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SYSTEMATIC REVIEW

Effect of Angiotensin-Converting Enzyme Inhibitors on Physical Function in Elderly Subjects: A Systematic Review and Meta-Analysis

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Abstract

Background Sarcopenia has been accepted as a new geriatric syndrome, which will become a common and important public health challenge. And angiotensin-converting enzyme inhibitors (ACEIs) have been shown to improve exercise capacity in elderly without heart failure.

Objectives To evaluate the effect of angiotensin-converting enzyme inhibitors (ACEIs) on physical function in elderly.

Data Sources The Cochrane Library, PubMed, EMBASE and Web of Science were searched.

Eligibility Criteria All researches included were randomized controlled trials (RCTs) which compared any kind of ACEIs with placebo or other anti-hypertensives in elderly, and provided empirical data of grip strength and 6-min walk distance change from baseline.

Study Appraisal and Synthesis Methods Risk of bias was systematically assessed by using the Cochrane risk of bias tool. Data of grip strength and 6-min walk distance change from baseline were collected and mean differences (MDs) were calculated along with 95 % CI (confidence interval) by using a random effects model.

Results In 3 RCTs including 337 elderly participants, ACEIs ($n = 178$) did not significantly improved 6-min walk distance (13.45, 95 % CI: −16.71 to 43.61; $P = 0.38$) versus placebo or other antihypertensives ($n = 159$). In 3 RCTs including 499 elderly participants, grip strength was not significantly different (−0.67, 95 % CI: −1.53 to 0.19; $P = 0.12$) between ACEIs ($n = 260$) and placebo or other antihypertensives ($n = 239$).

Limitations There exists only 4 RCTs and the number of participants is limited. Pooling of data were from different trials including different participant characteristics. And intervention is not strictly consistent.

Conclusion This study shows that ACEIs can not significantly improve walk distance or the age-related decline of muscle strength for older participants in clinical trials.

Key Points

Sarcopenia has been accepted as a new geriatric syndrome and angiotensin-converting enzyme inhibitors (ACEIs) have been shown to improve exercise capacity among older patients without heart failure.

In this work, we evaluated the effect of angiotensin-converting enzyme inhibitors (ACEIs) on physical function in elderly subjects without heart failure and found that ACEIs can not significantly improve walk distance or the age-related decline of muscle strength for the elderly in clinical trials.

It remains unclear if ACEIs can be used us an appropriate treatment for sarcopenia, which needs more research. This review highlights the need of more data from studies involving measurements of muscle mass.

1 Introduction

Initially suggested by Rosenberg in 1989 [1], sarcopenia has been accepted as a new geriatric syndrome [2], with definitions of incorporating an age-related decline in

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muscle function (defined by muscle strength or physical performance) as well as skeletal muscle mass [3, 4]. And sarcopenia has been reported to affect more than approximately 600 million elderly individuals ≥60 years of age in the year 2000 worldwide. To the year 2050, the number is estimated to rise to 2 billion [3]. It will become a common and important public health challenge as the proportion of aged population rapidly increase in worldwide, associated with reduced physical capability, subsequent disability, falls, bone fracture and frailty, which lead to poorer quality of life, increases morbidity and mortality [1, 5–11]. Sarcopenia will also become an economic burden to healthcare services: the healthcare costs attributable to sarcopenia in the USA in 2000 were estimated to be $18.5 billion [12]. Therefore, identifying interventions that improving physical function represents one of the primary goals of geriatric medicine. To date, the therapeutic intervention attempting to improve muscle function has got progressive exercise training [13]. there is evidence of a beneficial effect of progressive exercise training on muscle strength and gait speed [14, 15]. However, the elderly are more likely to interrupt an exercise program because of being unwilling to do exercise training or diseases. So it is limited by the high attrition rates and low long-term compliance. Therefore, it's important to search for other strategies to prevent sarcopenia.

Cardiovascular disease which is common in elderly may contribute to sarcopenia because of reducing blood supply to skeletal muscle [16, 17]. And that Renin–angiotensin–aldosterone system (RAAS) blocking drugs may avoid this deleterious effect. Angiotensin converting enzyme inhibitors (ACEIs) have been demonstrated to improve in physical function in patients with congestive heart failure in a variety of studies [18]. Recent evidence suggests that ACEIs may improve physical function through the direct effects on the risk factors for sarcopenia, rather than blood-pressure-lowering effects. The pathogenesis of sarcopenia remains to be not fully understood. There are several identified risk factors that may be involved in the onset and progression of sarcopenia: inadequate nutrition, hormonal factors, chronic state of inflammation, oxidative stress, declines in neural function, apoptosis [19, 20], reduced protein synthesis [21], loss of mitochondrial function [22], reduced satellite cell function [23] and telomere length [24]. And many studies have indicated ACEIs treatment improved insulin sensitivity [25], protected against age-related mitochondrial dysfunction [26], decreased the mRNA expression of markers of inflammation and oxidative damage [27, 28]. So the effect of ACEIs for sarcopenia is promising. In clinical trials ACEIs have been shown to improve exercise capacity in elderly [29]. But there are also reports that ACEIs therapy can not enhance physical function the among older people. So far, its therapeutic value has not been widely accepted because conclusions are inconsistent and even conflicting in clinic [30]. The current review is aimed at synthetically evaluating the effect of ACEIs on physical function in elderly subjects by synthesized and analyzing the results from research papers.

2 Methods

2.1 Inclusion and Exclusion Criteria

Our meta-analysis of randomized controlled trials were reported in accordance with the PRISMA statement. The studies included had to meet all the following criteria: (1) randomized controlled trials which compared any kinds of ACEIs with placebo or with other anti-hypertensives (CCBs, b-blockers or diuretics); (2) all the patients in experiments were more than 60 years old; (3) minimum period of treatment with ACEIs was more than 4 weeks or 1 month; (4) articles published in English. Studies were excluded based on any of the following reasons: (1) the experiment was on the animals, (2) the data of grip strength and 6-min walk distance change from baseline could not be obtained in the article, (3) the study had no control group, (4) the articles were abstracts, letters, editorials and expert opinions, reviews without original data.

2.2 Literature Search Strategy

Studies published from 2000 to 2015, were mainly searched in the Cochrane Library, PubMed, EMBASE and Web of Science in English. The following keywords were used: "Angiotensin-Converting Enzyme Inhibitors", "ACEI", "ACE inhibitors", "physical function", "sarcopenia", "gait speed", "walk distance", "grip strength" and "elderly" (see "Appendix").

2.3 Study Selection and Data Abstraction

Two reviewers (Zhou, Xu) reviewed all searched studies including the title, the abstract then full texts for potentially eligible studies independently. Different articles with the same authors were check carefully to avoid overlapping of patients. The authors of articles would be contacted for full texts if necessary. To improve reliability of the present research, two authors (Zhou, Xu) extracted data from included articles independently. When there was disagreement, the both reviewers discussed with each other or with third reviewer (Xiao) to reach a consensus. The following data were extracted in each article: first author, year of publication, country, number of the patients in

experimental group and control group, age and sex of participants, ACEIs type and dose, duration of treatment, controls type and dose, and the data of grip strength and 6-min walk distance change from baseline. The data of grip strength and 6-min walk distance change from baseline were presented alone, or derived by calculating the raw data in articles. If the article showed the data of left and right hand grip strength respectively, we would get the weighted average.

2.4 Assessment of Methodological Quality

The methodological quality of the studies included was assessed by the instructions given in the Cochrane Handbook for Systematic Reviews of Intervention which comprises 5 domains (7 items): selection bias measured by how the sequence was generated and the allocation was concealed, performance bias measured by blinding of the participants, detection bias measured by blinding of the outcome assessment, attrition bias measured by how discontinuations and missing data were handled, and reporting bias measured by the outcomes reported. In addition, risk of other bias can be measured including imbalances, conflict of interest, etc [31]. The risk of bias in each trial was assessed as "high" or "low".

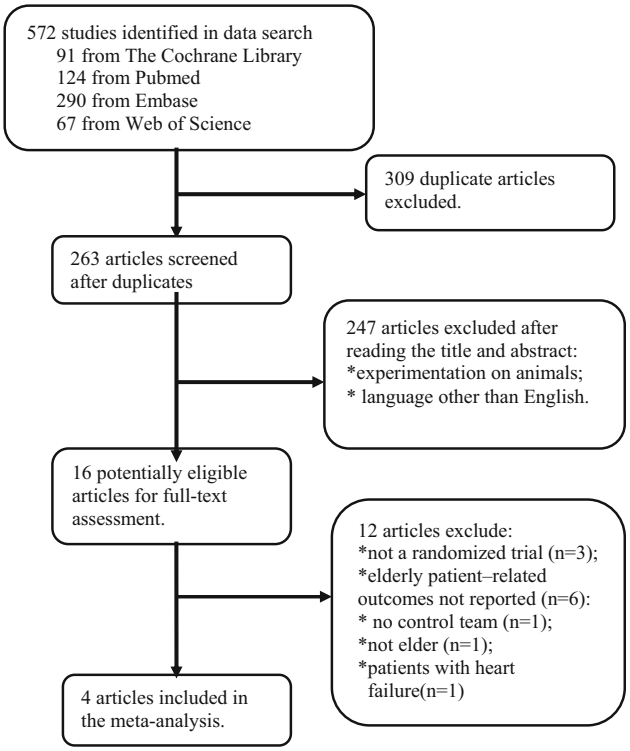

Fig. 1 Study selection flow

2.5 Data Analysis

Mean difference (MD) was measured along with 95 % CI for continuous variables. The heterogeneity was examined by both Chi-squared test and I^2 statistics. And meta-analysis were pooled in random-effects models because of the presence of heterogeneity between studies. The heterogeneity was considered statistically significant when $P < 0.05$ or $I^2 > 50$ %. The sensitivity analysis was conducted excluding each study at a time and then detecting the efficiency. If the results didn't change significantly, the results would be considered as robust. The analysis was performed by using RevMan 5.2.4 software.

3 Results

3.1 The Flow of Trial and Characteristics of Included Studies

The detail flow diagram of articles selection was shown in Fig. 1. A total of 263 articles were found after duplications removed, of which 16 potentially eligible articles were for full-text assessment. Based on the inclusion and exclusion criteria, 12 articles were excluded [32–43] and the rest 4 articles included in our meta-analysis [29, 30, 44, 45]. The main characteristics of randomized clinical trials of included articles were shown in Table 1 and characteristics of participants were shown in Table 2. In total, there are 337 elderly participants for 6-min walk distance while 499 elderly participants for grip strength in the meta-analysis. The methodological quality of included articles is shown in Fig. 2.

Table 1 Main characteristics of randomized clinical trials

References	Country	Intervention	*n* (intervention/control)	Control	Follow-up	Exercise (intervention)
Bunout et al. [44]	Chile	ENalapril 10 mg/day	50/32	Nifedipine	9 months	No
Sumukadas et al. [30]	UK	Perindopril 4 mg/day	83/77	Placebo	20 weeks	Yes
Sumukadas et al. [29]	UK	Perindopril 4 mg/day	45/50	Placebo	20 weeks	No
Cesari et al. [45]	Italy	Fosinopril 40 mg/day	127/130	Placebo	6 months	No

n number, *UK* United Kingdom, *mg* milligram

Table 2 Characteristics of participants

References	Mean age Intervention/control	Female/male Intervention/control	BMI (Kg/m^2) Intervention/control	Diagnosis and comorbidities	Walking capacity[a,b] (m) Intervention/control	Grip strength[a] (kg) Intervention/control	Condition	Concomitant treatments
Bunout et al. [44]	75 ± 4/75 ± 4	38/12/21/11	NK	Stage I HT	0.25 ± 159.6/−19.4 ± 138.9	−0.6 ± 14.8/−0.3 ± 15.0	NK	NK
Sumukadas et al. [30]	76.3 ± 7.3/75.1 ± 6.2	52/31/42/35	28.0 ± 5.3/29.2 ± 5.5	HT; OA; AP; pulmonary disease; DM; PAD; AF	29.6 ± 74.9/36.4 ± 59.2	1.0 ± 3.5/1.0 ± 5.2	Mobility impairment	Beta blockers; calcium antagonist; diuretics; analgesics
Sumukadas et al. [29]	78.7 ± 6.2/78.3 ± 6.9	32/13 / 34/16	67.11 ± 4.9/66.1 ± 12.4	HT; CAD; PAD; stroke; DM; Parkinson's disease	24.6 ± 51.2/−6.8 ± 51.2	NK	Mobility impairment	Diuretic; beta blockers; calcium antagonist; nitrate; statin
Cesari et al. [45]	65.9 ± 7.2/66.0 ± 7.6	56/71/53/77	28.9 ± 4.7/29.0 ± 4.8	CAD; cancer; DM; HT; pulmonary disease; PAD; stroke; GU	NK	−2.7 ± 26.7/−1.4 ± 27.0	NK	NK

AF atrial fibrillation, *AP* angina pectoris, *BMI* body mass index, *CAD* coronary artery disease, *DM* diabetes mellitus, *GU* gastric ulcer, *HT* hypertension, *NK* not known, *OA* osteoarthritis, *PAD* peripheral arterial disease

[a] Change from baseline

[b] Six-min walking distance

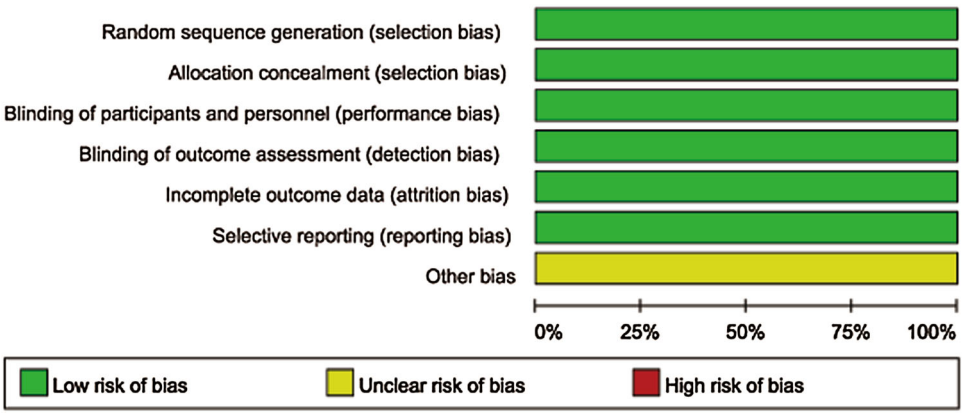

Fig. 2 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

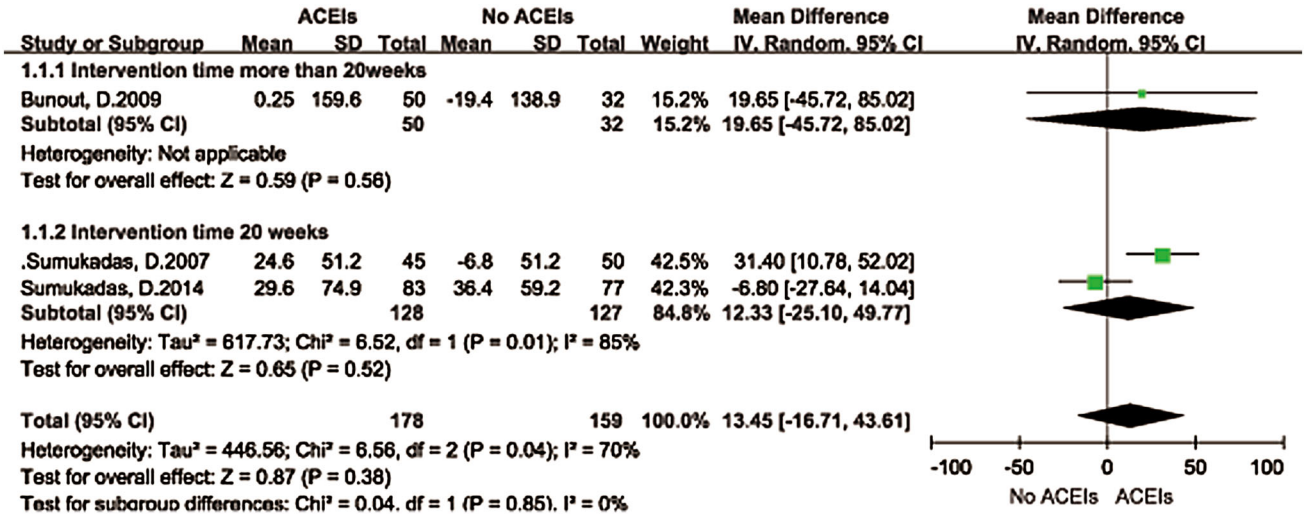

Fig. 3 Forest plot of comparison ACEIs with no ACEIs for 6-min walk distance. The mean of 6-min walk distance is the change in 6-min walk distance with or without ACEIs, and *SD* represents the change in 6-min walk distance after therapy. *Total* represents the total number of patients. *SD* standard deviation, *IV* inverse variance, *df* degrees of freedom, *CI* confidence interval

3.2 Risk of Bias Within Studies

As shown in Fig. 2, the quality of articles included was satisfactory. All studies had detailed description of randomization, allocation concealment methods, double-blinding and adequate reporting on loss to follow up and withdraw.

3.3 Effect of ACEIs on 6-Min Walk Distance and Grip Strength

The forest plots of comparison between ACEIs and no-ACEIs for 6-min walk distance and grip strength were shown in Figs. 3 and 4. Overall, 3 trials assessed the effect of ACEIs for 6-min walk distance compared to placebo or other antihypertensives [29, 30, 44]. These studies included 337 patients, of which 178 patients received ACEIs while 159 patients received placebo or other antihypertensives. A random effect model showed that ACEIs could not significantly improve 6-min walk distance (13.45, 95 % CI: −16.71 to 43.61; $P = 0.38$) versus placebo or other antihypertensives (Fig. 3). In 3 RCTs including 499 elderly participants, of which 260 patients received ACEIs and 239 patients received placebo or other antihypertensives [30, 44, 45], grip strength was not significantly different (−0.67, 95 % CI: −1.53 to 0.19; $P = 0.12$) between ACEIs and placebo or other antihypertensives.

3.4 Heterogeneity

Study on the effects of heterogeneity is key to know the possible influencing factors on accurate estimates in statistics and to evaluate whether merging different studies is appropriate. I^2 of 6-min walk distance and grip strength

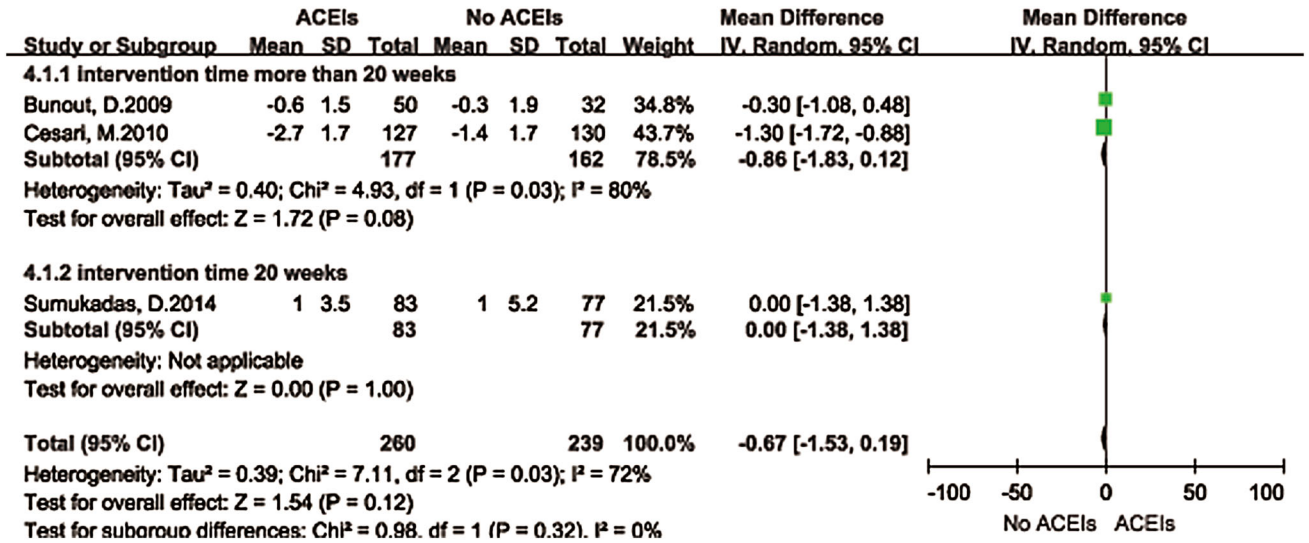

Fig. 4 Forest plot of comparison ACEIs with no ACEIs for grip strength. The mean of grip strength is the change in grip strength with or without ACEIs, and *SD* represents the change in grip strength after therapy. *Total* represents the total number of patients. *SD* standard deviation, *IV* inverse variance, *df* degrees of freedom, *CI* confidence interval

compared between ACEIs and no-ACEIs were 73, 72 %, implicating there being significant heterogeneity.

3.5 Sensitivity Analysis for Heterogeneity

We explained this heterogeneity by using sensitivity analysis. Sensitivity analysis with 6-min walk distance compared between ACEIs and no-ACEIs showed that the result had marked change from primary analysis when excluding one study [30] from analysis while the result of grip strength showed similarity to the primary analysis. when we excluded this study, I^2 of 6-min walk distance between ACEIs and no-ACEIs changed from 73 to 13 %, which showed that this study had influence on heterogeneity.

4 Discussion

One report has shown that there is a mean loss of 230 and 500 g/year of fat free mass among healthy women and men more than 70 years old [46]. It's important to search for the way to prevent sarcopenia and improve physical function in elderly subjects. The current study, derived from 4 randomized studies, is the first meta-analysis to assess the effect of ACEIs on physical function in elderly. Main findings of our meta-analysis is that 6-min walk distance and grip strength were not significantly different between ACEIs and placebo or other antihypertensives for old people.

Gait speed and grip strength have been used in EWGSOP diagnosis for sarcopenia. In clinic, gait speed is usually assessed by measuring the time taken to walk a set distance or the walk distance in a limited time at usual pace. Older people with slow gait speed have been found to be at an increased risk of subsequent disability, falls, cognitive decline, hospitalization, and mortality, as well as stroke and heart failure [47–50]. Grip strength has been recommended as the most practical method of measuring muscle strength which can predict the measured health outcomes while quadriceps strength can not [51]. Grip strength showed an association with quality of life, disability, mortality, hospitalization [51–53]. Many studies have shown that ACEIs have favorable effect on physical function. The mechanisms for effects of ACEIs on skeletal muscle may be concluded as muscle fiber type effect which determines a shift of the myosin-heavy chains of leg skeletal muscle from type II toward type I, Anti-inflammatory effect, nutritional effect, effects on angiogenesis and metabolic effect [54]. Our result showed that ACEIs could not improve gait speed and grip strength significantly, indicating that ACEIs could not improve physical function in elderly, which was inconsistent with the results from animal experiments [55–58]. The reasons for this phenomenon may relate to the short tintervening time and limitations of this meta-analyses.

One report showed that the elderly using ACEIs derived more functional benefit from a exercise intervention than nonusers which indicated that exercise might be used to stimulate certain adaptations to pharmaceuticals [33]. Similarly, it was reported that the ACEIs combined with exercise improved in physical performance but there was no effect when used ACEIs alone in rodents [59–61]. However, Sumukadas et al showed that ACEIs did not enhance the effect of exercise training on physical function

among functionally impaired older people [30]. Whether or not combination ACEIs with exercise can improve in physical performance needs more research. Genetic studies also show that the ACE system may be involved in skeletal muscle function. People with the II genotype of the ACE gene have lower ACE activity and have been found to have a better endurance performance and better anabolic response to exercise training, as compared with individuals with the DD genotype which is associated with a higher ACE activity [62]. In a prospective study, participants with ACE II genotype showed a significant increase in both fat and lean mass compared to those with the DD genotype in response to the same exercise [63]. And it demonstrated that enhanced responsiveness to exercise among people with ACE II genotype perhaps was mediated by an increase in muscle strength. At the same time, it indicated that the effect of ACE system for physical function might have some relationship to exercise. Regarding the role of ACEIs status and intervention in physical performance in elderly persons, it needs more study.

The strengths of our review include that all researches included are RCTs only, and we excluded case-control and cohort studies to guarantee the quality. The methodological quality was satisfactory which increased the reliability of the results. As we all know, ACEIs can improve physical performance of patients with diastolic heart failure. We excluded the participants with heart failure in order to assure the reliability of the results. And there are many limitation of the study. One is the high heterogeneity among included studies. These may contribute to heterogeneity: different drugs used in research, different intervening interval and weather or not combined with exercise. Another limitation is that there exists only 4 RCTs and the number of participants is limited. In addition, pooling of data were from different trials with different participant characteristics. Some of the participant in the included trials are health people while some are disable. Full details of the characteristics of the elderly participants and the adverse of drug were not reported. Meanwhile the outcome indicators in the study were measured by people, which could produce system bias. The topic is new, and we want to bring recent researches into the article. We searched the studies published from 2000 to 2015, which is likely introducing temporal bias. Diagnostic criteria for sarcopenia includes physical performance (such as gait speed), muscle strength and muscle mass. But only one of the studies included has the data of muscle mass. The muscle mass is usually measured by dual energy X-ray absorptiometry (DXA) which may be more objective and reliable. Further research should include the measurement of muscle mass in order to show the effect of drugs for sarcopenia better.

5 Conclusion

The current meta-analysis found that treatments with ACEIs can not significantly improve 6- min walk distance and do not work on grip strength compared with placebo or other antihypertensives. That whether or not ACEIs can be used as an appropriate treatment for sarcopenia needs more research. This review highlights the need of more data from studies involving measurements of muscle mass. Further studies are required to improve our understanding of the mechanisms of sarcopenia's effect.

Compliance with Ethical Standards

Conflict of interests Our work was supported by grants from the National Key Clinical Specialties Construction Program of China (No. [2013]544). Ling-shan Zhou, Ling-jie Xu, Xue-qing Wang, Yi-huan Huang, Qian Xiao have no competing, conflicting interests to report.

Appendix

Search strategy

("Angiotensin-Converting Enzyme Inhibitors" **OR** "Angiotensin Converting Enzyme Inhibitors" **OR** ACEI **OR** "ACE inhibitors" **OR** "antihypertensive") **AND** ("physical function" **OR** sarcopenia **OR** "exercise performance " **OR** "gait speed" **OR** "muscle strength" **OR** "grip strength") **AND** ("old people" **OR** elderly **OR** aged).

("Angiotensin-Converting Enzyme Inhibitors"**[Mesh]**) **AND** ("physical function" **OR** sarcopenia **OR** "exercise performance" **OR** "gait speed" **OR** "muscle strength" **OR** "grip strength") **AND** ("old people" **OR** elderly **OR** aged).

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