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FULL REVIEW

Effect of renin–angiotensin–aldosterone system blockade in adults with diabetes mellitus and advanced chronic kidney disease not on dialysis: a systematic review and meta-analysis

Ionut Nistor[1,2], Johan De Sutter[3], Christiane Drechsler[2,4], David Goldsmith[5], Maria Jose Soler[6], Charles Tomson[7], Andrzej Wiecek[8], Mihaela-Dora Donciu[1], Davide Bolignano[2,9], Wim Van Biesen[10] and Adrian Covic[1]

[1]Nephrology Department, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania, [2]ERBP Methods Support Team, Ghent University Hospital, Ghent, Belgium, [3]Maria Middelares Ziekenhuis, Ghent, Belgium, [4]Division of Nephrology, University Hospital Würzburg and Comprehensive Heart Failure Center, Würzburg, Germany, [5]Renal and Transplantation Department, Guy's Hospital, London, UK, [6]Department of Nephrology, Hospital del Mar, Barcelona, Spain, Institut Hospital del Mar of Medical Research (IMIM), Barcelona, Spain, [7]Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne, UK, [8]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland, [9]Institute of Clinical Physiology, National Council of Research, Reggio Calabria, Italy and [10]Renal Division, Ghent University Hospital, Ghent, Belgium

Correspondence and offprint requests to: Wim Van Biesen; E-mail: Wim.VanBiesen@UGent.be

ABSTRACT

The presumed superiority of renin–angiotensin–aldosterone system (RAAS)-blocking agents over other antihypertensive agents in patients with diabetes to delay development of end-stage kidney disease (ESKD) has recently been challenged. In addition, there is ongoing uncertainty whether RAAS-blocking agents reduce mortality and/or delay ESKD in patients with diabetes and chronic kidney disease (CKD) stages 3–5. In this subgroup, there might be an expedited need for renal replacement therapy (RRT) when RAAS-blocking agents are used. We conducted a meta-analysis of randomized controlled trials (RCTs) of at least 6-months duration in adult patients with diabetes who also have non-dialysis CKD stages 3–5. RCTs comparing single RAAS-blocking agents to placebo or alternative antihypertensive agents were included. Outcomes of interest were all-cause mortality, cardiovascular morbidity, progression of renal function, ESKD and adverse events. A total of nine trials ($n = 9797$ participants with CKD stages 3–5) fit our inclusion criteria. There was no difference between the RAAS group and control group regarding all-cause mortality {relative risk [RR] = 0.97 [95% confidence interval (CI) 0.85–1.10]}, cardiovascular mortality [RR = 1.03 (95% CI 0.75–1.41)] and adverse events [RR = 1.05 (95% CI 0.89–1.25)]. There was a trend for a favourable effect for non-fatal cardiovascular events [RR = 0.90 (95% CI 0.81–1.00)] and a lower risk of the composite endpoint need for RRT/doubling of serum creatinine [RR = 0.81 (95% CI 0.70–0.92)] in the RAAS-blocking agents group versus the con-

trol group. We found evidence that in patients with diabetes mellitus and CKD stages 3–5, treatment with RAAS-blocking agents did not result in a clear survival advantage. The effect on renal outcomes did depend on the selected outcome measure. However, we did not find evidence that the use of RAAS-blocking agents expedited the need for RRT in patients with CKD stages 3–5.

Keywords: angiotensin II, diabetes mellitus, diabetic kidney disease, guidelines, predialysis

INTRODUCTION

Diabetes substantially reduces life expectancy, with cardiovascular disease being the leading cause of mortality, accounting for 50% of all causes of death [1–3]. The odds ratio of having chronic kidney disease (CKD) for patients with versus without (type 2) diabetes is 2.5; furthermore, at least 20% of patients with diabetes mellitus (DM) have CKD stages 3–5 [4, 5]. The combination of advanced CKD and diabetes is linked with increased mortality, an association that is amplified as there is progression to end-stage kidney disease (ESKD) [6].

Because of the presumed ability of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) to reduce at the same time all-cause mortality, cardiovascular risk and progression of nephropathy, most current renal and DM guidelines recommend ACEIs/ARBs as first-line drugs for diabetic patients with CKD [1, 7]. However, several guideline groups acknowledge that there are limitations in the evidence base and therefore the evidence level is mostly rated as low or of moderate quality [1, 7–9], particularly for CKD stages 3–5 [10–12]. In fact, some small studies including populations with more advanced CKD suggest that withholding renin–angiotensin–aldosterone system (RAAS)-blocking agents may actually reverse the decline in glomerular filtration rate (GFR) and retard the start of renal replacement therapy (RRT) [13, 14]. Potential cardiovascular protection may be counter balanced by the potential worsening of renal function and the need to start RRT earlier. It can also be questioned whether administering RAAS-blocking agents to patients with already advanced cardiovascular and renal damage will still result in a survival advantage.

A recent meta-analysis including only studies comparing RAAS blockers to other antihypertensive agents did not support an advantage for RAAS blockade with regard to total or cardiovascular mortality, nor for progression of CKD [15]. However, this study did not focus on patients with advanced CKD. The network meta-analysis of Palmer *et al.* [16] reported a protective effect of RAAS blockade, but the overwhelming majority of this effect was due to studies comparing RAAS-blocking agents to placebo. As such, this study was not really able to assess the place of RAAS inhibitors as compared with other antihypertensive agents. In addition, this study found a higher risk of hyperkalaemia in the RAAS inhibitor group, raising a potential concern for the use of these drugs in patients with more advanced CKD.

To answer these questions, we conducted a systematic review and meta-analysis to investigate both hard and surrogate renal and cardiovascular endpoints in patients with DM and CKD stages 3–5 who were receiving any form of RAAS-blocking treatment in a randomized controlled trial (RCT). Our specific objective was to evaluate if there is a beneficial effect on cardiovascular events or mortality that exceeds potential renal adverse events (decrease in GFR, expedited need for RRT and hyperkalaemia events).

MATERIALS AND METHODS

Our systematic review included RCTs of at least 6 months duration, comparing single RAAS-blocking agents (only ACEIs, ARBs or renin inhibitors, but not in combination) with either placebo or an alternative antihypertensive agent in patients with DM and moderate or severe CKD [stages 3–5 or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2]. We also included studies presenting pre-planned post hoc analyses of RCTs if they analysed a subgroup including our population of interest and maintained the initial randomization frame or if they provided an interaction analysis for patients with DM and CKD stages 3b–5 as defined according to the Kidney Disease: Improving Global Outcomes definition as abnormalities of kidney structure or function present for >3 months, with implications for health [17]. It was staged based on eGFR (mL/min/1.73 m^2) as follows: 45–59, stage 3a; 30–44, stage 3b; 15–29, stage 4; <15, stage 5 [17]. When different subgroups of patients with advanced CKD were available, the data were extracted only for those with eGFR <45 mL/min/1.73 m^2.

We included all available studies that met the inclusion criteria regarding the design, population and intervention, irrespective of the reported outcomes. We did not put restrictions on language. Studies that included only participants on haemodialysis (HD), peritoneal dialysis (PD) or renal transplant were excluded, as well as studies with $<30\%$ of patients with DM, unless results were presented separately for our population of interest or an interaction analysis was provided. The primary analysis was performed once with studies comprising both patients with and without DM (overall) and once with studies including only patients with DM. Also, several subgroup analyses were performed for studies with placebo treatment versus with other antihypertensive treatment in the control arm, for studies with or without high risk of bias or for studies stratified by type of RAAS-blocking agent (ACEI versus ARB).

Finally, meta-regression analysis was conducted to assess the impact on the effect estimates of studies with $<100\%$ diabetes patients for major outcomes of interest: all-cause mortality and the composite outcome need for RRT/doubling of serum creatinine.

Search strategy

Two reviewers searched MEDLINE (1950–November 2016), Embase and Cochrane Central Register of Controlled Trials (1991–November 2016) according to a standardized protocol (see Supplementary Table S1 for search terms used in strategies for this review) [18]. Citations identified from electronic databases were supplemented by manually reviewing reference lists of clinical practice guidelines, review articles and relevant

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studies. Searches for available data in other sources of grey literature (abstracts, conference proceedings, unpublished studies, databases of industrial companies, US Food and Drug Administration or European Medicines Agency) was performed. A first search for studies was run to January 2014 and updated to November 2016 afterwards. When possible, we contacted investigators of included trials to obtain missing or incomplete data for key outcomes.

Data extraction, risk of bias and quality of evidence

Data extraction was performed independently by two reviewers (I.N., E.D.) using standard data extraction forms and included in a database table; any disagreements between reviewers were resolved in consultation with a third reviewer (A.C.).

Data on the characteristics of the trials, participants, interventions and hard and surrogate endpoints were extracted. We planned that missing or unclear information would be searched within the study protocol or within the original trial (for the post hoc RCTs). Any full text in a language other than English would be translated. As a significant proportion of the included studies reported both cardiovascular and renal outcomes in a pre-specified composite manner, data for the renal and cardiovascular outcomes of interest were extracted only from studies that analysed these outcomes separately. When more than one article for a study was found, we used only the references with the most complete data, or both if they reported different types of outcomes.

Risk of bias was explored according to the Cochrane Handbook for Systematic Reviews of Interventions for the following domains: selection bias (random sequence generation, allocation concealment), performance bias (blinding of the participants and personnel), detection bias (blinding of assessment of outcome), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias (significant different group comparisons, funding sources, early termination of a trial) [19]. We considered trials to have a high selective reporting bias when data on all-cause and cardiovascular mortality outcomes were not provided or were provided in an inadequate manner (data that could not be included in a meta-analysis) [19].

Quality of evidence was explored according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for the following limitations: study limitation [lack of concealment allocation, lack of blinding, important loss to follow-up, no intention-to-treat (ITT) analysis, early discontinuation of the trial, selective reporting], inconsistent results (heterogeneity or variability in results), indirectness of evidence (use of only one of two active drugs, differences between populations/interventions/outcomes of interest), imprecision (for trials including a relatively small number of patients or events, wide confidence intervals) and publication bias (failure of the investigators to report studies) [20].

We evaluated the following types of outcome measures:

(i) All-cause mortality
(ii) Cardiovascular mortality
(iii) Non-fatal cardiovascular events
(iv) Renal outcomes:
- Dichotomous—evaluating the number of events: need for RRT/doubling of serum creatinine or a composite of these
- Continuous—changes from baseline values and end-of-treatment values: serum creatinine (mg/dL), creatinine clearance (CrCl) (mL/min/1.73 m^2), eGFR (mL/min/1.73 m^2)

(v) Adverse events:
- Hypotension
- Hyperkalaemia
- Total number of reported adverse events

Statistical analysis

For dichotomous outcomes, the relative risk (RR) and 95% confidence interval (CI) were calculated. For continuous outcomes, the mean difference (MD) and 95% CI was calculated. The effect estimates were summarized using random effects analysis. The heterogeneity was evaluated using the Cochrane chi-squared (χ^2) test on $N - 1$ degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test with 95% CI. We considered low heterogeneity as an I^2 value $<25\%$, moderate heterogeneity as an I^2 value of 26–74% and important heterogeneity as an I^2 value $\geq 75\%$. For the meta-regression analysis, $P < 0.05$ was considered significant. All statistical analyses were performed using Review Manager, version 5.20 and Comprehensive Meta-Analysis software, version 2.

RESULTS

Our original search yielded 1089 articles. Based on titles and abstracts, 819 citations were excluded. Based on full-text assessment of the remaining 270 articles, 9 trials reported in 11 references were included in the final analysis. Details of the reasons for inclusion and exclusion are provided in Figure 1. Of the included studies, seven were RCTs [21–27] and four were post hoc analyses of the following RCTs: RENAAL [28], IDNT [29], ALLHAT [30] and CASE-J [31]. Overall, the entire meta-analysis comprised 9797 participants (data were extracted only once when reports were available both as an RCT and as a post hoc analysis if there was more than one publication of the same trial).

Study characteristics

There were five trials that compared ACEIs [21–24, 30] with placebo or with other antihypertensive treatments. Of these, four studies enrolled only patients with type 2 DM [21–24], while one study [30] was conducted in a mixed population with 33.3% of patients having type 2 DM. Six trials used an ARB [25–29, 31]; of these, five studies enrolled only patients with type 2 DM [25–29] and one study [31] included a mixed population with 48.2% of patients having type 2 DM (Table 1). We did not find any study using direct renin inhibitors as monotherapy in patients with DM and moderate to advanced CKD. Overall, there were two studies that included mixed populations of both patients with and without diabetes, while the remaining nine

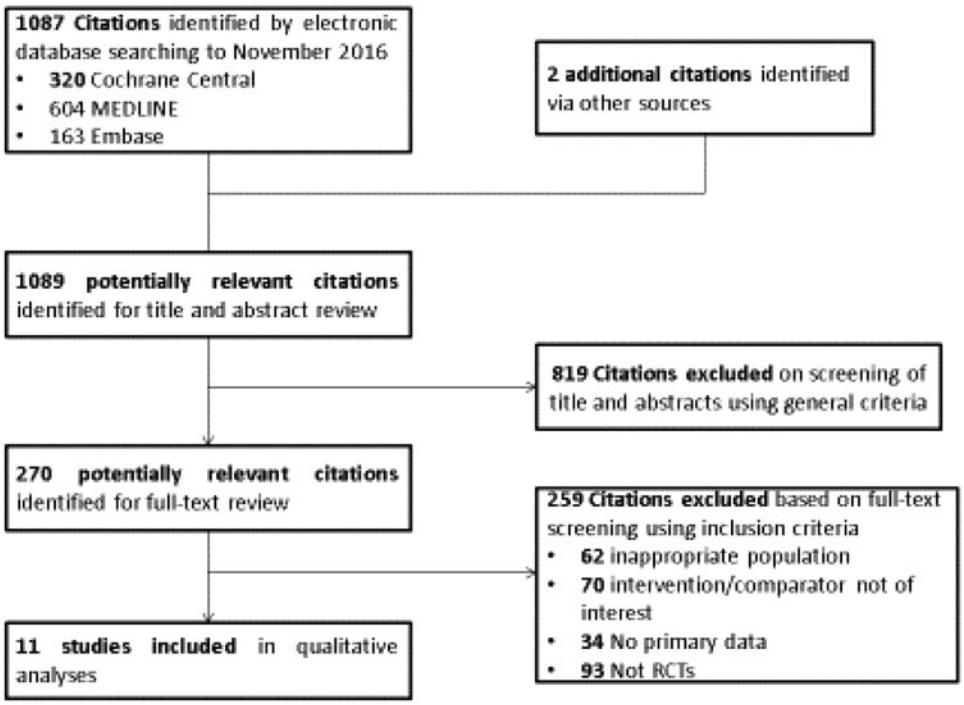

FIGURE 1: Flow chart of the search strategy and inclusion and exclusion criteria.

included only patients with diabetes. All studies except one (ALLHAT) [30] included patients who had some degree of proteinuria at baseline—most studies reporting values of ∼1 g/day. For the ALLHAT study, this information was not reported [30].

Of the five studies investigating ACEIs, there were three studies comparing ACEIs with placebo [22–24] and two studies comparing ACEIs with other antihypertensive drugs (amlodipine, nitrendipine, chlorthalidone) [21, 30]. Of the six studies investigating ARBs, two studies compared ARBs with placebo [26, 28], two studies compared ARBs with other antihypertensive drugs (amlodipine) [27, 31] and two studies [25, 29] compared ARBs versus a two-arm control group (placebo and other antihypertensive treatment) (Table 1). The ACEI studies used, in general, minimum to moderate doses of the study drug: 2.5 mg/day benazepril [22], 5 mg/day ramipril [21], 20 mg/day fosinopril [23], 4 mg/day perindopril [24]. Only one trial [30] used the maximum dosage (40 mg/day lisinopril). All of the ARB studies except one used the maximum doses of the intervention drug: 100 mg/day losartan [26–28], 300 mg/day irbesartan [25, 29], but only 12 mg/day candesartan [31].

Quantitative analysis

Comparing ACEIs/ARBs with placebo/other antihypertensive treatment, the evaluated outcomes showed the following results:

(i) All-cause mortality: analysing the overall population, we did not find any significant difference between the two groups for this outcome [four studies, 5309 participants, RR = 0.97 (95% CI 0.85–1.10)] and no heterogeneity ($\chi^2 = 1.38$; $I^2 = 0\%$) (Figure 2).

(ii) Cardiovascular mortality: we found only two studies reporting data for this outcome. No difference was found between the intervention and control groups [two studies, 3748 participants, RR = 1.03 (95% CI 0.75–1.41)], with moderate heterogeneity ($\chi^2 = 3.49$; $I^2 = 43\%$) (Figure 2).

(iii) Non-fatal cardiovascular events: in the overall population there was a trend towards a favourable effect estimate for the ACEI/ARB group, with a 10% reduction in the risk of developing non-fatal CV events [three studies, 6138 participants, RR = 0.90 (95% CI 0.81–1.00)] with no heterogeneity ($\chi^2 = 0.54$; $I^2 = 0\%$) (Figure 3).

(iv) Renal outcomes: for the composite dichotomous outcome need for RRT/doubling of serum creatinine, we found in the overall population a 19% risk reduction in favour of the intervention arm [five studies, 5202 participants, RR = 0.81 (95% CI 0.70–0.92)] with no heterogeneity ($\chi^2 = 2.11$; $I^2 = 0\%$) (Figure 4). When analysing diabetic patients only, we found a consistent protective effect for the RAAS-blocking therapy, with a 22% reduction in the risk for the composite dichotomous outcome need for RRT/doubling of serum creatinine [four studies, 3314 participants, RR = 0.78 (95% CI 0.67–0.90)] and no heterogeneity ($\chi^2 = 0.04$; $I^2 = 0\%$) (Figure 4).

For the continuous outcome of change in eGFR/CrCl values, we did not find a difference in the effect estimates between the groups [four studies, 2074 participants, MD = −0.09 (95% CI −2.75–2.57)] in the overall group. Of note, there was moderate heterogeneity that might be explained by the variance in the different techniques used by each study for renal function assessment and by using different time points for renal function assessment for this outcome ($\chi^2 = 12.64$; $I^2 = 68\%$) (Figure 5).

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Table 1. Baseline characteristics of the included studies

Trial	Intervention	Control group	Study duration (weeks)	Total patients (*n*)	Mean age (years)	Men (%)	Baseline renal function and intervention group	Type of DM	
								Type 1	Type 2
Fogari *et al.* (1999) [21]	Ramiprill	Nitrendipine	96	107	58 ± 1	100	Serum creatinine (mg/dL): 2.0 ± 0.4; CrCl (mL/min/1.73 m^2): 44.4 ± 8; UAE (g/24 h): 0.79 ± 0.04	–	•
IDNT [25, 29]	Irbesartan	Placebo, amlodipine	124.8	1715	59.3 ± 7.1	66.4	Serum creatinine (mg/dL): 1.67 ± 5.4; UPE (g/24 h), median: 2.9 (IQR 1.6–5.4)	–	•
RENAAL [26, 28]	Losartan	Placebo	163.2	1513	60 ± 7	63.1	Serum creatinine (mg/dL): 1.9 ± 0.5. UACR (mg/g): 1237	–	•
Suzuki *et al.* (2002) [22]	Benazepril	Placebo	48	72	NS	38.8	UPE (g/24 h): 1.2 ± 0.6	–	•
Tong *et al.* (2006) [23]	Fosinopril	Placebo	73.7	38	65 ± 6	65.7	Serum creatinine (mg/dL): 2.07 ± 0.53; CrCl (mL/min/1.73 m^2): 34.8 ± 9.8; UAE (g/24 h), median: 1.52 (IQR 0.19–4.6)	–	•
Guo *et al.* (2009) [27]	Losartan	Amlodipine	24	41	59.2 ± 7.0	43.9	eGFR (mL/min/1.73 m^2): 53.65 ± 7.70; UPE (g/24 h), median: 1.80 (IQR 0.8–3.6)	–	•
Heerspink *et al.* (2010) (ADVANCE) [24]	Perindopril-Indapamide	Placebo	206.4	2033	68.3 ± 6.4	42.5	eGFR (mL/min/1.73 m^2): 51.0 ± 7.8 UACR (μg/mg), median: 19.4 (IQR 8.0–64.5)	–	•
Rahman *et al.* (2005) (ALLHAT) [30]	Lisinopril	Chlorthalidone, amlodipine	288	1888	70.6 ± 7.9	NS	eGFR (mL/min/1.73 m^2): 49.2 ± 9.0	–	•
Saruta *et al.* (2009) (CASE-J) [31]	Candesartan	Amlodipine	153.6	2390	65.6 ± 10.3	51.7	eGFR < 60 (mL/min/1.73 m^2); positive urinary protein tests by dipstick analysis	–	•

IQR, interquartile range; UACR, urinary albumin:creatinine ratio; UAE, urinary albumin excretion; UPE, urinary protein excretion.

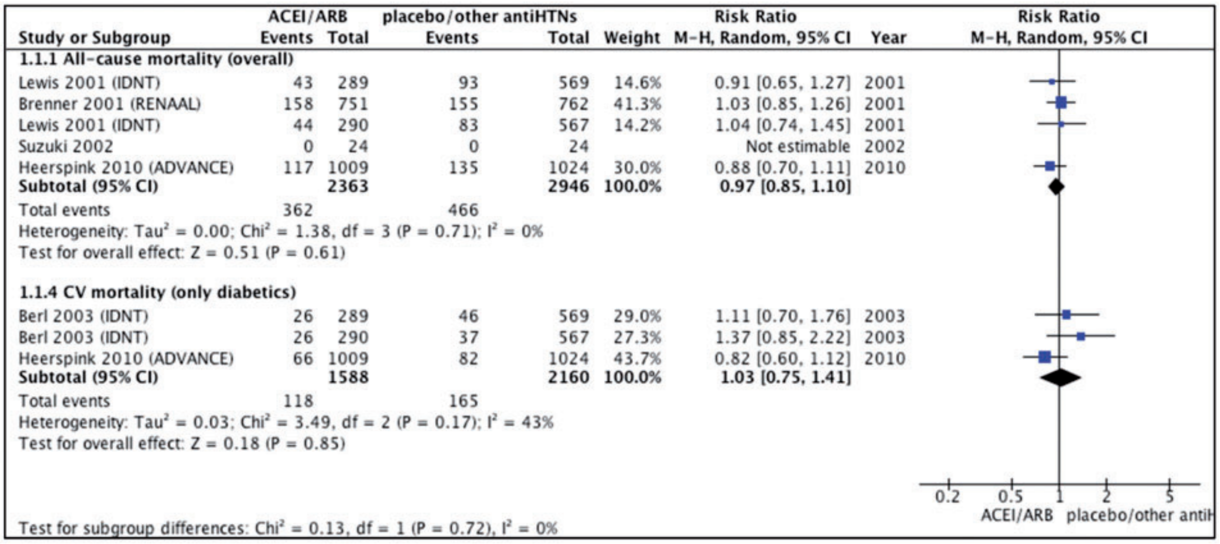
ACEI/ARB placebo/other antiHTNs Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year M-H, Random, 95% CI
1.1.1 All-cause mortality (overall)
Lewis 2001 (IDNT) 43 289 93 569 14.6% 0.91 [0.65, 1.27] 2001
Brenner 2001 (RENAAL) 158 751 155 762 41.3% 1.03 [0.85, 1.26] 2001
Lewis 2001 (IDNT) 44 290 83 567 14.2% 1.04 [0.74, 1.45] 2001
Suzuki 2002 0 24 0 24 Not estimable 2002
Heerspink 2010 (ADVANCE) 117 1009 135 1024 30.0% 0.88 [0.70, 1.11] 2010
Subtotal (95% CI) 2363 2946 100.0% 0.97 [0.85, 1.10]
Total events 362 466
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
1.1.4 CV mortality (only diabetics)
Berl 2003 (IDNT) 26 289 46 569 29.0% 1.11 [0.70, 1.76] 2003
Berl 2003 (IDNT) 26 290 37 567 27.3% 1.37 [0.85, 2.22] 2003
Heerspink 2010 (ADVANCE) 66 1009 82 1024 43.7% 0.82 [0.60, 1.12] 2010
Subtotal (95% CI) 1588 2160 100.0% 1.03 [0.75, 1.41]
Total events 118 165
Heterogeneity: Tau² = 0.03; Chi² = 3.49, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 0.18 (P = 0.85)
0.2 0.5 1 2 5
ACEI/ARB placebo/other antiH
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

FIGURE 2: All-cause mortality and CV mortality: ACEIs/ARBs versus placebo/other antihypertensive treatment.

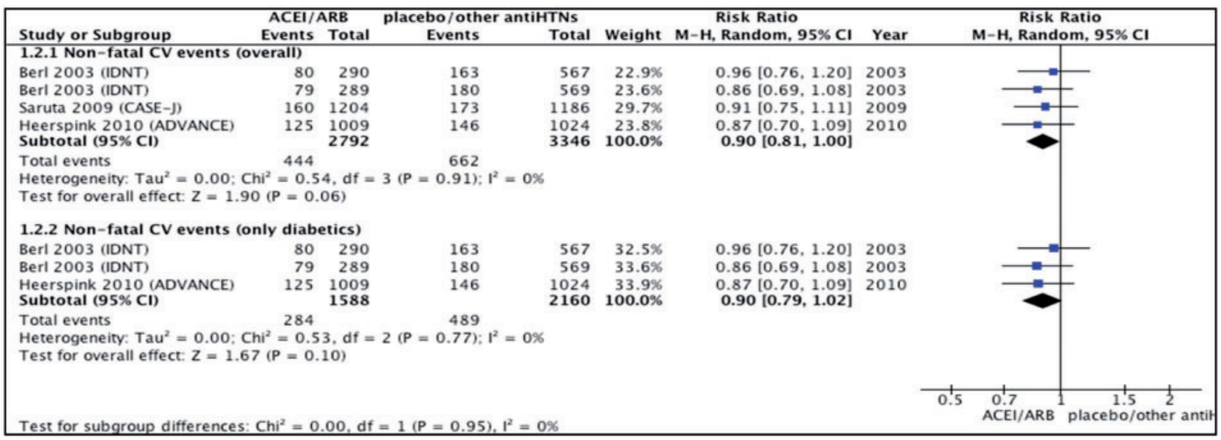
ACEI/ARB placebo/other antiHTNs Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year M-H, Random, 95% CI
1.2.1 Non-fatal CV events (overall)
Berl 2003 (IDNT) 80 290 163 567 22.9% 0.96 [0.76, 1.20] 2003
Berl 2003 (IDNT) 79 289 180 569 23.6% 0.86 [0.69, 1.08] 2003
Saruta 2009 (CASE-J) 160 1204 173 1186 29.7% 0.91 [0.75, 1.11] 2009
Heerspink 2010 (ADVANCE) 125 1009 146 1024 23.8% 0.87 [0.70, 1.09] 2010
Subtotal (95% CI) 2792 3346 100.0% 0.90 [0.81, 1.00]
Total events 444 662
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)
1.2.2 Non-fatal CV events (only diabetics)
Berl 2003 (IDNT) 80 290 163 567 32.5% 0.96 [0.76, 1.20] 2003
Berl 2003 (IDNT) 79 289 180 569 33.6% 0.86 [0.69, 1.08] 2003
Heerspink 2010 (ADVANCE) 125 1009 146 1024 33.9% 0.87 [0.70, 1.09] 2010
Subtotal (95% CI) 1588 2160 100.0% 0.90 [0.79, 1.02]
Total events 284 489
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.10)
0.5 0.7 1 1.5 2
ACEI/ARB placebo/other antiH
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%

FIGURE 3: Non-fatal CV events: ACEIs/ARBs versus placebo/other antihypertensive treatment.

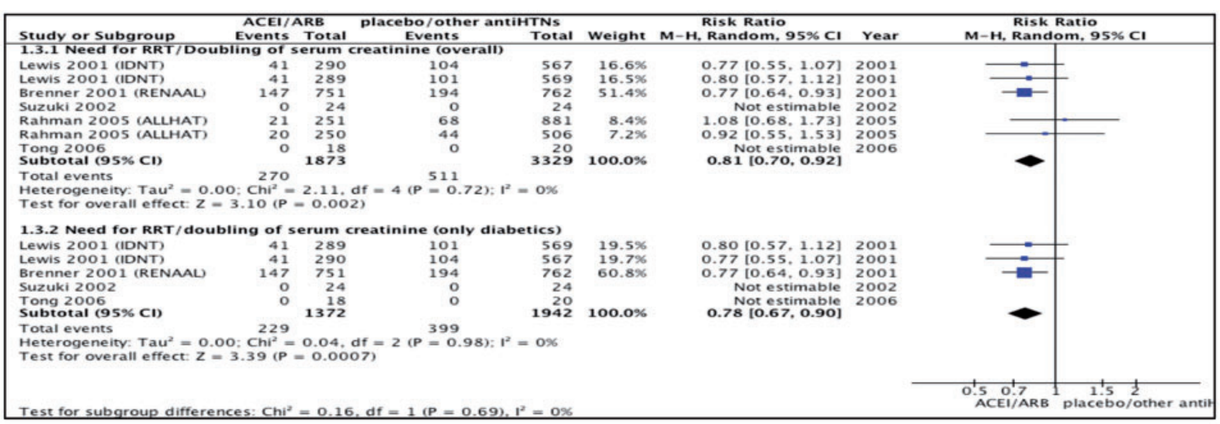
ACEI/ARB placebo/other antiHTNs Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year M-H, Random, 95% CI
1.3.1 Need for RRT/Doubling of serum creatinine (overall)
Lewis 2001 (IDNT) 41 290 104 567 16.6% 0.77 [0.55, 1.07] 2001
Lewis 2001 (IDNT) 41 289 101 569 16.5% 0.80 [0.57, 1.12] 2001
Brenner 2001 (RENAAL) 147 751 194 762 51.4% 0.77 [0.64, 0.93] 2001
Suzuki 2002 0 24 0 24 Not estimable 2002
Rahman 2005 (ALLHAT) 21 251 68 881 8.4% 1.08 [0.68, 1.73] 2005
Rahman 2005 (ALLHAT) 20 250 44 506 7.2% 0.92 [0.55, 1.53] 2005
Tong 2006 0 18 0 20 Not estimable 2006
Subtotal (95% CI) 1873 3329 100.0% 0.81 [0.70, 0.92]
Total events 270 511
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.10 (P = 0.002)
1.3.2 Need for RRT/doubling of serum creatinine (only diabetics)
Lewis 2001 (IDNT) 41 289 101 569 19.5% 0.80 [0.57, 1.12] 2001
Lewis 2001 (IDNT) 41 290 104 567 19.7% 0.77 [0.55, 1.07] 2001
Brenner 2001 (RENAAL) 147 751 194 762 60.8% 0.77 [0.64, 0.93] 2001
Suzuki 2002 0 24 0 24 Not estimable 2002
Tong 2006 0 18 0 20 Not estimable 2006
Subtotal (95% CI) 1372 1942 100.0% 0.78 [0.67, 0.90]
Total events 229 399
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.39 (P = 0.0007)
0.5 0.7 1 1.5 2
ACEI/ARB placebo/other antiH
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%

FIGURE 4: Need for RRT/doubling of serum creatinine: ACEIs/ARBs versus placebo/other antihypertensive treatment.

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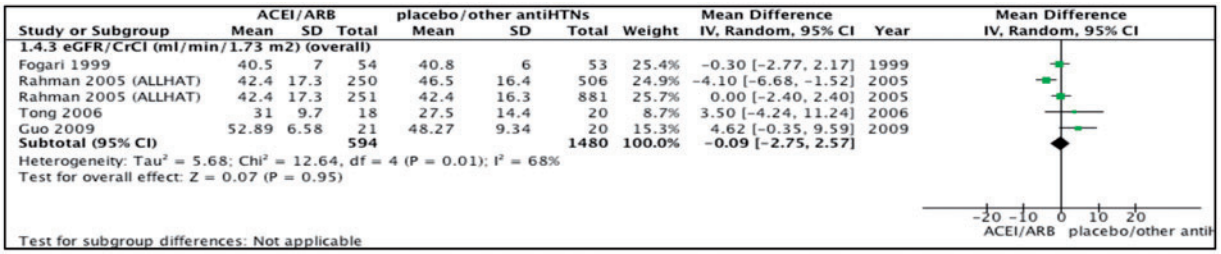

FIGURE 5: eGFR/CrCl (ml/min/1.73 m^2), end-of-treatment values: ACEIs/ARBs versus placebo/other antihypertensive treatment.

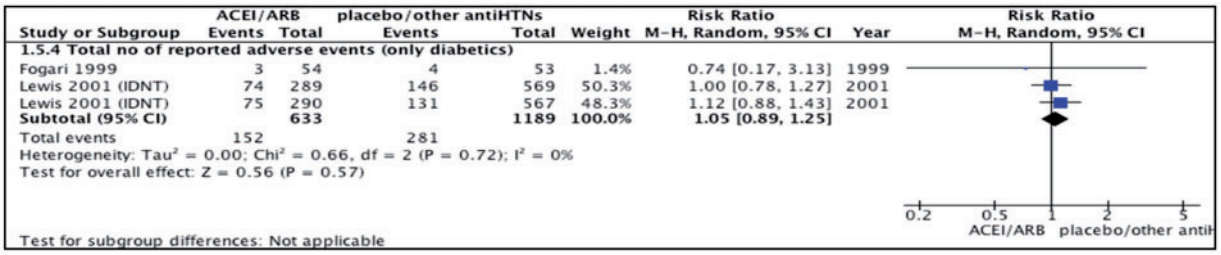

FIGURE 6: Total number of reported adverse events: ACEIs/ARBs versus placebo/other antihypertensive treatment.

(v) Adverse events: only two studies, conducted in patients with DM, reported data for the total number of adverse events and found no difference between groups [two studies, 1822 participants, RR = 1.05 (95% CI 0.89–1.25)] (Figure 6). A trend towards a higher overall rate of serious adverse events was observed in individuals with CKD, independent of the intervention group, as reported by the ADVANCE authors [24].

Subgroup analysis and investigation for sources of heterogeneity

We planned to analyse the variability in effect size caused by studies comparing ACEIs/ARBs versus placebo or versus other antihypertensive medications to explore whether the effect is attributed to the antihypertensive effect itself or whether ACEIs/ARBs have a protective effect on top of their blood pressure–lowering effect. However, in reality, only one study performed a separate analysis for ACEIs/ARBs versus placebo (the IDNT trial); for all the other studies, it was impossible to extract data of RAAS-blocking agents versus placebo, as the placebo arm allowed the use of antihypertensive medication except RAAS-blocking agents.

We also performed a subgroup analysis stratified by the type of RAAS agent used in the intervention arm versus controls. When trials using ACEIs as the intervention were evaluated separately, data could be analysed only for the all-cause mortality outcome, showing no difference between the ACEI and control groups [two studies, 2081 participants, RR = 0.88 (95% CI 0.70–1.11)] (Supplementary Figure S7). When studies were analysed for ARBs as the intervention, there was a 22% reduction in the risk of reaching the composite outcome of need for RRT/doubling of serum creatinine [two studies, 3228 participants, RR = 0.78 (95% CI 0.67–0.90)] (Supplementary Figure S2). In this subgroup analysis of studies using ARBs as an intervention, we did not find a difference for the outcomes all-cause mortality and non-fatal cardiovascular events [two studies, 3228 participants, RR = 1.01 (95% CI 0.87–1.17) and two studies, 3105 participants, RR = 0.91 (95% CI 0.80–1.03), respectively] (Supplementary Figures S3 and S4).

Other subgroup analysis was intended, stratifying patients according to CKD stages (eGFR ≤ 45 versus 45–60 mL/min/1.73 m^2). However, it could not be performed, as the included studies did not state the exact number of patients for each CKD stage, asserting only the CKD stages 3–5 status of the participants.

For the majority of outcomes there was no heterogeneity present. The only outcomes where we found moderate heterogeneity were the cardiovascular mortality outcome ($I^2 = 43\%$) and the change in eGFR/CrCl outcome ($I^2 = 68\%$). Due to the small number of included studies, there was no possibility to further explore possible sources of heterogeneity in these outcomes.

Finally, we performed a univariate random-effects meta-regression analysis. We found no difference in the effect estimates of RAAS-blocking agents on the dichotomous composite outcome of need for RRT/doubling of serum creatinine (P = 0.24; Q = 1.35; df = 1.00) when accounting for studies including <100% of patients with DM (Supplementary Figure S5).

Qualitative analysis

Only a small number of studies reported data for further relevant renal outcomes and adverse events. More specifically, changes in CrCl and/or eGFR (mL/min/1.73 m^2) from baseline values were reported by only two studies: Tong *et al.* [23], weekly changes in CrCl; and Guo *et al.* [27], monthly evaluations during the entire follow-up period in eGFR. There was a striking lack of data reported on major adverse events: the number of cases that developed hyperkalaemia during the study period were reported by only one study [25], changes in baseline potassium values were not reported by any of the included studies and potassium values at the end of treatment were reported by two studies, Suzuki *et al.* [22] (data for only the intervention

group) and Tong *et al.* [23]. Also, the specific number of patients that developed hypotension throughout the study period was reported by one study [24]. In the majority of the studies, adverse events were addressed either as part of composite endpoints or they were not reported at all.

Quality assessment was performed for all 11 studies, which reported data on the nine included trials (RENAAL and IDNT trials reported different outcomes in different references). Overall, the quality of the included studies was suboptimal. For seven studies, the randomization was unclear [21–23, 26–28, 30] and was at low risk of bias in four studies [24, 25, 29, 31]. Allocation concealment was unclear for all of the included studies. Blinding of the patients and personnel was unclear for nine studies [21–29] and was at low risk of bias for two studies [30, 31]. Attrition bias was found to be low for nine studies [22–29, 31] and high for two studies [21, 30]. Nevertheless, selective reporting was high for the majority of the trials, except for the two IDNT post hoc analyses [25, 29] and the ADVANCE post hoc study [24]. Also, 73% of the included studies were considered as having a high risk of bias on other bias domains (funding bias [23–26, 28–31], early discontinuation for the RENAAL trial and post hoc analysis [26, 28] and imbalance in baseline characteristics [24]) (Supplementary Figures S6 and S7). Results were largely similar in the sensitivity analysis when excluding trials with a high risk of bias. Publication bias was assessed for all-cause mortality, cardiovascular mortality and need for RRT/doubling of serum creatinine, showing an unequal distribution of the studies, consistent with possible bias regarding small sample size and both negative and positive studies (Supplementary Figures S8 and S9).

The GRADE quality of evidence assessment showed that on all outcomes we had moderate (all-cause mortality and need for RRT/doubling of serum creatinine) and low quality of evidence (CV mortality, non-fatal CV events and total number of reported adverse event outcomes) (Table 2).

DISCUSSION

We conducted a systematic review and meta-analysis to investigate the alleged beneficial impact and safety of RAAS-blocking agents on cardiovascular and renal outcomes in the setting of patients with DM and CKD stages 3–5 or eGFR <45 mL/min/1.73 m^2). Overall, our results included nine studies ($n = 9797$ participants with CKD stages 3b–5) reporting data for this growing population. There was no difference between the RAAS-blocking agents and control groups regarding all-cause or cardiovascular mortality. There was a trend for a favourable effect for RAAS-blocking agents for non-fatal cardiovascular events and a lower risk for the composite outcome of need for RRT/doubling of serum creatinine when RAAS-blocking agents were used. It was not possible, however, to assess whether this effect was due to better control of hypertension or to the RAAS inhibition per se. Also, regarding the benefits of ACEI versus ARBIs on renal and cardiovascular mortality, there are insufficient data, as only three trials used a head-to-head comparison between these two types of agents (DETAIL, ONTARGET, ORIENT) [32–35], suggesting an overall insignificant difference between ACEIs and ARBs in patients with diabetic nephropathy stages 3b–5.

Although there are several previously published meta-analyses and systematic reviews evaluating the effects of RAAS-blocking agents in patients with diabetes [15, 16, 36–41], none focused on patients with advanced CKD stages 3b–5. One of the meta-analyses evaluated outcomes with use of renin–angiotensin system (RAS) blockers compared with other antihypertensive agents in patients with diabetes. When compared with other antihypertensive agents, RAS blockers were associated with a similar risk of death, cardiovascular death or major cardiovascular events. The authors concluded that in people with diabetes, RAS blockers are not superior to other antihypertensive drugs at reducing the risk of hard cardiovascular and renal endpoints [15]. However, only end-stage renal disease (ESRD) was evaluated as an outcome, whereas doubling of serum creatinine was not considered a 'hard' renal endpoint. No subgroup analysis was in people with diabetic nephropathy.

Catalá-López *et al.* [36] published a network meta-analysis in adults with diabetes and focused on the comparisons of different RAS blockers. They showed similar effects of ACEIs and ARBs on major cardiovascular and renal outcomes [36]. No impact of CKD as a comorbidity or impact of the level of eGFR was reported.

A different network meta-analysis of randomized trials comparing blood pressure–lowering agents in adults with diabetic

FULL REVIEW

Table 2. Summary of findings

Outcome	Trials reporting more than one event/total no. of trials included	No. of patients included	Median treatment duration (weeks)	Relative effect	95% CI	Quality of evidence*
1. All-cause mortality (overall)	3/4	5309	135.6	0.97	0.85–1.10	Moderate
2. CV mortality (only diabetics)	2/2	3748	165.6	1.03	0.75–1.41	Low
3. Non-fatal CV events (overall)	3/3	138	161.6	0.90	0.81–1.00	Low
4. Need for RRT/doubling of serum creatinine (overall)	3/5	5202	139.5	0.81	0.70–0.92	Moderate
5. eGFR/CrCl (mL/min/1.73 m^2), end of treatment (overall)	4/4	2074	120.4	−0.09	−2.75–2.57	Very low
6. Total no. of reported adverse events (overall)	2/2	1822	110.4	1.05	0.89–1.25	Low

kidney disease found that no drug regimen was more effective than placebo for reducing all-cause mortality. Only an ARB (alone or combined with an ACEI) was significantly better than placebo for prevention of ESKD [16]. However, most of this effect was attributed to studies comparing RAAS blockade to placebo, and the evidence evaluating head-to-head comparisons or other combinations was low.

Finally, a different meta-analysis found that after stratification by type of RAAS-blocking agent, only ACEI and not ARB treatment reduced the risk of all-cause and cardiovascular mortality in patients with DM [41]. In the population with DM and CKD stages 3b–5 we could not confirm these results, as for this subpopulation there were mainly studies using ARBs as the intervention (with a cumulative weight of 76.2). Thus the absence of a positive effect on mortality by ACEIs in our meta-analysis should not be considered as conflictive with the general literature.

There are several major differences between these previous reports (discussed above) and our current meta-analysis. First, we were able to include significantly more trials, some of them published only recently [23, 24, 27, 30, 31]. Second, we allowed studies comparing RAAS-blocking agents to placebo as well as to other antihypertensive treatments, and most importantly, we focussed on patients with diabetes and CKD stages 3–5.

We confirm and extend results from a recent prospective study assessing the effectiveness and safety of ACEI/ARB treatment in 28 497 adults with late, pre-dialysis, stage 5 CKD—53% of these patients had diabetes [42]. The use of ACEIs/ARBs was associated with a lower risk for long-term dialysis [hazard ratio (HR) = 0.94 (95% CI 0.91–0.97)] and for the composite outcome 'long-term dialysis or death' [HR = 0.94 (95% CI 0.92–0.97)].

Based on the evidence included in this meta-analysis and reviews mentioned above, the European Best renal Practice Diabetes Guideline Development Group recommended that adults with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2 or on dialysis) and diabetes who have a cardiovascular indication (heart failure, ischaemic heart disease) should be treated with an ACEI at the maximally tolerated dose (1B) [18]. The guideline development group suggest an RCT on the impact of on mortality, cardiovascular outcomes and evolution to ESRD withdrawing or maintaining RAAS inhibitors in patients already taking them for a cardiac indication when their CKD progresses to an eGFR <45 mL/min/1.73 m^2.

Fortunately, results of an ongoing trial may be available in the future [43]. The STOP-ACEi trial (trial registration: current controlled trials, ISRCTN62869767), an investigator-led multicentre, open-label, randomized controlled clinical trial of 410 participants with advanced (stage 4 or 5) progressive CKD receiving ACEIs, ARBs or both. Patients will be randomized in a 1:1 ratio to either discontinue ACEIs, ARBs or a combination of both (experimental arm) or continue ACEIs, ARBs or combination of both (control arm). The results of this trial will show whether discontinuation of ACEIs/ARBs can improve or stabilize renal function in patients with advanced progressive CKD.

There are several limitations to the conclusions of our meta-analysis that are inherent to the studies included. First, it should be emphasized that the degree of renal impairment can be an important effect modifier for hard endpoints in patients with diabetic nephropathy. Most RCTs evaluating relevant cardiovascular and renal outcomes in patients with diabetes do not include patients with CKD stages 3b–5. In our current meta-analysis, none of the studies included CKD stages 4–5. Although in the IDNT and RENAAL study serum creatinine was 1.6 ± 0.5 mg and 1.9 ± 0.5 mg, respectively, whereas in ADVANCE it was stipulated that 2000 patients had an eGFR <60 mL/min,1.73 m^2, we do not know how many patients had an eGFR <45 mL/min/1.73 m^2. As such, our analysis does not allow a firm conclusion on the effect of RAAS inhibitors in patients with diabetes and CKD stages 4–5. It can be postulated that any potential beneficial effect would be lower and adverse effects such as hyperkalaemia would be more prevalent, but data to support this are lacking. Another limitation is related to the influence of proteinuria. Most of the included studies were done on patients with medium to severe proteinuria at baseline and we believe that our results cannot be extrapolated to patients without proteinuria. Also, due to a lack of sufficient data, we were unable to perform a subgroup analysis adjusting on the level of proteinuria and explore the impact of proteinuria on the outcomes.

It is unclear how far the results of our meta-analysis may be generalized to the overall population of patients with diabetes and advanced renal impairment not due to diabetic nephropathy. A recent systematic review found that a substantial portion of patients with diabetes and kidney disease do not have diabetic nephropathy, but have some other primary kidney disease [44]. In addition, in IDNT, renovascular disease was an exclusion criterion, whereas in ADVANCE, patients had a trial with perindopril before inclusion; in RENAAL, only tolerant patients were included. As such, all patients who could potentially be harmed or have a deterioration of their kidney function by the use of RAAS-blocking agents were excluded before the start of the trial (selection bias).

In most studies there is a residual difference in blood pressure control between the RAAS-blocking group and the control group. It is thus uncertain how much of the effect is due to a difference in achieved blood pressure control rather than a pure RAAS-blocking effect.

The most important strength of this meta-analysis is that it is based on a systematic search of medical databases, data extraction and analysis of all current and the most recent information on the effects of RAAS-blocking agents in the specific population of patients with CKD stages 3b–5 and diabetes. To our knowledge, this is the first time a meta-analysis has been done in this specific population.

CONCLUSION

In conclusion, we found in this meta-analysis that treatment with RAAS-blocking agents, either ACEIs or ARBs, has favourable effects on renal outcomes in patients with DM and CKD stages 3–5, but only if the renal outcome is assessed as a composite outcome of need for RRT/doubling of serum creatinine and not when it was expressed as the evolution of GFR. Unfortunately, a lack of data precludes making firm conclusions

on their impact on mortality outcomes and also hampers interpretation of the differential impact of the class of RAAS-blocking agent. There is a considerable risk of selection bias in the included studies, focussing on patients with true diabetic nephropathy and excluding patients with comorbidities known to lead to poor tolerance of RAAS-blocking agents. Furthermore, there is an underreporting of potential adverse events, whereas our population of interest is at increased risk of these side effects.

As such, the question of whether to prescribe or withhold RAAS-blocking agents in patients with DM and CKD stages 3–5 cannot be answered with confidence based on the available evidence.

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SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

A.W.: member of advisory boards or received honoraria for lectures from Amgen, Fresenius, Astellas, Apotex, TEVA and Pharmacosmos; A.C.: received speakers honoraria from Amgen, Roche, Fresenius Medical Care and Abbott; I.N.: none to declare; J.D.S.: none to declare; C.D.: none to declare; D.G.: received speakers honoraria from Roche, Amgen, Vifor, Takeda and Sandoz; M.J.S.: none to declare; C.T.: none to declare; M.-D.D.: none to declare; D.B.: none to declare; W.V.B.: none to declare.

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