STATE OF THE ART REVIEW

Effect of calcium channels blockers and inhibitors of the renin-angiotensin system on renal outcomes and mortality in patients suffering from chronic kidney disease: systematic review and meta-analysis

Hong-Jin Zhaoa,b*, Yan Lib,c*, Shan-Mei Liud, Xiang-Guo Sunb, Min La, Yan Haoa, Lian-Qun Cuia and Ai-Hong Wanga

aDepartment of Cardiology, Provincial Hospital affiliated to Shandong University, Ji’nan, P.R.China; bDepartment of Obstetrics and Gynecology, Child & Family Research Institute, University of British Columbia, Vancouver, British Columbia, Canada; cDepartment of Obstetrics and Gynecology, Peking University Third Hospital, Beijing, P.R. China; dDepartment of Nephrology, Linyi City Yishui Central Hospital, Yishui, Linyi, Shandong, P.R. China; eDepartment of Pediatrics, Linyi City Yishui Central Hospital, Yishui, Linyi, Shandong, P.R. China

ABSTRACT

Background: The renoprotective effect of inhibitors of renin-angiotensin system (RAS) has been identified through placebo-controlled trials. However, the effect of calcium-channel blockers (CCBs) on renal system is still controversial. Our current meta-analysis includes available evidences to compare the effect of dihydropyridine CCBs and ACEIs or ARBs on renal outcomes and mortality. We also further investigate whether CCBs can be used in combination with inhibitors of RAS to improve the prognosis of patients with chronic kidney disease (CKD).

Methods and results:

Electronic databases were searched up to July 2012, for clinical randomized controlled trials, assessing the effect of dihydropyridine CCBs on the incidence of end-stage renal disease (ESRD) and all-cause mortality in contrast to ACEIs or ARBs. Eight clinical trials were included containing 25,647 participants. ESRD showed significantly higher frequency with CCBs therapy compared with ACEIs or ARBs therapy, though blood pressure was decreased similarly in both groups in every trial (OR, 1.25; 95% CI, 1.05–1.48; \( p = 0.01 \)). In contrast, there was no significant difference in the incidence of all-cause mortality between these two groups, though ACEIs or ARBs exhibited better renoprotective effect compared to CCBs (OR, 0.96; 95% CI, 0.89–1.03; \( p = 0.24 \)).

Conclusions: CCBs did not increase all-cause mortality incidence in patients with CKD though they displayed weaker renoprotective, compared to ACEIs or ARBs therapy. Our results suggest the combination of a CCB and an ACEI or ARB should be a preferable antihypertensive therapy in patients with CKD, considering their higher effect in decreasing blood pressure and fewer adverse metabolic problems caused.

ARTICLE HISTORY

Received 13 January 2016
Revised 1 March 2016
Accepted 7 March 2016
Published online 7 April 2016

KEYWORDS

All-cause mortality; angiotensin-converting enzyme inhibitor; angiotensin-II receptor blocker; calcium-channel blocker; chronic kidney disease; end-stage renal disease

Introduction

Hypertension accounts for nearly 30% of end-stage renal disease (ESRD) in the United States.1 Effective blood pressure control has been well accepted as a clinical strategy to slow down the progression of chronic kidney disease (CKD) to ESRD.2,3 Calcium-channel blockers (CCBs) and inhibitors of renin-angiotensin system (RAS) are the most common and effective antihypertensive agents, especially the latter including angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been proven to protect renal system in addition to those benefits resulted from lowering blood pressure alone.4 Based on a large body of evidence from clinical studies, international guidelines have endorsed the opinion that inhibitors of the RAS should be the first-line antihypertensive therapy in patients with diabetic and nondiabetic nephropathy because of their protective effect in slowing down the progression of CKD to ESRD. But for many patients with hypertension as well as CKD, one ACEI or ARB is not enough to decrease blood pressure to an ideal level. Moreover, if we just increase the dose of ACEI or ARB or combine ACEI and ARB to get a nice blood pressure control, some metabolic problems especially hyperkalemia will appear, which send patients with CKD to very dangerous conditions.5 Dihydropyridine CCBs, effective antihypertensive agents with little possibility to cause metabolic problems, could be used in combination with inhibitors of RAS to enhance the efficiency of lowering blood pressure for patients with CKD. However, the
effects of CCBs on renal diseases drawn from current the available clinical data are quite contradictory: bene-
ficial, neutral, even adverse.6–8

To assess the action of CCBs on the progression of CKD, we undertook a systematic review and meta-analy-
ysis of clinical randomized controlled trials investigating the effects of CCBs on renal outcomes and all-cause mortalit
y compared with ACEIs or ARBs.

**Methods**

**Search and selection process**

We did a computerized search of the Pub Med, Cochrane Library, reviews, and reference lists of relevant papers. The search strategy was supplemented manually by reviewing reference lists and querying investigators working in this field. Included studies met the following four criteria: (1) Studies had to be clinical randomized controlled trials, and the parallel-design in multicenter would be better; (2) Studies examined the effect of dihy-
dropyridine CCBs on the progression of renal disease and all-cause mortality compared with that of ACEIs or ARBs at similar blood pressure control in CKD patients associated with hypertension and/or diabetes mellitus. If maximum tolerated doses of the blinded drug failed to effect the assigned blood pressure goal, additional drugs could be added: furosemide, doxazosin, metopro-
lol, clonidine, hydralazine, minoxidil and so on; (3) Progression of renal disease was assessed by using the incidence of ESRD, which is defined as the necessary for kidney transplantation, hemodialysis or a serum creatin-
ine concentration of about 5.0 mg per deciliter, even renal death. All-cause mortality was also taken into
account; (4) Studies had to have a minimum follow-up of two years and at least 100 participants. Only studies published as full-length articles in English-language journals were included.

Two reviewers (Hong-Jin Zhao and Yan Li) masked to the study authors and journals in which the studies were published, independently extracted data from published sources and determined whether the trials met the inclusion criteria. Disagreements were resolved by joint review and consensus.

**Data extraction**

Two reviewers, (Hong-Jin Zhao and Yan Li), independ-
ently extracted data from published sources regarding methodological features, the numbers of treated patients, mean follow-up exposure, patients’ characteristics and the occurrence of the following two outcomes: ESRD and all-cause mortality. If relevant information could not be extracted, the study authors were con-
tacted by e-mail, with a reminder after 30 days. Uncertainties were resolved by joint review and consensus.

**Statistical analysis**

Meta-analyses of the trial results are presented as pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) calculated using the Mantel–Haenszel method for CCBs compared with ACEIs or ARBs. A p val-
ues less than 0.05 were considered statistically signifi-
cant; all tests and CIs were two-sided. Analyses were
carried out by using Review Manager statistical software (Review Manager version 5.0.21.0; The Nordic Cochrane Center, Rigs Hospitalet). The appropriation of pooling the results from individual studies was assessed using the $I^2$ test for heterogeneity. The $I^2$ value describes the percentage of total variation across studies due to heterogeneity rather than chance, and we considered $I^2$ more than 50% to indicate significant heterogeneity among the trials. All analyses were initially assessed using a fixed-effects model, and if heterogeneity across studies was observed, the analyses were repeated using a random-effects model, which includes a measure of variance in the calculation of pooled results. Publication bias was assessed using a funnel plot of effect size against standard error.

**Results**

**Study selection**

As shown in Figure 1, a total of 526 potentially eligible studies were identified, of which 504 were excluded after reviewing the study titles, leaving 22 studies for a more detailed evaluation. Of these 22 studies, 14 studies were excluded for the following reasons: duplicate data in 4 studies; there were 3 studies concerning renal outcomes but no ESRD or all-cause mortality; two studies were not randomized controlled trials; all the participants in two studies were hemodialysis patients; one study was about the survival only in kidney transplant patients; the number of participants in two trials was less than 100; Totally, eight studies were therefore included in this meta-analysis.

**Study characteristics and quality**

The baseline characteristics of eight included studies including a total of 25,647 patients were shown in Table 1. All included studies were randomized controlled trials (RCT) published in English, six of which
were prospective RCT in multiple clinical centers with higher quality.

Quantitative data synthesis and analyses
Data related to blood pressure and the outcomes of ESRD as well as all-cause mortality during follow-up is documented in Table 2.

ESRD showed significantly higher frequency with CCBs therapy compared with ACEIs or ARBs therapy, though blood pressure was decreased similarly in the CCBs group and ACEIs group in every trial (OR, 1.25; 95% CI, 1.05–1.48; \( p = 0.01 \)) (Figure 2).

In contrast, there was no significant difference in the incidences of all-cause mortality between the two groups, though ACEIs or ARBs exhibited obvious renoprotective effect (OR, 0.96; 95% CI, 0.89–1.03; \( p = 0.24 \)) (Figure 3).

Publication bias
This was assessed with two funnel plots, which are available from us on request. The funnel plots for ESRD and all-cause mortality during follow-up were symmetric, suggesting the absence of publication bias.

Discussion
Although similar blood pressure responses in two groups of every trial at the end of follow-up, ACEIs or ARBs reduced ESRD more effectively than CCBs. Hypertension is known as an essential risk factor for CKD and can promote the progression of CKD to ESRD. High systemic pressure transmitted to the renal microvasculature, causing increased renal intraglomerular filtration and subsequent hypertensive renal damage.22 African–American study of kidney disease and hypertension (AASK) revealed that renal death happened less frequently in a relatively lower blood pressure group of patients treated with amlodipine, suggesting the renoprotective effect of dihydropyridine CCBs through antihypertensive action.23 To the contrary, some experts believe that BP reduction achieved by CCBs provides the expected renoprotective effect because blockades of the “L” type Ca\(^{2+}\) channels lead to vasodilation of the preglomerular arteriole, rendering high renal glomerular
filtration pressure that will impair the vascular wall and promote protein excretion called proteinuria that will further enhance the damage to the renal function while they reduce BP. On the other hand, inhibitors of RAS might effectively lower filtration pressure to improve glomerular pore size, reducing proteinuria to attenuate renal damage through inhibiting angiotensin II which has strong vasoconstrictive effect on postglomerular vasculature. These different effects on the renal microvasculature between these two types of antihypertensive drugs may partly explain why ACEIs or ARBs can slow down the progression of CKD to ESRD much more effectively than CCBs.

The accumulation of bradykinin (BK) has been confirmed as a factor to the renal protection in ACEI group. It has been well known that ACEI can delay the degradation of BK, leading to the increment of BK throughout the body that is responsible for frequent cough in some patients treated with ACEI. However, the insulin-like effect of BK helps the improvement of insulin sensitivity, subsequently attenuating the pernicious effects of hyperglycemia to the renal microvasculature in diabetic patients. Furthermore, besides BK, ACEI can also induce the increment of angiotensin 1–7 rendering reduction of plasminogen activator inhibitor-1, which is another risk factor for the renal function, whereas CCBs have no such additional benefits on renal outcomes. Though ACEIs or ARBs can significantly decrease the occurrence of ESRD, showing obvious renoprotective effects of major cardiovascular events and mortality, the risk of ACEIs or ARBs-associated anemia and especially hyperkalemia definitely contributed to mortality. Therefore, the risk of ACEIs or ARBs-associated anemia and especially hyperkalemia definitely contributed to mortality, especially in diabetic patients.

Though inhibitors of RAS show obvious renoprotective effects in keeping blood pressure in the optimal level, the incidence of diabetes, hypertension, and cardiovascular disease is still rising in the world. Therefore, the combination of the ACEI and ARB to enhance the renoprotective effects of the ACEIs or ARBs therapy is of great significance in the treatment of kidney diseases.

### Table 1. Study characteristics comparing the therapeutic benefits and risks of CCBs therapy versus ACEIs or ARBs therapy.

| Clinical trials | Year | Agent and daily dose (mg) | n | Age* (years) | Men (%) | Mean follow-up | SBP* (mm Hg) | DBP* (mm Hg) | Diabetes | HT | RCT | Multi-center |
|----------------|------|--------------------------|---|--------------|---------|----------------|--------------|--------------|-----------|----|-----|--------------|
| FACET          | 1998 | amlodipine (10 mg/day)   | 191 | 63.3 (04)    | 55.5    | 3.5 years      | 171 (1)      | 94 (1)       | Y         | Y  | Y   | N            |
| ARD            | 1998 | fosinopril (20 mg/day)   | 189 | 62.8 (05)    | 63.5    | 3.5 years      | 170 (1)      | 95 (1)       | Y         | Y  | Y   | N            |
| STOP-2         | 1999 | felodipine 2.5 mg or isradipine 2–5 mg daily | 2196 | 75.9 | 34.0 | 54 months | 194 | 98 | Y | Y | Y | N |
| AASK           | 2001 | amlodipine (5-10 mg/day) | 211 | 54.4 (10.7) | 59.9 | 36 months | 150.0 (25.3) | 95.7 (14.1) | Y | Y | Y | Y |
| Lewis          | 2002 | amlodipine (10 mg/day)   | 567 | 59.1 (79.2) | 65    | 30.8 months   | 159 (19)    | 87 (11)      | Y | Y | Y | N |
| Marin          | 2001 | irbesartan (300 mg/day)  | 579 | 59.3 (71.1) | 63    | 31.7 months   | 160 (20)    | 87 (11)      | N | Y | Y | N |
| ALLHAT         | 2005 | amlodipine (2.5, 5, and 10 mg/day) | 3213 | 66.1 (79) | 45.6 | 4.9 years | 146.1 (15.9) | 84.7 (10.3) | P | Y | Y | Y |
| ALLHAT         | 2005 | fosinopril (10-30 mg/day) | 129 | 53.1 (14)    | 60.9   | >3 years      | 155 (17)    | 96 (11)      | N | Y | Y | Y |
| Marin          | 2001 | amlodipine (5-10 mg/day) | 131 | 57.5 (12.9) | 60    | 2.9 years     | 165.2 (16.6) | 102.5 (7.1) | N | Y | Y | N |

*Values are mean (SD).

Notes: Values are mean (±SD). SBP and DBP: systolic and diastolic blood pressure; HT: hypertension; RCT: randomized controlled trial; Y: yes; N: no; P: partial.
blood pressure control, the serum potassium concentration would be significantly increased which may be lethal to patients, especially when the renal function was not optimal. Another adverse effect of high dose ACEI or ARB therapy is severe anemia, partly resulted from the reduction of angiotensin II which is known to stimulate erythropoietin in certain circumstances. ACEIs or ARBs has been suggested as the first choice to control blood pressure in patients with CKD. However, it does not mean CCBs cannot be considered as a part of the combination of antihypertensive therapy. Shokei et al. have proved that the combination of ARB and CCB exhibited greater efficacy in preventing cardiovascular events in CKD patients.

### Figure 2
Risk of ESRD in patients receiving CCBs therapy or ACEIs/ARBs therapy. The meta-analysis of ESRD showed significantly more events with CCBs therapy compared with ACEIs or ARBs therapy (OR, 1.25; 95% CI, 1.05–1.48; P = 0.01). CI indicates confidence interval; OR: odds ratio; ESRD: end-stage renal disease; CCBs: calcium-channel blockers; ACEIs: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin-II receptor blockers.

### Figure 3
Risk of all-cause mortality in patients receiving CCBs therapy or ACEIs/ARBs therapy. There was no significant difference in the incidence of all-cause mortality between the two groups (OR, 0.96; 95% CI, 0.89–1.03; P = 0.24). CI: confidence interval; OR: odds ratio; CCBs, calcium-channel blockers; ACEIs: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin-II receptor blockers.
compared with high dose ARB alone. Furthermore, ACEIs or ARBs combined with CCBs has been shown to particularly reduce the risk of hyperkalemia and other metabolic problems.

In conclusion, CCBs did not increase all-cause mortality in patients with CKD though they displayed less renoprotection effect in reducing the occurrence of ESRD, compared with ACEIs or ARBs therapy. Although the long-term efficacy of the combination of a CCB and an ACEI or ARB therapy needs further confirmation, our results suggest this combined antihypertensive therapy could be a more preferable antihypertensive therapy in patients with CKD, considering its effective blood pressure controlling, an assured antiproteinuria effect and fewer adverse metabolic problems.

Acknowledgements

Dr. Hong-Jin Zhao and Yan Li contributed to the data extraction from the literature, statistical analysis and the writing of this paper. Dr. Shan-Mei Liu, Xiang-Guo Sun, Min Li and Yan Hao contributed to statistical analysis and helped gather references for the manuscript. Dr. Lian-Qun Cui and Ai-Hong Wang contributed to design, direction, and supervision of data analysis and revision of the manuscript.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding information

This work was supported by research grants from the Natural Science Foundation of Shandong Province [2010ZR81488].

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