CLINICAL RESEARCH STUDY

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The Effect of Calcium Channel Blockers on Moderate or Severe Albuminuria in Diabetic, Hypertensive Patients

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ABSTRACT

OBJECTIVES: Inhibitors of the renin-angiotensin system are recommended for the management of albuminuria in patients with hypertension and diabetes mellitus, but there is little consensus about alternative therapies. Calcium channel blockers are recommended for the management of hypertension, but the data are controversial regarding their role in patients with albuminuria. This review was designed to assess the efficacy of calcium channel blockers compared with inhibitors of the renin-angiotensin system in decreasing albuminuria in diabetic, hypertensive patients with nephropathy.

METHODS: We searched MEDLINE, Embase, CENTRAL, and ClinicalTrials.gov for records that compared calcium channel blockers to inhibitors of the renin-angiotensin system and reported pre- and postintervention albuminuria measurements. Two reviewers independently screened abstracts for randomized, controlled trials in adults. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to select 29 trials from 855 records. We synthesized the data through a random-effects model.

RESULTS: We analyzed data from 2113 trial participants with hypertension and diabetes mellitus who had the equivalent of ≥30 mg/day of urinary albumin excretion. Inhibitors of the renin-angiotensin system were more effective than calcium channel blockers in decreasing albuminuria (standardized difference in means −0.442; confidence interval, −0.660 to −0.225; $P < .001$). This finding was independent of the blood pressure response to treatment. There was no difference between the 2 drug classes regarding markers of renal function.

CONCLUSIONS: Inhibitors of the renin-angiotensin system are superior to calcium channel blockers for the reduction of albuminuria in nephropathy due to hypertension and diabetes mellitus. The net clinical benefit, however, is small.

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KEYWORDS: Albuminuria; Calcium channel blockers; Diabetic nephropathy; Hypertension; Renin-angiotensin system blockers

INTRODUCTION

Diabetic nephropathy is characterized by albuminuria, the severity of which is proportional to the individual's cardiovascular risk.[1] Because angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-II receptor blockers (ARB) decrease both urinary albumin excretion and the progression of diabetic nephropathy, these have become the preferred initial drug therapy for hypertension in diabetics.[2]

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However, ACEI/ARB therapy can be limited by adverse effects and a limited efficacy in controlling systemic blood pressure,[3,4] and there is little consensus about which therapy is the best alternative to ACEI/ARB in patients with proteinuria due to hypertension and diabetes. Although any lowering of systemic blood pressure would be expected to reduce proteinuria by a reduction in glomerular pressure, the net effect of any antihypertensive agent would also depend on concurrent effects on intrarenal hemodynamics. The evidence that short-acting nifedipine actually causes a transitory increase in proteinuria as well as diuresis, likely due to its effect on afferent renal vasodilatation, has thus raised theoretical concerns that longer-acting calcium channel blockers (CCBs) might have an adverse effect on proteinuria reduction and renoprotection, as clearly shown for dihydropyridine CCBs in nondiabetic hypertensive patients with renal disease.[5] Despite this, CCBs have been reported to improve urinary albumin excretion when added to an ACEI/ARB in nondiabetic subjects,[6,7] however, the data are not conclusive.[8] Similarly, a number of studies have suggested that CCBs might be as effective as ACEI/ARB for the management of albuminuria in patients with diabetes and chronic kidney disease.[9-19] To our knowledge, no pooled analysis has assessed the effect of CCB on albuminuria in patients with kidney disease due to hypertension and diabetes. The purpose of this review is to address this gap by determining the efficacy of CCB compared with ACEI/ARB in decreasing urinary albumin excretion in diabetic, hypertensive patients with moderately or severely increased albuminuria.

CLINICAL SIGNIFICANCE

- Therapy with inhibitors of the renin-angiotensin system is superior to therapy with calcium channel blockers for albuminuria in patients with hypertension and diabetes.
- However, while statistically significant, the difference between both therapies may not be clinically significant, and calcium channel blockers may be a reasonable alternative to inhibitors of the renin-angiotensin system when these are not tolerated.

METHODS

Study Selection

We included randomized, controlled clinical trials that studied diabetic, hypertensive adults (age ≥18 years) with a baseline urinary albumin excretion of ≥30 mg/day or equivalent. The intervention of interest was therapy with a CCB for a minimum of 4 weeks with a comparison group comprised of participants receiving an ACEI or ARB.

We required the following data from the studies: baseline characteristics, and baseline and postintervention measurements of the urine albumin excretion. We accepted the urine albumin-creatinine ratio as a surrogate where reported. Cross-over clinical trials, interventional studies without randomization, observational studies, and case reports were excluded from this review.

The primary outcome was the within-group change from baseline in the urinary albumin excretion. When more than one measurement was obtained, we used the measurement obtained at the highest tolerated dose of the intervention. The secondary outcomes were the postintervention estimated glomerular filtration rate, serum creatinine, and blood pressure.

Search Methodology

We searched MEDLINE, Embase, the Cochrane Central Register of Control Trials (CENTRAL), and ClinicalTrials.gov on September 19, 2018 for studies in humans that were published from database inception until the search date. We did not apply language or geographic restrictions.

The search strategies were modeled on the one designed for MEDLINE (see Supplementary Material, available online) and were combined with adaptations of the Highly Sensitive Search Strategy described in the Cochrane Handbook for Systematic Reviews of Interventions.[20] Finally, we searched the reference list of related reviews to identify additional studies.

Data Collection, Synthesis, and Analysis

We matched references by title, author names, location and setting, and number of participants to avoid duplicate publications. We used the outcome data from the publication with the most complete follow-up when a study had multiple reports; methodology and baseline characteristics data were supplemented using information from prior publications when necessary. Two investigators used Rayyan QCRI[21] to screen all records independently. Disagreements were resolved by consensus with a third reviewer. We retrieved full texts for the selected abstracts and re-assessed the studies according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to determine final inclusion.

EHC and PDL extracted the data independently with a standard data collection form, and a cross-check was performed. When eligible studies were missing tabulated or directly reported outcome data, 2 attempts were made to contact corresponding authors by e-mail. However, we did not receive any response from the authors. When feasible, we extracted the data from available graphics using the measuring tool available in Acrobat Reader DC (Adobe Systems, McLean, Va),[22,23] using the methods described in the Supplementary Material.

When the urinary albumin excretion was reported in μg/min or μg/24 h, it was converted to mg/24 h. When the urinary albumin-creatinine ratio was reported in mg albumin/mg creatinine, it was converted to mg albumin/g creatinine; when it was reported in μg albumin/mg creatinine, the units were changed to the equivalent mg albumin/g creatinine;

and when it was reported in mg albumin/mmol creatinine, it was converted to mg albumin/g creatinine (by dividing by 0.113). When serum creatinine was reported in μmol/L, it was converted to mg/dL (by multiplying by 0.011).

Some studies presented the urinary albumin excretion as geometric means. Geometric means and anti-log standard deviation (SD) and geometric means and 95% confidence intervals (CI) were converted to the mean and SD of the logarithmic scale of the values through the formulae described by Higgins et al.[24] If the data were presented as geometric means and tolerance factor, interquartile range or range of values, we imputed the SD from the average SD of studies with similar baseline population, measurement method and scale, and time periods, as described in the Cochrane Handbook.[20] When median and interquartile ranges were provided, the arithmetic mean and SD were calculated using the formulas proposed by Luo et al[25] and Wan et al,[26] respectively. If the arithmetic mean was provided, but the SD was not, the latter was calculated using the standard error or the CI, as described in the Cochrane Handbook.[20]

The outcome data were imported into Comprehensive Meta-Analysis v.3.3 (BioStat Solutions, Inc., Frederick, Md) for analysis. The data are expressed as mean ± SD. Studies reporting the urinary albumin excretion as an arithmetic mean were pooled separately from studies reporting it as a geometric mean. The data were combined using the random-effects model and a 2-sided $P < .05$ was considered significant; results are presented as the standardized difference in means (SMD) with 95% CI. We performed standard chi-squared tests to assess heterogeneity. Statistically significant heterogeneity was defined as $P \leq .1$. We interpreted the level of heterogeneity using I^2 as low (<35%), moderate (35%-55%), or high (>55%). To identify possible sources of heterogeneity, we performed prespecified subgroup analyses by the duration of diabetes, the method of measurement of the urinary albumin excretion, and the level of baseline albuminuria, and post hoc subgroup analyses by the degree of postintervention blood pressure control, age at enrollment, and number of participants in each study arm. We also performed sensitivity analyses by performing one-study-removed analyses and meta-regression, and by comparing the results of the analyses using different correlation coefficients.

The risk of bias of the included studies was assessed independently by 2 reviewers during the data-collection process, and disagreements were resolved by consensus with a third reviewer. We assessed the following domains: randomization and allocation concealment, to assess selection bias; blinding of the study personnel, to assess performance bias; blinding of the outcome assessor, to assess detection bias; incomplete outcome reporting, to assess attrition bias; and selective outcome reporting, to assess selective reporting bias. We also assessed the funding source as an additional domain to determine if the study was funded by a member of the pharmaceutical industry, which could introduce bias. Each domain was classified as being at low, high, or uncertain risk of bias, and a summary assessment was generated using Review Manager v.5.3 (The Cochrane Collaboration).[27] We used funnel plots to assess potential publication bias when ≥10 studies contributed to a meta-analysis and used Egger et al's test[28] to assess the relationship between sample size and effect size. Duval and Tweedie's trim-and-fill method[29] was used to further evaluate and adjust for publication bias.

RESULTS

Study Selection, Characteristics, and Quality

Our search of MEDLINE, Embase, and CENTRAL yielded 885 records. We selected and retrieved 134 full-text articles for review after the screening process and identified 29 reports of clinical trials that met the inclusion criteria (Figure 1).[9-19,30-47] The most remarkable exclusions were 8 studies that reported proteinuria, but not albuminuria; 2 studies in which the baseline albuminuria levels were below the prespecified threshold for this review; and 1 study in which the baseline blood pressure was not in the hypertensive range (see Supplementary Material). The data were not directly reported in 3 studies,[19,30,31] and we did not receive a response from the authors, so the values were extracted from the graphics.

The pooled cohort included 2113 participants (1554 men) with hypertension and diabetic nephropathy who were followed for a median of 12 months (range 3-60 months). The characteristics of the included studies are summarized in Table 1[9-16,19,30-44] and Table 2.[17,18,45-47] The median age in the included studies was 57 years (range 38-63.1 years) and the median body mass index was 27.4 kg/m^2 (range 22.7-31.0 kg/m^2). The median systolic and diastolic blood pressures at baseline were 160.0 mm Hg (range 141.6-184.0 mm Hg) and 93.5 mm Hg (range 50.0-104.4 mm Hg), respectively. All studies except one[31] achieved similar blood pressure reduction between groups (0.043; CI, −0.055-0.141; $P = .387$; $I^2 = 1.93\%$). However, it is worth noting that only 8 studies[11,15,31,37-40,42] achieved a postintervention blood pressure <140/90 mm Hg and only 2 studies[36,38] achieved <130/90 mm Hg in both groups. The median duration of diabetes in the included studies was 9.2 years (range 4.8-32.1 years) and the median glycosylated hemoglobin Ac was 7.2% (range 6.8%-9.8%). While most studies included participants with type 2 diabetes, 5 studies[12,13,39,44,46] included patients with only type 1 diabetes, and 2 studies[16,30] included both; 3 studies did not differentiate between diabetes types.[9,37,42]

Most studies measured urinary albumin excretion on a 24-h collection, however, 7 studies measured it on an overnight urinary collection. The urinary albumin-creatinine ratio was measured on 3 timed urinary samples in 4 studies. The most commonly evaluated CCB was amlodipine (10 studies), followed by nifedipine (5 studies) and nitrendipine (4 studies).

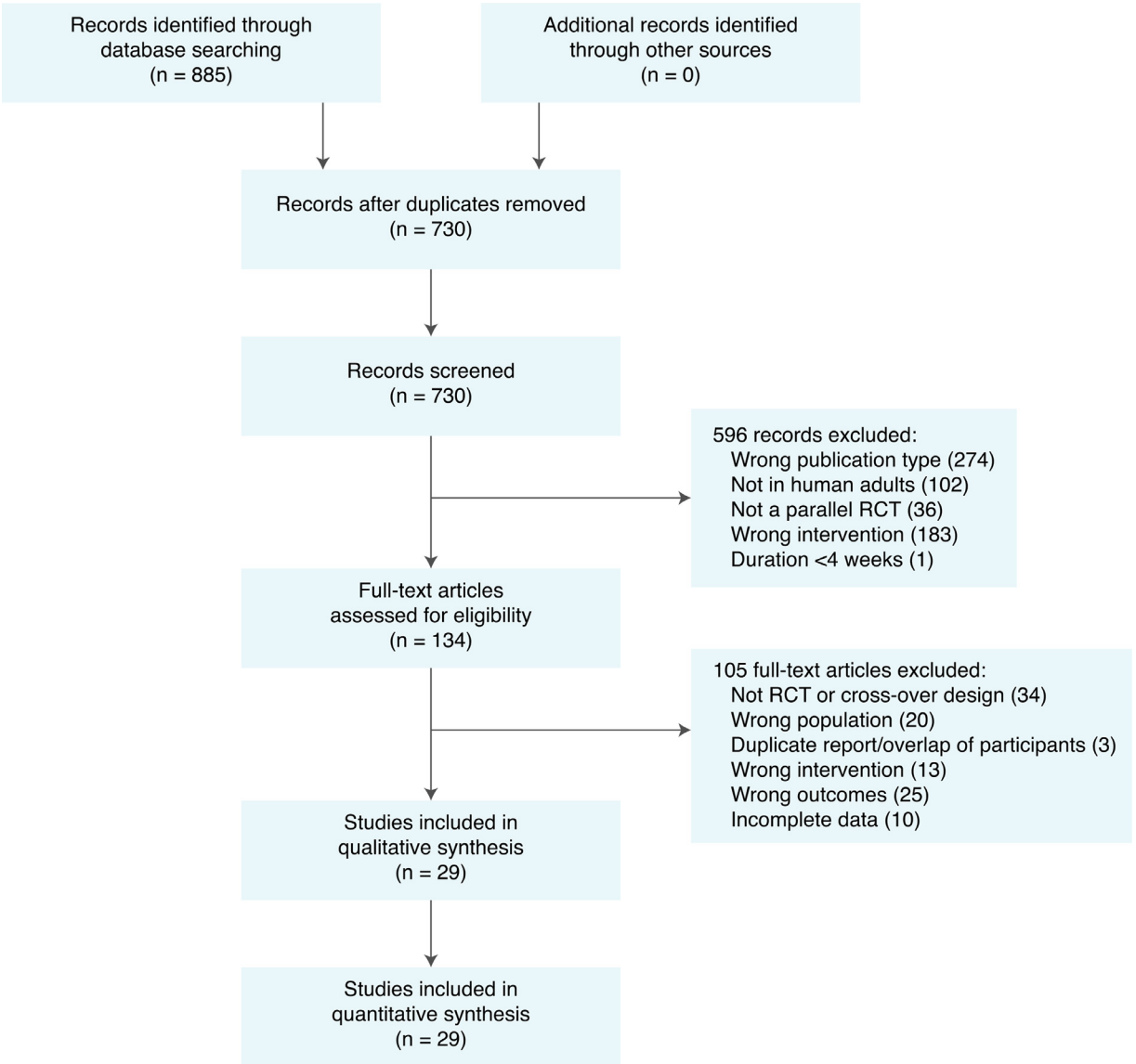

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrating the study selection process.

Pooled Effect of CCB on Urinary Albumin Excretion

We recorded the pre- and postintervention values for the urinary albumin excretion and used the correlation coefficient reported by Dalla Vestra et al[34] to assess the change between values in each group. This coefficient (0.559) was confirmed through sensitivity analyses by comparing the results of analyses using coefficients of 0, 0.5, and 0.9 without observing a significant change in the results.

There was high heterogeneity between studies ($P < .001$; $I^2 = 75.6\%$; $\tau = 0.421$), so a random-effects meta-analysis was used for quantitative synthesis. The use of ACEI/ARB resulted in a greater decrease in albuminuria than CCB (SMD −0.442; CI, −0.660 to −0.225; $P < .001$; see Figure 2) in diabetic, hypertensive individuals. This represents a difference of 0.442 mg albumin/g creatinine. This estimate did not vary in the one-study-removed analysis. We also performed sensitivity analysis by excluding 2 studies[31,35] with outlying SMDs; the effect estimate did not change significantly (SMD −0.304; CI, −0.457 to −0.151; $P < .001$).

Subgroup analyses were only performed using studies with arithmetic means due to the low number of studies reporting in geometric means (see Table 3). In a prespecified subgroup analysis, we found that therapy with CCB performed similarly as therapy with ACEI/ARB in the studies in which the mean level of albuminuria was ≥300 mg/24 h. This was consistent with the results of the meta-regression, which suggested that the severity of albuminuria was a potential source of heterogeneity. While the effect of ACEI/ARB and CCB was also similar in subgroup analyses of studies with a mean blood pressure <130 mm Hg, a mean age <50 years, or urinary albumin:creatinine ratio as

Table 1 Baseline Characteristics of the Included Studies with Arithmetic Mean

Source (First Author Name, Year)	Country	Treatment (mg/day)	Comparison (mg/day)	Additional therapy	Follow-Up (months)	N	Mean Age (years)	Males (%)	Baseline Blood Pressure (mm Hg)	Baseline sCr (mg•dL^{-1})	Baseline GFR	Baseline Albuminuria*	CCB RASI	Postintervention Albuminuria*	CCB RASI
Ferrier 1992[16]	Switzerland	Verapamil (240-480)	Enalapril (20-40)	NR	7.5	54	NR	NR	NR	NR	NR	167[c] (404)	135[c] (300)	251[c] (806)	163[c] (601)
Slataper 1993[9]	USA	Diltiazem	Lisinopril	NR	18	20	52.5	NR	NR	NR	60[a]	2900[d] (1,260)	3300[d] (1,260)	1600 [d] (940)	1900 [d] (940)
Norgaard 1993[12]	Denmark	Isradipine (5)	Spirapril (6)	NR	6	15	42.5	60.0	154/91	1.02	86[a]	1614[d] (1,558)	1476[d] (810)	1860[d] (1,857)	1442[d] (1,077)
O'Donnell 1993[13]	UK	Nifedipine (20-80)	Lisinopril (2.5-20)	NR	4.75	28	51.9	78.6	166/99	1.29	107[a]	1544[d] (1,308)	1064[d] (915)	1413[d] (1,472)	928[d] (1,390)
Josefsberg 1995[37]	Canada	Nitrendipine (10-40)	Enalapril (5-40)	NR	8	21	54.2	14.3	146/50	NR	NR	64[d] (40)	85[d] (50)	80[d] (65)	45[d] (29)
Agardh 1996[32]	Multinational	Nifedipine (40-80)	Lisinopril (10-20)	Furosemide	12	335	58.5	71.3	162/98	1.06	100[a]	105 [d] (75)	101 [d] (72)	145 [d] (318)	81 [d] (137)
Bouhanick 1996[33]	France	Nicardipine (100)	Captopril (50)	NR	24	111	57.0	58.6	160/94	0.94	94[a]	54[d] (86)	30[d] (55)	45[d] (72)	89[d] (182)
Velussi 1996[42]	Italy	Amlodipine (5-10)	Cilazapril (2.5-5)	Furosemide	36	18	55.5	83.3	184/95	1.02	NR	59[d] (19)	83[d] (40)	41[d] (11)	70[d] (43)
Fogari 1997[10]	Italy	Amlodipine (10)	Enalapril (20)	NR	12	50	53.9	100.0	160/101	NR	90[a]	88[d] (30)	100[d] (35)	72[d] (26)	79[d] (34)
Sawicki 1997[39]	Germany	Felodipine (5-15)	Ramipril (1.25-3.75)	Doxazosin Furosemide	24	21	39.0	100.0	142/86	1.46	65[a]	1000[d] (1100)	1000[d] (1300)	1600[d] (1100)	800[d] (1000)
Tatti 1998[41]	Italy	Amlodipine (10)	Fosinopril (20)	NR	42	380	63.1	59.5	171/94	1.00	NR	35[d] (20)	29[d] (20)	19[d] (19)	19[d] (19)
Bakris 1998[15]	USA	Verapamil (180-360)	Trandopril (2-8)	Furosemide	12	37	59.4	67.6	174/104	NR	7[b]	604[d] (187)	616[d] (202)	42[d] (152)	399[d] (176)
Fogari 1999[35]	Italy	Nitrendipine (10-20)	Ramipril (2.5-5)	No	24	51	56.3	NR	166/102	NR	44[a]	768[d] (39)	792[d] (40)	618[d] (30)	536[d] (33)
Shiba 2000[40]	Japan	Manidipine (10)	Delapril (60)	NR	24	18	61.0	105.6	154/85	0.86	NR	106[c] (77)	79[c] (67)	187[c] (224)	63[c] (40)
Baba 2001[19]	Japan	Nifedipine (20-60)	Enalapril (5-20)	Furosemide	24	436	60.1	50.5	162/68	0.77	105[a]	99[d] (75)	97[d] (68)	124[d] (182)	138[d] (55)
Kopf 2001[30]	Germany	Nitrendipine (20-40)	Perindopril (4-8)	Indapamide	12	46	52.1	NR	160/79	NR	103 [b]	70[d] (29)	109[d] (38)	80[d] (52)	74[d] (42)
Fogari 2002[43]	Italy	Amlodipine (5-15)	Fosinopril (10-30)	No	48	309	62.8	56.6	160/99	1.00	NR	96[d] (64)	98[d] (67)	62[d] (33)	46[d] (25)
Bakris 2002[31]	USA	Amlodipine (5)	Benazepril (10)	HCTZ	9	27	59.6	59.3	154/98	NR	83[b]	124[d] (25)	113[d] (28)	79[d] (26)	23[d] (27)
Dalla Vestra 2004[34]	Italy	Lecarnidipine (10-20)	Ramipril (5-10)	HCTZ	12	180	59.0	71.7	155/92	0.85	NR	125[d] (78)	96[d] (61)	99[d] (106)	68[d] (94)
Fogari 2005[36]	Italy	Manidipine (10-20)	Lisinopril (10-20)	No	24	121	60.2	48.8	148/90	NR	93[b]	82[d] (38)	79[d] (37)	52[d] (23)	42[d] (20)
Krimholtz 2005[44]	UK	Amlodipine (5-10)	Candesartan (8-18)	NR	6	26	47.5	57.7	NR	NR	92[a]	49[c] (46)	50[c] (39)	38[c] (45)	46[c] (59)
Ohno 2007[14]	Japan	Amlodipine (2.5-5)	Losartan (25-100)	NR	3	35	57.7	57.1	160/85	NR	78[a]	298[d] (416)	352[d] (557)	323[d] (415)	276[d] (466)
Pan 2015[38]	China	Amlodipine (10)	Losartan (100)	Diuretic, β/α blocker	12	130	59.6	24.6	146/85	NR	68[a]	213[e] (57)	218[e] (56)	206[e] (50)	159[e] (56)
Kim 2017[11]	Korea	Amlodipine (5)	Valsartan (80)	Thiazide	6	68	54.1	70.6	147/90	NR	NR	41[c] (67)	39 (71)	33 (55)	30 (52)

CCB = calcium channel blockers; GFR = glomerular filtration rate; n = sample size; HCTZ = hydrochlorothiazide; NR = not reported; RASI = renin-angiotensin system inhibitor; sCr = serum creatinine; UACR = urinary albumin-creatinine ratio; UAE = urinary albumin excretion.

*Arithmetic mean (SD).

[a]GFR value reported as mL/min.

[b]GFR value reported as mL/min/1.73 m^2.

[c]UACR value expressed as mg-albumin/g-creatinine.

[d]UAE value expressed as mg/24-h.

[e]UAE value expressed as mmol/L in a 24-h urine collection.

Table 2 Baseline Characteristics of the Included Studies with Geometric Mean

Source (First Author Name, Year)	Country	Treatment (mg/day)	Comparison (mg/day)	Additional therapy	Follow-Up (Months)	n	Mean Age (Years)	Males (%)	Baseline Blood Pressure (mm Hg)	Baseline sCr ($mg \bullet dL^{-1}$)	Baseline GFR	Baseline Albuminuria*	CCB RASI	Postintervention Albuminuria*	CCB RASI
Crepaldi 1995[18]	Italy	Nifedipine (20-40)	Lisinopril (20-40)	Atenolol	6	162	56.3	48.1	161/97	NR	103[a]	6.13[b]	6.46[b]	7.52[b]	6.71[b]
Mosconi 1996[45]	Italy	Nitrendipine (10-40)	Enalapril (5-20)	NR	27	13	NR	NR	153/96	NR	65[a]	5.64[b]	6.36[b]	4.07[b]	3.46[b]
Chan 2000[17]	China	Nifedipine (40-80)	Enalapril (10-40)	Indapamide Furosemide	60	102	58.1	NR	169/93	0.02	75[a]	7.09[b]	7.01[b]	8.23[b]	7.48[b]
Tarnow 2000[46]	Denmark	Nisoldipine (20-40)	Lisinopril (10-20)	Furosemide	48	48	38.0	66.7	155/95	1.23	85[a]	21.41[b]	27.22[b]	22.18v[b]	20.53[b]
Yasuda 2005[47]	Japan	Amlodipine (2.5-10)	Losartan (25-100)	NR	3	87	61.5	41.4	161/94	1.21	NR	18.13[b]	18.36[b]	18.34[b]	15.93[b]

CCB = calcium channel blockers; GFR = glomerular filtration rate; n = sample size; NR = not reported; RASI = renin-angiotensin system inhibitor; sCr = serum creatinine.
*Geometric mean.
[a]GFR value reported as mL/min/1.73 m^2.
[b]Urinary albumin excretion value expressed as mg/24-h.

the method of albuminuria detection, the number of studies included in these analyses was low.

Pooled Effect of CCB on Markers of Renal Function and Blood Pressure

The estimated postintervention glomerular filtration rate was reported in 16 studies. The effect of ACEI/ARB on glomerular filtration rate did not differ significantly from that of CCB (SMD −0.076; CI, −0.321-0.169; $P = .543$). Similarly, in the 11 studies that reported the postintervention serum creatinine levels, we found a similar effect of ACEI/ARB and CCB on this clinical marker (SMD 0.034; CI, −0.148-0.216; $P = .711$).

The postintervention blood pressure was reported in 21 studies. Similar blood pressure lowering was achieved between both intervention groups, in both systolic (SMD 0.043; CI −0.055-0.141; $P = .387$) and diastolic (SMD 0.050; CI −0.046-0.146; $P = .305$) measurements.

Risk of Bias in the Included Studies

Approximately half of the studies had random sequence generation, but most did not report allocation concealment. While most studies were blinded, 4 were open label and 14 did not report blinding of the outcome assessors. Importantly, the funding source was uncertain in 16 studies. The risk-of-bias summary table can be found in the Supplementary Material. The funnel plot for the primary outcomes suggested there was no publication bias (Figure 3). We confirmed this finding through Egger's test ($P = .2610$). The trim-and-fill method suggested 3 studies were missing to the left of the mean, which did not affect the previous effect estimates significantly (−0.511; CI, −0.628 to −0.426).

DISCUSSION

In this meta-analysis of 29 randomized clinical trials, we pooled data from 2113 participants and found that ACEI/ARB are superior to CCB for the reduction of albuminuria in patients with hypertension and diabetes. This finding appears to be independent of the degree of reduction in blood pressure achieved with these drugs. We did not see a significant difference in renal function after therapy with ACEI/ARB or CCB (as indicated by postintervention estimated glomerular filtration rate and serum creatinine level). To the best of our knowledge, this is the first pooled analysis comparing renal endpoints between ACEI/ARB and CCB in this group of patients with an increased risk of progressive renal disease.

Although our findings suggest that ACEI/ARB are statistically more effective than CCB in reducing albuminuria, it should be noted that the net clinical effect is small, as the SMD between both groups was only 0.44 mg/24 h. Further, in the subgroup of studies with severe albuminuria, CCB therapy resulted in a similar reduction in the degree of albuminuria as ACEI/ARB. This small net clinical effect is consistent with the findings of a meta-analysis of 19

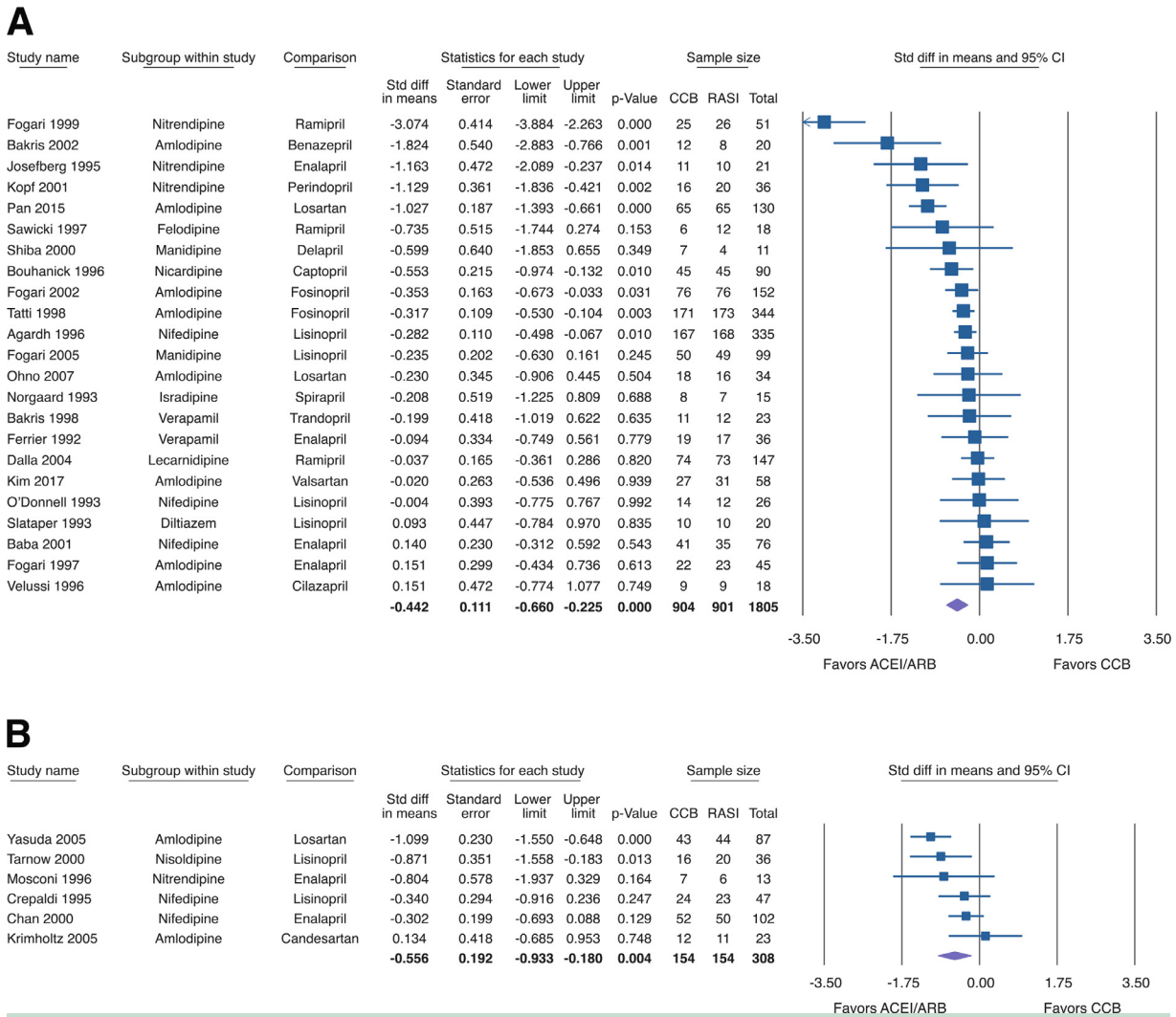

Figure 2 Pooled effect of ACEI/ARB and CCB on urinary albumin excretion. Forest plot for the change in urinary albumin excretion in response to therapy in studies reporting an (**A**) arithmetic and (**B**) geometric mean. Squares represent SMD for each clinical trial and bars represent 95% CI. The pooled estimate of the meta-analysis is represented with a diamond. ACEI/ARB were more effective than CCB in reducing urinary albumin excretion. ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CCB = calcium channel blockers; CI = confidence intervals; RASI = renin-angiotensin system inhibitor; SMD = standardized difference in means.

randomized clinical trials, which revealed that ACEI/ARB are not superior to other antihypertensives at reducing cardiovascular or renal endpoints in hypertensive, diabetic patients who do not have albuminuria.[48] Consequently, while these findings support the common practice of favoring ACEI/ARBs in patients with hypertension and diabetes who have albuminuria, they also indicate that CCB may provide a similar clinical benefit, especially in cases with intolerance or a lack of response to ACEI/ARBs.

We believe that our analysis is sufficiently robust to support these conclusions. We used explicit eligibility criteria and conducted a comprehensive search. All records were reviewed in duplicate, as was the process of data extraction and the assessment of the risk of bias. All the included studies are randomized, controlled trials with a parallel design and an adequate methodology, and most were blinded studies. Our sensitivity analyses confirmed the accuracy of our findings, and standard tests indicated that our results were free from publication bias.

Nonetheless, this study should be interpreted in the context of its limitations. We did not have access to individual patient data, and several studies had small sample sizes. The main limitation of this review is the high statistical heterogeneity among the included studies. Aside from the severity of baseline albuminuria, which is already known to affect the response to ACEI/ARB, we identified 2 sources of heterogeneity: the method of measurement of albuminuria and the mean age of the study participants. Most studies used a 24-hour urine collection to determine the level of albuminuria and this subgroup had the highest heterogeneity ($I^2 = 84.6\%$), which is consistent with the known technical difficulties of this measurement method. The fact that

Table 3 Effect Estimates in Subgroup Analyses of Studies with Arithmetic Means

	N	Effect Estimate	95% CI		*P* Value	Between-Group *P*	*P* for Heterogeneity	I^2 (%)
			Lower Limit	Upper Limit				
Blood pressure						—		
<140 mm Hg	8	−0.579	−1.002	−0.156	.007		< .001	70.0
<130 mm Hg	2	−0.634	−1.411	0.142	.109		.004	88.0
UAE measurement method						< .001		
24-h collection	15	−0.540	−0.862	−0.217	.001		< .001	82.3
UACR	3	−0.550	−1.240	0.139	.118		.177	42.2
Overnight UAE	5	−0.244	−0.445	−0.043	.017		.274	22.1
Level of baseline UAE†						< .001		
Moderately increased	16	−0.366	−0.559	−0.173	< .001		< .001	66.0
Severely increased	7	−0.624	−1.475	0.226	.150		< .001	86.1
Mean age						< .001		
<50 years	2	−0.474	−1.190	0.242	.195		.471	0.0
≥50 years	20	−0.460	−0.695	−0.225	< .001		< .001	78.7
Duration of diabetes:						< .001		
<10 years	11	−0.525	−0.934	−0.116	.012		< .001	83.9
≥10 years	9	−0.485	−0.830	−0.140	.006		.001	69.0
Study group ≥30 participants	8	−0.335	−0.538	−0.132	.001	—	.002	69.3

CI = confidence interval; n = number of studies; UACR = urinary albumin-creatinine ratio; UAE = urinary albumin excretion.
*Statistical significance.
†Moderately increased albuminuria indicates 30-300 mg/24 h or equivalent. Severely increased albuminuria indicates >300 mg/24 h or equivalent.

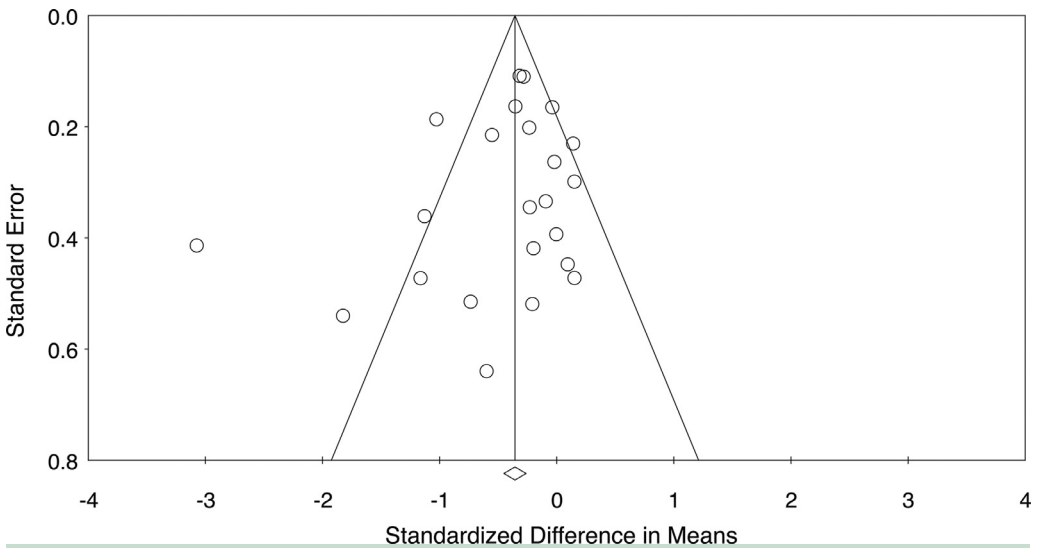

Figure 3 Funnel plot of the primary outcome. The graphic plots the study weights against the standardized difference in means for the change in urinary albumin excretion in studies with an arithmetic mean. The circles represent the included studies and the diamond represents the pooled estimate. The plot is in line with Egger's test and the trim-and-fill test in suggesting there was no publication bias in this review.

the studies that used the urinary albumin-creatinine ratio method had a lower heterogeneity ($I^2 = 35.8\%$) and did not show a significant difference in the primary outcome between both therapies raises concerns about the accuracy of the 24-hour urinary collection in other studies. Due to the inherent limitations of subgroup analyses, any differences between these 2 groups are not conclusive.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.05.039.

SUPPLEMENTARY MATERIAL

Contents

MEDLINE Search Strategy

- "randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]
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- ("Benazepril"[Supplementary Concept] OR benazepril [Title/Abstract]) OR ("Ramipril"[Mesh] OR ramipril [Title/Abstract]) OR ("Lisinopril"[Mesh] OR lisinopril [Title/Abstract]) OR ("Enalapril"[Mesh] OR enalapril [Title/Abstract]) OR ("Captopril"[Mesh] OR captopril [Title/Abstract]) OR ("Trandolapril"[Supplementary Concept] OR trandolapril[Title/Abstract]) OR ("Perindopril"[Mesh] OR perindopril[Title/Abstract]) OR ("Zofenopril"[Supplementary Concept] OR zofenopril[Title/Abstract])
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- #13 NOT #14

Remarkable Excluded References

These were reports in which there were incomplete data, or data were pooled to include normotensive and hypertensive patients, patients with normal and mild microalbuminuria, or patients with moderate to severe microalbuminuria.

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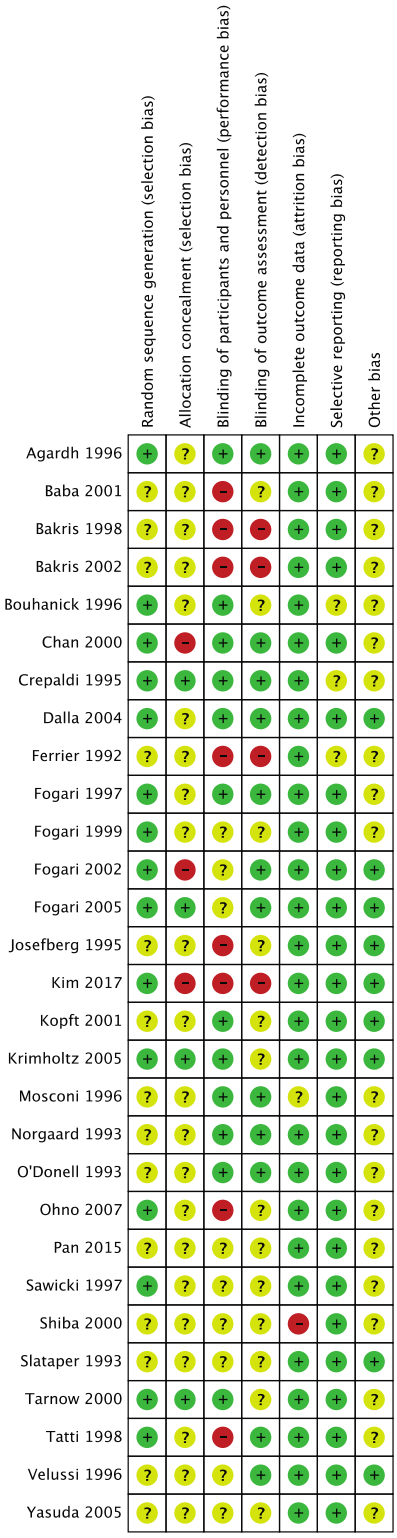
Risk-of-Bias Figure



Data Extraction from Graph

- Open the file using Adobe Acrobat Reader DC (Adobe Systems, McLean, Va)
- Click on **TOOLS** and then select **MEASURES**
- Click on **MEASURING TOOL** and measure Y axis from beginning to end
- Right click over the document and select **CHANGE SCALE RATIO AND PRECISION**. Set the scale ratio precision values. For example, if Y axis represents blood pressure levels (0 mm Hg to 200 mm Hg) and the distance measured from Y axis begging to the end is 2.1 in. Set the scale ratio and precision as 2.1 in = 200 mm Hg.
- Now that scale ratio precision has been set, use **MEASURING TOOL** to measure distances from Y axis beginning to all points for which you need values.