Short- and long-term treatment with angiotensin-converting enzyme inhibitors or calcium channel blockers for the prevention of diabetic nephropathy progression: A meta-analysis

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Received May 21, 2020; Accepted October 14, 2020

DOI: 10.3892/etm.2020.9446

Abstract. Treatments with angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (CCBs) may delay the development of albuminuria in patients with early diabetic nephropathy. However, evidence in the literature has not been consistent. The present meta-analysis aimed to compare the short- and long-term therapeutic effects of ACE inhibitors and CCBs (when used separately) for preventing the progression of nephropathy in patients with diabetes mellitus. A comprehensive search of various databases was performed from inception until March 2015 for studies in the Chinese and English languages. Randomized controlled trials (RCTs) comparing the efficacy of ACE inhibitors with that of CCBs in patients with early diabetic nephropathy were considered. A total of 12 RCTs were included with a total of 947 patients. ACE inhibitors were indicated to be more effective in reducing the albumin excretion rate than CCBs after short-term treatments (<6 months) [mean difference (MD), 32.35; 95% confidence interval (CI), 31.62-33.07; P<0.00001]. There was no difference in serum creatinine values after treatment with either drug (MD, 8.7; 95% CI, -21.5-38.91; P=0.57). Data from six studies were used to compare long-term treatment effects (≥1 year). In terms of progression to normoalbuminuria, a marginal difference was obtained between the two drugs with better outcomes with ACE inhibitors [odds ratio (OR), 0.70; 95% CI, 0.49-1.00; P=0.05]. There was no statistically significant difference between ACE inhibitors and CCBs regarding the progression from microalbuminuria to macroalbuminuria (OR, 1.78; 95% CI, 0.82-3.87; P=0.15). In conclusion, the present study indicated that the antiproteinuric efficacy of CCBs may be less than that of ACE inhibitors after short-term treatment in patients with DN. However, both types of drugs are equally effective in reducing the progression of microalbuminuria to macroalbuminuria in the long term.

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Key words: angiotensin-converting enzyme inhibitors, calcium channel blockers, meta-analysis, early diabetic nephropathy

Introduction

Diabetes mellitus is a common metabolic disease with increasing prevalence worldwide. According to a global study published in 2004, the disease affected 150 million adults in 2000 and that number is expected to increase to 350 million by 2030 (1). Diabetic nephropathy (DN) affects 20-40% of all patients with diabetes mellitus and is one of the most important microvascular complications resulting in increased morbidity and mortality (2). DN causes irreversible proteinuria and kidney damage and is one of the principal causes of end-stage renal disease in this population (3). In addition, DN is frequently accompanied by a steadily increasing blood pressure and a slow but progressive loss of kidney function. Once the kidney function begins to decline, it may deteriorate by ~10% per year if left untreated. Microalbuminuria is a vital marker for the development of DN. Therefore, early DN with an albumin excretion rate (AER) ranging between 20 and 200 μg per min (30-300 mg/24 h) is an important stage in the progression of nephropathy. Effective treatment in this phase may reverse the albuminuria and reduce the incidence of end-stage renal disease.

Antihypertensive drugs are able to effectively diminish DN progression. Angiotensin-converting enzyme (ACE) inhibitors, which belong to the class of renin-angiotensin system (RAS) blockers, are recommended as the primary antihypertensive drugs. In addition to inhibiting the RAS

system, thereby producing a hypotensive effect, they also decrease proteinuria, preserve the glomerular filtration rate and limit the progression to renal failure (4,5). However, the efficacy of other antihypertensive agents, in particular that of calcium channel blockers (CCBs), to confer similar effects on albuminuria has not been clarified and the clinical importance of the selection of different antihypertensive drugs remains elusive. The Melbourne Diabetic Nephropathy Study Group (MDNSG) reported similar efficacies for the ACE inhibitor perindopril and the CCB nifedipine for preventing the development from macroalbuminuria to microalbuminuria in patients with types 1 and 2 diabetes after long-term treatment (6). However, comparisons of short-term treatments with ACE inhibitors and CCB in patients with early DN have not provided any consistent results (5,7-9). Therefore, the purpose of the present study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing the efficacy of ACE inhibitors and CCBs after short- or long-term treatments for patients with early diabetic nephropathy to elucidate their efficacy to prevent nephropathy.

Materials and methods

Search strategy. Guidelines of the Cochrane handbook were followed during the conduct of this study (10). A comprehensive search of the PubMed, ScienceDirect, Embase, Cochrane Library, Chinese National Knowledge Infrastructure, China Biomedical Literature database and Wanfang digital periodical full-text databases from inception to June 2020 was performed. The language of publication was restricted to Chinese and English. The following key words were used for the literature search: 'Angiotensin-converting enzyme inhibitors'; 'ACE inhibitors'; 'calcium channel blockers'; 'CCB'; 'antihypertensive drugs'; 'nifedipine'; 'amlodipine'; 'lercanidipine'; 'manidipine'; 'enalapril'; 'fosinopril'; 'delapril'; perindopril'; 'ramipril'; 'diabetes mellitus'; 'diabetic nephropathy'; 'albuminuria'; 'creatinine'; 'kidney failure' and 'renal failure'. In addition, the references of included studies and pertinent review articles were manually searched to retrieve any additional studies.

Study selection. The following inclusion criteria were applied: i) RCTs comparing ACE inhibitors and CCBs for the treatment of early DN; ii) studies including adult patients of either gender with primary type 1 or type 2 diabetes mellitus with or without hypertension; and persistent microalbuminuria (AER between 20 and 200 μg/min or 30 and 300 mg/24 h); iii) studies providing data of the study groups, including the baseline and follow-up period; iv) outcomes of the study were to include AER and serum creatinine (Scr) for short-term treatments, as well as the number of patients with improvements in albuminuria for long-term treatments. Studies comparing ACE inhibitors and CCBs for patients other than DN were excluded. Non-RCTs, retrospective studies, case series, case reports and studies not reporting relevant outcome data were also excluded.

Data extraction and quality evaluation. The following data were extracted independently in a standardized manner from all eligible studies: Authors, publication year, sample size, study duration, intervention and outcomes. Data on AER and Scr levels were extracted for short-term treatments and the number of patients improving (developing macroalbuminuria or normal albuminuria) for long-term treatments.

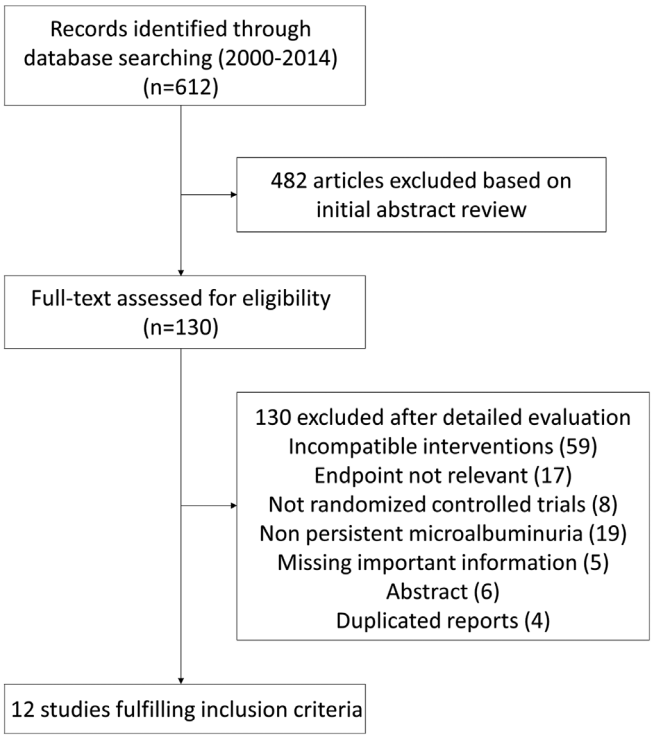

Figure 1. Flow chart of study selection.

The quality of each RCT was assessed using the Cochrane Collaboration risk assessment tool (11). Studies were rated as having low risk, high risk or unclear risk of bias in the following categories: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

Data analysis. Quantitative and qualitative analyses of the collected data were performed. Odds ratios (OR) were calculated for categorical variables and mean differences (MD) for continuous variables with 95% confidence intervals (CI). Review manager [version 5.3; 2014; Nordic Cochrane Centre (Cochrane Collaboration)] was used for the statistical analyses. Heterogeneity of the included studies was assessed using the I^2 test. I^2 values of <50% were considered to represent low heterogeneity and a fixed-effects model was used. For I^2 values of ≥50%, heterogeneity was considered to be significant and a random-effects model was used. $P \leq 0.05$ was considered to indicate statistical significance. Publication bias was to be assessed using funnel plots if there were >10 studies in a meta-analysis (10).

Results

Study characteristics. Fig. 1 presents the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of the study. The search yielded a total of 612 citations. After serial selection and evaluation, 12

Table I. Details of included studies.

Authors (year)	Country	Sample size CCB/ACEI	Study design	Age		Male sex (%)		Intervention measures		Glycosylated Hb_{1c} (%)		Baseline 24h AER (mg/24 h)		Baseline Scr (mg/dl)		Duration		Outcomes	Refs.
				CCB	ACEI	CCB	ACEI	CCB/dose (mg/d)	ACEI/dose (mg/d)	CCB	ACEI	CCB	ACEI	CCB	ACEI	Short-term	Long-term		
Rachmani *et al* (2000)	Israel	13/11	Randomized, single-blind cross-over	56.8±8.9	56.8± 8.9	54	54	Nifedipine/30	Enalapril/10	7.98±1.6	7.98±1.6	52.9±0.8	52.9±80.8	1±0.2	1±0.2	4W	-	AER	(12)
Fogari *et al* (2000)	Italy	55/52	Double-blind, randomized, parallel-group prospective	67.8±11	68.2± 12	NR	NR	Amlodipine/5-10	Fosinopril/ 10-20	6.9±1.8	7±2	96.59± 56	98.2±58	NR	NR	6M	-	AER	(13)
Shiba *et al* (2000)	Japan	7/6	Randomized	61±10.7	61± 8.1	56.3	43.5	Manidipine/10	Delapril/60	8.5±1.8	7.8±1.4	NR	NR	NR	NR	6M	-	AER	(14)
Luque Otero *et al* (2005)	Spain	37/40	Multicenter, randomized, double-blind	64±11	60±11	51	58.6	Manidipine/10	Enalapril/10	6.7±1.4	6.2±1	NR	NR	1.01± 0.18	0.97± 0.21	24W	-	Scr	(9)
Gao and Chang (2006)	China	9/8	Randomized	NR	NR	NR	NR	Amlodipine/2.5-5	Enalapril/ 5-10	NR	NR	106.3± 40.8	106.7± 41.8	1.04± 0.24	1.08± 0.26	12W	-	AER, Scr	(15)
Hu and Yang (2014)	China	50/50	Randomized digits table	71.3±2.4	71.2± 2.5	64	62	Amlodipine/2.5	Enalapril/20	NR	NR	NR	NR	NR	NR	1M	-	AER, Scr	(5)
Chan *et al* (2000)	HK,China	13/21	Randomized double-blind	56.2±9.9	60± 9.3	NR	NR	Nifedipine/40-80	Enalapril/ 10-40	7.32±1.11	7.7±1.17	NR	NR	NR	NR	-	5Y	Num	(16)
Baba *et al* (2001)	Japan	53/64	Randomized	60.2±8.9	59.9± 8.6	48.7	52.4	Nifedipine/20-60	Enalapril/ 5-20	7.5±1.7[a]	7.7±1.8[a]	45±5[a]	42±5[a]	0.77± 0.22[a]	0.76± 0.22[a]	-	2Y	Num	(17)
Jerums *et al* (2001)	Australia	13/10	Randomized	28±4	35±5	69.2	60	Nifedipine/20-80	Perindopril/ 2-8	9.1±0.7[a]	8.5±0.3[a]	NR	NR	84±6[ab]	87±6[ab]	-	3Y	Num	(19)
Fogari *et al* (2002)	Italy	103/102	Multicenter, open-labeled, randomized, prospective, parallel-group	62.6±8.5	63.1± 9.1	56.3	59.8	Amlodipine/5-15	Fosinopril/ 10-30	6.9±1.5	7.1±1.6	95.5±64.1	98.2±67.3	1±0.5	1±0.5	-	4Y	Num	(8)
Dalla Vestra *et al* (2004)	Italy	89/91	Multicentric, randomized, double-blind, active controlled, parallel-group	58±7	60±7	NR	NR	Lercanidipine/10-20	Ramipril/ 5-10	NR	NR	NR	NR	NR	NR	-	1Y	Num	(18)
Jerums *et al* (2004)	Australia	27/23	Prospective, randomized, open, blinded endpoint	55±2	50±2	74	60	Nifedipine/20-80	Perindopril/ 2-8	8.1±0.4[a]	8±0.4[a]	NR	NR	87±4[ab]	71±4[ab]	-	6Y	Num	(7)

Values are expressed as the mean ± standard deviation unless otherwise indicated. [a]Values are expressed as the mean ± standard error; [b]Units: μmol/l. HK, Hong-Kong; Num, number of patients progressing to macroalbuminuria or normoalbuminuria; W, weeks; M, months; Y, years; CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitor; Hb, hemoglobin; Scr, serum creatinine; AER, albumin excretion ratio; NR, not reported.

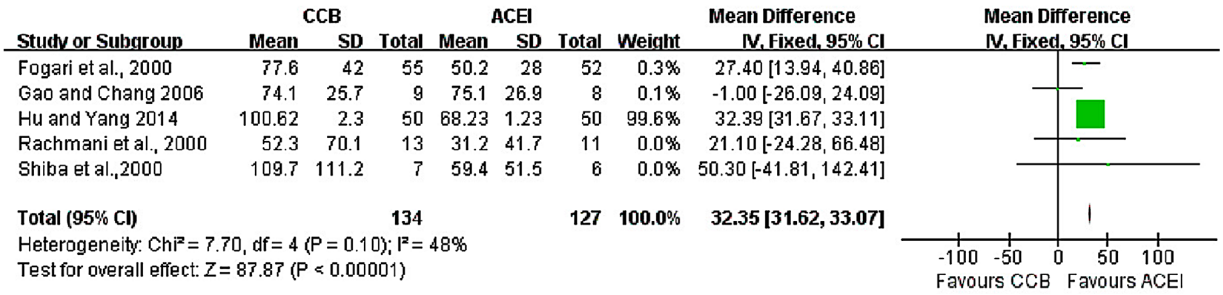

Figure 2. Effect of ACE inhibitors and CCB on the albumin excretion rate. IV, inverse variance; SD, standard deviation; df, degrees of freedom; ACE, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

studies (5,7-9,12-19) were included in the meta-analysis with a total of 947 participants from six different countries (Table I). A total of 10 studies were in English and two in Chinese. Treatments were classified as short-term (course of treatment, <6 months) or long-term (≥1 year) for the meta-analysis. The interventions in the experimental groups of the 12 studies included ACE inhibitors (perindopril, enalapril, delapril, fosinopril, lisinopril, ramipril) and those in the control groups included CCBs [amlodipine, sustained-release nifedipine (tablets), manidipine, lercanidipine].

Results of the meta-analysis

Effect of short-term treatment. A total of six RCTs (5,9,12-15) reported on short-term treatments with ACE inhibitors and CCBs with a total of 338 participants. Of these, five studies (5,12-15) reported AERs. The results indicated that ACE inhibitors were more effective in reducing AER than CCBs (fixed-effects model analysis: MD, 32.35; 95% CI, 31.62-33.07; P<0.00001; I^2=48%; Fig. 2). A total of three studies (5,9,15) reported Scr values. The analysis indicated no statistically significant difference in Scr values between the two groups (random-effects model analysis: MD, 8.7; 95% CI, -21.5-38.91; P=0.57; I^2=97%; Fig. 3).

Effect of long-term treatment. A total of six studies (7,8,16-19) with long-term treatments included 609 patients with early DN and reported data on the progression to normoalbuminuria. The present meta-analysis indicated a marginally significant difference between the two groups, with better outcomes with ACE inhibitors (fixed-effects model analysis: OR, 0.70; 95% CI, 0.49-1.00; P=0.05; I^2=44%; Fig. 4). The P-value happened to be marginally significant, which may be considered to point to a lack of a distinct difference

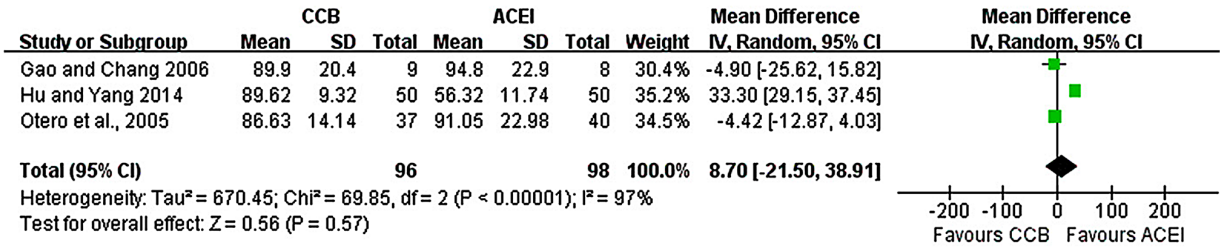

Figure 3. Effect of ACE inhibitors and CCB on serum creatinine. IV, inverse variance; SD, standard deviation; df, degrees of freedom; ACE, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

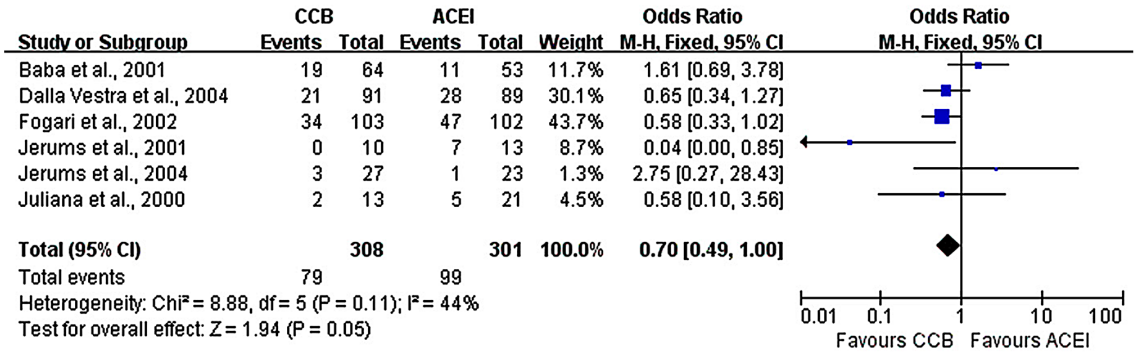

Figure 4. Effect of ACE inhibitors and CCB on the progression to normoalbuminuria. df, degrees of freedom; ACE, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers; M-H, Mantel-Haentzel.

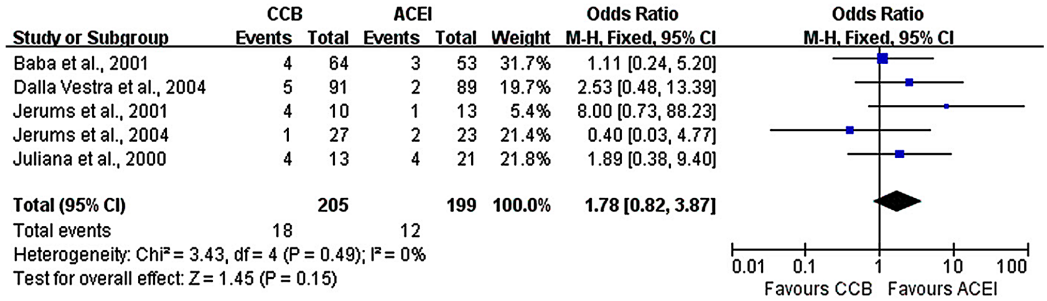

Figure 5. Effect of ACE inhibitors and CCB on the progression to macroalbuminuria. df, degrees of freedom; ACE, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers; M-H, Mantel-Haentzel.

between the two groups, but the issue requires to be analyzed in further studies with larger sample sizes. Furthermore, five studies (7,16-19) reported data on the progression to macroalbuminuria. No difference between ACE inhibitors and CCBs was obtained regarding the progression from microalbuminuria to macroalbuminuria (fixed-effects model analysis: OR, 1.78; 95% CI, 0.82-3.87; P=0.15; I^2=0%; Fig. 5).

Adverse events. Only three studies reported the number of adverse events in both study groups (9,13,17). While two studies (9,13) mentioned the number of patients with adverse events, one trial reported the total number of adverse in the entire cohort (17). Due to this heterogeneity, no meta-analysis was performed and only a detailed, qualitative comparison is provided in Table II. None of the studies reporting adverse events indicated any statistically significant differences between the two groups. In studies describing adverse events, ankle edema was the most common side-effect with CCBs, while cough was the most common adverse event with ACE inhibitors.

Methodological quality. The results of the risk of bias evaluation of the included studies are presented in Table III. The majority of studies did not provide any information on the exact methods of randomization and allocation concealment. Blinding was not performed in any of the included studies. None of the trials were pre-registered. The overall quality of the studies was deemed to be moderate.

Discussion

The blockade of RAS is essential for treating albuminuria in patients with diabetes mellitus, as hyperactive RAS is thought to have a pivotal role in the pathophysiology of renal failure (20). As angiotensin receptor blockers, ACE inhibitors are recommended as the primary antihypertensive drugs in patients with diabetes (21). They reduce albuminuria to a greater extent than other antihypertensive agents and are first-choice drugs for treating patients with diabetes and early

Table II. Details of adverse events reported in the included studies.

Authors (year)	Total number of patients with adverse events		Description of adverse events (frequency, %)		Refs.
	CCB	ACEI	CCB	ACEI	
Rachmani *et al* (2000)	NR	NR	NR	NR	(12)
Fogari *et al* (2000)	7	6	Ankle edema (5.4) Headache (1.3) Palpitation (1.3) Flushing (1.3)	Cough (4) Headache (2.7) Gastric intolerance (1.3)	(13)
Shiba *et al* (2000)	NR	NR	NR	NR	(14)
Luque Otero *et al* (2005)	35	44	Ankle edema (11.3) Hot flushes (5.7) Mild dizziness (3.8)	Cough (10.3)	(9)
Gao and Chang (2006)	NR	NR	NR	NR	(15)
Hu and Yang (2014)	NR	NR	NR	NR	(5)
Chan *et al* (2000)	NR	NR	NR	NR	(16)
Baba *et al* (2001)	33	34	NR	NR	(17)
Jerums *et al* (2001)	NR	NR	NR	NR	(19)
Fogari *et al* (2002)	NR	NR	NR	NR	(8)
Dalla Vestra *et al* (2004)	NR	NR	NR	NR	(18)
Jerums *et al* (2004)	NR	NR	NR	NR	(7)

NR, not reported; ACE, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

Table III. Authors' judgment of risk of bias in included studies.

Included trials (Refs.)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Rachmani *et al* (12)	Unclear risk	Unclear risk	Low risk	High risk	Low risk	Unclear risk
Fogari *et al* (13)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Shiba *et al* (14)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Luque Otero *et al* (9)	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk
Gao and Chang (15)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Hu and Yang (5)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Chan *et al* (16)	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Baba *et al* (17)	Low risk	Unclear risk	High risk	High risk	High risk	Unclear risk
Jerums *et al* (19)	Unclear risk	Unclear risk	High risk	Low risk	High risk	Unclear risk
Fogari *et al* (8)						
Unclear risk	Unclear risk	High risk	High risk	High risk	Unclear risk	
Dalla Vestra *et al* (18)	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Jerums *et al* (7)	Low risk	Unclear risk	High risk	Low risk	High risk	Unclear risk

nephropathy (22). They are also regarded as particularly effective for limiting renal-disease progression due to their possible kidney function benefits that are separate from their systemic blood pressure effects. Treatment with angiotensin receptor blockers has been associated with reduced intraglomerular pressure, decreased filtration fraction and glomerular filtration membrane permeability improvements that reduce urinary protein excretion (23). However, the use of only one class of antihypertensive agent is frequently unable to achieve target blood pressure levels and may not be sufficient to reduce albuminuria or proteinuria. Additional antihypertensive drugs are indispensable to obtain target blood pressure levels and

kidney protection benefits. CCBs are another group of drugs that not only reduce blood pressure but are also efficacious for the management of albuminuria.

Several types of CCBs are available and have been classified according to their biological half-life, drug delivery systems and blocking channel types. In addition, a novel class of dihydropyridines has been added as CCBs with sympathetic nerve effects (24). Furthermore, at least five subtypes based on electrophysiological and pharmacological characteristics exist, namely the L-, N-, P/Q-, R- and T-types (25,26). Several studies have assessed the effects of ACE inhibitors and CCBs in reducing albuminuria when used for patients with DN; however, the results have been conflicting, with certain trials indicating a better antialbuminuric effect with ACE inhibitors (16,19,27), while others reported no differences between the two therapies with long-term treatment (7,28-30).

The present review comparing the renal protective effects of CCB with those of ACE inhibitors analyzed data from 12 RCTs with 6 trials reporting outcomes after short-term treatment and another 6 studies reporting outcomes of long-term therapy. The results of the present meta-analysis indicate that CCBs may be less effective than ACE inhibitors after short-term treatment, but there were no significant differences between the two groups of drugs in terms of the progression of microalbuminuria to macroalbuminuria and only a marginally favorable result with ACE inhibitors for progression to normoal buminuria as the treatment time was prolonged. The earlier renoprotective effect of ACE inhibitors has been suggested to be independent of the antihypertensive action of the drug (8). ACE inhibitors exert their antiproteinuric effect by two mechanisms. They not only reduce the efferent arteriolar resistance and subsequently the glomerular hydraulic pressure but also have nonhemodynamic actions such as enhancing selectivity of the glomerular barrier, compensatory growth of residual nephrons and activation of the renal interstitium with scar formation. These factors are thought to contribute to the earlier renoprotective effects of ACE inhibitors (8,13,14).

The results of the present study also indicated that CCBs and ACE inhibitors have similar long-term effects. The antiproteinuric effect of CCBs only with long-term treatment and a lack of any significant short-term effects may be attributed to the reduction of systemic blood pressure with long-term treatment and absence of any intrinsic effects of the drug (13). Studies indicated that long-term renoprotective actions of antihypertensive drugs are proportional to the reduction in blood pressure for both DN and non-DN (13,31,32). It is known that different CCB channel types reduce the production of oxygen-free radicals that inhibit the vasoconstrictive effects of thromboxane A2 (33). By their blocking mechanism, CCBs thereby cause significant lowering of systemic arterial pressure by relaxing the afferent glomerular arterioles (31). This action results in alteration of intraglomerular pressure and AER, depending upon the equilibrium between preglomerular vasodilation and systemic BP reduction (31,32).

Data on adverse events were not available from all included studies in the present review. However, of the studies collecting these data, none reported any statistically significant difference in the incidence of adverse events between the two groups. Numerous studies have focused on the combination of RAS blocking agents and CCBs to achieve a complementary effect and reduce the incidence of side effects (34,35). Studies have revealed that combination therapy with RAS blockade agents and certain CCBs produces a greater reduction in AER than either drug used as monotherapy (8,34-36). Thus, CCBs as supplementary therapies may be a good alternative for patients that have absolute or relative contraindications against RAS blockers and to diminish side effects of the drug used as monotherapy (34-36).

While the efficacy of CCBs and ACE inhibitors for the prevention of diabetes was not one of the outcomes of the present review, an increasing amount of research has evaluated the effect of antihypertensive drugs on the incidence of diabetes. It has been reported that CCBs inhibit proapoptotic β-cell thioredoxin-interacting protein expression and thereby improve β-cell survival and function (37). A meta-analysis of RCTs by Noto *et al* (37), however, has reported that CCBs are not significantly associated with the reduction of the incidence of diabetes. They also reported that ACE inhibitors have the lowest association with a reduced risk of diabetes amongst antihypertensive drugs.

In the present meta-analysis, the CCBs used in all trials were of the dihydropyridine class, but non-dihydropyridine CCBs have demonstrated better reductions in urinary proteins for patients with diabetic nephropathy (38). Furthermore, the albuminuria reduction effects were also different when comparing different types of CCBs (38,39). However, the CCB with the best albuminuria/proteinuria reduction remains to be identified.

Of note, the present review had certain limitations. There was inter-study heterogeneity amongst the included studies with respect to sample size, choice of drug, dosage, duration of follow-up and study outcomes. This may limit the generalization of the present results. Furthermore, it also limited the possibility to assess the role of different drugs and dosages on the study outcomes. In addition, the limited number of studies analyzed along with the relatively small sample size of certain trials may have underestimated the true treatment effect in the present meta-analysis. As another limitation, not all RCTs provided adequate information on the methods of randomization and allocation concealment. Furthermore, blinding was not performed in all trials. Finally, a lack of rigorous methodology may have skewed the outcomes of the trials.

In view of these limitations, there is a requirement for further RCTs with larger sample sizes to identify the most beneficial intervention strategy for patients with early DN. Future studies should be high-quality, incorporating rigorous methods of randomization, allocation concealment and blinding, and also standardize the dose of the drugs to reduce bias in their results. Studies should also record and compare the adverse events of both drugs to provide high-quality comparative evidence regarding the safety of the drugs. In addition, further studies are required comparing the effects of different classes of CCB vs. ACE inhibitors for the management of patients with DN.

To conclude, the present review provided up-to-date and comprehensive level-1 evidence comparing the short- and long-term therapeutic effects of ACE inhibitors and CCBs for preventing the progression of nephropathy in patients with diabetes mellitus. The results of the present study indi-

cated that the antiproteinuric efficacy of CCBs may be less than that of ACE inhibitors after short-term treatments in patients with DN. However, both types of drugs have similar efficacy in reducing the progression of microalbuminuria to macroalbuminuria after long-term treatment. Thus, in clinical practice, ACE inhibitors may be useful when early antiproteinuric action is required; however, either drug may be used for long-term action. There is a requirement for further studies to provide robust evidence.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JLL, JRL and ML conceived and designed the study. QT and WL collected data and performed data analysis. JLL and JRL wrote the draft of this manuscript. ML edited the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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