The Validity of Drug Effects on Proteinuria, Albuminuria, Serum Creatinine, and Estimated GFR as Surrogate End Points for ESKD: A Systematic Review

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Rationale & Objective: Proteinuria, albuminuria, and serum creatinine level are widely used as surrogate end point measures of end-stage kidney disease (ESKD). We evaluated the correlation between antihypertensive drug effects on surrogate renal end points and ESKD.

Study Design: Systematic review.

Setting & Participants: Randomized controlled trials of blood pressure–lowering therapy.

Selection Criteria for Studies: Trials of pharmacological blood pressure–lowering strategies reporting drug effects on albuminuria, proteinuria, or serum creatinine level and ESKD through March 26, 2018.

Analytical Approach: Bayesian bivariate meta-analysis to calculate correlations between drug effects on surrogate end points and drug effects on ESKD. Risks of bias were adjudicated using the Cochrane tool.

Results: 22 randomized controlled trials involving 69,642 participants were eligible. Risks of bias in the included trials were frequently unclear due to incomplete reporting. Relative risk for ESKD was statistically significant in 1 of 29 (3.4%) treatment comparisons. There appeared to be little or no correlation between antihypertensive drug effects on serum creatinine level, albuminuria, proteinuria, and the corresponding effects on ESKD. All correlations had wide 95% credible intervals that included the null effect.

Limitations: Low power due to infrequent outcomes of ESKD and incomplete data reporting in primary trials.

Conclusions: The association between antihypertensive drug effects on doubling of serum creatinine level and albuminuria or proteinuria with ESKD in treatment trials is not sufficiently certain to enable the confident use of these markers to guide clinical or regulatory decision making.

Complete author and article information provided before references.

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Chronic kidney disease (CKD) is estimated to affect between 10% and 15% of the population[1,2] and is associated with premature death and end-stage kidney disease (ESKD).[3] Blood pressure–lowering treatment is used to prevent progressive failure of kidney function and ESKD. However, compared with cardiovascular disease and death, ESKD is a substantially less frequent outcome of CKD and requires trials to include large numbers of participants with follow-up over several years.[4] In addition, progression of kidney disease is often heterogeneous and the time elapsed between diagnosis and progression to ESKD can be variable, leading to difficulty identifying higher risk patients for inclusion in clinical trials.[5] The variability in progression to kidney failure and the relative infrequency of long-term dialysis therapy or kidney transplantation during a person's lifetime has challenged the conduct of trials to provide definitive evidence for the effectiveness of treatments to prevent CKD progression.

Surrogate markers of kidney function have been proposed to increase trial feasibility by shortening trial duration and reducing the sample size needed to definitively identify treatment benefit.[6,7] Renal measures including urine albumin and protein excretion rates have been widely used as surrogate markers to predict patient-centered outcomes of interest, theoretically occurring earlier on the causal pathway of drug effect. Proteinuria and albuminuria are used as trial end points because excretion is consistently associated with progressive kidney disease in a dose-dependent manner.[8]

Previous meta-analyses of observational studies and randomized clinical trials have proposed that albuminuria may predict ESKD.[9,10] However, determining the predictive utility of surrogate biomarkers on risks for ESKD across available trials can be challenging due to heterogeneity in drug effects on both intermediary and patient-centered end points. Bayesian bivariate meta-analysis is a methodology that measures the correlation between 2 outcomes (in this case, surrogate and patient-centered renal end points) simultaneously across available clinical trials to offer information about whether changes in a surrogate marker are correlated with those on a patient-centered outcome of interest.[11]

In this study, we used Bayesian bivariate meta-analysis methods to evaluate the correlation between blood pressure–lowering drug effects on doubling of serum creatinine level, halving of glomerular filtration rate (GFR), and measures of albuminuria and proteinuria with ESKD.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] The meta-analysis was conducted using a prespecified protocol (Item S1), although was not prospectively registered.

Data Sources and Searches

Relevant clinical trials were identified using a highly sensitive search of MEDLINE (1946 through March 21, 2018), Embase (1980 through March 23, 2018), and the Cochrane Library CENTRAL database (through Issue 2 of 12, 2018) using a search strategy designed by an information specialist (Table S1) without language restriction. Reference lists from systematic reviews identified in the search were manually screened to identify additional potentially relevant studies.

Study Selection

Randomized controlled trials comparing pharmacological blood pressure–lowering interventions with a second pharmacological or nonpharmacological intervention, placebo, or standard care were considered. Potentially eligible studies were included if data were extractable for risks for ESKD together with surrogate renal outcomes (urine albumin or protein excretion, doubling of serum creatinine level, or halving of GFR). Trials involving children and those in which trial follow-up was shorter than 12 weeks were excluded.

Retrieved records from the search strategy were screened by 2 authors (S.C.P. and M.R.) and any discrepancies were resolved by discussion. The full text of all potentially relevant trials was reviewed by the same authors to identify studies that met eligibility criteria.

Data Extraction and Quality Assessment

Published reports for each eligible trial were obtained and data were extracted by one author (M.R.) and double-checked by a second (S.C.P.). Risk of bias was adjudicated using Cochrane methods considering the following methodological domains: sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment (for clinical outcomes), attrition, and other potential sources of bias (sponsor involvement in data analysis, or authorship; imbalance between treatment comparisons; and/or premature termination of trial).[13]

Surrogate outcomes of interest were urine albumin excretion, urine protein excretion, progression of albuminuria, regression of albuminuria, doubling of serum creatinine level, or halving of estimated GFR (eGFR). We included absolute albumin or protein excretion per unit of time or excretion standardized per unit of urinary creatinine and included dichotomous outcomes as defined by investigators (regression or progression of albuminuria, doubling of serum creatinine, halving of eGFR). The patient-centered outcome of interest was ESKD (defined as eGFR < 15 mL/min/1.73 m^2, long-term dialysis therapy, and/or kidney transplantation). Because measurements of proteinuria and albuminuria were reported using various measures, including relative to urinary creatinine, we have harmonized all end points to a single measure of milligrams per day of excretion. We followed the methods reported by Lambers Heerspink et al[10] to convert protein excretion rate per day to albumin excretion rate by multiplication of the protein excretion by 0.6, recognizing that total daily protein excretion of 500 mg/d is approximately equal to 300 mg/d of albumin.

To avoid the double counting of participants in studies that evaluated a single drug intervention in 2 or more arms (eg, several doses of a single drug in 3 different study arms), event data for the binary outcomes (ESKD or progression or regression of albuminuria, doubling of serum creatinine level, halving of eGFR) were combined for all intervention arms of the same drug. We extracted data from the highest dose treatment arm for continuous outcomes (urine albumin or protein excretion).

Data Synthesis and Analysis

For each study, summary statistics for the continuous renal end points or the proportion of the study population in each arm experiencing regression or progression of albuminuria, doubling of serum creatinine level, halving of eGFR, or ESKD were extracted. Because there was inconsistency in the statistical measures used to report continuous outcomes (mean and standard deviation, median and interquartile range, or mean of log-transformed variables [geometric means]), the approximations described by Wan et al[14] and Higgins et al[15] were used to compute standardized mean difference as the measure of effect for biomarkers reported in a continuous scale. For dichotomous outcomes, the ratio of the proportions (relative risk) was calculated as the measure of effect.

Scatterplots were generated for drug effects on ESKD (relative risk) on the vertical axis and effects on surrogate renal outcomes (dichotomous or continuous) on the horizontal axis. The area of each plotted point estimate was proportional to the sample size, and 95% confidence intervals were shown for each point estimate. In scatterplots, point estimates consistent with beneficial drug effects for both outcomes (lower risk for ESKD, doubling of serum creatinine, halving of eGFR, and lower albumin or protein excretion rate or progression of albuminuria) were observed in the lower left quadrant. For plots of the association between ESKD and regression of albuminuria, point estimates consistent with beneficial drug effects on both outcomes were observed in the lower right quadrant.

Correlation between treatment effects on surrogate end points (standardized mean difference or log relative risk) and ESKD (log relative risk) was computed using bivariate random-effects meta-analysis.[16] As in a systematic review we have reported previously,[17] within-study correlations between drug treatment effects on surrogate and clinical end points were not reported in individual studies. Hence, we used the approach described by Riley et al[16] that estimates a single correlation parameter that incorporates both the between- and within-study correlations to reduce imprecision in correlation estimates in the presence of few data.[16] This correlation was estimated assuming a bivariate normal distribution for log relative risk for ESKD and the drug effect on the corresponding surrogate end point.

Although a single regression line showing the relationship between drug effects on surrogate measures and ESKD would have aided interpretation of the findings, the 2 components of the correlation (between study and within study) were inseparable and therefore estimating and plotting such a regression line in the scatterplots was not possible.

The model was fitted using a Bayesian approach with uninformative normal—N(0, 1,000)—priors for the mean log relative risk and standardized mean difference; uninformative uniform—U(0, 10,000)—priors for the variance components and an uninformative uniform—U(−1, 1)—prior for the correlation. Four Markov chain Monte Carlo chains of 100,000 iterations each were used to compute the posterior distributions, after 10,000 burn-in iterations. Gelman and Rubin[18] diagnostics and inspection of trace plots were used to check for convergence of Markov chain Monte Carlo chains.

A 95% credible interval was calculated for all correlation estimates. The Bayesian 95% credible interval was interpreted as having a 95% probability of including the true correlation. An interval that excluded zero indicated that a statistically significant correlation was present between treatment effects on surrogate and clinical outcomes. Preplanned subgroup analyses were conducted to assess treatment correlations according to CKD category, baseline proteinuria (normal or mildly increased, moderately increased, or severely increased), and the presence of diabetes. All statistical analyses were conducted in R (R Foundation for Statistical Computing) using the JAGS package.

Results

The electronic search strategy identified 4,791 records. Eighteen additional records were identified from reference lists in retrieved systematic reviews (Fig 1). Overall, 22 randomized trials involving 69,643 participants met the review eligibility criteria (Table 1).[19-40]

The trials were published between 1994 and 2017 and included between 24 and 8,576 participants allocated to a treatment (median of 455). Follow-up time ranged from 4 to 72 (median, 36) months. Mean study eGFR at baseline was reported in 16 (72.7%) trials and was < 30 mL/min/1.73 m^2 in 2 studies, 30-45 mL/min/1.73 m^2 in 3 studies, 45-60 mL/min/1.73 m^2 in 5 studies, and 60-90 mL/min/1.73 m^2 in 6 studies. Mean systolic blood pressure at baseline ranged between 108 and 167 mm Hg. The proportion of participants with diabetes was reported in 16 (73%) studies; of these, 11 included only participants with diabetes, whereas diabetes was an exclusion criterion in 3 studies (n = 240). Baseline levels of proteinuria or albuminuria were reported in 19 trials and ranged from normal or mildly increased in 2 trials (albumin excretion rate equivalent of < 30 mg/d), moderately increased in 13 trials (30-300 mg/d), and severely increased in 3 trials (> 300 mg/d).

Overall, 1,627 participants progressed to ESKD, 2,394 experienced doubling of serum creatinine level (15 trials), and 10 experienced halving of GFR (1 trial). Progression of albuminuria was reported to occur in 1,510 participants (5 trials), regression of albuminuria was reported to occur in 2,203 participants (2 trials), and a continuous outcome measure for proteinuria or albuminuria was reported for 6,220 participants (9 trials).

Risks of Bias

Risks of bias were frequently high or uncertain due to incomplete methodological reporting (Figs S1 and S2). Methodological reporting of the random sequence generation was consistent with low risk of bias in 9 (41%) studies, and treatment allocation was concealed adequately in 11 (50%) studies. In 13 (59%) studies, both participants and investigators were blinded to treatment allocation, whereas in 12 (55%) studies, outcome assessment was blinded. In 10 (45%) studies, attrition from follow-up was low risk of bias. In 9 (41%) studies, there were additional issues that indicated a possibly high risk of bias from other sources. Reported sources of funding are reported in Table S2.

Effect Sizes for Surrogate Outcomes and ESKD

For patient-centered end points, the relative risk for ESKD was statistically significant in 1 of 29 (3.4%) treatment comparisons (Fig S3). For drug effects on surrogate renal outcomes, the risk estimate was statistically significant in 4 of 21 (19%) treatment comparisons for doubling of serum creatinine level (Fig S4), 0 of 1 for halving GFR (Fig S5), 2 of 7 for progression of albuminuria (Fig S6), 2 of 2 for regression of albuminuria (Fig S7), and 8 of 17 (47%) for any continuous measure of albuminuria or proteinuria (Fig S8).

Correlations of Effect Sizes

Scatterplots for drug effects on ESKD and corresponding drug effects on surrogate renal outcomes are shown in Figures 2 to 4. There were few studies reporting drug effects on both surrogate and patient-level outcomes in a format extractable and combinable for meta-analysis.

In scatterplots, there appeared to be a weak association between doubling of serum creatinine level and ESKD (Fig 2). Data for halving of GFR were sparse. Visual inspection of scatterplots showing the association between progression or regression of albuminuria with risks for ESKD did not indicate any correlation between end points (Fig 3). Similarly, data were scant for albuminuria or proteinuria as continuous end points, with highly uncertain correlations between surrogate markers and ESKD (Fig 4).

These observations for the association between surrogate end points and ESKD were confirmed by bivariate meta-analysis showing small to moderate between-study correlations (range, −0.41 to 0.66) in analyses with sufficient data points. All 95% credible intervals included

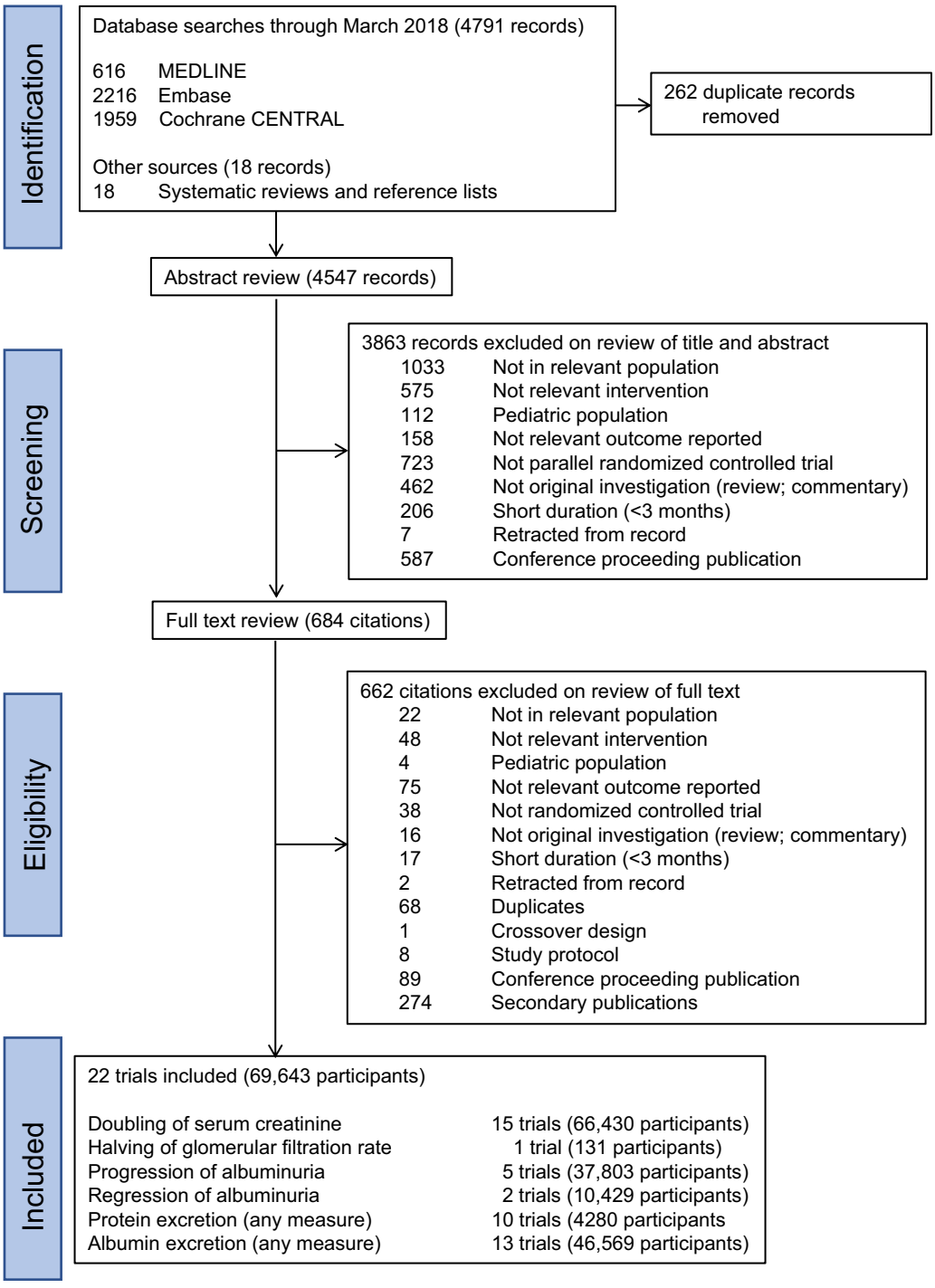

Figure 1. Flow chart shows identification of eligible studies.

zero, consistent with the possibility of no correlation. In meta-analysis including all albuminuria or proteinuria end points combined, the correlation between the standardized mean differences for surrogate outcomes and ESKD was 0.40 (95% credible interval, −0.56 to 0.86).

Subgroup and Sensitivity Analyses

Correlations between drug effects on surrogate end points and ESKD were not estimable or imprecise within subgroup analyses according to the presence of diabetes, CKD category, or level of baseline proteinuria.

Discussion

In this systematic review of randomized trials, there appeared to be limited correlation between drug effects on surrogate renal end points and ESKD. Correlation estimates were imprecise and of low certainty. Estimates were

Table 1. Characteristics of Included Studies

Study	N	Intervention	Dose	Duration, mo	Baseline Population Characteristics								
					Age, y[a]	Men	CVD	CKD	DM	eGFR[b]	PER[b]	ACR[c]	SBP, mm Hg[a]
AASK[19] (2002)	217	Amlodipine	5-10 mg/d	36-72	54.5 (10.7)	60.4%				45.8 (12.9)			150 (25)
	436	Ramipril	2.5-10 mg/d		54.4 (10.9)	61.5%				45.4 (12.8)			151 (23)
	441	Metoprolol	50-200 mg/d		54.9 (10.4)	61.5%				45.8 (13.4)			150 (24)
Abe[20] (2010)	118	Benidipine	2-8 mg/d	12	67.5 (11.9)	64.4%		100%	52.5%	27.9 (17.4)			151.9 (15.2)
	115	Cilnidipine	5-20 mg/d		67.3 (12.9)	66.9%		100%	51.3%	26.8 (16.1)			151.6 (16.1)
ALTITUDE[21] (2016)	4,274	Aliskiren	300 mg/d	32.9	64.4 (9.9)	68.7%				57.0 (21.9)			137.3 (16.7)
	4,287	Placebo			64.6 (9.6)	67.4%				57.0 (23.0)			137.3 (16.2)
ASCEND[22] (2010)	478	Avosentan	50 mg/d	4	61 (9.1)	67.2%	28.2%	100%	100%	33.2 (10.9)		166.5 [85.80-284.5] mg/mmol	137 (14.3)
	455	Avosentan	25 mg/d		61.2 (8.8)	69.2%	31.4%	100%	100%	33.8 (11.2)		160.9 [82.45-274.35] mg/mmol	137.1 (13.8)
	459	Placebo			60.8 (8.9)	66.2%	32.5%	100%	100%	33.0 (10.6)		173.2 [89.85-319.45] mg/mmol	135.4 (5.1)
ATTEMPT-CVD[23] (2016)	615	Telmisartan	20-80 mg/d	36	66 (9)	58.4%	32.7%			72.4 (19.6)		25.5 [11.4-97.1] mg/g	151 (15)
	613	Non-ARB			66 (10)	58.1%	32.5%			73.1 (19.8)		26.6 [11-85.3] mg/g	150 (14)
Cinotti[24] (2001)	66	Lisinopril	5-10 mg/d	24	49.6 (10.8)	69%		100%	0%	36.2 (6.8)	0.35 (0.15) mg/min		141 (27.4)
	65	Std therapy			52.1 (11)	62%		100%	0%	35.4 (7.1)	0.36 (0.11) mg/min		142.2 (24.2)
	120	Telmisartan	80 mg/d		61.2 (8.5)	72.5%	49.2%	100%	100%	91.4 (21.5)			152.6 (16.6)
DIABHYCAR[25] (2004)	2443	Ramipril	1.25 mg/d	48	65.2 (8.4)	69.6%	77.6%		100%				145.8 (15.0)
	2,469	Placebo		48	65 (8.3)	70.1%	73.6%		100%				145.1 (15.2)
	166	Placebo		13	58.6 (13.8)	66%	6.6%	100%		68.6 (13.6)		156.8 (133.6) mg/g	138.8 (12.6)
Fried 2013[26] (2013)	724	Losartan + lisinopril	100 mg/d + 10-40 mg/d	12	64.5 (7.9)	98.8%	38%	100%	100%	53.7 (16.2)			136.9 (16.5)
	724	Losartan + placebo	100 mg/d	12	64.7 (7.7)	99.6%	38.3%	100%	100%	53.6 (15.5)			137 (16.0)
	166	Benazepril + amlodipine	20-40 mg/d + 5-10 mg/d	12	57.7 (10.9)	65.7%			100%	91.6 [47.1-180]		56.9 [10.3-570] mg/g	150 (13.3)
Hannedouche 1994[27] (1994)	52	Enalapril	5-10 mg/d	36	52 (14.4)					18.6 (7.9)	2.2 (0.3) g/d		167 (21.6)
	48	Acebutolol or atenolol	400 or 10 mg/d	36	50 (14.4)					21.0 (11.6)	2.2 (0.3) g/d		166 (13.9)

(Continued)

Table 1 (Cont'd). Characteristics of Included Studies

Study	N	Intervention	Dose	Duration, mo	Baseline Population Characteristics								
					Age, y[a]	Men	CVD	CKD	DM	eGFR[b]	PER[b]	ACR[c]	SBP, mm Hg[a]
IDNT[28] (2001)	579	Irbesartan	70-300 mg	32.2	59.3 (7.1)	65%	27%		100%		2.9 [1.6-5.4] g/d		160 (20)
	567	Amlodipine	2.5-10 mg		59.1 (7.9)	63%	30%		100%		2.9 [1.6-5.2] g/d		159 (19)
	569	Placebo			58.3 (8.2)	71%	29		100%		2.9 [1.8-5.2] g/d		158 (20)
Kanno[29] (2006)	45	Candesartan + ACE inhibitor	2-12 mg/d	37.2	60.3 (11.9)	60%		100%	0%		1.78 (0.67) g/d		140 (20.1)
	45	ACE inhibitor			59.9 (12.0)	60%		100%	0%		1.61 (0.74) g/d		135 (13.4)
Lewis[30] (1999)	63	MAP 92 mm Hg		24	37 (7)	46%		100%	100%	62	1.0 g/d		
	66	MAP 100 mm Hg			37 (8)	48%		100%	100%	64	1.1 g/d		
NAVIGATOR[31] (2017)	4,631	Valsartan	160 mg/d	74.4	64 (7)	50%	24.8%	10.8%		81 (19)		7.1 (4.4-14.2) mg/g	139 (18)
	4,675	Placebo			64 (7)	48.7%	23.9%	11.2%		80 (19)		7.1 (4.5-14.7) mg/g	140 (17)
ONTARGET[32] (2008)	8,576	Ramipril	10 mg	56	66.4 (7.2)	72.8%	74.4%		36.7%	73.7 (19.3)		0.81 (0.78-0.84) mg/mmol	141.8 (17.4)
	8,542	Telmisartan	80 mg		66.4 (7.1)	73.7%	74.5%		38%	73.6 (19.9)		0.83 (0.80-0.86) mg/mmol	141.7 (17.2)
	8,502	Ramipril + telmisartan	80 + 10 mg/d		66.5 (7.3)	73.5%	74.7%		37.9%	73.4 (19.5)		0.81 (0.78-0.84) mg/mmol	141.9 (17.6)
ORIENT[33] (2011)	282	Olmesartan	10-40 mg/d	36	59.1 (8.1)	70.6%	21.3%		100%			192.3 [87.1-339.4] mg/mmol	141.7 (17)
	284	Placebo			59.2 (8.1)	67.6%	11.6%		100%			191.2 [98.4-352.9] mg/mmol	140.8 (18)
PRONEDI[34] (2013)	28	Irbesartan	150 mg/d	32	67.9 (8.0)	75%		100%	100%	46 (16)			154 (19)
	35	Lisinopril	10 mg/d	32	68.7 (6.8)	70%		100%	100%	48 (14)			153 (18)
	70	Lisinopril + irbesartan	5 + 75 mg/d	32	63 (8.5)	78%		100%	100%	50 (25)			152 (20)
REIN[35] (1997)	78	Ramipril	1.25 mg/d	42	48.9 (13.6)	85%		100%		40.2 (19.0)	5.6 (2.8) g/d		149.8 (17.8)
	88	Placebo		42	49.7 (13.6)	73%		100%		37.4 (17.5)	5.1 (2.0) g/d		148 (17.3)
RENAAL[36] (2001)	751	Losartan	50-100 mg/d	42	60 (7)	61.5%	10%		100%			1,237	152 (19)
	762	Placebo		42	60 (7)	64.8%	12.3%		100%			1,261	153 (20)
ROADMAP[37] (2011)	2232	Olmesartan	40 mg/d	48	57.7 (8.8)	47%	34.5%		100%	85.0 (17.0)		4 [2-7]	137 (16)
	2215	Placebo		48	57.8 (8.6)	45.3%	32.3%		100%	84.7 (17.3)		3 [2-7]	136 (15)

(Continued)

Table 1 (Cont'd). Characteristics of Included Studies

Study	N	Intervention	Dose	Duration, mo	Baseline Population Characteristics								
					Age, y[a]	Men	CVD	CKD	DM	eGFR[b]	PER[b]	ACR[c]	SBP, mm Hg[a]
Tarnow[38] (2000)	24	Lisinopril	10-20 mg/d	48	41 (9)	62.5%		100%	100%				108 (14.7)
	24	Nisoldipine	20-40 mg/d		35 (6)	70.8%		100%	100%				105 (9.8)
TRANSCEND[39] (2008)	2,954	Telmisartan	80 mg/d	56	66.9 (7.3)	56.7%	74.8%		35.8%	71.8 (19.9)		0.68 (0.65-0.72) mg/mmol	140.7 (16.8)
	2,972	Placebo			66.9 (7.4)	57.4%	74.3%		35.6%	71.7 (19.9)		0.66 (0.63-0.70) mg/mmol	141.3 (16.4)
VIVALDI[40] (2008)	443	Telmisartan	80 mg/d	12	60.9 (9.2)	63%		100%	100%	48.4 (23.0)	2.7 g/d[d]		147.6 (15.6)
	442	Valsartan	160 mg/d		61.4 (9.1)	65.2%		100%	100%	48.6 (22.3)	2.86 g/d[d]		148.5 (15.5)

Note: Blank cells indicate data were not available.

Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin-creatinine ratio; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; PER, protein excretion rate: SBP, systolic blood pressure; SD, standard deviation; std, standard (conventional).

[a]Values given as mean (SD).

[b]Values given as mean (SD) or median [quartile 1-quartile 3].

[c]Values given as mean (SD), median [quartile 1-quartile 3], or geometric mean (95% confidence interval).

[d][author needs to supply].

uncertain although drug effects on surrogate renal end points were statistically significant in one-fifth to one-half of treatment evaluations in trials, whereas drug treatment significantly lowered risks for ESKD in < 5% of treatment comparisons available in trials. Correlations between surrogate and patient-centered outcomes were imprecise or inestimable when adjusted for the presence of diabetes, CKD category, or baseline proteinuria. Taken together, these findings suggest that there is very low-certainty evidence that drug effects on surrogate markers of kidney function at the level of randomized trials are robust correlates of ESKD. Additional high-quality randomized trials demonstrating that treatment targeted to lower albuminuria or proteinuria or reducing changes in serum creatinine levels prevents ESKD are required before these end points can be used with confidence as therapeutic end points to inform research and clinical decision making.

The finding of a weak evidentiary basis for albumin or protein excretion and serum creatinine level as end points to measure drug effectiveness on kidney outcomes in trials of blood pressure lowering is consistent with a previous meta-analysis that concluded that proteinuria is weakly predictive of ESKD.[9] In that meta-analysis of 27 randomized trials in a range of interventions and involving nearly 100,000 participants, a treatment effect ratio (TER) defined as the relative drug effect on ESKD divided by the relative drug effect on the surrogate end point was 0.82 for proteinuria (a TER value close to 1 indicates better agreement between treatment effects). Notably, there was evidence that results from individual trials were heterogeneous beyond a level that might be expected by chance and that was not explained by study characteristics, including patient age, kidney function, blood pressure, or type of study intervention. This heterogeneity in treatment effects on surrogate and clinical end points within and between studies constrained the generation of a summary TER to assess end-point validity. Measurement of a TER can be useful when the surrogate marker represents the principal biological pathway to the clinical end point, whereas bivariate meta-analysis measures the association between 2 outcomes without requiring that 2 markers are measuring the same biological or clinical process.

The paucity of evidence supporting proteinuria as a valid surrogate trial end point to predict subsequent need for dialysis or transplantation observed in the current study does not confirm the conclusions from a National Kidney Foundation and US Food and Drug Administration workshop that concluded that proteinuria could be recommended as a surrogate for kidney disease progression only in selected circumstances, such as when drug effects lead to large clinical changes in protein excretion (eg, complete remission of severely increased albuminuria).[6] As in the findings of that workshop, the present study showed that there is considerable heterogeneity in the methods used to measure proteinuria and albuminuria in clinical trials, which limited the inclusion of available data observations within meta-analyses and resulted in considerable

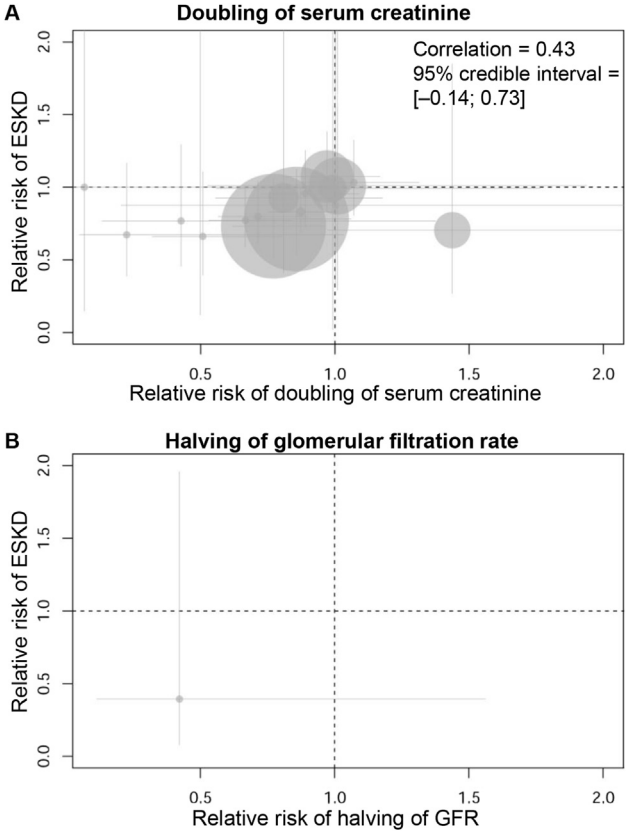

Figure 2. Study-level assessment of the correlation between relative antihypertensive drug effects on measures of creatinine and glomerular filtration rate (GFR) and end-stage kidney disease (ESKD). Each point represents the association between the relative drug effects on measures of (A) doubling of serum creatinine level or (B) estimated GFR (horizontal axis) and the relative risk for ESKD (vertical axis) within a single study. A point estimate indicating a relative beneficial effect of the active treatment compared with the comparator treatment (lower risk for ESKD and lower risk for doubling of serum creatinine or halving of GFR) would be observed in the lower left quadrant. The 95% confidence interval is shown for each point estimate. The correlation of effects of drug treatment on albuminuria, serum creatinine level, or GFR and ESKD estimated using Bayesian bivariate metaregression is shown together with the 95% credible interval. A 95% credible interval that includes zero is consistent with no statistical evidence of correlation. A correlation was not calculated when there were fewer than 3 studies reporting the combined end points.

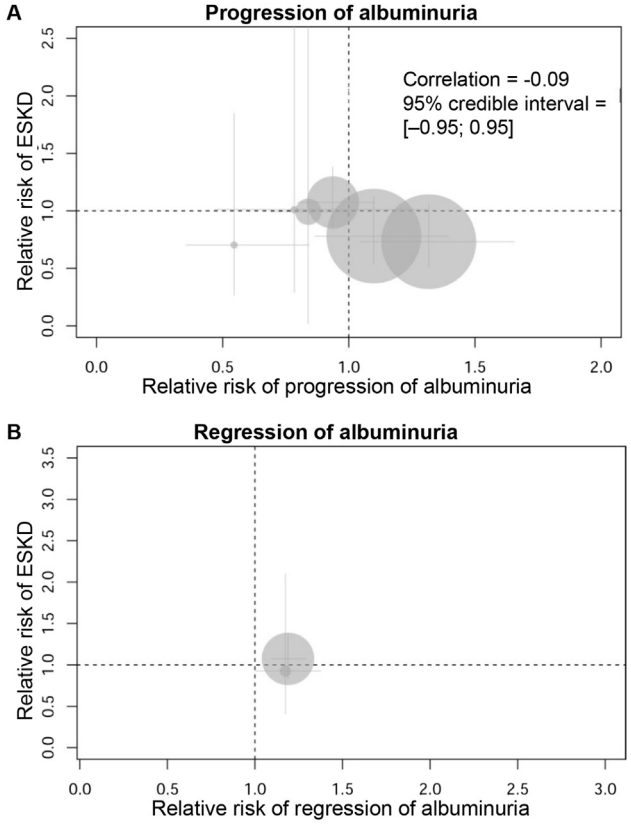

Figure 3. Study-level assessment of the correlation between relative drug effects on surrogate measures of progression or regression of albuminuria and end-stage kidney disease (ESKD). Each point represents the association between the relative drug effects on measures of (A) progression of albuminuria or (B) regression of albuminuria on the horizontal axis and the relative risk for ESKD (vertical axis) within a single study. A point estimate indicating a relative beneficial effect of the active treatment compared with the comparator treatment (lower risk for ESKD and progression of albuminuria) would be observed in the lower left quadrant. A point estimate indicating a relative beneficial effect of the active treatment compared with the comparator treatment (lower risk for ESKD and regression of albuminuria) would be observed in the lower right quadrant. The area of each point is proportional to the sample size of the contributing study. The 95% confidence interval is shown for each point estimate. The correlation of the effects of drug treatment on albuminuria and ESKD estimated using Bayesian bivariate metaregression is shown together with the 95% credible interval. A 95% credible interval that includes zero is consistent with no statistical evidence of correlation. A correlation was not calculated when there were fewer than 3 studies reporting the combined end points.

imprecision in correlation estimates. Standardized measures of surrogate renal outcomes (albuminuria and/or proteinuria) in future trials could improve the understanding of these outcomes as predictors of patient-level renal outcomes. In addition, pragmatic trials testing routine clinical decision making with a focus on patient-centered renal outcomes may obviate the need for reliance on surrogate markers of kidney function as trial end points.[41]

The current study contrasts with the findings from the REASSURE (Reducing Albuminuria as Surrogate Endpoint) Consortium that used univariate random-effects metaregression to examine the effects of a range of interventions on albuminuria and reported that a 30% reduction in proteinuria or albuminuria was associated with a 23.7% (95% confidence interval, 11.4%-34.2%) lower risk for ESKD.[10] Notably, a 30% reduction in albuminuria was achieved in < 10% of trials and the timeframe over which treatment effects on albuminuria were measured was not provided. In that study, numerous

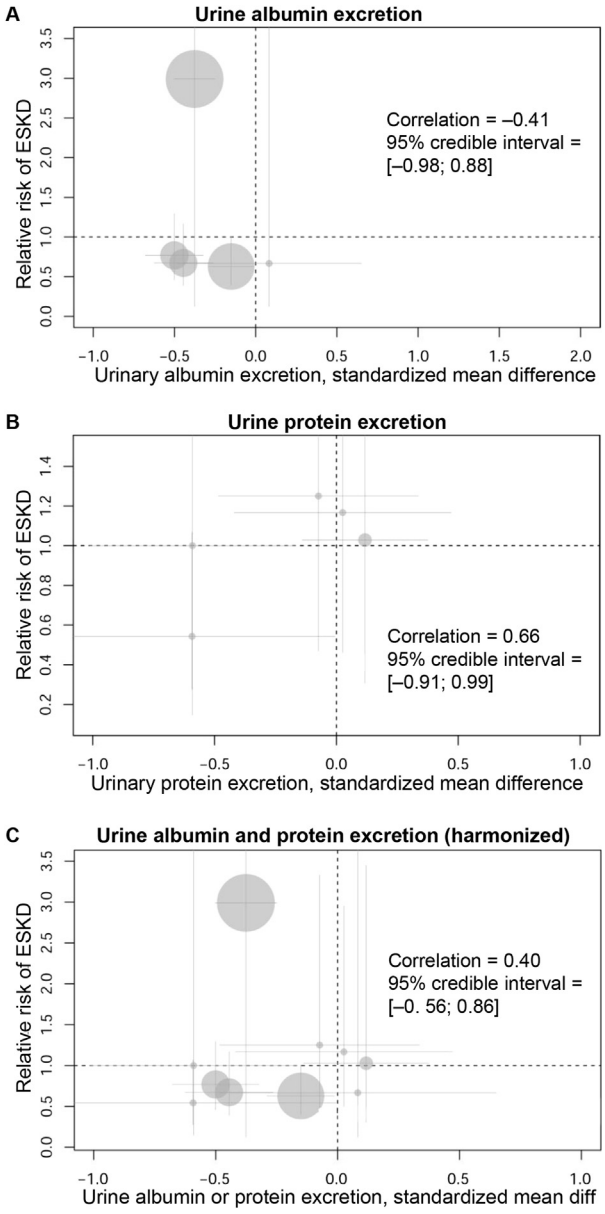

Figure 4. Study-level assessment of the correlation between relative drug effects on surrogate measures of albuminuria or proteinuria and end-stage kidney disease (ESKD). Each point represents the association between the relative drug effects on measures of (A) albumin excretion, (B) protein excretion, or (C) albumin or protein excretion on the horizontal axis and the relative risk for ESKD (vertical axis) within a single study. A point estimate indicating a relative beneficial effect of the active treatment compared with the comparator treatment (lower risk for ESKD and lower protein or albumin excretion) would be observed in the lower left quadrant. The area of each point is proportional to the sample size of the contributing study. The 95% confidence interval is shown for each point estimate. The correlation of the effects of drug treatment on proteinuria and ESKD estimated using Bayesian bivariate metaregression is shown together with the 95% credible interval. A 95% credible interval that includes zero is consistent with no statistical evidence of correlation. A correlation was not calculated when there were fewer than 3 studies reporting the combined end points. Abbreviation: Diff, difference.

measures of albuminuria or proteinuria were combined into a single surrogate end point for analysis. In our analyses, each renal surrogate end point was considered individually, and this approach constrained the statistical power of analyses. However, when all reported surrogate outcomes were included in a single meta-analysis, there was no evidence of a strong correlation between surrogate and clinical outcomes and the 95% credible interval included the possibility of the null effects. Although the REASSURE study indicates a potential association between surrogate renal end points and risks for ESKD, the results require evaluation using random treatment allocation to differing albuminuria targets in which both the benefits and harms of treatment are systematically captured. An earlier study showing that treatment targeted to reduce proteinuria to protein excretion < 0.3 g/d was associated with fewer episodes of ESKD compared with historical controls supports the need for randomized trials of proteinuria lowering to test efficacy against longer term renal outcomes.[42]

Our finding of an imprecise correlation of doubling of serum creatinine level with ESKD is consistent with a previous meta-analysis of GFR decline involving 37 trials across a range of interventions.[43] In that review, there appeared to similar hazards of GFR decline (40% or 30%) and of a composite of treated kidney failure, untreated kidney failure, or doubling of serum creatinine level throughout study follow-up. However, there was imprecision in the estimates indicating that a GFR decline during treatment might plausibly predict a range of risks for ESKD. As in this present study, the authors identified low statistical power for many trials.

Although our study was conducted using a search strategy design by an information specialist, considered the quality of the available evidence, and used a Bayesian bivariate meta-analytical approach to simultaneously consider surrogate and patient end points, the study has limitations. First, the risks of bias in included studies were often unclear or high, reducing certainty in treatment estimates within and across studies. Second, analyses included few studies, leading to considerable imprecision in estimates. Importantly, a possible correlation between treatment effects on surrogate renal markers and clinical end points could not be excluded. Reporting bias was possible due to the number of potentially eligible studies that were excluded due to a lack of extractable outcome data. To overcome the paucity of data, an individual patient-data meta-analysis could be conducted. The advantages of individual patient-level information are to facilitate standardization of outcomes and analyses across studies, provide more detailed derivation of end point measures, and offer longer follow-up time, additional studies without published data, and adjustment for potential confounding factors. Third, trials were limited to those evaluating blood pressure therapies to maximize homogeneity in treatment effects between studies, at the expense of

statistical power in the analyses. A wider range of treatments may have increased statistical power and the generalizability of the findings. Fourth, changes in albuminuria (standardized mean difference ≤ 0.5) during treatment were relatively modest and may not have provided a sufficient biological effect to affect risks for kidney failure in the longer term. Finally, subgroup analyses were constrained by few studies; the correlation between surrogate and hard end points in specific clinical settings such as patients with advanced kidney disease or in the presence of diabetes was not examinable.

In conclusion, there is no high-certainty evidence demonstrating the validity of serum creatinine level, eGFR, albuminuria, or proteinuria to estimate risks for ESKD in trials of blood pressure–lowering therapy. The correlation between antihypertensive drug effects on serum creatinine level, albuminuria, or proteinuria and ESKD is not sufficiently certain to enable confident use of these markers to guide clinical decision making or test the effectiveness of treatments to prevent ESKD.

Supplementary Material

Figure S1: Risk of bias in individual studies.

Figure S2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure S3: Pairwise treatment comparisons for drug effects on ESKD.

Figure S4: Pairwise treatment comparisons for drug effects on doubling of serum creatinine.

Figure S5: Pairwise treatment comparisons for drug effects on halving of GFR.

Figure S6: Pairwise treatment comparisons for drug effects on progression of albuminuria.

Figure S7: Pairwise treatment comparisons for drug effects on regression of albuminuria.

Figure S8: Pairwise treatment comparisons for drug effects on urine albumin or protein excretion rate.

Table S1: Search strategy.

Table S2: Reported sources of funding in included studies.

Item S1: Prespecified protocol for the meta-analysis.

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