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# Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis

Michel Burnier[a], Shanyan Lin[b], Luis Ruilope[c], Giovanni Bader[d], Sharanbasappa Durg[e] and Patrick Brunel[d]

[a]Service of Nephrology, University Hospital, University of Lausanne, Lausanne, Switzerland; [b]Huashan Hospital, Fudan University, Shanghai, China; [c]Autonoma University, Madrid, Spain; [d]Novartis Pharma AG, Basel, Switzerland; [e]Molecular Connections (P) Ltd., Bengaluru, India

**ABSTRACT**

**Objective:** Angiotensin receptor blockers (ARB) are among the recommended first-line treatment options in patients with hypertension and chronic kidney disease (CKD). This meta-analysis evaluated the effect of ARB on blood pressure (BP) and renal function in patients with concomitant hypertension and CKD with or without diabetes.

**Methods:** Literature search was performed in PubMed/MEDLINE, EMBASE and BIOSIS to identify parallel-group, randomized controlled trials (≥8 weeks) reporting the effects of ARB on office systolic/diastolic BP (SBP/DBP), estimated glomerular filtration rate (eGFR), serum creatinine (SCr), creatinine clearance (CrCl) or proteinuria in adults with hypertension and CKD. Mean difference (MD, generic inverse variance) with 95% confidence intervals (CIs) was used to report an outcome.

**Results:** Among the 24 studies identified, 19 evaluated ARB as monotherapy, 4 evaluated ARB as combination therapy and one evaluated ARB both as monotherapy and combination therapy. Median (range) duration of the studies was 12 (1.84–54.0) months. ARB monotherapy significantly ($p < 0.01$) reduced BP (treatment ≥1 year: SBP [MD: −14.84 mmHg; 95% CI: −17.82 to −11.85]/DBP [−10.27 mmHg; −12.26 to −8.27]) and proteinuria (≥1 year [−0.90 g/L; −1.22 to −0.59]). Results were consistent for combination therapy. In these studies, non-significant changes were observed for eGFR, CrCl and SCr. The impact of SBP changes on eGFR was not significant; however, studies were of a relatively short duration.

**Conclusion:** ARB had a favorable impact on BP and renal parameters such as proteinuria with monotherapy as well as with combination therapy, highlighting their potential benefits in patients with hypertension and CKD. During the short follow-up of these studies, no significant change in eGFR was observed.

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Angiotensin receptor blocker; chronic kidney disease; creatinine clearance; hypertension; proteinuria

## Introduction

Hypertension and chronic kidney disease (CKD) are global health issues [1] with a strong cause and effect relationship [2]. Both hypertension and CKD are associated with a high risk of cardiovascular (CV) morbidity and mortality [3]. Hypertension together with proteinuria contributes to the progression of CKD [4,5], resulting in an increased CV and all-cause mortality [6,7].

Blood pressure (BP) control in patients with CKD reduces the likelihood of progression to end-stage renal disease (ESRD) and the occurrence of CV events [8]. Therefore, guidelines recommend a target BP of ≤140/90 mmHg with careful monitoring of adverse events (AEs) in CKD patients with proteinuria <1 g/24 h and lower targets in those with proteinuria >1 g/24 h [9–11]. Most recently, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) clinical practice guidelines recommended an aggressive BP goal of <130/80 mmHg in all hypertensive patients including those with CKD [12].

The renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in controlling BP and renal function. Angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEIs) have been shown to be effective in lowering BP, slowing the progression of both diabetic and nondiabetic

CONTACT Michel Burnier michel.burnier@chuv.ch Service of Nephrology and Hypertension, University Hospital, University of Lausanne, Rue du Bugnon 17, 1011 Lausanne, Switzerland

Supplemental data for this article can be accessed here.

renal disease, reducing proteinuria, and reducing the risk of overt nephropathy [13–21]. In addition, studies such as the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study (IRMA-2), Irbesartan in Diabetic Nephropathy Trial (IDNT), Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) have demonstrated that the renoprotective effects of ARB in patients with diabetic nephropathy are partially independent of their antihypertensive effect [22–25]. These renoprotective benefits beyond the BP-lowering effects support the recommendations to use ARB or ACEIs in patients with hypertension and CKD, particularly when they have proteinuria. Therefore, guidelines recommend initiating antihypertensive treatment with an ARB or ACEI, either as monotherapy or in combination with existing treatments, as first-line therapy for patients with CKD [9,11,12,26,27]. Even in patients with advanced CKD, ARB and ACEIs are effective in delaying the disease progression [28,29].

Early meta-analysis and network meta-analysis [30,31] have demonstrated that blocking the renin–angiotensin system with ACEIs or ARB has beneficial effects on BP and proteinuria and may be the best approach to prevent ESRD in diabetic and nondiabetic CKD. The benefits of ACEIs or ARB on renal outcomes in placebo-controlled trials appear to result mainly from a BP-lowering effect, while additional renoprotective actions beyond lowering BP remain uncertain in diabetes [30]. However, these meta-analyses included patients with or without hypertension and with or without reduced glomerular filtration rate (GFR) [30,31].

Therefore, we performed a systematic review and meta-analysis evaluating the effects of ARB on office BP, renal function, and proteinuria when prescribed as a monotherapy or in combination with other antihypertensives in patients presenting hypertension and CKD.

## Methods

### Systematic literature search strategy

We adopted the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines to perform this systematic review [32]. A literature search from the earliest available date to July 2017 was performed in the PubMed/MEDLINE, EMBASE, and BIOSIS databases using MeSH terms (Emtree in case of EMBASE)/keywords: monotherapy, ("losartan" OR "eprosartan" OR "valsartan" OR "irbesartan" OR "tasosartan" OR "candesartan" OR "telmisartan" OR "olmesartan medoxomil" OR "azilsartan medoxomil" OR "fimasartan" OR ("angiotensin receptor blocker" OR "ARB")) AND "hypertension" AND "chronic kidney disease;" dual therapy, ("losartan" OR "eprosartan" OR "valsartan" OR "irbesartan" OR "tasosartan" OR "candesartan" OR "telmisartan" OR "olmesartan medoxomil" OR "azilsartan medoxomil" OR "fimasartan" OR ("angiotensin receptor blocker" OR "ARB")) AND ("calcium channel blocker" OR "diuretic") AND "hypertension" AND "chronic kidney disease". The literature search was limited to clinical trials (to restrict nonhuman studies such as preclinical, in vitro and in vivo) and English language to retrieve more relevant hits.

### Inclusion and exclusion criteria

The studies that met the following criteria were included: (1) adult patients with hypertension and CKD with or without diabetes and who were treated with ARB; (2) parallel-group randomized controlled trials (RCTs) $\geq$8 weeks in duration; (3) studies that reported at least one of the following outcomes: systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated GFR (eGFR), serum creatinine, creatinine clearance (CrCl) and proteinuria. Exclusion criteria included observational studies, crossover RCTs, studies not reported in English, or manuscripts without any full-text available. However, conference abstracts with relevant data for the aforementioned outcomes were included. We also excluded most studies, which included diabetic and nondiabetic patients with hypertension and CKD, when the results were not presented separately for patients with or without diabetes.

### Parameters

The identified studies were analyzed for BP (SBP and DBP) and renal parameters (eGFR, CrCl, serum creatinine, and proteinuria).

### Data extraction

The reviewers independently screened for potentially relevant article titles and abstracts based on the inclusion criteria. Whenever necessary, the full-text articles were also retrieved. The authors were independently involved in all stages of study selection and data extraction. Disagreements between reviewers, if any, were resolved by a discussion to obtain a consensus.

### Assessment of risk of bias in included studies

The risk of bias of eligible trials, published as full-texts, was assessed using the Cochrane collaborations tool. The risk of bias tool covered selection bias, performance bias, detection bias, attrition bias, and reporting bias. We assigned judgments of low, unclear or high risk of bias under the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Disagreements were resolved by consensus.

### Data analysis

Meta-analysis (post-treatment versus pre-treatment) and meta-regression were carried out in R statistical software (version 3.4.1; https://www.r-project.org) using the meta and metafor packages. We used mean difference (MD, generic inverse variance [IV]) with 95% confidence intervals (CIs) to pool all available data for an outcome in a single forest plot. Serum creatinine values, where reported as µmol/L, were converted to mg/dL (1 mg/dL = 88.4 µmol/L) for analysis. The amount of heterogeneity was assessed by $I^2$ test (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity) [33]. However, a random-effects model was used in all outcomes as the selected studies differed in the mixes of participants, interventions and treatment duration [34]. For analysis, post-pre standard deviation (SD) was converted to standard error (SE) [35]. For studies that reported results only in graphical format, the numerical values were extracted from the graphs using Adobe® Reader® XI inbuilt measuring tool, version 11.0.06 (Adobe Systems Incorporated, San Jose, California, USA). Analysis was carried out for studies with durations ≥8 weeks to <1 year and ≥1 year. In all the analyses, a $p$-value <0.05 (two-tailed test) was considered statistically significant.

## Results

### Study selection and description of included studies

The electronic search retrieved 679 records; 415 unique records were screened after excluding 264 duplicate records. Of the 415 records screened, 165 full-text articles were assessed for eligibility and 24 studies met the inclusion criteria. There was no disagreement about the inclusion of studies among the authors. Figure 1 depicts the process of identifying relevant studies.

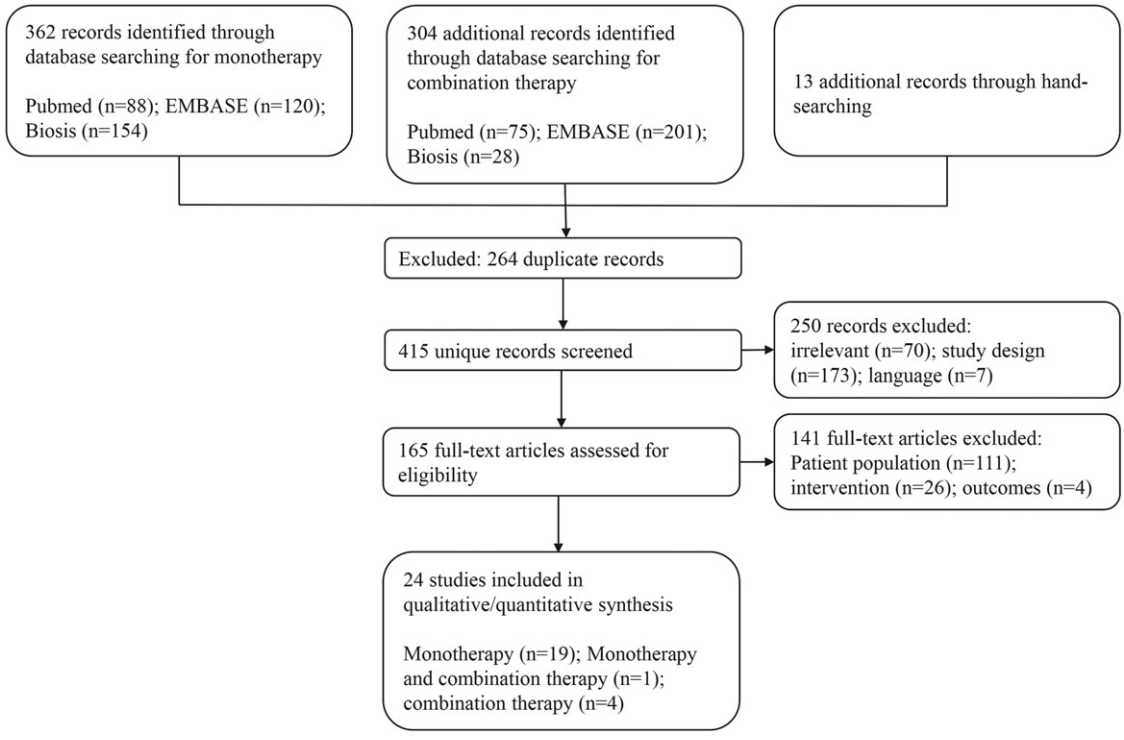


Figure 1. Flowchart for the identification of studies.

### Characteristics of selected studies

The characteristics of the 24 studies [22–25,36–55] included in the meta-analysis are shown in Table 1. These studies were published between 1998 and 2017, with sample sizes ranging from 9 to 1715 subjects. The median duration of the studies was 12 months ranging between 1.84 months and 54.0 months. ARB as monotherapy were evaluated in 19 studies and 4 studies evaluated ARB in combination with other antihypertensive drugs. One study evaluated ARB both as monotherapy and combination therapy. Further, out of all the included studies, only five studies [24,25,38,40,45], which were of 3 years duration, evaluated the effect of ARB on CV events, ESRD, and deaths; therefore, these parameters were not included in the present analysis.

### Antihypertensive effects of ARB in patients with hypertension and CKD

#### Effect on SBP

Figure 2 presents the effects of an ARB treatment on SBP in patients with hypertension and CKD. Overall results suggested that ARB as monotherapy or in combination with other antihypertensive agents significantly ($p < 0.01$) reduced the SBP. Monotherapy with an ARB for ≥8 weeks to <1 year resulted in a significant reduction of SBP (MD: −12.60 mmHg; 95% CI, −18.53 to −6.67; $p < 0.01$). Monotherapy with an ARB for ≥1 year also significantly decreased SBP (MD: −14.84 mmHg; 95% CI, −17.82 to −11.85; $p < 0.01$), and the reduction in SBP with ARB monotherapy for ≥1 year was numerically greater than that with ARB monotherapy for ≥8 weeks to <1 year (≥1 year versus ≥8 weeks to <1 year: MD, −2.24 mmHg; 95% CI, −8.88 to 4.40; $p = 0.51$). Moreover, combination treatment of ARB with diuretics (HCTZ) for ≥8 weeks to <1 year was also significant ($p < 0.01$) in reducing the SBP with a greater effect than ARB alone (MD: −18.00 mmHg; 95% CI, −20.86 to −15.14). ARB treatment in combination with calcium channel blockers (CCBs) or diuretics (hydrochlorothiazide [HCTZ]) for ≥1 year resulted in a significant ($p < 0.01$) reduction in SBP in patients with hypertension and CKD (MD: −13.07 mmHg; 95% CI, −18.93 to −7.22).

#### Effect on DBP

In patients with hypertension and CKD, ARB induced a significant ($p < 0.01$) reduction in DBP (Figure 3). ARB monotherapy for ≥8 weeks to <1 year lowered the DBP by −6.52 mmHg (95% CI, −11.27 to −1.77; $p < 0.01$). The results were consistent for ARB monotherapy for ≥1 year with an MD of −10.27 mmHg (95% CI, −12.26 to −8.27; $p < 0.01$). However, the reduction in DBP observed with ≥1 year of ARB monotherapy was greater compared with ARB monotherapy for ≥8 weeks to <1 year (≥1 year versus ≥8 weeks to <1 year: MD, −3.75 mmHg; 95% CI, −8.90 to 1.40; $p = 0.15$). ARB in combination with HCTZ for ≥8 weeks to <1 year also demonstrated a significant reduction in the DBP (MD: −10.0 mmHg; 95% CI, −11.50 to −8.50; $p < 0.01$). When ARB are prescribed in combination with CCBs/diuretics (HCTZ) for ≥1 year, a significant reduction in DBP was also found (MD: −9.70 mmHg; 95% CI, −13.22 to −6.17; $p < 0.01$).

### Effects of ARB on renal parameters in patients with hypertension and CKD

#### Effects on proteinuria

ARB treatment in patients with hypertension and CKD significantly lowered proteinuria ($p < 0.01$) (Figure 4). ARB monotherapy for ≥8 weeks to <1 year reduced proteinuria by a mean of −0.60 g/L (95% CI, −0.93 to −0.26; $p < 0.01$). The results were consistent for ARB monotherapy for ≥1 year (MD: −0.90 g/L; 95% CI, −1.22 to −0.59; $p < 0.01$). The results were consistent for ≥8 weeks to <1 year of treatment with ARB in combination with HCTZ (MD: −1.40 g/L; 95% CI, −1.71 to −1.09; $p < 0.01$). Further, ARB in combination with CCBs/diuretics (HCTZ) for ≥1 year induced a significant reduction in proteinuria (MD: −0.33 g/L; 95% CI, −0.46 to −0.20; $p < 0.01$).

#### Effect on serum creatinine

Treatment with ARB in patients with hypertension and CKD did not induce any significant change in serum creatinine levels in the selected studies (Figure 5). ARB monotherapy resulted in a nonsignificant increase in serum creatinine levels in patients treated for ≥8 weeks to <1 year (MD: 0.30 mg/dL; 95% CI, −0.69 to 1.29; $p = 0.55$) as well as in those treated for ≥1 year (MD: 0.02 mg/dL; 95% CI, −0.46 to 0.51; $p = 0.92$). Similarly, ARB in combination with CCBs/diuretics (HCTZ) for ≥1 year treatment duration also demonstrated non-significant increase in serum creatinine levels (MD: 0.01 mg/dL; 95% CI, −0.02 to 0.04; $p = 0.48$). However, treatment with ARB/diuretic (HCTZ) combination for ≥8 weeks to <1 year of

**Table 1.** Characteristics of the studies included in this meta-analysis.

| Study number | Author, year | Design | N | Patients | Treatment | Outcomes measured |
|---|---|---|---|---|---|---|
| 1 | Parving et al. 2001 [22] | 2 y, DB, RCT | 590 | Hypertensive patients with type 2 diabetes and microalbuminuria aged between 30 and 70 years; albumin excretion rate of 20–200 μg/minute in two of three consecutive, sterile, overnight urine samples; SCr of no more than 1.5 mg/dL for men and no more than 1.1 mg/dL for women | Irb 150 and 300 mg/d | Time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a UAE rate that was greater than 200 μg/minute and at least 30% higher than the baseline level |
| 2 | Lewis et al. 2001 [23] | 2.6 y, DB, RCT | 1715 | Patients aged between 30 and 70 y, with type 2 diabetes mellitus, hypertension, proteinuria, and UPE of at least 900 mg/24 h; SCr of 1.0–3.0 mg/dL in women and 1.2–3.0 mg/dL in men | Irb titrated from 75 to 300 mg/d; Aml titrated from 2.5 to 10 mg/d | SBP, DBP, SCr, and serum potassium. Primary composite outcome (doubling of SCr the onset of end-stage renal disease or death from any cause), secondary composite outcome (death from CV causes, nonfatal MI, heart failure resulting in hospitalization, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle) |
| 3 | Brenner et al. 2001 [24] | 3.4 y, DB, RCT | 1513 | Patients with type 2 diabetes and nephropathy aged between 31 and 70 y; SCr of 1.3–3.0 mg/dL in men weighing more than 60 kg | Los 50 mg/d, increased to 100 mg/d after 4 w if BP is >140/90 mmHg | Primary composite outcome (doubling of SCr, ESRD, or death), secondary composite outcome included morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal disease |
| 4 | Imai et al. 2011 [25] | 3.2 y, DB, RCT | 566 | Patients with type 2 diabetes with overt nephropathy aged between 30 and 70 y; UACR >33.9 mg/mmol (>300 mg/g) in the first morning urine sample; SCr concentration of 1.0–2.5 mg/dL in women and 1.2–2.5 mg/dL in men | Olm 10 mg; increased to 20 mg if BP is >130/85 mmHg after 4 w after randomisation or at any time thereafter, with further titration to 40 mg, if necessary, upon which additional antihypertensive agents including diuretics, β blockers, CCBs and α blockers could be used | SBP, DBP, UACR, SCr, and serum potassium. Primary composite outcome (doubling of SCr, ESRD and death), secondary composite outcome (CV outcomes, changes in renal function and proteinuria) |
| 5 | Zinellu et al. 2016 [36] | 6 m, RCT | 24 | CKD hypertensive patients aged >18 y (BP ≥140/90 mmHg, plasma LDL-C concentrations >100mg/dL (without concomitant hypolipidemic drugs), and presence of proteinuric CKD (CrCl >20 mL/min/1.73m$^2$ combined with a UPE rate >0.3 g/24 h, without evidence of urinary tract infection or overt heart failure [NYHA class III or more]). Patients were of CKD stage 3 or 4, not receiving dialysis | Tel (80 mg/day) vs Tel (40 mg/d) + Rami (5 mg/d) | SBP, DBP, SCr, eGFR, proteinuria, carotid IMT, total LMW thiols, reduced LMW thiols, thiols redox status |

(*continued*)

**Table 1.** Continued.

| Study number | Author, year | Design | N | Patients | Treatment | Outcomes measured |
|---|---|---|---|---|---|---|
| 6 | Nakamura et al. 2008a [37] | 1 y, RCT | 30 (15 to each arm) | Nondiabetic CKD patients (aged ≥20 y) with hypertension and moderate renal insufficiency. SBP 161 ± 9 mmHg; DBP 97 ± 6 mmHg; SCr 1.7 ± 0.3 mg/dL | Tel (40 mg/d) vs Aml (5 mg/d) | SBP, DBP, SCr, 24 h CrCl, UPCR, carotid IMT, brachial-ankle PWV, total cholesterol, triglyceride, IL-6, MMP-9 |
| 7 | Nakamura et al. 2005 [38] | 3.1 y, OL, RCT | 141 (Cand, n = 69; Conventional therapy, n = 72) | Patients aged 60 to 75 y with previously treated or untreated hypertension who had renal insufficiency (SBP >140 mmHg; DBP >90 mmHg; mean SCr >1.2 to <2 mg/dL) | Cand (7.12 ± 1.56 mg daily in the patients with past history of CVD or 6.99 ± 1.22 mg daily in the patients without past history of CVD) vs conventional therapy | Primary CV event (hospitalization due to MI, stroke, or CHF), SBP, DBP, HR, BUN, SCr, eGFR, CV events, deaths |
| 8 | Sharma et al. 2005 [39] | 12 w, prospective, OL | 82 | Adults with DBP 90–109 mmHg and stable CKD were enrolled: mild/moderate (CrCl 30– 74 mL/min/1.73 $m^2$), severe (CrCl <30 mL/min/1.73 $m^2$) or requiring maintenance hemodialysis | Tel 40 mg/d for 4 weeks. Tel 80 mg/d was given after 4- or 8-week treatment if DBP was ≥85 mmHg | SBP, DBP, UPCR, urinary Cr, CrCl |
| 9 | Hou et al. 2007 [40] | 3 y, prospective, OL | 360 | Patients aged 18 to 70 y, had CKD (non-diabetic), and had not received ACEI or ARB for at least 6 w before screening; A SCr level of 1.5 to 5.0 mg/dL (133 to 442 μmol/L); CrCl 20 to 70 mL/min/1.73 $m^2$ with variations of <30% in 3 m; diagnosis of nondiabetic renal disease; persistent overt proteinuria (urinary protein excretion of >1.0 g/d for ≥3 m without any evidence of urinary tract infection or overt heart failure | Benz 10 mg/d vs Los 50 mg/d. Patients who continued to show inadequate BP control (i.e. a SBP >130 mmHg and/or a DBP >80 mmHg), had an additional antihypertensive agent (diuretic, CCB, β-blockers, centrally acting agent, or a combination of these medications, excluding an ACEI and ARB) added to their treatment regimen | SBP, DBP, serum Cr, eGFR,UPCR, CrCl, CV events, ESKD, deaths |
| 10 | Aranda et al. 2005 [41] | 2 y, OL | 78 | Patients aged ≥18 y with nondiabetic proteinuric nephropathies | Tel (80 mg/d) vs Tel (80 mg BID) | SBP, DBP, fasting serum glucose, UA, SCr, potassium, LDL-C, HDL-C, triglycerides, Hct, hemoglobin, urine urea, UPCR, CrCl |
| 11 | Uneda et al. 2016 [42] | 24 w, OL | 36 (ARB group, n = 18; DRI group, n = 18) | Hypertensive patients with CKD who had already been treated with ARB | Val/Tel/Irb/Azl/Olm vs Ali (up to 300 mg/d) | SBP, DBP, cSBP, AI, ABI, BaPWV, HR, eGFR, SCr, UACR, UPCR, L-FABP, HbA1c, LDL, BNP, BUN, Uric acid, PRA, hs-CRP, pentosidine |
| 12 | Kaneshiro et al. 2009 [43] | 12 m, OL | 70 | Patients who had nondiabetic CKD (microalbuminuria and a eGFR >60 mL/min/1.73 $m^2$) and who had been treated with 160 mg/day (maximum dose allowed in Japan) of valsartan alone for their hypertension | Aml (2.5–10 mg/d) vs HCTZ (12.5 to 50 mg/d) added onto Val (160 mg/d) | SBP, DBP, Cr, UA, total cholesterol, triglycerides, HDL-C, LDL-C, CRP, PRA, PAC, PWV, UAE |
| 13 | Antlanger et al. 2017 [44] | 10 w prospective, randomized controlled exploratory trial | 24 | Nondiabetic, proteinuric CKD stage III or IV (defined by an eGFR [MDRD] of 15–59 mL/min); patients with proteinuria. Patients had SBP range >120 to <180 mmHg | Ali for 2 m (150 mg/d for 4 w followed by 300 mg/d for 4 w) vs Cand for 2 m (8 mg/d for 4 w followed by 16 mg/d for 4 w) | SBP, DBP, SCr, eGFR, UPCR, UACR, PRA, PAC, potassium |
| 14 | Woo et al. 2014 [45] | 3 y, Randomized OL study | 155 | Patients with CKD due to chronic glomerulonephritis, and not due to diabetic nephropathy, hypertensive nephrosclerosis, lupus nephritis or Henoch–Schönlein nephritis | Ali (150 mg/d) vs Los (100 mg/d) vs Ali (150 mg/d)+Los (100 mg/d) | SBP, DBP, SCr, eGFR, UPE, ESKD |

(*continued*)

**Table 1.** Continued.

| Study number | Author, year | Design | N | Patients | Treatment | Outcomes measured |
|---|---|---|---|---|---|---|
| 15 | Takenaka et al. 2012 [46] | 1 y OL, parallel group RCT | 67 | Hypertensive patients with CKD: taking an ARB and a CCB other than Aml or Azl, who were considered to have poor BP control (>130/80 mmHg on at least two visits) and eGFR >10 mL/min/1.73 $m^2$ | Other CCBs vs Aml (5 mg) or Azl (16 mg)+ARB (Olm, 20 mg; Los, 100 mg; Tel, 20 − 40 mg; Cand, 8 mg; Val, 80 − 160 mg) | SBP, DBP, eGFR, SCr, Al, BNP, UPE |
| 16 | Nakamura et al. 2008b [47] | 12 m OL, RCT | 30 (15 to each arm) | Nondiabetic hypertensive CKD patients mean aged 44.3 y with mild renal insufficiency (SBP 146 mmHg; DBP, 93 mmHg; mean SCr, 1.7 mg/dL; eGFR, 58.1 mL/min) | Tel (40 mg/d) vs Tel (80 mg/d) | SBP, DBP, urinary L-FABP excretion, UPE, urinary collagen IV, eGFR, SCr, HR |
| 17 | Crowe et al. 2003 [48] | 8 w prospective single-blind randomized study | 21 | Patients with proteinuria (>1 g/24 h) due to nondiabetic chronic renal failure (stable CrCl >20 mL/min) and mild to moderate hypertension (BP, 130/80 to <160/110 mmHg) | Los 50 mg/d for 4 w, then 100 mg/d for 4 w vs Los 50 mg/d for 8 w | Ambulatory BP, CCl, UPE, ERPF, eGFR, PRA, PAC, UPCR, serum and urine sodium, serum andurine potassium |
| 18 | Matsuda et al. 2003a [49] | 48 w RCT | 52 | Hypertensive (140 and/or 90 mmHg) patients with chronic renal disease (SCr <265 (range, 44–265) μmol/l or CrCl ≥30 (range, 30–121) mL/min/1.72$m^2$ | ACEI (Trand, 1 mg/d] or Peri, 2 mg/d]) vs ARB (Los, 25 mg/d or Cand, 4 mg/d) | SBP, DBP, 24 h CrCl, serum potassium, SCr, UPE, urinary $NO_x$ excretion |
| 19 | Matsuda et al. 2003b [50] | 96 w RCT | 62 | Patients with hypertension (SBP/DBP >140 and/or 90 mmHg) and proteinuria (>0.5 g/day). SCr level <265 μmol/l or CrCl >30 mL/min/1.72$m^2$ | Peri (2 mg/d) vs Trand (0.5 mg/d) vs Cand (4 mg/d) vs Los (25 mg/d) | SBP, DBP, SCr, CrCl, serum potassium, UPE, urinary $NO_x$ excretion |
| 20 | Plum et al. 1998 [51] | 6 m DB, RCT, placebo-controlled study | 9 | Patients with arterial hypertension, sitting DBP <105 mmHg, and SBP <180 mmHg); stable renal insufficiency with a SCr between 200 and 600 μmol/L; stable proteinuria of at least 500 mg/24 h; no increase of SCr over 30% within 6 m before the trial; no history of heart failure, malignancy, or any disorders requiring immunosuppressive therapy | Val (80 mg/d) vs placebo | Proteinuria, albuminuria, RBC, HB, Hct, WBC, Plt, serum sodium, serum potassium, serum calcium, serum phosphate, serum chloride, SCr, serum urea, serum bicarbonate, serum uric acid, urinary sodium, urinary potassium, FE sodium, FE potassium, eGFR, ERPF, FF, RVR |
| 21 | Tsygankova et al. 2012 [52] | 1 y RCT | 155 | Patients with CHF of different etiology and NYHA class II or III, with CKD stage I to III, and with uncorrected arterial hypertension | Ena (19.1 mg/d) vs Los (65.4 mg/d) vs Ali (274.5 mg/d) | SBP, DBP, microalbuminuria, eGFR |
| 22 | Nakamura et al. 2010 [40] | 1 y randomized OL study | 30 (15 to each arm) | Nondiabetic hypertensive CKD patients with mild to moderate renal insufficiency (mean age, 37 y); eGFR >60 mL/min/1.72$m^2$) and BP >130/85 mmHg | Tel (80 mg/d) vs Ena (10 mg/d) | SBP, DBP, Urinary L-FABP excretion, UPE, urinary ET-1, eGFR, SCr |
| 23 | Sowers et al. 2010 [54] | 12 w RCT | 469 | Patients aged ≥18 y on ARB (other than Val) for ≥28 d (with treatment-naive patients or patients not controlled on agents other than an ARB treated with olm 20 or 40 mg, respectively, for 28 d) and with uncontrolled MSSBP (≥150–<200 mmHg)<br>Patient groups were either diabetic or stage II CKD (eGFR ≥60–<90 mL/min/1.73$m^2$), or stage III CKD (eGFR ≥30–<60 mL/min/1.73 $m^2$) | Aml/Val 5/320 or 5/160 mg; increased to 10/320 mg in the intensive arm at week 2 and addition of HCTZ 12.5 mg to both arms at week 4; optional up-titration with HCTZ 12.5 mg at week 8 was allowed if MSSBP >140 mmHg | MSSBP |

(*continued*)

**Table 1.** Continued.

| Study number | Author, year | Design | N | Patients | Treatment | Outcomes measured |
|---|---|---|---|---|---|---|
| 24 | Praga et al. 2003 [55] | 20 w, DB, prospective, randomized study | 97 | Patients (aged >18 y) with nondiabetic nephropathies and proteinuria >1.5 g/24 h, hypertension (SBP >140–170 mmHg while sitting and/or a DBP >90–105 mmHg while sitting) and SCr ≤2.5 mg/dL | Los 50–100 mg + HCTZ 12.5–25 mg<br>Aml 5–10 mg + HCTZ 12.5–25 mg | SBP, DBP, HR, blood count, SCr, serum urea, serum sodium, serum potassium, serum bilirubin, serum alkaline phosphate, AST, ALT, glucose, UA, total cholesterol, HDL-C, triglycerides, plasma TGF-β, urine TGF-β |

ABI: ankle-brachial pressure index; ACEI: angiotensin-converting enzyme inhibitor; AI: augmentation index:; Ali: aliskiren; ALT: alanine aminotransferase; Aml: amlodipine; ARB: angiotensin receptor blocker; AST: aspartate aminotransferase; Azl: azelnidipine; Azil: azilsartan; BaPWV: brachialankle pulse wave velocity; Benz: benazepril; BID: twice a day; BNP: brain natriuretic peptide; BP: blood pressure; BUN: blood urea nitrogen; Cand: candesartan; CCB: calcium channel blocker; CHF: congestive heart failure; CKD: chronic kidney disease; Cr: creatinine; CrCl: creatinine clearance; CRP: C-reactive protein; cSBP: central systolic blood pressure; CVD: cardiovascular disease; d: day; DB: double-blind; DBP: diastolic blood pressure; DRI: direct renin inhibitor; eGFR: estimated glomerular filtration rate; Ena: enalapril; ERPF: effective renal plasma flow; ESKD: end-stage kidney disease; ET-1: urinary endothelin-1; FE: fraction excretion; FF: filtration fraction; h: hour; HbA1c: glycated hemoglobin; Hct: hematocrit; HCTZ: hydrochlorothiazide; HDL-C: high-density lipoprotein cholesterol; HR: heart rate: IL-6: interleukin-6; IMT: intima media thickness; Irb: irbesartan; LDL-C: low density lipoprotein cholesterol; L-FABP: urinary liver-type fatty acid-binding protein; LMW: low molecular weight; Los: losartan; m: month; MDRD: Modification of Diet in Renal Disease; MI: myocardial infarction; MMP-9: matrix metalloproteinase-9; MSSBP: mean sitting SBP; $NO_X$: nitrogen oxides; NYHA: New York Heart Association; OL: open label; Olm: olmesartan; PAC: plasma aldosterone concentration; Peri: perindopril; Plt: platelet; PRA: plasma renin activity; PWV: pulse wave velocity; Rami: ramipril; RAS: renin–angiotensin system; RBC: red blood cell; RCT: randomized controlled trial; RVR: renovascular resistance; SBP: systolic blood pressure; SCr: serum creatinine; Tel: telmisartan; TGF-β: transforming growth factor-β; Tran: trandolapril; UA: uric acid; UACR: urinary albumin creatinine ratio; UAE: urinary albumin excretion; UPCR: urinary protein creatinine ratio; UPE: urinary protein excretion; Val: valsartan; w: week; WBC: white blood cell; y: year.

treatment caused a significant ($p < 0.01$) increase in serum creatinine (MD: 0.20 mg/dL; 95% CI, 0.06 to 0.34) but the effect was modest and the observation was limited to one study of 50 patients.

### *Effect on eGFR and creatinine clearance*

ARB as monotherapy or in combination with other antihypertensive drugs did not induce any significant change in either eGFR (Figure 6) or CrCl (Supplementary Figure S1). ARB monotherapy for ≥8 weeks up to <1 year or for ≥1 year was not associated with any significant improvement or deterioration of eGFR. This was also the case when ARB were combined with CCBs or diuretics (HCTZ).

### *Impact of treatment duration on SBP changes*

Meta-regression analysis demonstrated no significant impact of ARB treatment duration on the SBP changes (estimate: 0.03; SE: 0.08; 95% CI, −0.14 to 0.19, $p = 0.76$; Supplementary Figure S2). A significant heterogeneity was observed among the studies ($I^2$=95.04%).

### *Impact of SBP changes on eGFR*

Meta-regression result demonstrated that there was no significant impact of SBP change on eGFR changes (estimate: 0.07; SE: 0.11: 95% CI, −0.14 to 0.28; $p = 0.53$; $I^2$=8.96%; Supplementary Figure S3).

### *Risk of bias*

The quality of the included studies was evaluated by the risk of bias assessment in the 22 full-text publications (Supplementary Figures S4 and S5). The overall risk of bias, across the six items of the Cochrane instrument, was judged to be low (Supplementary Figure S4). Within individual studies, however, two [39,41] had high-risk in random sequence generation and one [39] in allocation concealment. In addition, in some studies, details of the methods for generating the random sequence [36,42,44,47–51,53] and allocation concealment [36,41,42,44,47–50,55] were not provided, and outcome data were incomplete [41,44] (Supplementary Figure S5).

## Discussion

The major observations of this meta-analysis of studies that investigated the BP and renal effects of ARB in patients with concomitant hypertension and CKD

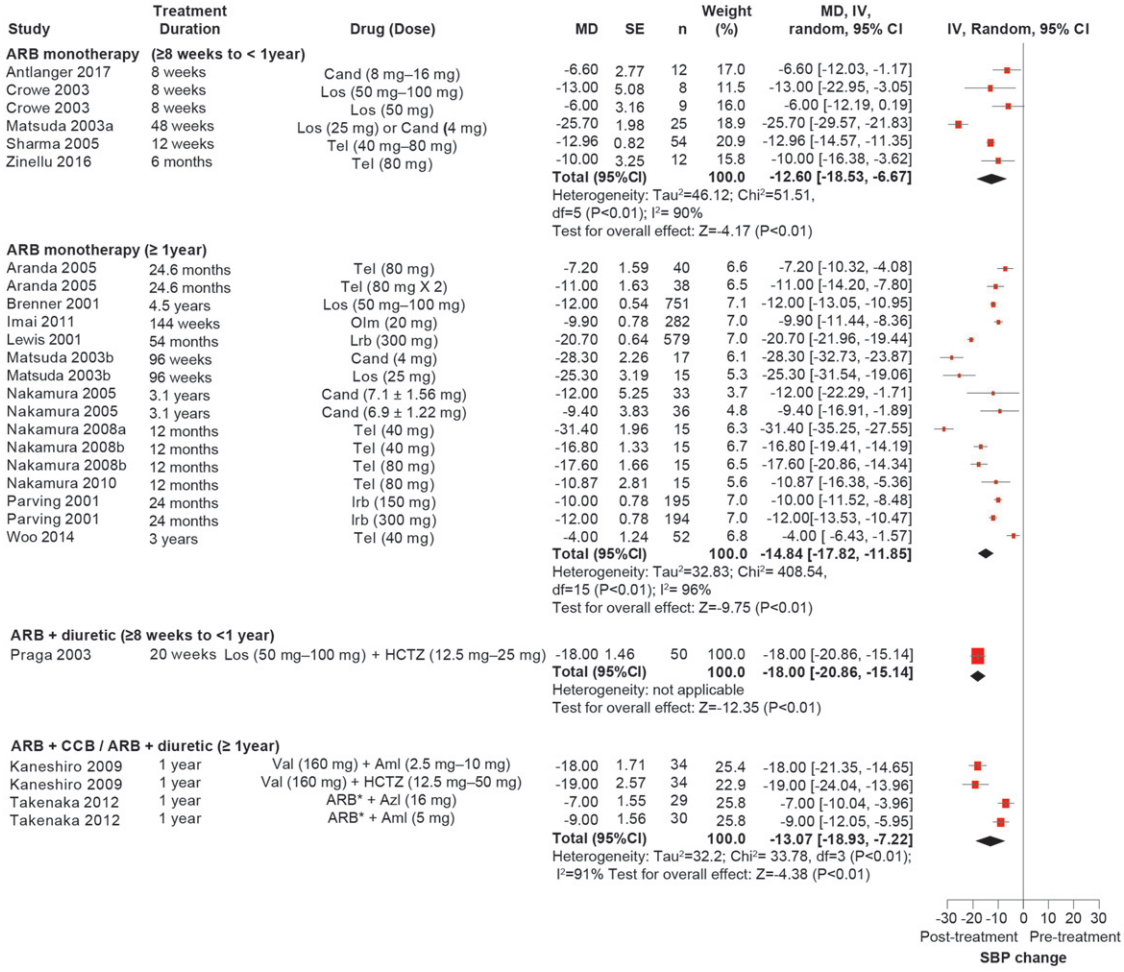


**Figure 2.** Effect of ARB on SBP reduction in patients with hypertension and CKD. *ARB (Olm, 20 mg; Los, 100 mg; Tel, 20 – 40 mg; Cand, 8 mg; Val, 80 – 160 mg). Aml: amlodipine; ARB: angiotensin receptor blocker; Azl: azelnidipine; Cand: candesartan; CCB: calcium channel blocker; CI: confidence interval; CKD: chronic kidney disease; HCTZ: hydrochlorothiazide; IV: inverse variance; Los: losartan; MD: mean difference; Olm: olmesartan; SBP: systolic blood pressure; SE: standard error; Tel: telmisartan; Val: valsartan.

are the following: firstly, ARB given as monotherapy or prescribed in combination with CCBs/diuretics (HCTZ) significantly lowered BP; secondly, ARB induced a significant reduction in proteinuria; and thirdly, ARB were not associated with significant changes in eGFR.

There are two major components to slowing the rate of progression of CKD: (1) treatment of the underlying disease whenever possible, and (2) treatment of risk factors for progression, mainly systemic hypertension, which leads to glomerular hyperfiltration, and proteinuria [56–62]. Treatment of hypertension in CKD patients is primarily aimed at achieving recommended BP targets by selecting the best class of drugs that have demonstrated antihypertensive efficacy and properties that may go above and beyond their BP-lowering effect. In this context, as proteinuria has been associated with the progression of renal disease in both nondiabetic and diabetic patients with CKD [63,64], the ability of hypertensive drugs to reduce proteinuria in addition to lowering BP, is another criteria for selecting drug treatments in CKD [61]. Indeed, studies such as the Modification of Diet in Renal Disease Study (MDRD) [65], and African American Study of Kidney Disease (AASK) [66], demonstrated that higher baseline proteinuria was associated with a faster eGFR decline. Similarly, in the Ramipril Efficacy in Nephropathy (REIN) study, proteinuria was correlated with eGFR decline and progression of ESRD [67]. Moreover, the RENAAL study conducted in patients with diabetic nephropathy reported baseline urine albumin-creatinine ratio as a strong independent predictor of ESRD [68]. Furthermore, IDNT reported similar findings in diabetic nephropathy patients [69]. For these many reasons, both European and American hypertension

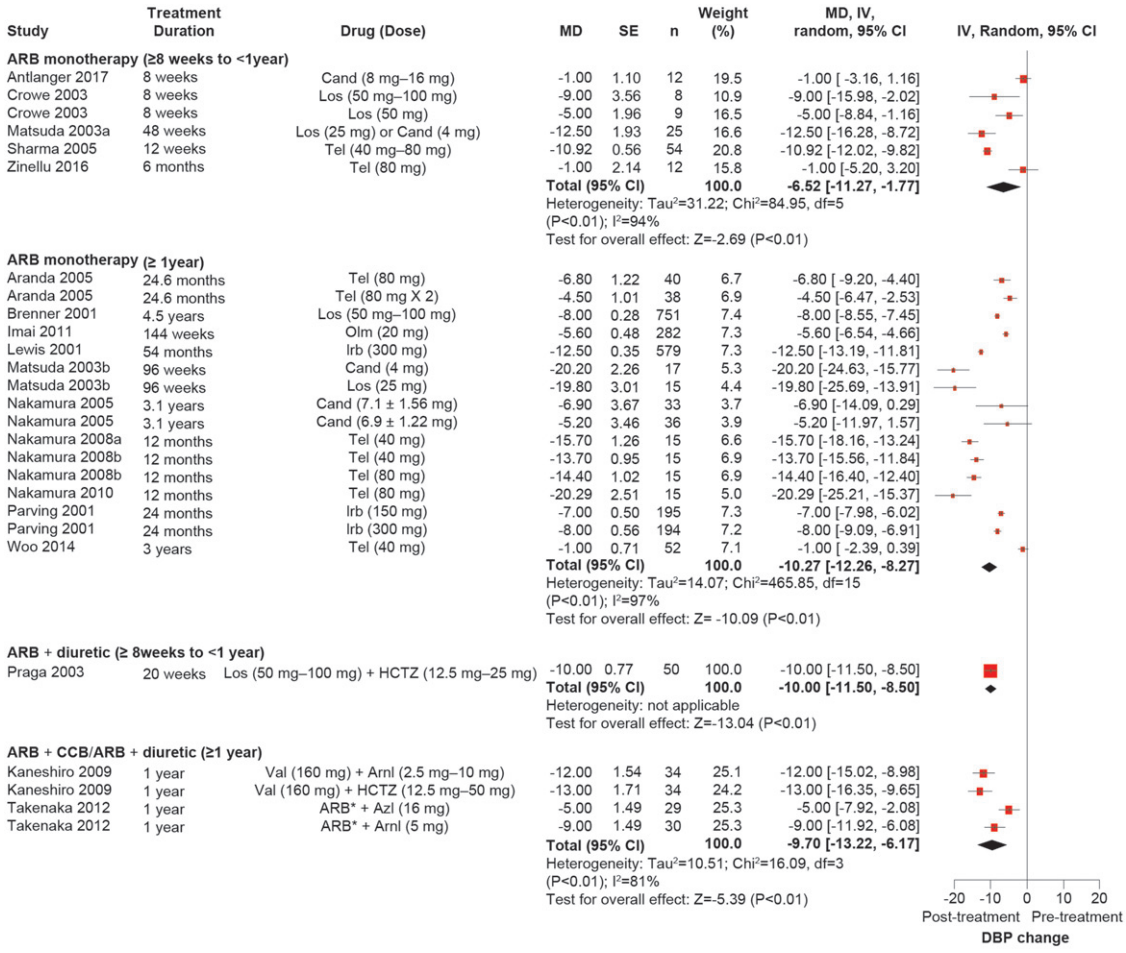


**Figure 3.** Effect of ARB on DBP reduction in patients with hypertension and CKD. *ARB (Olm, 20 mg; Los, 100 mg; Tel, 0 – 40 mg; Cand, 8 mg; Val, 80 – 160 mg). Aml: amlodipine; ARB: angiotensin receptor blocker; Azl: azelnidipine; Cand: candesartan; CCB: calcium channel blocker; CI: confidence interval; CKD: chronic kidney disease; DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide; IV: inverse variance; Los: losartan; MD: mean difference; Olm: olmesartan; SE: standard error; Tel: telmisartan; Val: valsartan.

guidelines recommend the use of blockers of the renin-angiotensin system as first-line therapy in patients with hypertension and CKD [11–12].

One objective of our meta-analysis was to evaluate the effect of ARB as monotherapy or in combination with other antihypertensive agents on systolic and diastolic BP in patients presenting strictly hypertension and CKD. Our results confirm that ARB, as monotherapy or in combination therapy, are effective in reducing both SBP and DBP with a slightly greater effect in patients treated for more than 1 year. Uncontrolled BP is a risk factor for worsening of renal function through an increase in the intraglomerular pressure and impaired glomerular filtration, leading ultimately to ESRD [70–75]. Patients with CKD and a normal BP level have better preservation of GFR than hypertensive patients; lower BP targets (≤130/80 mmHg) are associated with better renal outcomes in patients with CKD and high proteinuria [72]. Therefore, treatment of hypertensive patients with CKD is primarily aimed at BP control and limiting proteinuria to delay progression to ESRD [75].

DBP has been reported to be significantly correlated with the progression of renal failure in patients with chronic glomerulonephritis; the progression rate of renal failure in patients with DBP <90 mmHg was significantly lower than that in patients with DBP >90 mmHg [76]. In another study, it was reported that the improvement in DBP from 93 to 90 mmHg in patients with renal failure was associated with retardation in the progression of chronic renal failure [77]. Furthermore, DBP <90 mmHg was associated with a slower rate and risk of progression to ESRD [78,79]. In another study, nisoldipine demonstrated a beneficial effect on the progression of renal failure in patients with renal insufficiency; in this study, there was no significant difference in SBP, but a significant reduction in DBP from 90 to 85 mmHg ($P < 0.03$) was reported [79]. Therefore, the control of DBP

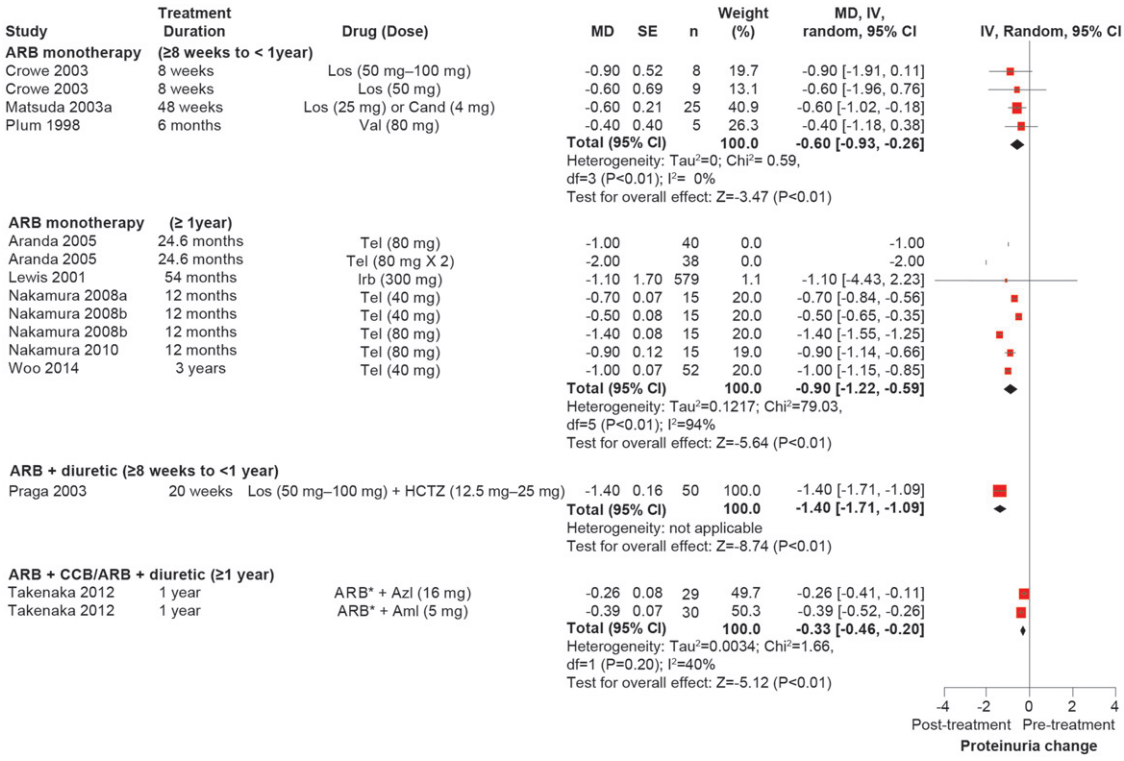


**Figure 4.** Effect of ARB on proteinuria in patients with hypertension and CKD. *ARB (Olm, 20 mg; Los, 100 mg; Tel, 20–40 mg; Cand, 8 mg; Val, 80–160 mg). Aml: amlodipine; ARB: angiotensin receptor blocker; Azl: azelnidipine; Cand: candesartan; CCB: calcium channel blocker; CI: confidence interval; CKD: chronic kidney disease; HCTZ: hydrochlorothiazide; IV: inverse variance; Los: losartan; MD: mean difference; Olm: olmesartan; SE: standard error; Tel: telmisartan; Val: valsartan.

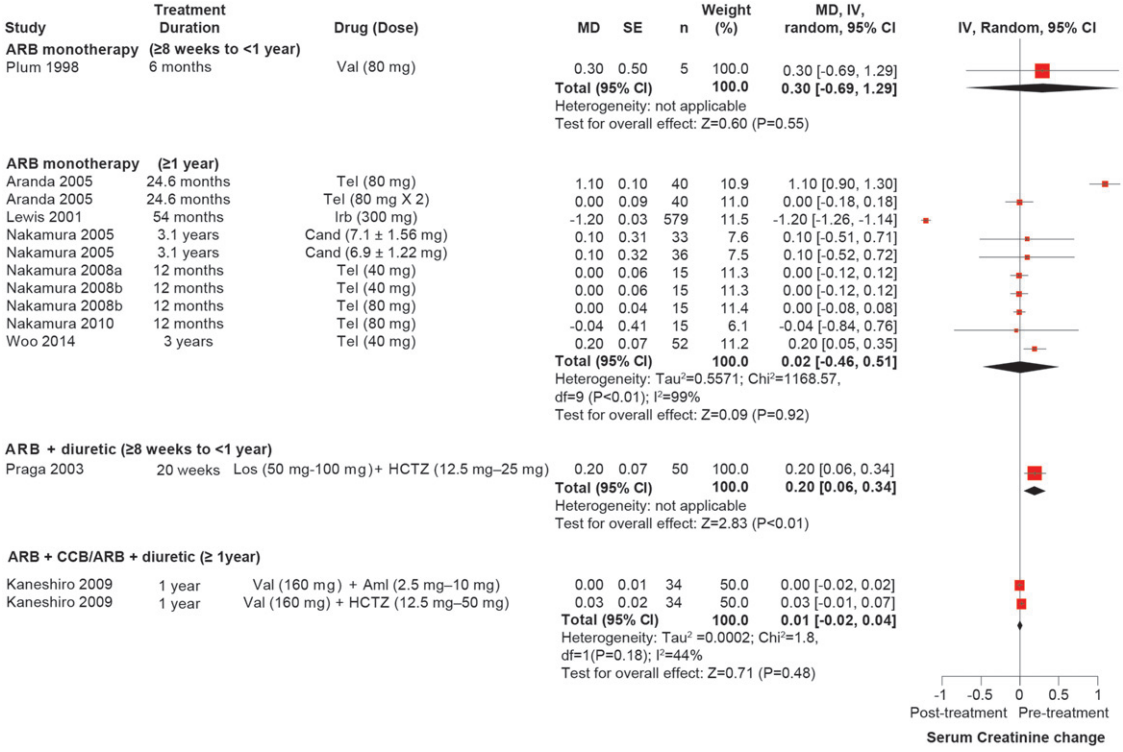


**Figure 5.** Effect of ARB on serum creatinine levels in patients with hypertension and CKD. Aml: amlodipine; ARB: angiotensin receptor blocker; Cand: candesartan; CCB: calcium channel blocker; CI: confidence interval; CKD: chronic kidney disease; HCTZ: hydrochlorothiazide; IV: inverse variance; Los: losartan; MD: mean difference; SE: standard error; Tel: telmisartan; Val: valsartan.

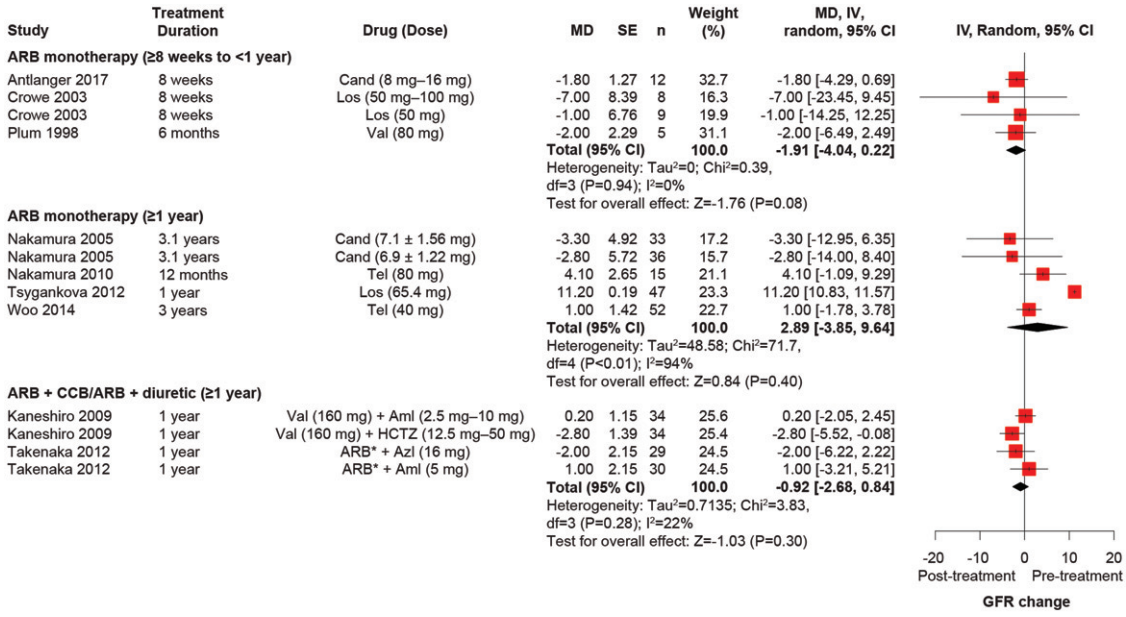


**Figure 6.** Effect of ARB on eGFR in patients with hypertension and CKD. *ARB (Olm, 20 mg; Los, 100 mg; Tel, 20–40 mg; Cand, 8 mg; Val, 80–160 mg). Aml: amlodipine; ARB: angiotensin receptor blocker; Azl: azelnidipine; Cand: candesartan; CCB: calcium channel blocker; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; IV: inverse variance; HCTZ: hydrochlorothiazide; Los: losartan; MD: mean difference; Olm: olmesartan; SE: standard error; Tel: telmisartan; Val: valsartan.

(<90 mmHg) may be as important as SBP to preserve renal function or to retard the progression of chronic renal failure. The results of our meta-analysis demonstrated that ARB significantly reduced DBP in patients with hypertension and CKD, highlighting their potential benefits in these patients. However, one has to mention that the ideal systolic and diastolic BP to target in CKD remains controversial. Indeed, SBP levels below 110-120 mmHg have been associated with a worsening of renal function and with an increased mortality in patients with moderate to severe CKD, suggesting a J-curve [81–83].

Proteinuria has been reported to be an independent factor in renal disease progression. Clinical trials have shown renoprotective effects of proteinuria reduction and suggest that antiproteinuric treatment maximizes renoprotection [18,62–64]. Results from the MDRD revealed a tight association between proteinuria and rate of eGFR decline [65]. Renal protection achieved by lowering of BP depended primarily on the level of initial proteinuria [67]. Secondary analysis of data from IDNT confirmed that baseline proteinuria is an important risk factor for renal failure in patients with type 2 diabetes and overt nephropathy [69]. In the present meta-analysis, ARB as monotherapy at recommended and at maximal doses were found to reduce proteinuria in patients with hypertension and CKD. ARB monotherapy for 8 weeks to 1 year or >1 year demonstrated a significant reduction in proteinuria in patients with hypertension and CKD. Further, ARB in combination with other antihypertensive drugs (CCBs/diuretics) provided an even greater decrease in proteinuria. Treatment with ARB in combination with diuretics for >1 year demonstrated greater reduction in proteinuria than that for a treatment duration <1 year. These results suggest that the beneficial antiproteinuric effect of ARB in patients with hypertension and CKD is preserved and even amplified over time. ARB and ACEIs are known to be more effective than other antihypertensive drugs in reducing proteinuria mainly because they lower both systemic BP and the intraglomerular pressure vasodilating the efferent arterioles [57]. The antiproteinuric effect of ARB has been demonstrated in patients with diabetic and nondiabetic CKD and is dose-dependent even when using very high doses, which do not lower BP more than conventional doses [41,84–87]. Thus, the Diovan Reduction Of Proteinuria (DROP) study reported that valsartan at its higher dose (640 mg/day) provided a greater reduction in microalbuminuria than the lower dose (160 mg/day) in hypertensive patients with type 2 diabetes mellitus and urinary albumin excretion rate of $20-700$ μg/min [87]. In the Strategies for Management of ART (SMART) trial, patients who received candesartan (128 mg/day) showed a significantly greater reduction (mean difference 33%) in proteinuria at 30 weeks than those who received

16 mg/day [84] and very high doses of irbesartan (up to 900 mg/day) were found to more effective in lowering proteinuria than lower doses of 300 mg/day [85]. A previous meta-analysis suggested that ARB treatment improved proteinuria over the short-to-medium term and prevented the progression of proteinuria/albuminuria over the medium term [88]. Another meta-analysis compared the effects of monotherapy and combination therapy with RAAS blockers on proteinuria and concluded that the ARB reduced proteinuria, independent of the degree of proteinuria and underlying disease [18].

Serum creatinine and the derived calculation of eGFR and CrCl are the common markers used to define CKD and to evaluate the progression of CKD towards ESRD. It has been well demonstrated that there is an acute renal hemodynamic effect following initiation of the RAAS blockade, which leads to an acute reduction in GFR. This phenomenon is due to the reduction in systemic and intraglomerular pressures. This initial decline is inversely correlated with renal function decline during the long-term follow-up; the greater the acute GFR fall, the slower the rate of long-term GFR decline and the risk of death [89,90]. The same is true for the early decline in proteinuria [91]. In this meta-analysis, ARB as monotherapy or in combination with other antihypertensive agents did not significantly influence serum creatinine, eGFR, or CrCl, which may trigger the question of some stabilization of renal function. However, the impact of ARB on eGFR is highly variable. Further, in this meta-analysis, we did not observe any significant impact of the decrease in SBP on eGFR changes among patients with hypertension and CKD; However, one has to acknowledge that most studies were of too short duration to assess long-term changes in eGFR. Several large clinical trials performed essentially in patients with type 2 diabetes and CKD have demonstrated the ability of ARB to retard the progression towards ESRD without any significant impact on total mortality [92].

Similar to other meta-analyses, this review was limited by the data (both quantity and data type) availability and accessibility. Rigid inclusion criteria were used for this meta-analysis that minimized the potential of bias during the selection process. Most of the studies included in this meta-analysis had small sample sizes and were conducted over a short duration (except five studies of 3 years duration), which limited our ability to evaluate the effects of ARB on CV events, ESRD, and deaths. The included studies were also of different treatment durations, which could have affected the treatment outcome. Different ARB were used in different studies, which increased the level of heterogeneity in this meta-analysis. Studies reporting the effect of ARB in combination with other antihypertensive agents were limited. Given the lack of consistency across studies in the collection of data, it has not been possible to analyze the relationships between BP, proteinuria, and eGFR.

In conclusion, this meta-analysis examined the effect of ARB on BP, proteinuria and renal function in patients with hypertension and CKD. ARB, as a monotherapy or in combination with other antihypertensive agents, demonstrated effective BP reduction and improved proteinuria in this patient population but without a clear effect on renal disease progression. These data suggest that ARB fulfill two important criteria to be recommended as first line therapy in hypertension and CKD. Few RCTs have shown the ability of ARB to retard the progression of nephropathy in type 2 diabetes but they did not affect total mortality significantly.

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## Disclosure statement

MB has received conference fees and research supports from Menarini, Sankyo, Sanofi, Novartis, and Servier. GB is an employee of Novartis and is therefore entitled to receive Novartis stocks and stock options. PB is a Novartis consultant entitled to get Novartis shares and participate to stock option plans. The remaining authors declare that they have no conflict of interest.

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