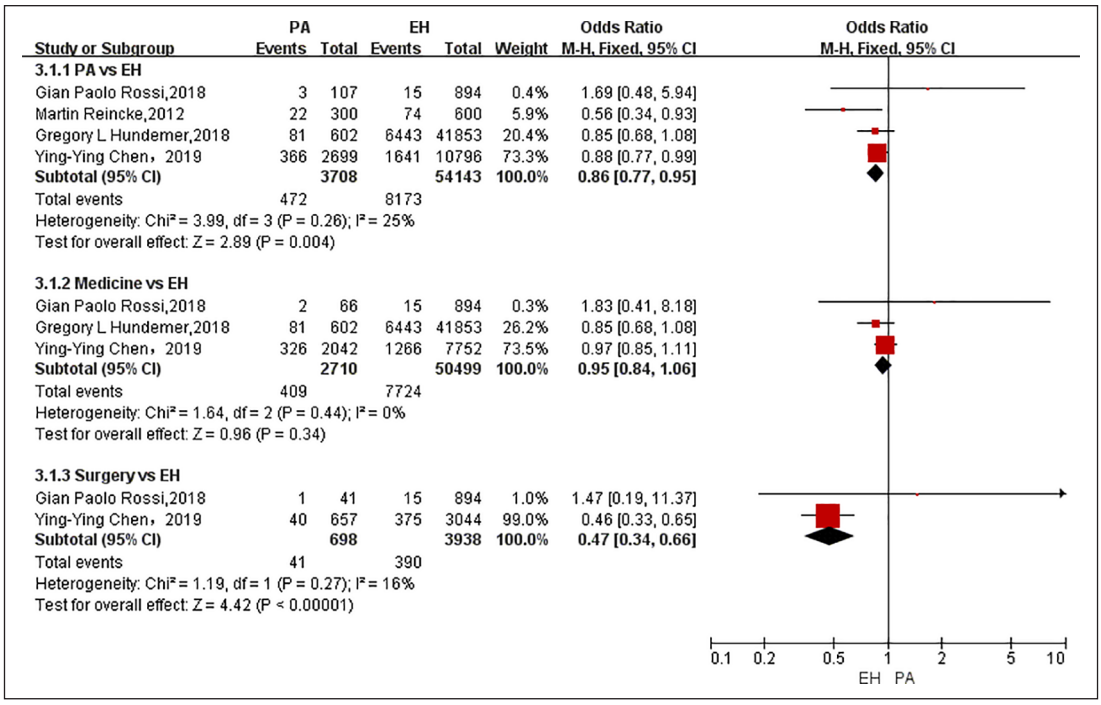

Figure 4. All-cause mortality in patients with primary aldosteronism (include surgery group and medical therapy group) versus essential hypertension.
Forest plot of the OR of all-cause mortality in treated patients with primary aldosteronism and essential hypertension. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95%CI); boxes, the weight of individual studies in the pooled analysis. Central squares of each horizontal line represent the OR for each study. Horizontal lines indicate the range of the 95%CI and the vertical line indicates an OR of 1.0 (which indicates no differences in the OR between the groups).
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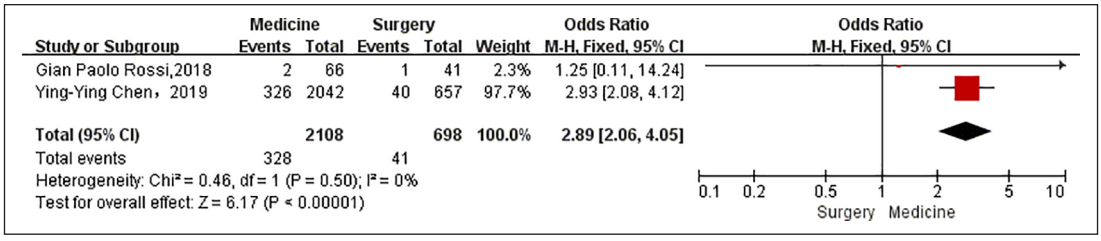

Figure 5. All-cause mortality in patients treated with surgery and medical therapy.
Forest plot of the OR of all-cause mortality in patients treated with medical therapy versus surgery. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95% CI); boxes, the weight of individual studies in the pooled analysis. Central squares of each horizontal line represent the OR for each study. Horizontal lines indicate the range of the 95% CI and the vertical line indicates an OR of 1.0 (which indicates no differences in the OR between the groups).
OR: odds ratio.

0.95; 95% CI 0.84–1.06; $p=0.34$) (Figure 4). The risk of all-cause mortality for patients with medically treated PA was 3-fold higher than those with surgically treated PA (OR 2.89: 95% CI 2.06–4.05: $p<0.001$) (Figure 5).

Discussion

In this meta-analysis of eight studies that evaluated CVD and all-cause mortality following targeted treatment of PA, we found a significantly higher risk of CVD in patients with treated PA than matched EH. In the subgroup analyses, the risk of CVD was significantly higher in patients who had medically treated PA compared to those with either EH or surgically treated PA. The risk of CVD in patients with surgically treated PA was similar to those with EH. On the other hand, the risk of overall mortality was lower in patients with treated PA compared with EH. Subgroup analyses demonstrated that the decreased risk of mortality was observed in patients with surgically treated PA when compared with patients with EH and medically treated PA, while the risk of mortality in patients with medically treated PA was similar to those with EH. Our results strongly advocate

for the early diagnosis and accurate identification of unilateral PA in patients who are surgical candidates and emphasises the importance of comprehensive cardiovascular risk management in medically treated patients.

It is well established that patients with PA display an increased cardiovascular risk compared to those with EH. Monticone et al.[24] conducted a systematic review and meta-analysis of 31 studies (about 95% of these were cross-sectional studies without treatment information) to compare the CVD risk between untreated PA and EH. The result showed that when compared to patients with EH, patients with PA display increased risks of stroke (OR 2.58: 95% CI 1.93–3.45), coronary artery disease (OR 1.77: 95% CI 1.10–2.83), atrial fibrillation (OR 3.52: 95% CI 2.06–5.99) and heart failure (OR 2.05: 95% CI 1.11–3.78). Targeted treatment in the form of unilateral adrenalectomy or MRA often leads to amelioration of aldosterone excess and improved blood pressure control. Considering these benefits, surgery and MRA may also be effective for improving outcomes such as CVD and death.

However, whether the risk of CVD is decreased in patients with surgically treated PA remains controversial. A study from the TAIPAI research group demonstrated lower risks of CVD and mortality in 754 surgically treated PA patients compared to a matched population with EH during 5.2-years of follow-up.[3] Another study from Italy enrolled 41 patients who received surgical treatment for PA and followed them for 11.8 years. No significant difference in CVD risk was observed between these surgically treated patients and 894 patients treated for EH.[4] In our meta-analysis of six longitudinal studies, we demonstrated that patients with treated PA had an increased risk of CVD mainly attributable to the higher risk in medically treated patients. The CVD risk in patients with surgically treated PA was comparable to those with EH and significantly lower than those with medically treated PA. Furthermore, the risk of all-cause mortality decreased by 50% in patients with surgically treated PA compared to those with EH. Our results suggest that surgical treatment of PA confers significant cardiovascular protection and reduces the risk of death in patients with PA. The pathophysiological changes of PA, including cardiac fibrosis, oxidative stress and chronic inflammation,[25–27] could be alleviated by targeted treatment. Frustaci et al.[28] compared the changes in cardiomyocytes in four male patients with aldosterone-secreting adrenal adenoma and cardiomyopathy (PACM) before and after adrenalectomy. With the normalisation of aldosterone levels, the diameter of cardiomyocytes reduced with disappearance of intracellular vacuoles, recovery of electron-density of cytosol and cell organelles,[28] down-regulation of mineralocorticoid receptors and aquaporin 1 channels. They found PACM to be a reversible entity, which suggests that myocardial hypertrophy can be alleviated after surgical treatment of PA, thereby reducing the risk of CVD.[28] The finding that cardiovascular risk in patients with surgically treated PA is not lower than EH may be caused by a combination of factors, including the variable rate of complete clinical success after surgery ranging from 17% to 62% (PASO);[29] concurrent EH and other metabolic diseases such as diabetes and dyslipidemia that persist after a surgical cure of PA;[30] and the presence of irreversible target organ damage in patients who suffered a long duration of PA prior to targeted treatment.[31] Furthermore, in Frustacid's study, myocardial fibrosis remained unchanged even after adrenalectomy, which suggests that some degree of myocardial damage is irreversible.[28]

Whether risks of CVD and mortality are higher or equal in patients with medically treated PA compared to those with EH are also controversial. Hundemer et al.[5] studied 602 MRA- treated patients and 41,853 patients with EH. After a 7-year follow-up, patients treated with MRA showed significantly higher risks of incident CVD and mortality than EH. Catena et al.[6] enrolled 54 medically treated PA and found no difference in CVD risk after 7.4 years of follow-up compared with EH. Our pooled results from four longitudinal studies demonstrated that the risk of CVD in medically treated PA was two-fold higher than treated-EH, while no statistical difference was observed in the risk of mortality. The cardiovascular protection of medical therapy in PA may be limited by the lack of adequate MRA dosing and therefore ongoing exposure to excess aldosterone. Hundemer et al.[5] found that 67% of medically treated patients had suppressed plasma renin activity (<1 g/l per h) at least 1 month after initiation of MRA therapy, which indicated insufficient mineralocorticoid receptor blockade and contributed to the significantly higher risks of incident CVD and mortality despite medical treatment. US Endocrine Society guidelines recommend that the starting dose for spironolactone should be 12.5–25 mg per day in a single dose, and the lowest effective dose should be set by gradually titrating upward if necessary, to a maximum dose of 100 mg/d.[1] Unfortunately, more than half of the included studies did not provide the dosage of MRA (Supplemental Table S4). Furthermore, aside from the study by Hundemer et al.,[5] none of the other studies reported on renin concentration or plasma renin activity as a marker of optimal MRA dosing. Another factor to consider in the medical treatment of PA is compliance. The need for long-term medications and side-effects associated with spironolactone treatment may reduce the actual dose of MRA taken. For example, a study from Italy indicated that MRA therapy was discontinued in 28% of patients with PA due to adverse effects.[32] Given the uncertainty about the adequacy of medical treatment in most studies, we cannot conclude that medical treatment is inferior in the management of PA.

The strength of our meta-analysis lies in the high quality of literature selected for analysis. Most of the articles received a quality score of higher than 5 points and were longitudinal studies published in the last 10 years. Importantly, surgically treated patients accounted for approximately 30%

of all the patients with PA and gave the study sufficient power to compare surgical PA treatment with both medical treatment and EH.

The main limitation of the meta-analysis is the small number of studies that evaluated mortality in PA. Therefore, the data on all-cause mortality should be interpreted with caution. We could not analyse individual CVD endpoints such as coronary heart disease, stroke, heart failure, lower limb vascular occlusion, atrial fibrillation because of lack of access to the original data. Data concerning the dose and adequacy of MRA treatment were limited, thus a definitive analysis of the impact of MRA therapy on CVD and mortality was not possible. Whilst the patient cohorts in the selected studies were all matched for age and sex, we do not have sufficient information to compare the blood pressure or age of patients who received surgical or medical treatment. An inherent limitation of the analysis is that older patients with more comorbidities are more likely to be given medical treatment and may therefore contribute to bias in our analysis. Lastly, patients who received medical treatment may have had unilateral PA that was not accurately diagnosed or did not qualify for surgery. However, the aim of this study is to compare the risk of CVD and all-cause mortality between two treatment strategies (surgery and medication), not the outcomes of the different subtypes of PA.

Conclusion

Patients with surgically treated PA have a decreased risk of CVD compared to patients with medically treated PA as well as a lower risk of all-cause mortality than those with EH. Medical treatment of PA, whilst associated with a higher risk of CVD compared to patients with EH, requires further evaluation where the adequacy of MRA dosing is assessed. Overall, this study strongly supports the early diagnosis and accurate subtyping of patients with PA who are candidates for curative surgical adrenalectomy; and the use of treatment targets such as renin together with stringent cardiovascular risk management in patients with medically treated PA.

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Author contributions

Jinbo Hu, Qifu Li and Ying Jing designed the study, oversaw the data collection and wrote the manuscript. Ying Jing and Kangla Liao contributed to the statistical expertise. Ruolin Li, Shumin Yang, Ying Song, Jun Yang and Wenwen He contributed to the writing of the manuscript. Ying Jing and Kangla Liao contributed to revise the manuscript. Jinbo Hu and Qifu Li are the guarantor of this work and, as such, have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read the journal's authorship agreement and that the manuscript has been reviewed by and approved by all named authors.

Declaration of conflicting interests

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Ethical approval

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Supplemental material

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