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Prevention of microalbuminuria using early intervention with renin-angiotensin system inhibitors in patients with type 2 diabetes: A systematic review

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Abstract

Hypothesis/objectives: Early prevention of diabetic nephropathy by way of blocking the renin-angiotensin system (RAS) in patients with normoalbuminuria seems rational, but trials have so far shown conflicting results. The present meta-analysis was undertaken to investigate if such treatment can prevent development of microalbuminuria.

Materials and methods: We searched MEDLINE, EMBASE and the Cochrane Library (2 June 2014) for randomised controlled trials, with a population of patients with type 2 diabetes and normoalbuminuria, comparing angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) to placebo. Studies had to have at least 50 participants in each arm and one year of follow-up. Random and fixed effect models were performed as well as trial sequential analysis.

Results: Six trials were included in the analysis (n=16,921). Overall risk of bias was variable. In a fixed model analysis ACE or ARB treatment was superior to placebo in relation to prevention of development of microalbuminuria, risk ratio 0.84 (95% confidence interval (CI) 0.79–0.88) p<0.001, I^2=23%, similar to random model results. Treatment also showed a trend towards a reduction in all-cause mortality(p=0.07).

Conclusions: We conclude that in patients with type 2 diabetes and normoalbuminuria, early intervention with ACEis or ARBs reduces the risk for development of microalbuminuria.

Keywords

Type 2 diabetes, microalbuminuria, renin angiotensin system, diabetic nephropathy, review

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Introduction

Of the global population of patients with type 2 diabetes, approximately half have signs of chronic kidney disease (CKD).[1] Any successful early intervention that reduces or delays progression in diabetic kidney disease is therefore expected to have a major impact on life expectancy and quality of life, as well as chronic care health economic costs. Primary prevention of microalbuminuria could be such an early intervention, that might truly prevent complications. This intervention would contrast to what is most frequently provided: treatment after the first signs of damage is present.

A major part of the chronic care of patients with type 2 diabetes is focused on the prevention of complications such as diabetic kidney disease. Specifically, the use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) is recommended[2] in the presence of microalbuminuria/moderately increased (urinary albumin creatinine ratio (UACR)>30 mg/g and

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<300 mg/g) or macroalbuminuria/severely increased (UACR>300 mg/g). The intervention leads to decreased albuminuria, prevents progression from microalbuminuria to macroalbuminuria and results in a reduced risk of cardiovascular disease (CVD), end stage renal disease (ESRD) and death.

Only a few studies have been conducted with primary prevention of albuminuria as outcome, and with conflicting results.[3–5] Currently there is no recommendation[2] for the use of renin-angiotensin system (RAS) inhibitors for primary prevention of the occurrence of albuminuria in patients with type 2 diabetes. Previous attempts to summarise studies, including a Cochrane analysis[6] have combined type 1 and type 2 diabetes, which may not be appropriate given the heterogeneity in kidney pathology. Diabetic nephropathy in type 1 diabetes is considered to be strictly a glomerular pathology with microalbuminuria as an early herald of molecular and cellular changes. In proteinuric type 2 diabetes, however, the causes of nephropathy are heterogenous.[7–9] This warrants a separate analysis in type 2 diabetes. In addition, the recent Cochrane analysis investigated antihypertensive treatment in general and not exclusively studies using ACEi or ARBs.[6]

The aim of our analysis was therefore not only to specifically assess the effect on development of microalbuminuria with intervention with an ACEi or ARB in patients with type 2 diabetes and normoalbuminuria, but also to try to assess whether further studies are needed. By presenting such a review of findings, we hope to assist clinicians in order to be better informed regarding treatment decisions.

Materials and methods

We searched MEDLINE, EMBASE and the Cochrane Library (2 June 2014), and search strings are included in the Supplementary Material. The protocol with details for this meta-analysis was published on the PROSPERO website (http://www.crd.york.ac.uk/PROSPERO/) (PROSPERO CRD42014009983) ahead of the initiation of the literature search. In summary, in order to be included in our analysis studies had to be double-masked randomised controlled trials, with a population of patients with type 2 diabetes and normoalbuminuria (UACR<30 mg/g) or urinary albumin excretion rate (UAER)<30 mg/24 h). In order to assess the effect of RAS inhibition, we only included studies comparing ACEi or ARB to placebo. At least one year of follow-up was considered necessary for evaluation of the effect on development of micro- or macroalbuminuria, and studies had to have at least 50 participants in each arm. The primary outcome for our analysis was development of micro/macroalbuminuria defined as UACR>30 mg/g or UAER>30 mg/24 h or corresponding converted units.

Our intention was also to investigate secondary outcomes including all-cause mortality, total CVD mortality (death from myocardial infarction, stroke and peripheral vascular disease) and CVD morbidity (non-fatal myocardial infarction, non-fatal stroke, amputation of lower extremity and coronary or peripheral revascularisation). In addition renal outcomes defined as doubling of baseline serum creatinine or progression to ESRD was investigated.

Selection of studies

An independent experienced librarian performed the initial literature search. Studies were included in the meta-analysis after full agreement between two authors (FP and ML).

Assessment of risk of bias in included studies

Two authors (FP and ML) independently assessed the risk of bias in each trial by means of the Cochrane Collaboration's risk of bias tool.

Measures of treatment effect

Data on dichotomous outcomes were statistically summarised as relative risks (RRs) with 95% confidence intervals (CIs).

Assessment of heterogeneity

A priori the authors evaluated clinical heterogeneity of the included trials. Heterogeneity was identified by visual inspection of the forest plots, by using a standard chi^2 test with a significance level of α=0.1. Heterogeneity was specifically examined with the I^2 statistic, where I^2 values of 0–40% indicate heterogeneity might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; and 75–100% may represent considerable heterogeneity.[10]

Assessment of overall effect on outcome

We used both a random effects model[11] and a fixed effect model[12] with no a priori consideration regarding which model to consider as primary model.

Data extraction and management

Two authors (FP and ML) independently extracted information on each trial using standard data extraction forms. The forms included data concerning trial design, participants, interventions and outcomes as detailed in the selection criteria described above.

Data synthesis

Statistical analysis was performed according to the statistical guidelines in the newest version of *The Cochrane handbook for systematic reviews of interventions*.[10]

Calculations and modelling were performed using the RevMan software version 5.3. The effect of treatment is calculated as risk ratios (RRs) and reported with 95% CIs, with a p-value <0.05 considered statistically significant.

Trial sequential analysis (TSA)

TSA is a methodology that combines an information size calculation (cumulated sample sizes of included trials) for meta-analysis with the threshold of statistical significance. TSA is a tool for quantifying the statistical reliability of data in a cumulative meta-analysis adjusting p-values for repetitive testing on accumulating data. TSA was conducted on the outcomes showing statistical significance in both random effects and fixed effect model.[13,14]

We applied TSA since it prevents an increase of the risk of type I error (less than 5%) due to potential multiple updating in a cumulative meta-analysis and provides important information in order to estimate the level of evidence of the experimental intervention. We applied trial sequential monitoring boundaries according to an information size suggested by the intervention effect estimated based on an a priori 10% relative risk reduction (RRR) employing α=0.05 and ß=0.20.

We used TSA version 0.9 beta for these analyses (Copenhagen Trial Unit, Trial Sequential Analysis (computer program), version 0.9 beta, Centre for Clinical Intervention Research, 2011, www.ctu.dk/tsa).

Subgroup analyses

Subgroup analyses according to hypertension status were initially planned for the primary outcome, but this approach was abandoned during the data analysis process owing to different and missing definitions of hypertension threshold in the included studies.

Results

A flow diagram of the numbers of studies identified and rejected at each stage in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15] can be seen as Figure 1. In brief, an experienced academic librarian searched and found 64 abstracts from MEDLINE, EMBASE and the Cochrane Library, and these underwent thorough evaluation in relation to inclusion criteria for this analysis. In addition, 1035 abstracts that were not captured in the initial search were screened, but no further studies fulfilling inclusion criteria were identified. Authors were not contacted for further data from any of the included studies.

We included six randomised controlled clinical trials[3–5,16–18] in our meta-analysis, and their characteristics can be seen in Table 1 (n=16,921 patients). Based on the inclusion criteria chosen for this analysis, the number of trials were considerably lower than a previous Cochrane metanalysis on the subject.[6] The overall risk of bias was variable (Figure 2).

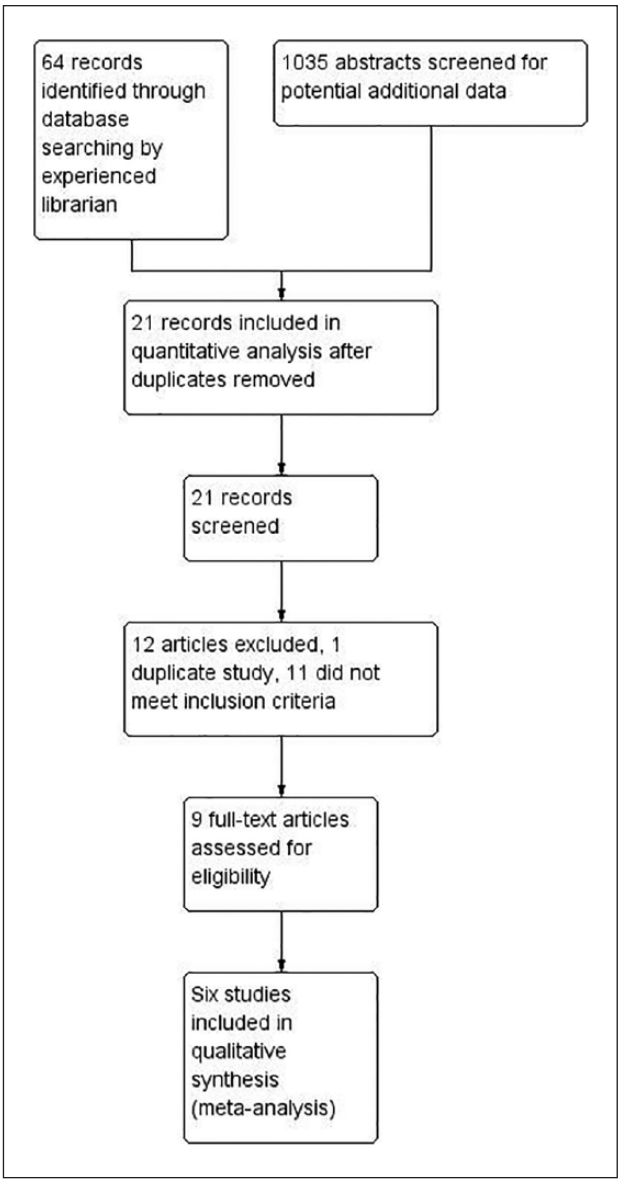

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart.

In fixed model analysis, ACEi or ARB treatment was superior to placebo in order to prevent development of microalbuminuria, with a risk ratio of 0.84 (95% CI 0.79–0.88) p<0.001. In the random model the results showed a risk ratio of 0.84 (0.78–0.91) p<0.001. There was no sign of heterogeneity in the risk ratio outcome with a I^2=23%, p=0.26. Forest plots are presented in Figure 3(a) and (b).

In the trials included as well as in the abstracts screened there were insufficient data available for the originally intended calculation of secondary outcomes, except for all-cause mortality shown in Figure 4, in which ACEi/

Table 1. Characteristics of the included studies.

Study	Year	Patients (*n*)	Follow-up (years)	RAS blocking agent	Daily dose (mg)	Hard renal outcome reported (yes/no)
Ravid et al.[16]	1998	156	6	Enalapril	10	No
MICROHOPE[17]	2000	3577[a]	4.5	Ramipril	10	Yes
BENEDICT[3]	2004	1204	3.6	Trandolapril	2	No
DIRECT 2[4]	2009	1905	4.7	Candesartan	32	No
ADVANCE[18]	2009	11,140	4.3	Perindopril	2	Yes
ROADMAP[5]	2011	4447	3.2	Olmesartan	40	Yes

RAS: renin-angiotensin system.
[a]Total no. of included patients in the study. Approximately 30% had microalbuminuria at baseline and were excluded from this analysis.

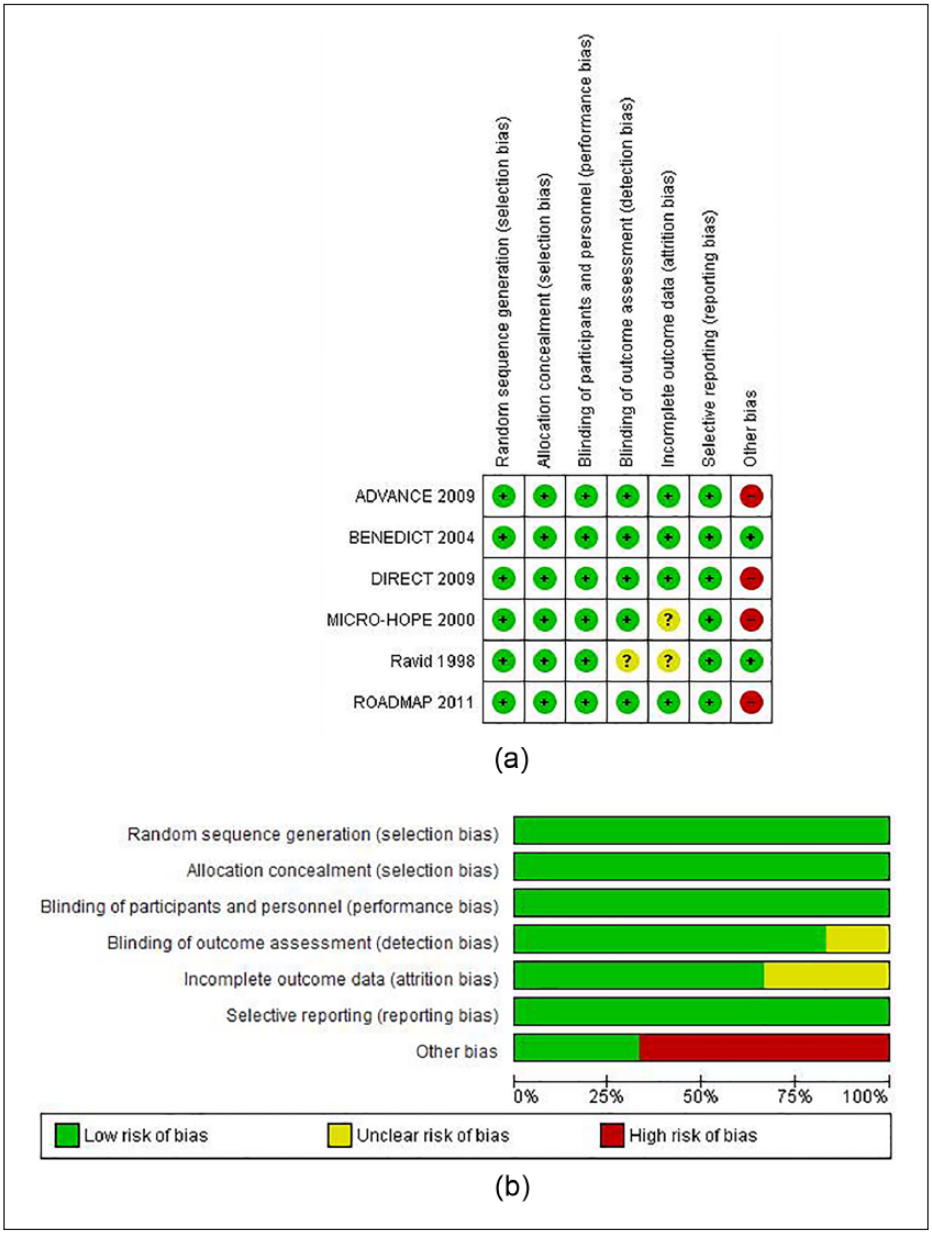

Figure 2. Risk of bias as evaluated by the authors. (a) risk of bias item for each included study. (b) risk of bias item presented as percentages across all included studies.

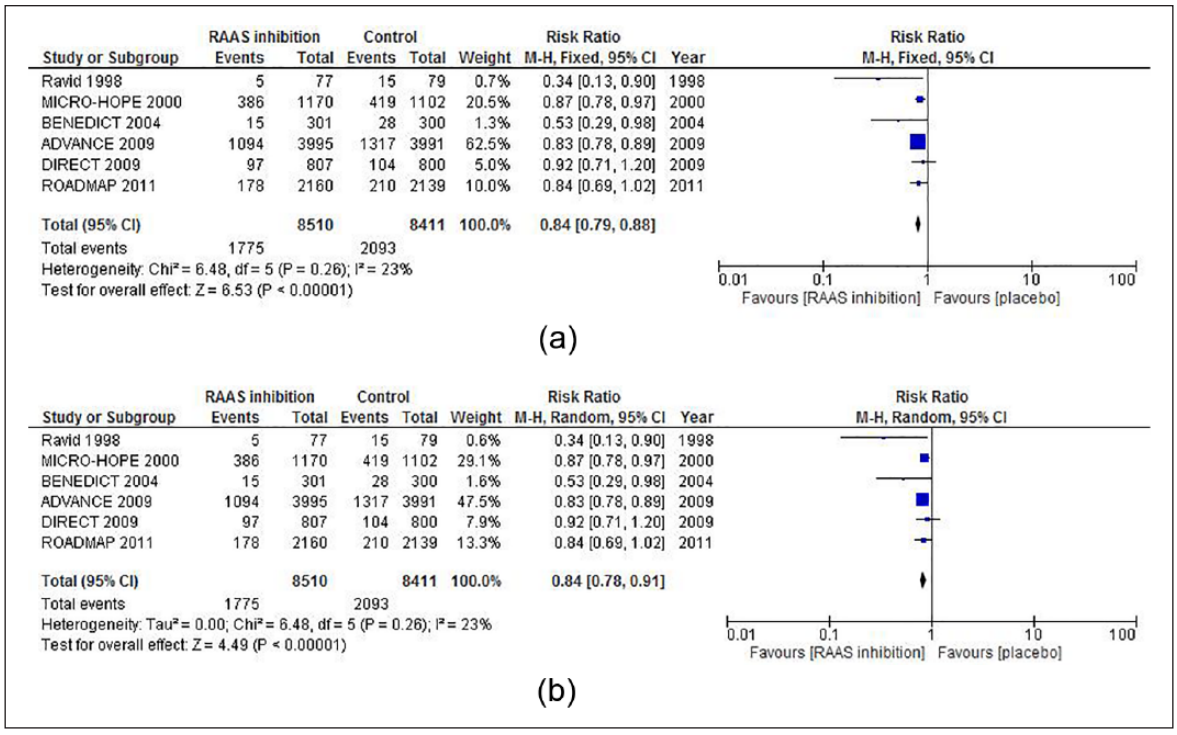

Figure 3. (a) Fixed and (b) random model forest plots of the effect of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy vs placebo to prevent microalbuminuria in type 2 diabetes.

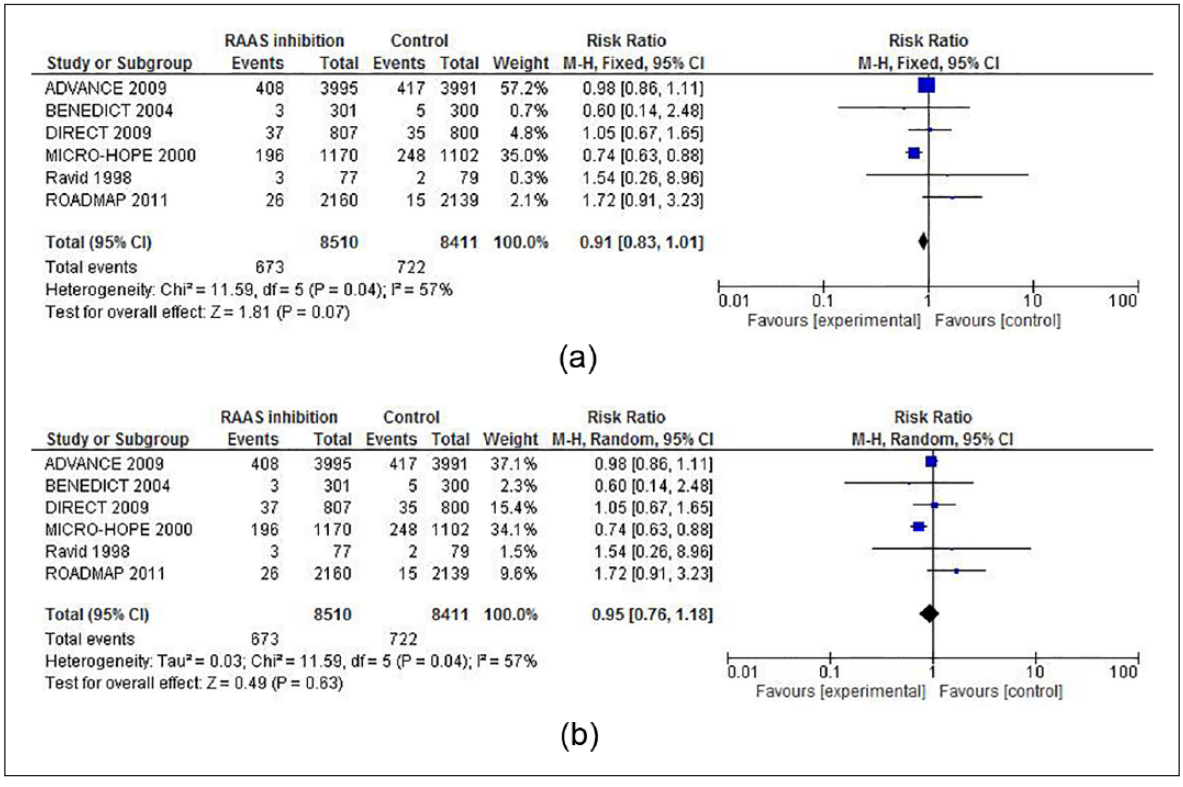

Figure 4. (a) Fixed and (b) random model forest plots of the effect of angiotensin-converting enzyme inhibitor (ACEi)/ angiotensin receptor blocker (ARB) therapy vs placebo on mortality in patients with type 2 diabetes and normoalbuminuria.

Table 2. Blood pressure and hypertension status at baseline as reported in the six included trials (values are mean (SD)).

Study	*n*	Baseline SBP		Baseline DBP		Baseline MAP		Hypertensive subjects (%)		Hypertension threshold (SD)
		Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	mm Hg
		mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg			
Ravid et al.[16]	156					98 ± 4 (84–105)	96 ± 4 (84–104)	0	0	140/90 (MAP 107)
ROADMAP[5]	4299	137 ± 16	136 ± 15	81 ± 10	80 ± 9			51	48	135/80
ADVANCE[18]	7986	145 ± 22	145 ± 21	81 ± 11	81 ± 11			68	69	140/90
DIRECT 2[4]	1607	123 ± 9	123 ± 9	75 ± 6	76 ± 7			62	62	130/85
BENEDICT[3]	601	151 ± 15	152 ± 15	87 ± 8	88 ± 7	109 ± 9	109 ± 9	100	100	130/85
MICROHOPE[a,17]	2272	142 ± 20	142 ± 20	80 ± 11	79 ± 11			58	54	160/90

BP: blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; SD: standard deviation.
[a]Mean BP values from full study population including approximately 30% with baseline microalbuminuria.

ARB treated tended to reduce mortality, RR 0.91(0.83–1.01) p=0.07.

The populations included in the six trials were a mix of normotensive and hypertensive, with differing definitions or thresholds for hypertension. The fraction of hypertensive subjects ranged from 0–100 %, see Table 2 for an overview of hypertension status in the six trials. It was not possible to conduct subgroup analysis of effect of the intervention according to baseline normotension vs hypertension, but approximately 38% of included patients were normotensive, or at least 31% if all subjects from the MICRO-HOPE study[17] are considered hypertensive.

Trial sequential analysis revealed a Z-value of 6.53 and an information size of 4163 patients (O'Brien two-sided 5% boundaries), indicating that the available studies and the available data in our analysis are sufficient to make these investigations and conclusions (Supplementary Material, Figure 1). For all secondary outcomes except all-cause mortality, numbers in the included studies were too small to be analysed in our review.

Discussion

In our meta-analysis of studies testing whether ACEi/ARB treatment, compared to placebo, can prevent development of microalbuminuria in type 2 diabetic patients, we identified six trials including 16,921 normoalbuminuric patients with type 2 diabetes. We found a 16% RR reduction for development of microalbuminuria in the ACE/ARB treatment group as compared to placebo groups. The findings were significant both in random effects and fixed effect models, although given the clinical heterogeneity of the studies, the random model probably can be considered the most robust. The risk ratio of 0.84 corresponds to a number needed to treat (NNT) of 25, meaning that for every 25 normoalbuminuric patients treated with ACEi/ARB, one case of microalbuminuria will be prevented or delayed (although the required treatment time needed cannot be determined from this analysis). From a recent paper from Schievink et al.[19] it is simulated that early RAS blockade intervention, as in the present analysis, can postpone ESRD by 4.2 years, compared to later stage interventions (3.6 and 1.1 years, for micro-and macroalbuminuria, respectively). Based on the TSA the available information size was found sufficient to support the inclusion, which means that it could be considered unethical to do further trials investigating this treatment compared to placebo.

The importance of change in albuminuria is evident from analyses of the IRMA2 study[20] and the Steno 2 study,[21] where reduction in albuminuria, and regression of micro- to normoalbuminuria translated into preserved kidney function. The primary outcome in our review is a surrogate outcome, and not a hard renal endpoint as i.e. ESRD, but the studies available do not have enough follow-up time to allow for hard renal endpoint evaluation. Our primary outcome is however frequently used clinically, and is a simple way to assess not only renal but also cardiovascular risk.

In type 2 diabetes the RAS is activated and has long been thought to play a major part in development of chronic vascular complications, including diabetic nephropathy and diabetic retinopathy. Following landmark studies like the IRMA2, RENAAL and IDNT trials,[22–24] RAS inhibition is widely accepted and recommended for patients with established micro- and macroalbuminuria, but the remaining issue of primary prevention is not yet solved. As evident from our literature search, only a few trials have reported this outcome, and not all were primarily designed with this aim, which could be part of the explanation for the diverging results.

The biochemical aim for inhibition of the RAS is to reduce the deleterious effects of the angiotensin II peptide, most importantly exerting its effects by binding to the angiotensin II receptor subtype 1 (AT1R). The ACEi will inhibit the angiotensin-converting enzyme in converting angiotensin I to angiotensin II, thereby lowering substrate for the AT1R. The ARB binds directly to the AT1R, thereby

preventing angiotensin II from activating the receptor. Reduced glomerular capillary hypertension has been demonstrated experimentally to minimise structural injury with mesangial expansion and fibrosis in the glomeruli leading to sclerosis, thereby slowing the development of glomerular leakage.[25]

Since Strippoli et al. published a systematic review on primary prevention of diabetic nephropathy in 2005,[26] several additional studies have been published, adding to the amount of evidence. Since larger studies are now available, we excluded smaller studies (n<100) in an attempt to minimise publication and reporting bias. The first large Cochrane review by Strippoli et al. in 2006 did not investigate primary prevention of diabetic kidney disease, but recently the Cochrane report was updated by Lv et al.[6] All antihypertensive treatment was analysed, despite the fact that most evidence and functional understanding regarding beneficial treatment come from RAS blocking drugs. Palmer et al.[27] published a network meta-analysis investigating blood pressure lowering agents in patients with diabetes and CKD. The overall conclusion was that ACEis and ARBs offer the best protection against progression to ESRD. The study included several relevant secondary outcomes, i.e. regression of albuminuria, but did not evaluate first occurrence of microalbuminuria, and thus we cannot compare to the findings in our analysis. Catalá-López et al.[28] performed a similar but more specific network meta-analysis on the effect on cardiorenal outcome of RAS blocking treatment in patients with diabetes, but incidence of microalbuminuria was not included as outcome. Recently, Bangalore et al.[29] published a somewhat different analysis comparing RAS blocking treatment with other types of antihypertensive treatment in diabetes. It was concluded that RAS offers no advantage compared other antihypertensive drugs in relation to all-cause mortality, CVD events and renal risk. However, placebo-controlled trials were excluded, and renal outcome only consisted of ESRD, leaving out doubling of baseline creatinine which is a generally accepted endpoint and frequently used in renal trials. No data on occurrence of microalbuminuria was included. Importantly, for all the abovementioned analyses, the authors made no distinction between nephropathy in type 1 and type 2 diabetes, thereby mixing conditions with different pathologies.[7–9]

We therefore performed the present systematic review only in patients with type 2 diabetes and normoalbuminuria, only comparing ACEis and ARBs to placebo, in order to get a cleaner picture of both patient populations and treatment. We hope this provides clinicians with more coherent information to use in a clinical setting.

Far from all patients with type 2 diabetes progress to diabetic nephropathy, and a future approach may be to select patients for early intervention based on risk markers. One such approach, using an urinary proteomic multimarker risk pattern, is ongoing (www.EU-PRIORITY.org), and may bring forth a more individualised preventive treatment in normoalbuminuric patients with type 2 diabetes.[30]

Our findings could have implications for future clinical practice. Side effects of RAS inhibitors are relatively mild and few in low-risk populations such as the study populations included, i.e. partly normotensive and well preserved kidney function. For instance, in the DIRECT study,[4,31] evaluating 5224 type 1 and type 2 diabetic patients, the occurrence of any serious adverse event, discontinuation due to adverse events or death were similar in the normotensive and hypertensive patients treated with RAS inhibition or placebo. Many hypertensive patients with type 2 diabetes will already be on RAS inhibitors, but extension of this to normotensive normoalbuminuric patients can now be contemplated. In addition, recent evidence from another meta-analysis suggests that RAS inhibitors can prevent and delay diabetic retinopathy in normotensive patients, further adding a reason for early initiation of treatment.[32] Current guidelines[2] do not recommend RAS inhibition in patients with normoalbuminuria, but our findings alongside the meta-analysis by Wang et al.[32,33] in diabetic retinopathy suggest that guidelines should be revised in order to further improve prevention of two major microvascular diabetic complications.

Owing to different definitions of hypertension, and since the included papers did not stratify participants or results according to hypertensive status, we did not compare normotensive and hypertensive subjects in our analysis, and this may not be relevant if most patients with elevated blood pressure will have this treatment applied anyway. Although it may well be that the major part of the effect found in our analysis is reserved to hypertensive patients, we cannot rule out a similar effect in normotensive subjects, making up approximately 38% of the analysed population. In fact many of the important renoprotective effects from RAS blocking treatment may well be related to other effects than those on systemic blood pressure, as seen in the IRMA 2, RENAAL and IDNT trials.[22–24]

Also we did not compare ACEi vs ARB due to data size, judging by the numbers needed in the comparative network meta-analysis by Palmer et al.[27] and the doses used in the included studies were not investigated in detail. However, the ONTARGET study,[34,35] the largest study so far, demonstrated that clinical effects are alike when compared head-to-head. There may be differences between optimal antiproteinuric doses between drugs that inhibit the RAS, and sometimes the optimal antiproteinuric dose is different from widely recommended antihypertensive doses.[36–38]

The included six trials used different endpoint definitions and methodology in relation to occurrence of microalbuminuria, but a recent paper looking at different endpoint definitions concludes that this has only minor

impact on the robustness of the outcome.[39] The authors performed a post-hoc analysis of four randomised controlled clinical trials and conclude that single urine collections at a study visit are sufficient to define a transition in albuminuria as endpoint in clinical trials. In addition, different ACEi/ARB treatments used may also add a certain degree of pharmacological heterogeneity, as seen in some of the few studies comparing different treatments in similar populations.[40,41] However, in terms of effect on development of microalbuminuria, there seems to be an effect of similar magnitude across different ACEi/ARBs.

We did not have the opportunity to analyse further secondary endpoints or safety and side effects along with the analysis of effect of ACEi/ARB treatment. This is an important limitation to our meta-analysis, especially if we want to promote this as standard early treatment of normotensive, normoalbuminuric patients in future guidelines. However all-cause mortality was insignificantly reduced, which at least speaks for the overall safety of early intervention. In addition, there are no clear signs from the reporting of adverse events in the included trials nor from a large trial in type 1 diabetes (the RASS trial)[42] or in prehypertension (the TROPHY study)[43] that there is a clinically significant increased frequency of hypotension and related side effects in normotensive populations treated with ACEi/ARBs. Depending on the definition of hypertension, a large proportion of patients with type 2 diabetes will be hypertensive anyway, as seen during follow-up in the DIRECT 2 trial, so treating normotension may not a frequent occurrence. Rather, it may be important to ensure that patients with type 2 diabetes receive treatment with ACEi or ARB as the first drug, whether the indication is hypertension or primary or secondary prevention of microvascular complications. It is however also important to point out that not all patients with type 2 diabetes will develop microalbuminuria, and not all patients diagnosed with nephropathy have true glomerular disease.[7–9] In addition, it could have been relevant to include to include studies using renin inhibitors, another RAS blocking treatment, but as no studies using renin inhibition in primary prevention have been performed or initiated, we did not include this in our review.

A future collaborative meta-analysis with individual patient-level data from the included six trials seems feasible and would allow for more detailed safety information, as well as time-to-event analyses for primary outcome. However, a comparison between one-stage and two-stage meta-analyses approach of clinical trials by Stewart et al.,[44] concluded that the two methods produce similar results.

Conclusions

In conclusion, we demonstrate that there is sufficient data available to conclude that inhibition of RAS using ACEis or ARBs can reduce the incidence of microalbuminuria, a risk marker for both renal disease and CVD, in patients with type 2 diabetes. This conclusion is, however, given with reservations since the populations included are heterogenous and a full safety analysis was not available.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FP reports having received research grants from Novartis and lecture fees from Novartis, Eli Lilly and Boehringer Ingelheim and having served as a consultant for Astra Zeneca and MSD. PR reports having received lecture fees from Novartis and Boehringer Ingelheim, and research grants from Novartis, has served as a consultant for Merck, and having equity interest in Novo Nordisk. H-HP reports having served as a consultant for Novartis, Merck, Pfizer and Sanofi-Aventis, having equity interest in Merck and Novo Nordisk and having received lecture fees from Novartis, Merck, Pfizer and Sanofi-Aventis. H-HP has received grant support from Novartis, AstraZeneca and Sanofi-Aventis. FP, ML and PR are employed at Steno Diabetes Center, Gentofte, Denmark. Steno Diabetes Center is an independent academic institution owned by Novo Nordisk A/S and The Novo Nordisk Foundation.

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