Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection: A Meta-Analysis

Hiddo J. Lambers Heerspink, Tobias F. Kröpelin, Jarno Hoekman, and Dick de Zeeuw, on behalf of the Reducing Albuminuria as Surrogate Endpoint (REASSURE) Consortium

Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

ABSTRACT

Albuminuria has been proposed as a surrogate end point in randomized clinical trials of renal disease progression. Most evidence comes from observational analyses showing that treatment-induced short-term changes in albuminuria correlate with risk change for ESRD. However, such studies are prone to selection bias and residual confounding. To minimize this bias, we performed a meta-analysis of clinical trials to correlate the placebo-corrected drug effect on albuminuria and ESRD to more reliably delineate the association between changes in albuminuria and ESRD. MEDLINE and EMBASE were searched for clinical trials reported between 1950 and April 2014. Included trials had a mean follow-up of ≥1000 patient-years, reported ESRD outcomes, and measured albuminuria at baseline and during follow-up. Twenty-one clinical trials involving 78,342 patients and 4183 ESRD events were included. Median time to first albuminuria measurement was 6 months. Fourteen trials tested the effect of renin-angiotensin-aldosterone-system inhibitors and seven trials tested other interventions. We observed variability across trials in the treatment effect on albuminuria (range, −1.3% to −32.1%) and ESRD (range, −55% to +35% risk change). Meta-regression analysis revealed that the placebo-adjusted treatment effect on albuminuria significantly correlated with the treatment effect on ESRD: for each 30% reduction in albuminuria, the risk of ESRD decreased by 23.7% (95% confidence interval, 11.4% to 34.2%; P=0.001). The association was consistent regardless of drug class (P=0.73) or other patient or trial characteristics. These findings suggest albuminuria may be a valid substitute for ESRD in many circumstances, even taking into account possible other drug-specific effects that may alter renal outcomes.

CKD receives growing attention as a major public health concern. Clinical practice guidelines advocate early detection and appropriate treatment based on the rationale that intervention in the early course of disease may be more advantageous.[1,2] To establish drug efficacy in clinical trials of progression of CKD doubling of serum creatinine and ESRD are used as clinical end points. However, progression of kidney disease to ESRD takes many years to manifest. Clinical trials enrolling patients at early stages of disease would therefore require a long follow-up or an impractical large sample size to establish drug efficacy. The use of surrogate end points may be a solution to this problem. However, rigorous validation is required before a surrogate end point is used in clinical trials. The criteria for validation are defined in the International Conference of Harmonization statistical principles of clinical trials.[3] First, prognostic evidence of the surrogate end point with patient outcome must be available. Second, a biologically plausible relationship between the surrogate and outcome should exist. Third, clinical

trial data must demonstrate that the effect of interventions that change the surrogate end point is directly associated with the same change in clinical outcomes. A typical example is BP, because high BP is associated with cardiovascular risk and reduction of BP, by whatever means, lowers cardiovascular risk.

Albuminuria has been proposed as a surrogate end point in clinical trials of CKD progression.[4] Multiple clinical studies have shown a strong and independent association between albuminuria and ESRD,[5] whereas experimental studies have documented the causal mechanisms through which increased urinary albumin leakage aggravates kidney damage.[6] In addition, analyses from several clinical trials have shown that the initial treatment-induced change in albuminuria predicts subsequent renal risk change.[7–12] Although the consistency of these studies supports the validity of albuminuria as a surrogate, the correlation analyses from randomized controlled trials between changes in albuminuria and ESRD were conducted *post hoc* and were no longer based on randomized comparisons. Therefore, the possibility that the lower risk of ESRD among patients with a reduction in albuminuria was caused by factors unrelated to the antialbuminuric effect of the intervention cannot be excluded. To minimize this type of bias, it is necessary to associate the placebo-controlled treatment effects on albuminuria with the placebo-controlled treatment effects on ESRD. This approach requires a combined analysis of multiple randomized controlled trials. A combined analysis of multiple clinical trials allows assessment of whether the reductions in albuminuria and ESRD are independent of the interventions that are used. If so, it would support the idea that the reduction in albuminuria is the determinant of renoprotection rather than the intervention *per se*.

Therefore, the aim of this study was to conduct a systematic review and meta-analysis to reliably examine the treatment effects of various interventions on an initial change in albuminuria as a predictor of the treatment effect on ESRD.

RESULTS

Literature Search and Characteristics of Studies

The combined literature search in EMBASE and MEDLINE *via* PubMed yielded 3412 articles, of which 626 articles were duplicates identified in both databases. Sixty-four articles were reviewed in full text on the basis of our inclusion criteria (Figure 1). Of these, 21 randomized clinical trials provided information on 78,342 patients and 4183 ESRD events and were eligible for inclusion. All trials were published in peer-reviewed journals. The majority of other studies identified by our search but not included in the meta-analysis were

randomized clinical trials in dialysis, renal transplant, or acute kidney populations or trials that had insufficient patient follow-up to be eligible.

Table 1 summarizes the characteristics of the included studies. These were reported between 1994 and 2013, with a sample size that ranged from 224 to 25,620 participants and total events accrued from 2 to 2141. Twelve studies were international multicenter trials.[13–24] Five studies were conducted in North America,[25–28] two studies were conducted in China,[29,30] one study was conducted in Italy,[31,32] and one study was conducted in Japan and Hong Kong.[33] Five studies assessed the effects of angiotensin-converting enzyme inhibitor (ACEI) treatment,[13,25,27,30,31] four studies examined the effects of an angiotensin receptor blocker (ARB),[18,21,33,34] one study assessed the effect of an ACEI or ARB,[29] and one study examined the effect of a combination of an ACEI with a diuretic.[14] Three studies assessed the effect of dual renin-angiotensin-aldosterone system (RAAS) blockade with either combined ACEI and ARB treatment[19,26] or a direct renin inhibitor as adjunct to ACEI or ARB.[15] Two studies evaluated a lipid-lowering intervention,[17,22] two studies assessed dietary protein restriction,[28] two studies assessed the effects of intensive BP control,[16,20] and one study examined the effects of a glycosaminoglycan.[23] The average age of the study participants ranged from 12 to 68 years and the proportion of men ranged from 28% to 93%. A total of 11 studies reported albuminuria as an albumin/creatinine ratio that ranged from 7.2 to 1900 mg/g. Ten other
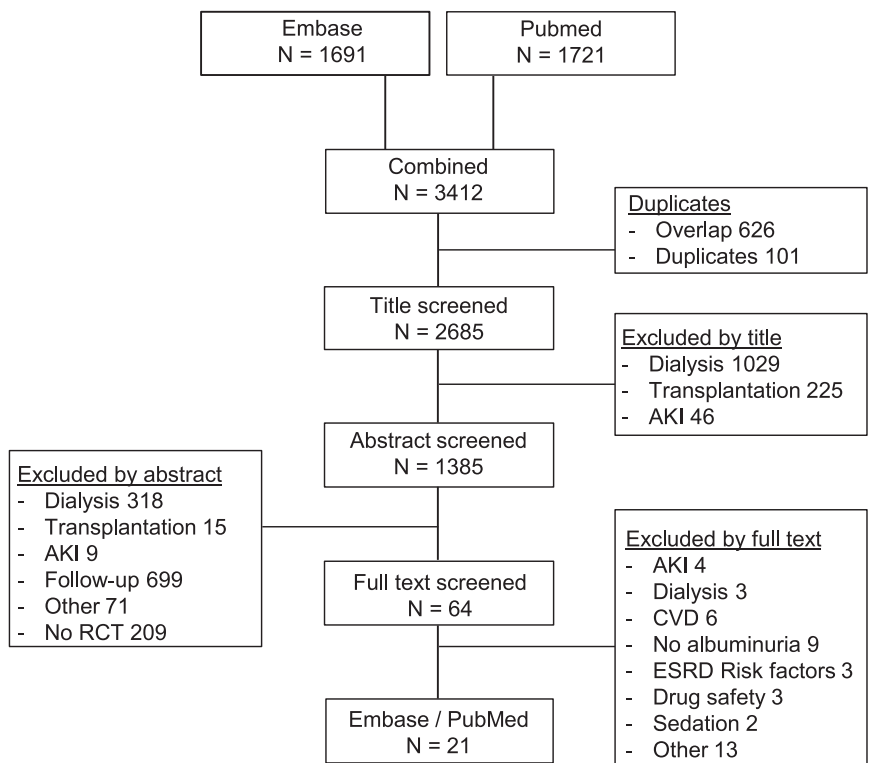
Figure 1. Identification process for eligible studies. CVD, cardiovascular disease; RCT, randomized controlled trial.

Table 1. Characteristics of randomized controlled trials reporting the effects of various agents on albuminuria and ESRD

Study Acronym (Year)	Patients (n)	ESRD Events (n)	Inclusion Criteria	Active Treatment	Control	Age (yr)	Female Sex (%)	eGFR (ml/min per 1.73 m²)	Albuminuria (mg/g)	Systolic BP (mmHg)	Albuminuria Change (%)
AASK (2001)[25]	1094	179	African-American with hypertensive nephrosclerosis	Ramipril	Metoprolol or Amlodipine	54.6	38.8	45.6	120.0	150.4	−23.3
ADVANCE (2001)[14]	11,140	46	Type 2 diabetes at CV risk	Perindopril and Indapamide	Placebo	66.0	42.5	72.2	15.0	145.0	−18.9
AIPRI (1999)[13]	583	2	Renal insufficiency	Benazepril	Placebo	51.0	72.0	42.6	1800.0	143.0	−30.4
ALTITUDE (2012)[15]	8561	234	Type 2 diabetes at cardiorenal risk	Aliskiren (+ ACEI or ARB)	Placebo (+ ACEI or ARB)	64.5	31.9	57.0	207.0	137.3	−11.0
BENAZEPRIL (2009)[30]	224	63	Nondiabetic nephropathy	Benazepril	Placebo	44.7	49.6	26.1	1700.0	152.4	−28.8
CSG-Captopril (2006)[27]	409	51	Type 1 diabetes and nephropathy	Captopril	Placebo	34.5	47.0	59.0	2746.9	138.5	−25.6
ESCAPE (2009)[16]	385	56	Children with nephropathy	Intensive BP control	Conventional BP control	11.5	40.7	45.9	1200.0	118.3	−16.4
FIELD (2005)[17]	9795	47	Type 2 diabetes at CV risk	Fenofibrate	Placebo	62.2	7.2	92.0	10.0	140.5	−13.9
IDNT (2001)[18]	1715	287	Type 2 diabetes and nephropathy	Irbesartan	Placebo or amlodipine	58.8	32.0	41.1	1900.0	159.0	−28.0
MDRD A (1994)[28]	584	58	Nondiabetic nephropathy with GFR 25–55 ml/min	Low protein diet	Conventional protein diet	52.0	40.0	38.6	200.0	131.0	−13.0
MDRD B (1994)[28]	255	136	Nondiabetic nephropathy with GFR 13–24 ml/min	Low protein diet	Conventional protein diet	52.0	40.0	18.5	710.0	133.0	−14.6
ONTARGET (2008)[19]	25,620	98	CV risk with end organ damage	Telmisartan and ramipril	Ramipril or telmisartan	66.4	26.8	69.2	7.2	141.8	−7.1
ORIENT (2011)[33]	566	152	Type 2 diabetes and nephropathy	Olmesartan	Placebo	59.2	30.9	42.9	1695.1	141.2	−32.1
VA-NEPHRON D (2013)[26]	1448	70	Type 2 diabetes and nephropathy	Losartan (+ lisinopril)	Placebo (+ lisinopril)	64.6	27.4	53.7	852.0	137.0	−19.6
REIN (1997/1999)[31,32]	352	73	Nondiabetic nephropathy	Ramipril	Placebo	49.5	23.6	42.9	3500.0	145.9	−29.3
REIN 2 (2005)[20]	338	72	Nondiabetic nephropathy	Intensive BP control with felodipine	Conventional BP control	53.8	25.1	35.0	2900.0	136.7	−11.4
RENAAL (2001)[21]	1513	341	Type 2 diabetes and nephropathy	Losartan	Placebo	60.0	36.8	35.0	1249.1	152.5	−31.9
ROAD (2007)[29]	339	26	Nondiabetic nephropathy	Antialbuminuric dose of ACEI or ARB	Conventional BP dose of ACEI or ARB	50.9	37.2	30.6	1800.0	150.2	−16.0

Table 1. Continued

Study Acronym (Year)	Patients (n)	ESRD Events (n)	Inclusion Criteria	Active Treatment	Control	Age (yr)	Female Sex (%)	eGFR (ml/min per 1.73 m²)	Albuminuria (mg/g)	Systolic BP (mmHg)	Albuminuria Change (%)
SHARP (2011)[22]	6247	2141	Diabetic and nondiabetic nephropathy	Simvastatin and ezetimibe	Placebo	62.0	37.4	26.6	206.5	139.0	−1.8
SUN-Macro (2012)[23]	1248	21	Type 2 diabetes and nephropathy	Sulodexide	Placebo	63.0	39.2	31.4	1389.3	138.0	−1.3
TRANSCEND (2008)[34]	5926	10	Patients intolerant to ACE inhibitors at CV risk	Telmisartan	Placebo	66.9	43.0	71.7	5.9	141.0	−28.0

AASK, African American Study of Kidney Disease and Hypertension; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CV, cardiovascular; AIPRI, ACE Inhibition in Progressive Renal Insufficiency; CSG, Collaborative Study Group; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; MDRD, Modification of Diet in Renal Disease; ORIENT, Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial; VA-NEPHRON D, Veterans Affairs Nephropathy in Diabetes; REIN, Ramipril Efficacy In Nephropathy; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SHARP, Study of Heart and Renal Protection; SUN-Macro, Sulodexide Macroalbuminuria Trial; TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.

studies measured total proteinuria, which ranged from 120 to 3500 mg/24 h. The mean baseline eGFR ranged from 19 to 92 ml/min per 1.73 m². All but one study provided information about the proportion of patients with diabetes (range, 0%–100%). Seven studies included patients with diabetic nephropathy,[15,18,21,23,26,27,33] and 10 studies included patients with nondiabetic nephropathy.[13,16,20,22,25,28,29,31,32] There were some minor differences in the definition of ESRD across studies. All studies defined ESRD as the need for chronic dialysis or transplantation. Four studies included a fixed serum creatinine threshold in the definition of ESRD,[17,18,23,33] whereas three other studies also included renal death in the definition of ESRD.[14,15,17] Study follow-up periods ranged between 11 and 56 months. Quality assessment revealed that all trials used a concealed treatment allocation, provided information on the participant flow throughout the study, compared baseline characteristics, and analyzed according to intention to treat (Supplemental Table 1). Across all published trials, the average Jadad score was 4.7 (range, 4–5). Formal statistical testing did not suggest the presence of publication bias (Begg's test, $P=0.81$; Supplemental Figure 2).
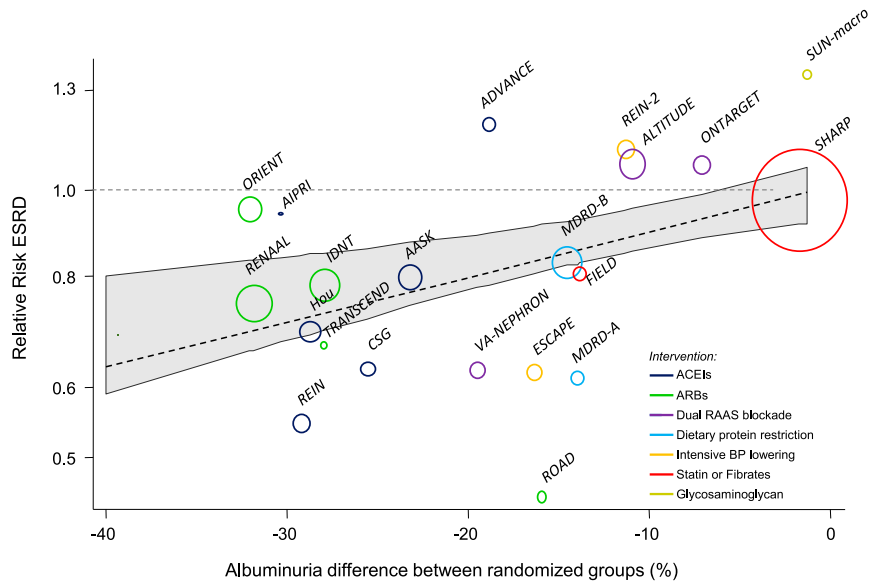
Effect of Treatment on Albuminuria and ESRD
The average albuminuria reduction between baseline and first albuminuria measurement was 19.2%. There was substantial variability in the treatment effects on albuminuria across all trials, ranging from −1.3% to −32.1%. Overall, active treatment reduced the risk of ESRD by 17% (95% confidence interval [95% CI], 8% to 25%) compared with control regimens (Supplemental Figure 1). A large variability in treatment effects on ESRD was observed, ranging from −55% to +35% across all studies. Formal statistical testing suggested significant heterogeneity in the magnitude of the treatment effect ($\chi^2=36.1$; $P=0.02$; $I^2 = 44.6\%$).

Association between Treatment Effects on Albuminuria and ESRD
The association between drug effects on albuminuria and ESRD was analyzed by meta-regression. This revealed that the treatment effects on albuminuria significantly correlated with the treatment effects on ESRD. For each 30% reduction in albuminuria, the risk of ESRD decreased by 23.7% (95% CI, 11.4% to 34.2%; $P=0.001$; Figure 2).

Figure 3 shows that the association between drug-induced changes in albuminuria and ESRD were consistent in various subgroup analyses. For each 30% reduction in albuminuria by drugs that intervene in the RAAS, the risk of ESRD decreased by 32% (95% CI, −55 to +2) compared with 39% (95% CI, −65 to +9) with drugs that do not intervene in the RAAS (Figure 3). There was no evidence to suggest a statistically significant difference in the association according to the duration of follow-up, size of the study, baseline albuminuria, eGFR, systolic BP, or between populations with diabetic nephropathy or nondiabetic nephropathy. Finally, a sensitivity analysis excluding the Study of Heart and Renal Protection, which contributed a large number of events to the meta-analysis, did not alter the conclusions. For each 30% reduction in albuminuria, the reduction in risk of ESRD was 27.4%

Figure 2. Univariate meta-regression exploring the association between the placebo-controlled treatment effect on albuminuria and the placebo-controlled treatment effect on ESRD events. Different types of interventions are indicated by different colors. The size of each circle is inversely proportional to the SEM of the treatment effect on ESRD. AIPRI, ACE Inhibition in Progressive Renal Insufficiency; MDRD, Modification of Diet in Renal Disease; CSG, Collaborative Study Group-Captopril Trial; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; VA-NEPHRON, Veterans Affairs Nephropathy in Diabetes Trial.

end point. Apart from the possibility that the increased risk of ESRD in these trials may be related to unintended off-target effects of the tested interventions,[35,36] our meta-analysis also unambiguously demonstrates that the reductions in albuminuria observed in these trials were too small to translate into clinical meaningful benefits. For example, in the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) trial, active treatment with the direct renin inhibitor aliskiren decreased albuminuria by 11% at month 6.[15] According to our meta-analysis, this would only translate into an 8% reduction of ESRD. Similarly, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), dual RAAS blockade decreased albuminuria by 7%,[19] a magnitude unlikely to translate into clinically relevant reductions in risk of ESRD. For new interventions, a 30% reduction in albuminuria on top of guideline-recommended care seems necessary to confer a realistically detectable renoprotective treatment effect.

The observed association between the treatment effect on albuminuria and ESRD was similar for various drug classes or dietary interventions. Although most of the studies tested drugs that intervened in the RAAS, the strength of the association between reductions in albuminuria and ESRD was not different with other interventions that decreased albuminuria. Moreover, the associations were consistent in various subpopulations with different patient characteristics or underlying diseases, supporting the generalizability of the results. Specifically, the strength of the association was not modified by baseline albuminuria, suggesting that reducing albuminuria both in the microalbuminuria and macroalbuminuria range is associated with renoprotection. We recognize, however, that the statistical power to reliably compare different drug classes as well as some subpopulations was small. Nevertheless, the results of this analysis demonstrate that the significant heterogeneity observed in the treatment effects on ESRD correlates with the heterogeneity in the treatment effects on albuminuria, suggesting that the short-term treatment effect on albuminuria predicts the long-term treatment effect on ESRD.

The results of this study are generalizable to the populations and interventions included in this study. Although our results were consistent in various subgroups, we cannot generalize to other populations or interventions. This implies that long-term clinical trials are required for drugs with novel albuminuria-lowering mechanisms of action to prove their renoprotective efficacy. We therefore propose that drug approval can be granted if a novel drug decreases albuminuria on the condition that subsequent long-term clinical trials using clinical end points

(95% CI, 0.7% to 46.9%; *P*=0.05). In addition, a sensitivity analysis that excluded trials with only cardiovascular risk populations[14,17,19,24] provided similar results: per 30% reduction in albuminuria, the reduction in risk of ESRD was 24.6% (95% CI, 11.6% to 35.7%; *P*=0.002). The effect estimate was again similar to our main analysis when trials with albuminuria measurements at ≥24 months of follow-up were excluded (hazard ratio for ESRD, 24.8%; 95% CI, −11.6% to 49.2%; *P*=0.11).
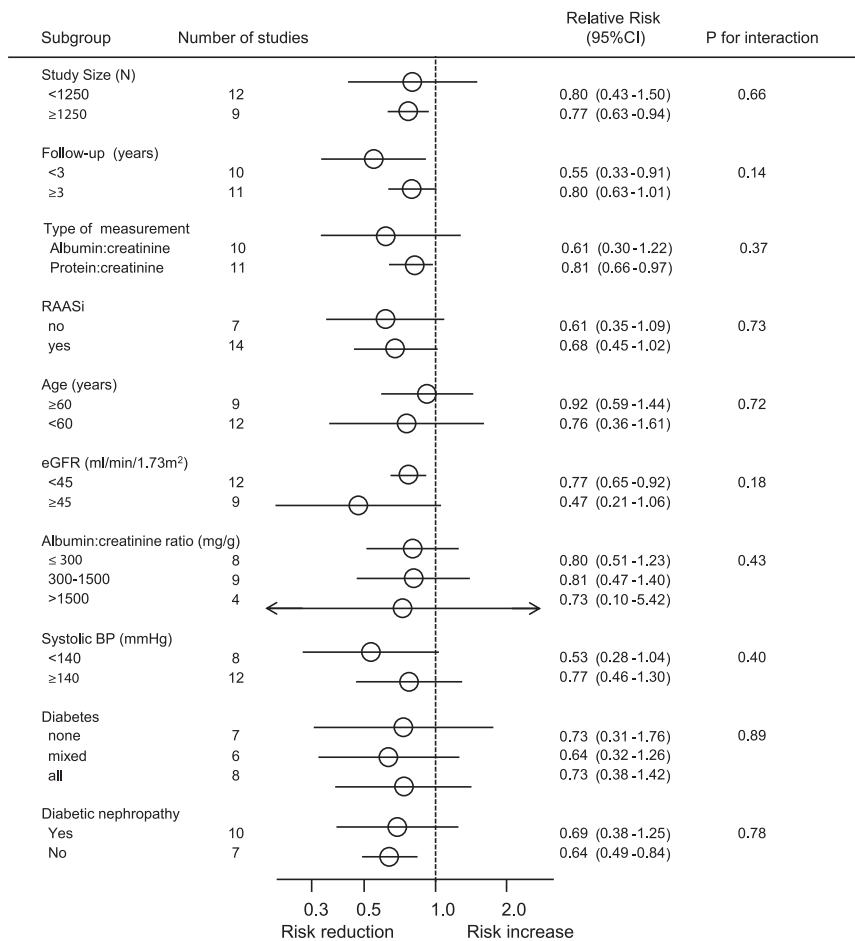
DISCUSSION

Albuminuria has been proposed as a surrogate end point in clinical trials of CKD progression. However, there is persistent uncertainty about the validity of albuminuria to substitute for hard clinical end points, which hampers its broad acceptance and application in daily practice of drug development, registration, and drug use. In this meta-analysis of randomized controlled trials, we have demonstrated a statistically significant association between drug effects on albuminuria and ESRD. The associations appear to be consistent across a range of drug classes used in the included studies and various patient characteristics. These results suggest that albuminuria could be a valid substitute for ESRD and support designing trials with different albuminuria targets to prospectively establish the validity of albuminuria as a surrogate end point.

Recent trials demonstrating that the drugs of investigation decreased albuminuria but did not decrease the risk of ESRD fueled discussions about the validity of albuminuria as a surrogate

Figure 3. Subgroup analysis for the effect of various interventions on albuminuria and ESRD events. Circles represent estimates of treatment effect on ESRD per 30% reduction in albuminuria. The horizontal line represents the 95% CI. The *P* interaction tested the consistency of the association in subgroups. RAASi, RAAS inhibitor.

NCT01858532) will further define whether albuminuria is a valid surrogate. In this trial, all eligible patients will start the trial with a 6-week treatment phase, during which the albuminuria response to the endothelin antagonist atrasentan will be established. Subsequently, patients are randomly assigned to atrasentan or matched placebo based on their albuminuria response. The randomization will be stratified for the different albuminuria responses. Accordingly, the SONAR trial will determine in a placebo-controlled manner whether the degree of albuminuria reduction with atrasentan is related to the degree of renoprotection. The trial will therefore further define whether albuminuria reduction is a necessary prerequisite for reducing renal morbidity and mortality.

The mechanisms through which albuminuria reduction delays renal disease progression is an area of great research interest. Since 1990, the hypothesis of a pathogenic role of altered glomerular permeability to macromolecules—and consequent protein overload to podocytes and tubular cells—in the pathogenesis and progression of glomerulosclerosis has been the subject of lively debate.[37] Recent data suggest that albuminuria *per se* is not just a marker of renal damage but may have a causal role in renal disease progression as well.[6] Within the kidney, increased glomerular filtration of albumin and other plasma macromolecules (*e.g.,* immunoglobulins, growth factors, complement components) increases the exposure of tubular cells to excessive albumin reuptake in proximal tubular cells, which in turn leads to the activation of multiple pathways that cause the release of vasoactive, inflammatory, and fibrotic substances.[38–40] Collectively, these processes result in tubulointerstitial damage and decreased nephron functionality.

Our results build upon a prior meta-analysis that sought to determine the validity of an early change in proteinuria as a surrogate end point for trials of kidney disease progression.[41] The meta-analysis included many small studies that were published before 2007. The meta-analysis showed that when all studies were grouped together by type of intervention, the treatment effects on proteinuria and the renal outcome were consistent, in line with our findings.[41] However, when studies were analyzed individually, the trial-level analysis showed no clear correlation between early changes in proteinuria and risk of doubling serum creatinine or ESRD, likely reflecting insufficient variation in drug effects and/or statistical power. Our

confirm the beneficial effect. These trials can also characterize the safety of the new agent, which often requires a much larger sample size than establishing drug efficacy in a surrogate outcome trial. These so-called conditional approval procedures thus balance timely access to novel interventions for patients while at the same time collect and provide adequate evolving information about the benefits and risks.

Few studies have prospectively assessed whether targeting of albuminuria delays progression of renal disease. The Renoprotection of Optimal Antiproteinuric Doses (ROAD) trial in patients with IgA nephropathy demonstrated that a regimen with either an ACEI or an ARB targeted to achieve a maximal antialbuminuric response is associated with marked better renal survival compared with a fixed maximal antihypertensive dose of these agents.[29] The Irbesartan Diabetic Nephropathy Trial (IDNT) trial showed that irbesartan decreased albuminuria compared with amlodipine at similar BP control and conferred renoprotection in patients with diabetes and nephropathy.[18] The Study of Diabetic Nephropathy with Atrasentan (SONAR) trial (ClinicalTrials.gov identifier

meta-analysis was prespecified to only include trials with >1000 patient-years of follow-up and/or >50 ESRD events to obtain sufficient statistical power, and included all large trials that were published after 2007. Analyzing the subgroup of studies included in the study by Inker *et al.* did not change our results. The differences between the previous meta-analysis and our meta-analysis may be explained by the difference in included studies, with exclusion of small studies in the prior analysis and inclusion of large recent trials in our meta-analysis. In addition, the correlation between errors in treatment effects on albuminuria and ESRD may have led to an overestimation of the reported association in the present meta-analysis. Because individual patient data were not available for all studies, we were unable to adjust for this.

Although we found a direct relation between drug-induced albuminuria reduction and renal outcome, we do not postulate that each drug-associated albuminuria reduction will ultimately result in renal protection. Several recent studies (in particular, dual RAAS blockade) have shown no renal protection despite albuminuria reduction.[15,26] Just like with other established surrogates, such as BP or cholesterol, a drug-induced fall will not offer cardiovascular/renal protection in the case that the intervention also induces negative effects (*e.g.,* hypotension, hyperkalemia). Thus, albuminuria reduction can only be a substitute for renal protection when the intervention is otherwise safe.

This study has limitations. First, studies included in the meta-analysis were not designed to target albuminuria, leading to potential less rigorous measurements and variability in treatment effects on this biomarker. Indeed, the individual trials showed considerable spread around the regression line. However, a similar spread across large clinical trials has been shown for other valid and clinically used surrogate end points such as BP and cholesterol.[42,43] It may be possible that the total exposure to albuminuria, as reflected by the area under the albuminuria curve, may be a better predictor of renal risk change than the change between two measurements. Second, some patients were lost to follow-up or reached an event before the postbaseline albuminuria measurement, which could have influenced the results. Finally, albuminuria was assessed after 24 months in five studies, whereas albuminuria was assessed within 6 months in all other studies. Because the effects of most anti–albuminuric interventions are present directly after treatment initiation, we assumed that the treatment effect at 24 months will likely resemble the effect after 6 months, although we cannot verify this assumption. However, a sensitivity analysis that excluded the five studies provided similar results.

In conclusion, short-term albuminuria reduction is associated with long-term renal protection across different interventions and populations. When considered in combination with observational studies demonstrating a strong association between albuminuria level and risk of kidney outcomes and experimental studies demonstrating the role of plasma macromolecules in causing kidney damage, we propose that albuminuria can be recommended as a surrogate end point in clinical trials for initial drug approval on the condition that long-term follow-up trials on clinical end points confirm the renoprotective effect of the agent.

CONCISE METHODS

Data Sources and Searches
We performed a systematic review of the available literature according to the Quality of Reporting of Meta-Analyses guidelines for the conduct of meta-analyses of intervention studies. Relevant studies were identified by computerized searches from the following data sources: MEDLINE *via* PubMed (from 1950 through April 2014) and EMBASE (from 1950 through April 2014), using relevant text words and medical subject headings that included all spellings of proteinuria or kidney diseases, drug therapy or drug effects, and ESRD (see Supplemental Appendix 1). The term *albuminuria* is used throughout this article and indicates abnormal excretion of urinary proteins including albumin. The search was limited to randomized controlled trials but was without language restriction. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Search of the ClinicalTrials.gov website was also performed to identify randomized trials that were registered as completed but not yet published. Requests for original data were made directly by contacting authors or principal investigators.

Study Selection
The literature search, data extraction, and quality assessment were conducted independently by two authors using a standardized approach (J.H. and T.F.K.). All completed randomized controlled trials that had >1000 patient-years of follow-up or >50 ESRD events and assessed the effects of different interventions on albuminuria and ESRD were eligible for inclusion. ESRD was defined as chronic dialysis or renal transplantation or renal death defined as death attributable to renal failure or need for RRT with no dialysis or renal transplantation applied in the definition of ESRD.

Data Extraction and Quality Assessment
Data extracted included patient characteristics (mean age, sex distribution, eGFR, albuminuria, systolic BP, diabetes status, cardiovascular disease status), follow-up duration, rates of outcome events, and type and dose of interventions. The initial albuminuria response was defined as the percentage change in albuminuria from baseline to the first measured albuminuria level during the trial. Summary measures of effects on ESRD outcomes were extracted from each study. Any disagreements in abstracted data were adjudicated by a third reviewer (H.J.L.H.). The quality of the included studies was assessed by the Jadad score.[44] The Jadad score is a tool used to systematically grade the quality of RCTs based on the presence and appropriateness of the blinding procedure, randomization, and handling of dropout and loss to follow-up.

Statistical Analyses
Individual study relative risks (RRs) and 95% CIs were extracted before data pooling. Summary estimates of RR ratios were obtained using a random effects model. The percentage of variability across studies

attributable to heterogeneity beyond chance was estimated using the I^2 statistic.[45] Univariate meta-regression was used to assess the association between the drug effect on albuminuria and ESRD. The consistency of the association was assessed by comparing summary results obtained from subsets of studies grouped by type of intervention (RAAS inhibitors versus non-RAAS inhibitors), number of enrolled patients, duration of follow-up, duration until first albuminuria measurement, and patient characteristics. For the purpose of subgroup analyses by baseline albuminuria, studies were categorized by study median data for the albumin/creatinine ratio. Some studies measured total protein excretion. The total protein excretion was converted to the albumin/creatinine ratio by multiplication of the total protein excretion by 0.6 since a total daily protein excretion of 0.5 g/d is approximately equal to 300 mg/g albumin/creatinine ratio.[46] Potential publication bias was assessed using the Begg's test and was represented graphically using funnel plots of the natural log of the RR versus its SEM. A two-sided P value of <0.05 was considered statistically significant for all analyses. All statistical analyses were performed with STATA software (version 9.2; StataCorp., College Station, TX).

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