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Systematic Review/Meta-analysis

Change in Proteinuria or Albuminuria as a Surrogate for Cardiovascular and Other Major Clinical Outcomes: A Systematic Review and Meta-analysis

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ABSTRACT

Background: There is ongoing controversy around the surrogacy of proteinuria or albuminuria, particularly for cardiovascular (CV) outcomes, which remain the leading cause of morbidity and mortality among patients with chronic kidney disease. We performed a systematic review and meta-analysis of the literature to assess the surrogacy of changing proteinuria or albuminuria for CV events, end-stage renal disease (ESRD), and all-cause mortality.

Methods: CENTRAL, EMBASE, and MEDLINE were searched (from inception to October 2017). All randomized controlled trials in adults that reported change in proteinuria or albuminuria and $\geq$ 10 CV, ESRD, or all-cause mortality events were included. We calculated treatment effect ratios (TERs), defined as the ratio of the treatment effect on a clinical outcome and the effect on the change in the surrogate outcome. TERs close to 1 indicate greater agreement between the clinical outcome and changing proteinuria or albuminuria.

Results: Thirty-six trials were included in the meta-analysis. We observed inconsistent treatment effects for proteinuria and CV events (20 trials; TER 1.11 [95% confidence interval (CI), 1.01-1.22]) with moderate heterogeneity ($I^2 = 51\%$, $P = 0.005$). Treatment effects on

RÉSUMÉ

Contexte : La question de savoir si la protéinurie et l'albuminurie sont des paramètres de substitution acceptables, en particulier pour les manifestations cardiovasculaires, qui demeurent la cause première de morbidité chez les patients atteints de néphropathie chronique, fait l'objet d'une controverse qui perdure. Nous avons réalisé une recension systématique et une méta-analyse de la littérature afin de déterminer si la variation de la protéinurie ou de l'albuminurie pouvait être utilisée comme paramètre d'évaluation à la place des manifestations cardiovasculaires, de l'insuffisance rénale terminale (IRT) et de la mortalité toutes causes confondues.

Méthodes : Une recherche a été effectuée dans les bases de données CENTRAL, EMBASE, et MEDLINE (de leur date de création à octobre 2017). Tous les essais cliniques randomisés et contrôlés menés chez l'adulte et rapportant la variation de la protéinurie ou de l'albuminurie ainsi qu'au moins 10 manifestations cardiovasculaires, l'IRT ou la mortalité toutes causes confondues ont été incluses. Nous avons calculé le rapport des effets du traitement (RET), défini comme étant le rapport de l'effet du traitement sur un paramètre clinique et de l'effet sur la variation du paramètre de substitution. Plus la valeur du

Chronic kidney disease (CKD) is common, with global prevalence estimates ranging between 8% and 16%, and is associated with an increased risk of cardiovascular (CV) morbidity and mortality.[1-3] Because of the high costs associated with treatment of advanced CKD and renal replacement therapies, interventions to slow CKD progression is a worldwide focus.[4] However, clinical end points used to test current and potential therapeutic strategies often require long periods of follow-up, which present major challenges in the design and conduct of such studies.

The search for surrogates for long-term clinical outcomes including CV events and end-stage renal disease (ESRD) has thus been a focus in CKD research.[5-7] Identification of these surrogates might allow for more efficient trials, potentially leading to increased strategies for effective risk reduction among individuals with CKD.[6,8] In large clinical cohorts, albuminuria grade, independent of estimated glomerular

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proteinuria or albuminuria were also inconsistent with the effects on all-cause mortality (21 trials; TER 1.17 [95% CI, 1.07-1.28]; $I^2 = 35\%$, P for heterogeneity = 0.06), although they were similar with the effects on ESRD (23 trials; TER 0.99 [95% CI, 0.88-1.13]; $I^2 = 9\%$, P for heterogeneity = 0.337).

Conclusions: Change in proteinuria or albuminuria might be a suitable surrogate outcome for ESRD. However, overall treatment effects on these potential surrogates are inconsistent and overestimate the treatment effects on CV events and all-cause mortality.

RET se rapproche de 1, plus forte est la concordance entre le résultat clinique et la variation de la protéinurie ou de l'albuminurie.

Résultats : Trente-six essais cliniques ont été inclus dans la méta-analyse. Nous avons observé une absence de concordance des effets du traitement entre la protéinurie et les manifestations cardiovasculaires (20 études; RET 1,11 [intervalle de confiance (IC) à 95 %, 1,01-1,22],) et une hétérogénéité modérée ($I^2 = 51$ %, $p = 0,005$). Les effets du traitement sur la protéinurie ou l'albuminurie ne concordaient pas non plus avec les effets sur la mortalité toutes causes confondues (21 études; RET 1,17 [IC à 95 %, 1,07-1,28]; $I^2 = 35$ %, p pour l'hétérogénéité = 0,06), mais concordaient avec ceux sur l'IRT (23 études; RET 0,99 [IC à 95 %, 0,88-1,13]; $I^2 = 9$ %, p pour l'hétérogénéité = 0,337).

Conclusions : La variation de la protéinurie ou de l'albuminurie pourrait être un paramètre de substitution de l'IRT approprié. Toutefois, les effets globaux du traitement sur ces paramètres de substitution potentiels ne sont pas concordants et les effets du traitement sur les manifestations cardiovasculaires et la mortalité toutes causes confondues sont surestimés.

filtration rate (eGFR), has been shown to be associated with progression to ESRD, CV events, and death.[9] Although change in albuminuria or proteinuria has been investigated as a potential surrogate outcome for ESRD in several meta-analyses,[6,7,10] trials reporting on the relationship between the change in proteinuria or albuminuria and subsequent CV events, the leading cause of morbidity and mortality among people with CKD, have been limited.[5-7]

Among adults, the validity of proteinuria and albuminuria change as a surrogate outcome for clinical outcomes is unclear and requires further exploration. With this in mind, in this systematic review and meta-analysis we assessed the association between change in proteinuria and albuminuria and adverse clinical outcomes including CV events, progression to ESRD, and all-cause mortality. Additionally, we examined the participant characteristics, interventions, and study characteristics that influenced the agreement between change of these potential surrogates and the clinical outcomes.

Methods

Data search strategy

We conducted this systematic review using a prespecified study protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for the conduct of meta-analyses of peer-reviewed and published randomized controlled trials (RCTs).[11] We searched 3 major electronic databases including MEDLINE via Ovid (1946 through October 2017), EMBASE (1980 through October 2017), and the Cochrane Central Register of Controlled Trials (CENTRAL, no date restrictions) using medical subject headings and text words that included "proteinuria," "albuminuria," "cardiovascular disease," "renal replacement therapy," "end-stage kidney disease," and "all-cause mortality" (Supplemental Table S1). Manual searching of reference lists from trials that met our inclusion criteria was performed to identify other relevant trials. We limited the search to RCTs but without restrictions on the type of intervention or language.

Study selection, data extraction, and quality assessment

Two authors (T.G.H. and H.T.-T.) independently screened the titles and abstracts. A third reviewer (M.J.) resolved any disagreement on the selection of trials. All completed RCTs, irrespective of intervention or comparator, conducted in adults (age $\geq$ 18 years) and reporting the outcome of change in proteinuria or albuminuria and any 1 of the following clinical outcomes were eligible for inclusion: ESRD (defined as the need for chronic dialysis, renal transplantation, or as defined by the authors), CV events (defined as fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or as defined by authors), or all-cause mortality. Trials had to have had at least 10 events to be eligible for inclusion. Trials that investigated patients with acute kidney injury, kidney transplantation, or incident ESRD were excluded. Published reports for each trial were obtained and selected information extracted. We collected data on change in proteinuria or albuminuria (from baseline to end of study; 24-hour proteinuria, urine albumin-to-creatinine ratio [UACR], urine protein-to-creatinine ratio [UPCR]; absolute and proportional; or as defined by authors), CV events (as defined by the authors), ESRD, and all-cause mortality.

Two authors (T.G.H. and H.T.-T.) independently extracted data on study characteristics, details of the intervention and comparator groups, and outcomes using a standard data extraction form that was piloted with several trials. A third reviewer (M.J.) cross-checked the data to ensure accuracy. In accordance with Cochrane Collaboration recommendations,[12] we investigated risk of bias by assessing for selection bias, performance bias, and detection bias, in addition to determining whether the study performed an intention to treat analysis. Additionally, publication bias was assessed with the Egger test.[13] Where publication bias was identified as being significant, the "trim and fill" method[14] was used to account for this.

Data synthesis and analyses

We assessed the association between change in proteinuria or albuminuria (from baseline to a study-defined time point) and subsequent clinical outcomes. For trials that reported

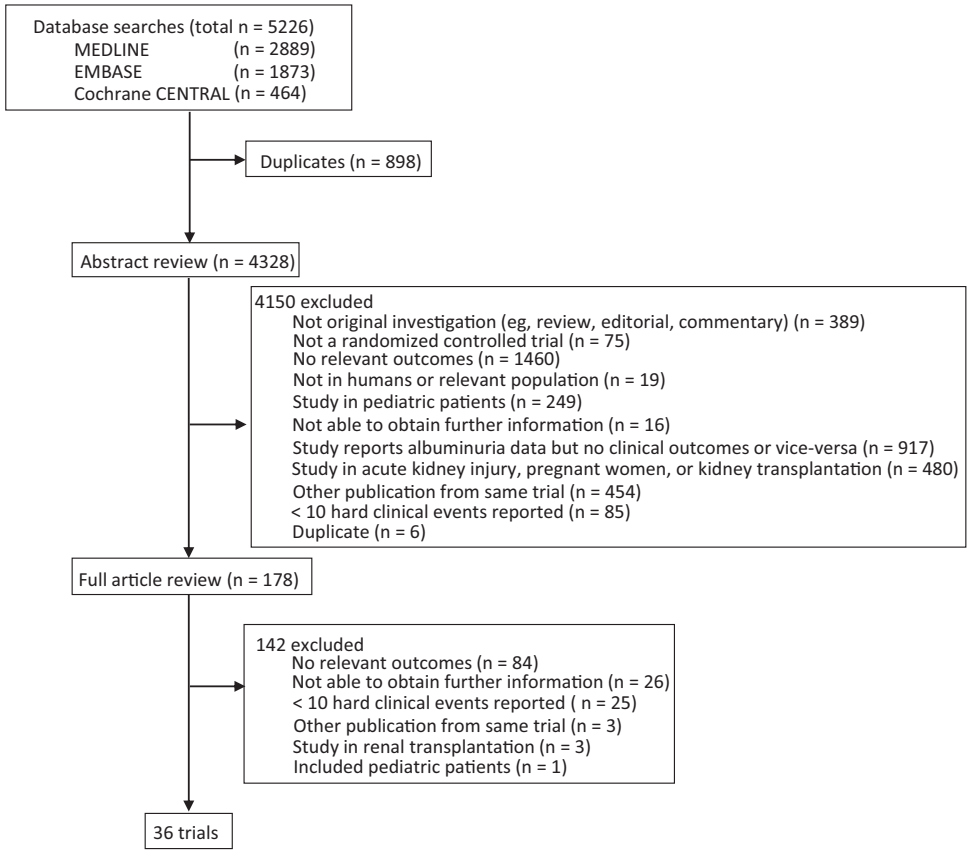


Figure 1. Identification of included randomized controlled trials.

categorical measures of proteinuria or albuminuria change, relative risks and corresponding 95% confidence intervals (CIs)[15] were calculated for each study before data pooling. In calculating the relative risk estimates we used total number of patients randomized in each group as the corresponding denominator. When continuous scales of measurement were used to assess the effects of treatment on proteinuria or albuminuria, we calculated weighted mean differences using end-of-trial mean values, their corresponding SDs, and treatment arm size. Where standard errors were provided, we calculated SDs on the basis of these values and the number of participants. To standardize quantification of urine albumin and protein excretion, measures were converted to 24-hour urine protein excretion for comparison using standardized conversion factors as per Kidney Disease Improving Global Outcomes guidelines and recent studies.[4,6,10]

To assess the association between change in proteinuria or albuminuria and clinical outcomes across the diverse group of trial interventions, we calculated the treatment effect ratio (TER) derived from baseline and end-of-trial urine protein or albumin results and the trial treatment effect on clinical outcomes, as per our previous study.[6] The use of TERs was on the basis of the rationale that the treatment effect on the surrogate would be proportional to that of the treatment effect on the risk of the clinical outcome. This is also part of the Prentice and Freedman criteria for validation of surrogate outcomes.[16,17] TERs close to 1 suggest greater agreement between the clinical outcome and change in proteinuria or albuminuria (the potential surrogate outcome). TERs > 1 suggest that change in proteinuria or albuminuria overestimates the change in clinical outcome, whereas TERs < 1 suggest that change in proteinuria or albuminuria underestimates the effect on clinical outcome. Data were pooled using a DerSimonian and Laird random effects model. Heterogeneity was assessed through the calculation of I^2 values and Cochran Q statistic. We conducted a number of prespecified stratified analyses to explore potential sources of heterogeneity for the 3 clinical outcomes of interest. For the ESRD and all-cause mortality outcomes, this included stratification of trials according to publication year, number of patients, median age, baseline eGFR, percentage of male participants, systolic blood pressure, and intervention types. For the CV event outcome, stratification according to publication year, number of patients, median age, baseline eGFR, percentage of male participants, systolic blood pressure, intervention types, CV event definitions, proportion of diabetic participants (2.5%-36.7% vs 100% [trial in diabetes]), baseline proteinuria (< 20 vs ≥ 20 mg/d), type of proteinuria measurement (UACR vs urine protein or albumin excretion), and follow-up duration (< 4 vs ≥ 4 years) were performed. Statistical analyses were performed with Stata software, version 9.2 (Stata Corp, College Station, TX).

Results

Search results and characteristics of included RCTs

After exclusion of duplicates, we identified 4328 articles for abstract review (Fig. 1), with 178 articles selected for full-text

Table 1. Baseline characteristics of the included trials

Intervention details/study	Inclusion criteria	Intervention	Control arm	Follow up, mean years	Study size, n	Mean age, years	Male sex, %	Mean baseline eGFR, mL/min/1.73 m^2	Baseline urine protein/albumin (measurement type)	Number of CV events	Number of ESRD events	Number of deaths
BP-lowering												
Zucchelli et al.[21]	Adults with CKD (SCr 1.8-5.0 mg/dL), HTN	Captopril	Nifedipine	3.0	121	55.0	57.9	30.5	10.0 g/d (UPE)	NR	21	1
Hannedouche et al.[22]	HTN, adults with CKD (SCr 200-400 µmol/L)	Enalapril	β-Blocker	3.0	100	51.0	53.0	NR	2.85 g/d (UPE); data available for 47 patients	NR	27	3
UKPDS 39[23]	HTN, adults with T2DM	Captopril	Atenolol	8.4	758	56.1	54.1	NR	Categorical albuminuria	107	8	134
GISEN-REIN-Stratum 1[24]	Normotensive and hypertensive adults with eGFR 20-70 mL/min/1.73 m^2, > 1 g/d of proteinuria not receiving an ACEi	Ramipril	Placebo	2.7	186	49.7	74.7	46.6	1.7 g/d (UPE)	6	27	1
ABCD[37]	40-74 years; T2DM; dBP > 90mmHg off of medications	Intensive (dBP < 75 mm Hg) target	Moderate (dBP 80-89 mm Hg) target	5.3	470	57.9	67.4	84.3	331.7 mg/d (UAE)	NR	NR	38
IRMA-2[34]	T2DM with hypertension, aged 30-70 years, with persistent microalbuminuria	Irbesartan (150 mg or 300 mg)	Placebo	2.0	590	58.0	68.5	109	55.5 µg/min (UAE)	26	NR	4
J-MIND[54]	CrCl > 30 mL/min and 24-hour UAE rate < 300 mg/d; sBP > 140 mm Hg and or dBP > 90 mm Hg without medication; HbA1c < 12%	Enalapril (5-20 mg/d)	Nifedipine (20-60 mg/d)	2.0	436	60.0	50.5	110	43.6 mg/d (UAE)	13	NR	NR
Marin et al.[26]	Adults with CKD (SCr 1.5-5 mg/dL) and hypertension	Fosinopril	Nifedipine	3.0	241	54.4	58.9	35.6	1.75 g per 24 hours (UPE)	NR	67	10
Fogari et al.[27]	T2DM, dBP 90-110 mm Hg, UAE 30-300 mg/d	Fosinopril or amlodipine	Fosinopril and amlodipine	4.0	309	62.5	56.6	89.6	97.1 mg/d (UAE)	19	NR	NR
ONTARGET[29,56]	Age ≥ 55 years; ≥ 1 of: CAD, PAD, cerebrovascular disease, or DM with end-organ damage	Ramipril or telmisartan or both	3 arms	4.7	25,620	66.4	73.3	75.6	0.81 mg/mmol (UACR)	4221	162	3068
TRANSCEND[30]	Age ≥ 55 years with documented CVD or DM with end-organ damage who could not tolerate ACEi	Telmisartan	Placebo	4.7	5926	66.9	57.0	NR	0.67 mg/mmol (UACR)	961	17	713

DEMAND[31]	Age > 40 years, hypertension and T2DM, UAE < 200 μg/min, SCr < 1.5 mg/dL	Manidipine and delapril	Placebo	3.8	380	60.8	65.2	99	5.9 μg/min (UAE)	18	NR	6
ROADMAP[32]	T2DM, normoalbuminuria, at least 1 cardiac risk factor	Olmesartan	Placebo	3.2	4447	57.7	46.1	84.9	6.1 mg/g (UACR)	190	0	41
PRONEDI[33]	Age > 35 years; T2DM; CKD diabetic nephropathy stage 2-3; UPCR 300 mg/g	Lisinopril or irbesartan	Lisinopril with irbesartan	2.7	133	65.5	76.3	48.6	1.3 g/g (UPCR)	NR	21	9
ATTEMPT-CVD[35]	Age 40-80 years, HTN, at least 1 CV risk factor	Telmisartan	Placebo	3.0	1228	66	58.2	72.7	26.0 mg/g (UACR)	25	1	0
NAVIGATOR post hoc[36]	≥ 1 CV risk factor (if age > 55 years) or known CV disease (if age > 50 years), and impaired glucose tolerance	Valsartan	Placebo	6.2	9306	64	50.6	80.5	7.1 mg/g (UACR)	1365	18	622
Lipid-lowering												
Endo et al.[39]	T2DM with clinical albuminuria (UAE > 300 mg/g)	Probucol and protein-restricted diet	Protein-restricted diet	2.4	102	59.6	55.9	NR	1468 mg/g (UACR)	NR	13	0
CARDS[57]	Age 40-75 years, T2DM with ≥ 1 of hypertension, retinopathy, albuminuria, smoker	Atorvastatin	Placebo	3.9	2838	61.6	68.0	64.2	9.73 mg/g (UACR)	210	NR	143
FIELD[40]	Age 50-75 years; T2DM; hyperlipidemia	Fenofibrate	Placebo	5.0	9795	62.2	62.7	87.7	1.12 mg/mmol (UACR)	1295	47	679
Diabetic therapy												
Bolton et al.[41]	T2DM age 22-50 years with retinopathy, nephropathy with > 500 mg/d UPE, and CrCl 40-90 mL/min	Pimagedine	Placebo	2.5	690	39.3	39.5	49.3	2.69 g/d (UPE)	NR	90	22
SAVOR[44]	T2DM with HbA1c 6.5%-12.0%, either established CV disease or multiple risk factors for vascular disease	Saxagliptin	Placebo	2.1	16,492	65.1	66.9	72.6	1.85 mg/mmol (UACR)	2093	372	768
BARI-2D post hoc[43]	Age > 25 years, T2DM, CAD with at least 1 lesion > 50% stenosis	Insulin	Not using insulin	5.0	1799	62.1	71.1	76.6	11.7 mg/g (UACR)	NR	35	NR

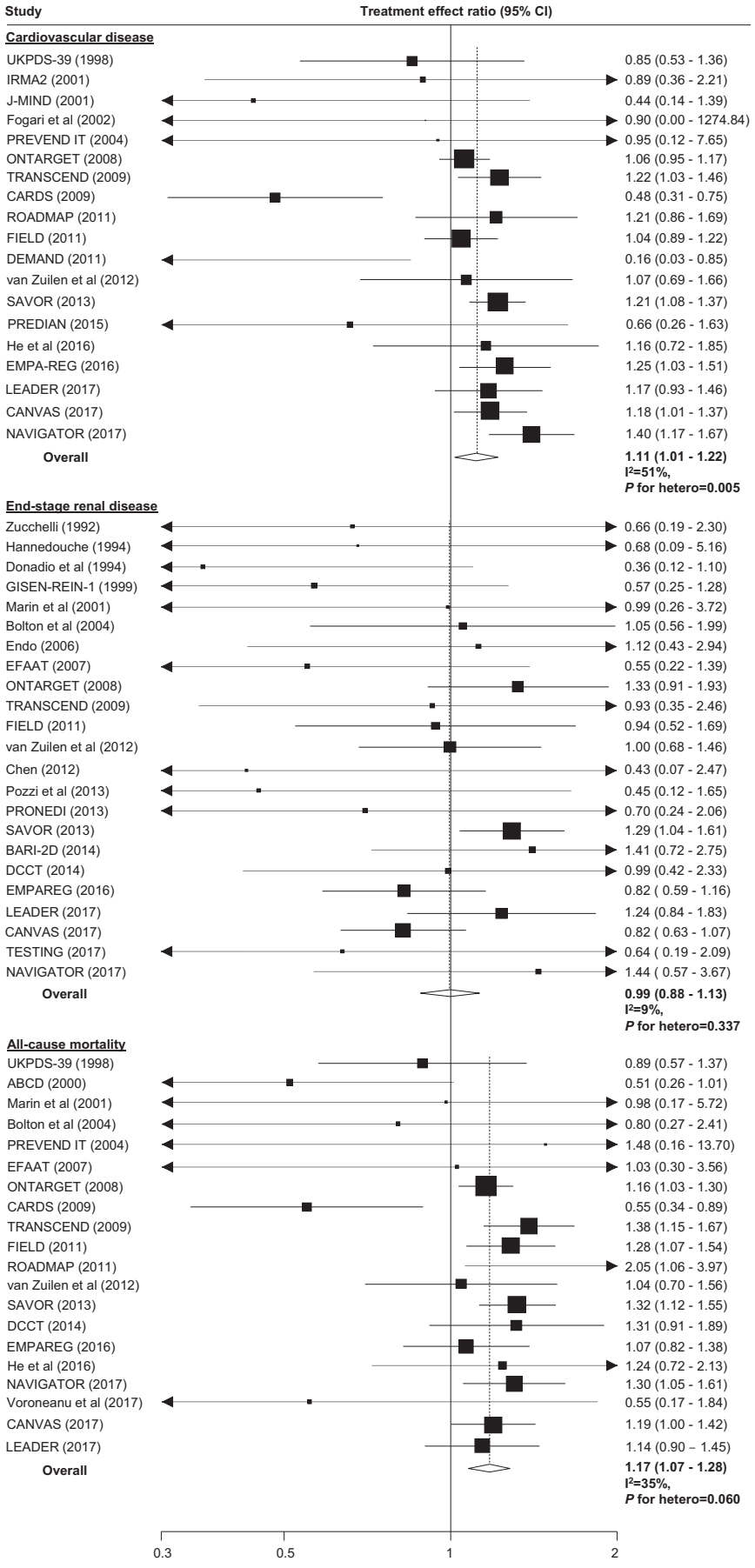
Continued

Table 1. Continued.

Intervention details/study	Inclusion criteria	Intervention	Control arm	Follow up, mean years	Study size, n	Mean age, years	Male sex, %	Mean baseline eGFR, mL/min/1.73 m^2	Baseline urine protein/albumin (measurement type)	Number of CV events	Number of ESRD events	Number of deaths
DCCT/EDIC post hoc[58]	Cohort 1: T2DM duration 1-5 years, AER < 40 mg/d, no retinopathy Cohort 2: T2DM 1-15 years, AER < 200 mg/d, at least 1 retinal microaneurysm	Intensive diabetes therapy	Conventional diabetes therapy	24.6	1441	26.9	52.8	126.1	Categorical albuminuria	NR	24	133
EMPA-REG OUTCOME,[81] EMPA-REG post hoc[82]	T2DM, with established CV disease, eGFR > 30 mL/min/m^2	Empagliflozin	Placebo	3.1	7020	63.2	71.6	74	Categorical albuminuria	772	152	463
He et al.—ADVANCE post hoc[49]	Adult patients with T2DM and hypertension from Chinese sites from the ADVANCE trial	Intensive glucose control	Standard glucose control	4.8	1888	65.0	51.3	NR	2.4 mg/mmol (UACR)	258	NR	115
LEADER[47]	T2DM with high CV risk	Liraglutide	Placebo	3.8	9340	64.3	64.3	80.4	190.2 mg/g (UACR)	1302	133	828
CANVAS[83] and CANVAS-R[46]	T2DM with high CV risk	Canagliflozin	Placebo	3.6	10,142	64.2	63.3	76.5	12.3 mg/g (UACR)	1011	249	681
Voroneanu et al.[48]	T2DM with > 500 mg/d proteinuria with maximum RAS blockade	Silymarin	Placebo	2.0	102	68.6	64.3	39.8	0.7 g/d (UPE)	NR	3	12
Treatment of glomerulonephritis												
Donadio et al.[20]	IgA nephropathy, with UPE ≥ 1g/d UPE, SCr < 265 µmol/L	Fish oil (12 g/d)	Olive oil	3.0	106	37.0	74.0	82	2.87 g/d (UPE)	NR	19	2
Pozzi et al. post-hoc[18]	IgA nephropathy with creatinine > 2.0 mg/dL and 1 g/d proteinuria	Steroids with azathioprine	Steroids	4.5	46	39.8	80.5	27	2.5 g/d (UPE)	NR	19	NR

TESTING[19]	IgA nephropathy with > 1 g/d of proteinuria and eGFR 20-120 mL/min/m^2after 3 months of conservative therapy	Methylprednisolone	Placebo	2.1	262	63.4	38.6	59.3	2.4 g/d (UPE)	NR	14	3
Other interventions												
PREVEND-IT[28]	UAE 15-300 mg per 24 hours, not hypertensive or hyperlipidemic	Fosinopril or pravastatin	Placebo	3.8	1728	51.2	64.9	NR	22.8 mg/d (UAE)	62	NR	19
EFAAT[50]	AA amyloidosis with renal involvement, > 1 g/d proteinuria or CrCl < 60 mL/min	Eprodisate	Placebo	2.0	183	51	42.1	58.7	3.2 g/d (UPE)	NR	20	10
van Zuilen et al.[51]	Adult patients with CrCl 20-70 mL/min	Nurse practitioner-directed care and usual care	Nephrologist-directed care	4.6	788	59.1	67.5	38.1	0.78 g/d (UPE)	80	109	98
Chen et al.[52]	Age 30-83 years; high-normal body lead burden (lead 80-600 μg); SCr ≤ 3.9 mg/dL	Lead chelation therapy	Dextrose	2.25	50	58.1	80.0	28.6	3.9 g/d (UPE)	NR	19	NR
PREDIAN[53]	Age > 40 years, T2DM, CKD stage 3-4, UAE > 30 mg per 24 hours, stable renal function	Pentoxyfylline	Control (not placebo)	1.97	169	69.8	53.8	37.4	1.05 g/d (UAE)	20	5	2

AA, amyloid A; ABCD, **A**ppropriate **B**lood Pressure **C**ontrol in **D**iabetes; ACEi, angiotensin-converting enzyme inhibitor; ADVANCE, **A**ction in **D**iabetes and **Va**scular Disease: Preterax and Diamicro**n** MR-**C**ontrolled **E**valuation; AER, albumin excretion rate; ATTEMPT-CVD, **A T**rial of **Tel**misartan **Prevent**ion of **C**ardio**v**ascular **D**iseases; BARI-2D, **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation **2 D**iabetes; BP, blood pressure; CAD, coronary artery disease; CANVAS, **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy; CANVAS-R, **CANVAS-R**enal; CARDS, **C**ollaborative **A**to**r**vastatin **D**iabetes **S**tudy; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; dBP, diastolic blood pressure; DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; DEMAND, **De**lapril and **Ma**nidipine for **N**ephroprotection in **D**iabetes; DM, diabetes mellitus; EFAAT, **E**prosidate **f**or **A**A **A**myloidosis **T**rial; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, **Empa**gliflozin Cardiovascular **Outcome** Event Trial in Type 2 Diabetes Mellitus Patients -**R**emoving **E**xcess **G**lucose; ESRD, end-stage renal disease; FIELD, **F**enofibrate **I**ntervention and **E**vent **L**owering in **D**iabetes; GISEN-REIN, Gruppo Italiano di Studi Epidemiologici in Nefrologia Ramipril Efficacy in Nephropathy; HbA1c, hemoglobin A1c; HTN, hypertension; IgA, immunoglobulin A; IRMA-2, **Ir**besartan in **M**icro**a**lbuminuria, Type 2 Diabetic Nephropathy; J-MIND, **J**apan **M**ulticenter **I**nvestigation of Antihypertensive Treatment for **N**ephropathy in **D**iabetics; LEADER, **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcome **R**esults; NAVIGATOR, **Na**teglinide and **V**alsartan in **I**mpaired **G**lucose **T**olerance **O**utcomes **R**esearch; NR, not reported; ONTARGET, **On**going **T**elmisartan **A**lone and in Combination With **R**amipril **G**lobal **E**ndpoint **T**rial; PAD, peripheral arterial disease; PREDIAN, **P**entoxifylline for **Re**noprotection in **Dia**betic **N**ephropathy; PREVEND-IT, **P**revention of **Re**nal and **V**ascular **End**stage Disease **I**ntervention **T**rial; PRONEDI, **Pro**gresion de **Ne**fropatia **Di**abetica; RAS, renin-angiotensin system; ROADMAP, **R**andomized **O**lmesartan **a**nd **D**iabetes **M**icro**a**lbuminuria **P**revention; SAVOR, **S**axagliptin **A**ssessment of **V**ascular **O**utcomes **R**ecorded in Patients with Diabetes Mellitus; sBP, systolic blood pressure; SCr, serum creatinine; T2DM, type 2 diabetes mellitus; TESTING, **T**herapeutic **E**valuation of **St**eroids in **I**gA **N**ephropathy **G**lobal; TRANSCEND, **T**elmisartan **R**andomised **A**ssessme**n**t **S**tudy in A**CE** Intolera**n**t Subjects With Cardiovascular **D**isease; UACR, urine albumin-to-creatinine ratio; UAE, urine albumin excretion; UKPDS, United Kingdom Prospective Diabetes Study Group; UPCR, urine protein-to-creatinine ratio; UPE, urine protein excretion.


Study
Treatment effect ratio (95% CI)
Cardiovascular disease
UKPDS-39 (1998) 0.85 (0.53 - 1.36)
IRMA2 (2001) 0.89 (0.36 - 2.21)
J-MIND (2001) 0.44 (0.14 - 1.39)
Fogari et al (2002) 0.90 (0.00 - 1274.84)
PREVEND IT (2004) 0.95 (0.12 - 7.65)
ONTARGET (2008) 1.06 (0.95 - 1.17)
TRANSCEND (2009) 1.22 (1.03 - 1.46)
CARDS (2009) 0.48 (0.31 - 0.75)
ROADMAP (2011) 1.21 (0.86 - 1.69)
FIELD (2011) 1.04 (0.89 - 1.22)
DEMAND (2011) 0.16 (0.03 - 0.85)
van Zuilen et al (2012) 1.07 (0.69 - 1.66)
SAVOR (2013) 1.21 (1.08 - 1.37)
PREDIAN (2015) 0.66 (0.26 - 1.63)
He et al (2016) 1.16 (0.72 - 1.85)
EMPA-REG (2016) 1.25 (1.03 - 1.51)
LEADER (2017) 1.17 (0.93 - 1.46)
CANVAS (2017) 1.18 (1.01 - 1.37)
NAVIGATOR (2017) 1.40 (1.17 - 1.67)
Overall 1.11 (1.01 - 1.22)
I²=51%,
P for hetero=0.005
End-stage renal disease
Zucchelli (1992) 0.66 (0.19 - 2.30)
Hannedouche (1994) 0.68 (0.09 - 5.16)
Donadio et al (1994) 0.36 (0.12 - 1.10)
GISEN-REIN-1 (1999) 0.57 (0.25 - 1.28)
Marin et al (2001) 0.99 (0.26 - 3.72)
Bolton et al (2004) 1.05 (0.56 - 1.99)
Endo (2006) 1.12 (0.43 - 2.94)
EFAAT (2007) 0.55 (0.22 - 1.39)
ONTARGET (2008) 1.33 (0.91 - 1.93)
TRANSCEND (2009) 0.93 (0.35 - 2.46)
FIELD (2011) 0.94 (0.52 - 1.69)
van Zuilen et al (2012) 1.00 (0.68 - 1.46)
Chen (2012) 0.43 (0.07 - 2.47)
Pozzi et al (2013) 0.45 (0.12 - 1.65)
PRONEDI (2013) 0.70 (0.24 - 2.06)
SAVOR (2013) 1.29 (1.04 - 1.61)
BARI-2D (2014) 1.41 (0.72 - 2.75)
DCCT (2014) 0.99 (0.42 - 2.33)
EMPAREG (2016) 0.82 (0.59 - 1.16)
LEADER (2017) 1.24 (0.84 - 1.83)
CANVAS (2017) 0.82 (0.63 - 1.07)
TESTING (2017) 0.64 (0.19 - 2.09)
NAVIGATOR (2017) 1.44 (0.57 - 3.67)
Overall 0.99 (0.88 - 1.13)
I²=9%,
P for hetero=0.337
All-cause mortality
UKPDS-39 (1998) 0.89 (0.57 - 1.37)
ABCD (2000) 0.51 (0.26 - 1.01)
Marin et al (2001) 0.98 (0.17 - 5.72)
Bolton et al (2004) 0.80 (0.27 - 2.41)
PREVEND IT (2004) 1.48 (0.16 - 13.70)
EFAAT (2007) 1.03 (0.30 - 3.56)
ONTARGET (2008) 1.16 (1.03 - 1.30)
CARDS (2009) 0.55 (0.34 - 0.89)
TRANSCEND (2009) 1.38 (1.15 - 1.67)
FIELD (2011) 1.28 (1.07 - 1.54)
ROADMAP (2011) 2.05 (1.06 - 3.97)
van Zuilen et al (2012) 1.04 (0.70 - 1.56)
SAVOR (2013) 1.32 (1.12 - 1.55)
DCCT (2014) 1.31 (0.91 - 1.89)
EMPAREG (2016) 1.07 (0.82 - 1.38)
He et al (2016) 1.24 (0.72 - 2.13)
NAVIGATOR (2017) 1.30 (1.05 - 1.61)
Voroneanu et al (2017) 0.55 (0.17 - 1.84)
CANVAS (2017) 1.19 (1.00 - 1.42)
LEADER (2017) 1.14 (0.90 – 1.45)
Overall 1.17 (1.07 - 1.28)
I²=35%,
P for hetero=0.060
0.3
0.5
1
2

review. From this review, 36 RCTs met the inclusion criteria. Table 1 summarizes the characteristics of the trials included. Study sizes ranged from 46 to 25,620 participants (135,661 participants in aggregate), with follow-up from 2 to 25 years. The mean age of study participants was between 27 and 67 years, with the proportion of male participants ranging from 40% to 81%. The mean eGFR (reported in 24 trials) ranged from 27 to 126 mL/min/1.73 m^2. Most trials were conducted in Canada, the United States, Europe, and Asia. Interventions were varied and included treatment of glomerulonephritis,[18-20] blood pressure-lowering therapies,[21-38] cholesterol-lowering therapies,[28,39,40] glucose-lowering therapies,[41-49] and other interventions including chemotherapy,[50] models of CKD care,[51] lead chelation,[52] and pentoxyfylline.[53] Of the 36 trials, 13 reported UACR, 12 reported daily urine protein excretion, 7 reported daily urine albumin excretion, 1 reported UPCR, and 3 reported categorical albuminuria.

The assessment of study risk of bias is summarized in Supplemental Table S2 and Supplemental Figure S1. Overall, there was adequate description of randomization in 47%, allocation concealment in 50%, intention-to-treat analysis in 75%, and loss of follow-up in 67%. These criteria were more consistently reported in trials in the past 10 years.

Change in proteinuria or albuminuria and outcomes

CV events. Twenty trials (109,200 participants and 14,048 events) were included in the meta-analysis. Of these, 10 trials assessed the effects of blood pressure-lowering interventions,[23,27,28,30,31,34-36,54-56] 3 assessed cholesterol-lowering therapies (**P**revention of **Re**nal and **V**ascular **End**-stage Disease **I**ntervention **T**rial [PREVEND-IT] assessed blood pressure and cholesterol-lowering therapies),[28,40,57] 5 assessed glucose-lowering therapy,[44-47,49] 1 assessed pentoxifylline use,[53] and 1 assessed CKD models of care.[51] Overall, the treatment effects on change in albuminuria and CV events were not consistent, and change in proteinuria or albuminuria overestimated the treatment effects on CV events (TER, 1.11; 95% CI, 1.01-1.22), with moderate heterogeneity ($I^2 = 51\%$; $P = 0.005$; Fig. 2).

ESRD. Twenty-three trials (99,889 participants) reported more than 10 ESRD events (1675 ESRD events total) and were included in the meta-analysis. Eight trials assessed blood pressure medication effects,[21,22,24,26,29,30,33,36,38,56] 2 assessed cholesterol-lowering therapies,[39,40] 7 assessed diabetic therapies,[41,43-47,58] 1 assessed models of CKD care,[51] 1 assessed immunosuppression,[19] 1 assessed chemotherapy,[50] and 1 assessed lead chelation.[52] Overall, the treatment effects on proteinuria or albuminuria were largely consistent with treatment effects on ESRD (TER, 0.99; 95% CI, 0.88-1.13), with no evidence of significant heterogeneity ($I^2 = 9\%$; $P = 0.337$; Fig. 2).

Mortality. Twenty trials (109,215 participants) reported more than 10 deaths (a total of 8597 deaths). Eight trials assessed blood pressure-lowering therapy,[21,23,26,28-30,36,37,55,56] 3 assessed cholesterol-lowering therapies (PREVEND-IT assessed blood pressure and cholesterol-lowering therapies),[28,40,57] 8 assessed glucose-lowering therapies,[41,44-49,58] 1 assessed chemotherapy,[50] and 1 assessed CKD models of care.[51] We observed significant differences in the treatment effect on proteinuria and albuminuria compared with the treatment effect on all-cause mortality, with change in proteinuria and albuminuria overestimating the treatment effect on mortality (TER, 1.17; 95% CI, 1.07-1.28). There was evidence of moderate, although not statistically significant, heterogeneity across the TERs ($I^2 = 35\%$; $P = 0.06$; Fig. 2).

Subgroup analyses

For the outcome of CV events we observed significant heterogeneity in the TERs according to age (< 62 vs ≥ 62 years; P for heterogeneity $= 0.023$; Fig. 3). We also observed substantial differences in the TER according to baseline systolic blood pressure (< 140 vs ≥ 140 mm Hg), although statistical significance was not reached (P for heterogeneity $= 0.067$). There was no evidence of

Figure 2. Treatment effect on change of proteinuria or albuminuria, cardiovascular events, end-stage renal disease, and mortality. The treatment effect ratio is the ratio of the relative risks of the clinical outcome and the relative treatment effect on proteinuria or albuminuria; a treatment effect ratio value close to 1 indicates better agreement between the treatment effects. The size of the boxes for the treatment effect ratios represent the weight of each study. Where trials reported urine albumin-to-creatinine ratio (UACR; mg/mmol), this has been converted to proteinuria in grams per day (UACR mg/mmol was converted to protein excretion mg/d [UACR mg/mmol $\times$ 10 [10 is the conversion factor]); where trials reported urinary protein to creatinine ratio (UPCR; g/g), this has been converted to proteinuria in grams per day (UPCR g/g was converted to UPCR mg/mmol [UPCR mg/g $\times$ 0.1131 (0.1131 is the conversion factor)]), and UPCR mg/mmol was converted to protein excretion mg/d (UPCR mg/mmol $\times$ 8.83 [8.83 is the conversion factor]). ABCD, **A**ppropriate **B**lood Pressure **C**ontrol in **D**iabetes; ATTEMPT-CVD, **A** **T**rial of **Telm**isartan **Preven**tion of **C**ardiovascular **D**iseases; BARI-2D, **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation **2** **D**iabetes; CARDS, **C**ollaborative **A**tor**v**astatin **D**iabetes **S**tudy; CANVAS, **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy; CANVAS-R, CANVAS-Renal; CI, confidence interval; DCCT/EDIC, **D**iabetes **C**ontrol and **C**omplications **T**rial/**E**pidemiology of **D**iabetes **I**nterventions and **C**omplications; DEMAND, **De**lapril and **Ma**nidipine for **N**ephroprotection in **D**iabetes; EFAAT, **E**prosidate **f**or **A**A **A**myloidosis **T**rial; FIELD, **F**enofibrate **I**ntervention and **E**vent **L**owering in **D**iabetes; GISEN-REIN, Gruppo Italiano di Studi Epidemiologici in Nefrologia Ramipril Efficacy in Nephropathy; IRMA-2, **Ir**besartan in **Micro**albuminuria, Type 2 Diabetic Nephropathy; J-MIND, **J**apan **M**ulticenter **I**nvestigation of Antihypertensive Treatment for **N**ephropathy in **D**iabetics; LEADER, **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcome **R**esults; NAVIGATOR, **Na**teglinide and **V**alsartan in **I**mpaired **G**lucose **T**olerance **O**utcomes **R**esearch; ONTARGET, **On**going **T**elmisartan **A**lone and in combination with **R**amipril **G**lobal **E**ndpoint **T**rial; PREDIAN, **P**entoxifylline for **Re**noprotection in **Dia**betic **N**ephropathy; PREVEND-IT, **P**revention of **Re**nal and **V**ascular **End**stage Disease **I**ntervention **T**rial; PRONEDI, Progresion de Nefropatia Diabetica; ROADMAP, **R**andomized **O**lmesartan **a**nd **D**iabetes **Micro**albuminuria **P**revention; SAVOR, **Sa**xagliptin **A**ssessment of **V**ascular **O**utcomes **R**ecorded in Patients with Diabetes Mellitus; TESTING, **T**herapeutic **E**valuation of **St**eroids in **I**g**A** **N**ephropathy **G**lobal; TRANSCEND, **T**elmisartan **R**andomised **A**ssessmen**t** **S**tudy in A**CE** Intoleran**t** Subjects With Cardiovascular **D**isease; UKPDS, United Kingdom Prospective Diabetes Study Group.

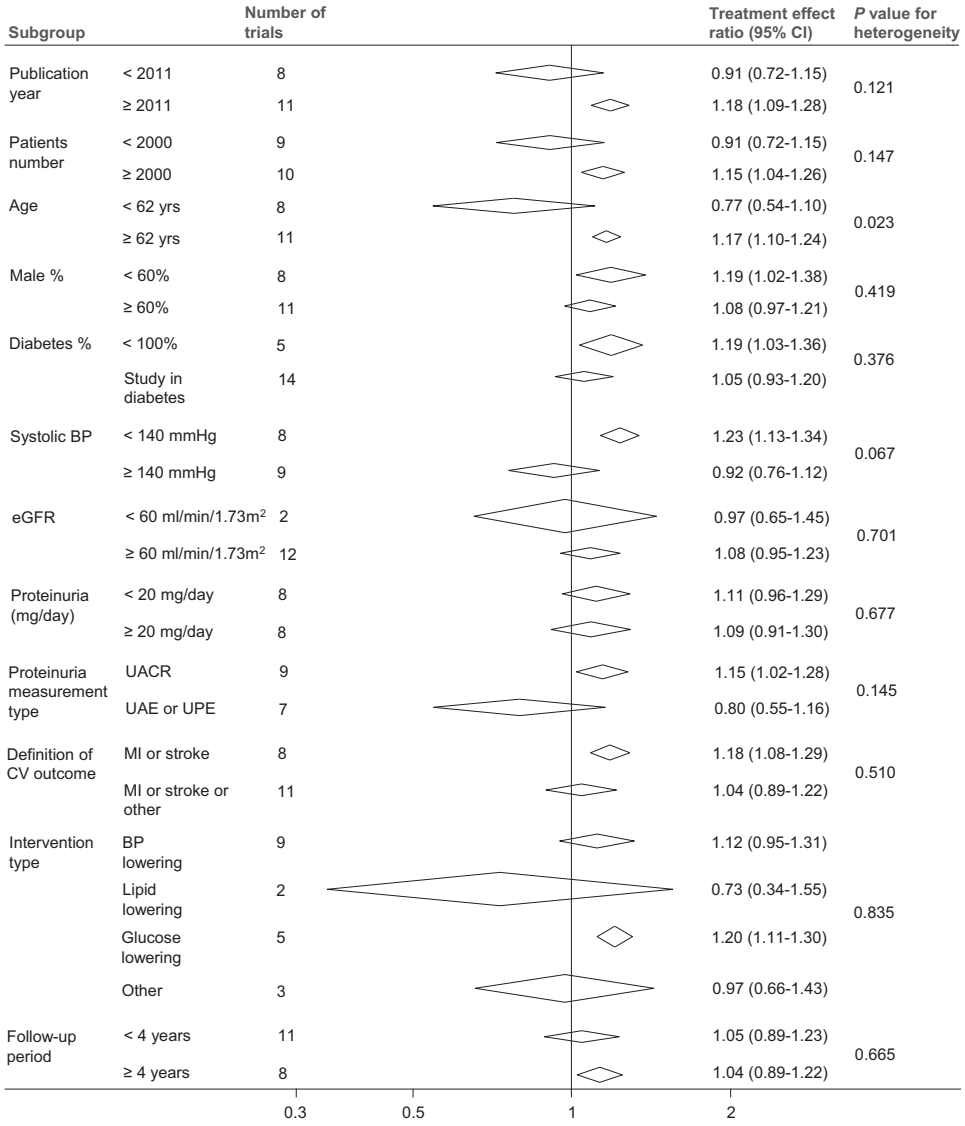


Figure 3. Subgroup analysis exploring the cardiovascular events meta-analysis. Heterogeneity was explored for the cardiovascular events outcome through subgroup analysis. Treatment effect ratios were pooled on the basis of subgroups and assessed for significant differences. BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; UACR, urine albumin-to-creatinine ratio; UAE, urine albumin excretion; UPE, urine protein excretion.

significant heterogeneity in the CV event TERs when trials were stratified according to publication year, trial size, sex, proportion of participants with diabetes, baseline eGFR, baseline proteinuria, type of proteinuria measure used, definition of CV outcome, intervention type, or follow-up period. We observed no evidence of significant heterogeneity in the TERs according to the assessed groupings for the outcomes of ESRD and all-cause mortality (Supplemental Figs. S2 and S3).

Publication bias

We analyzed included trials for publication bias for each of the clinical outcomes. There was evidence of potential publication bias for CV events (Egger test $P = 0.049$; Fig. 4A) and ESRD (Egger test $P = 0.028$; Fig. 4B). These results were unchanged when the "trim and fill" method was performed to account for this bias. There was no evidence of publication bias for the all-cause mortality outcome (Egger test $P = 0.186$; Fig. 4C).

Discussion

In our systematic review and meta-analysis we assessed the relationship between change in proteinuria or albuminuria and the risk of clinically important outcomes on the basis of RCTs across a range of interventions. Overall, our review indicates that the treatment effects for a range of interventions on change in proteinuria or albuminuria are generally consistent with the treatment effects on ESRD. However, we found that the treatment effects on change in proteinuria or albuminuria overestimated the treatment effects on CV events and all-cause mortality, suggesting uncertainty regarding the

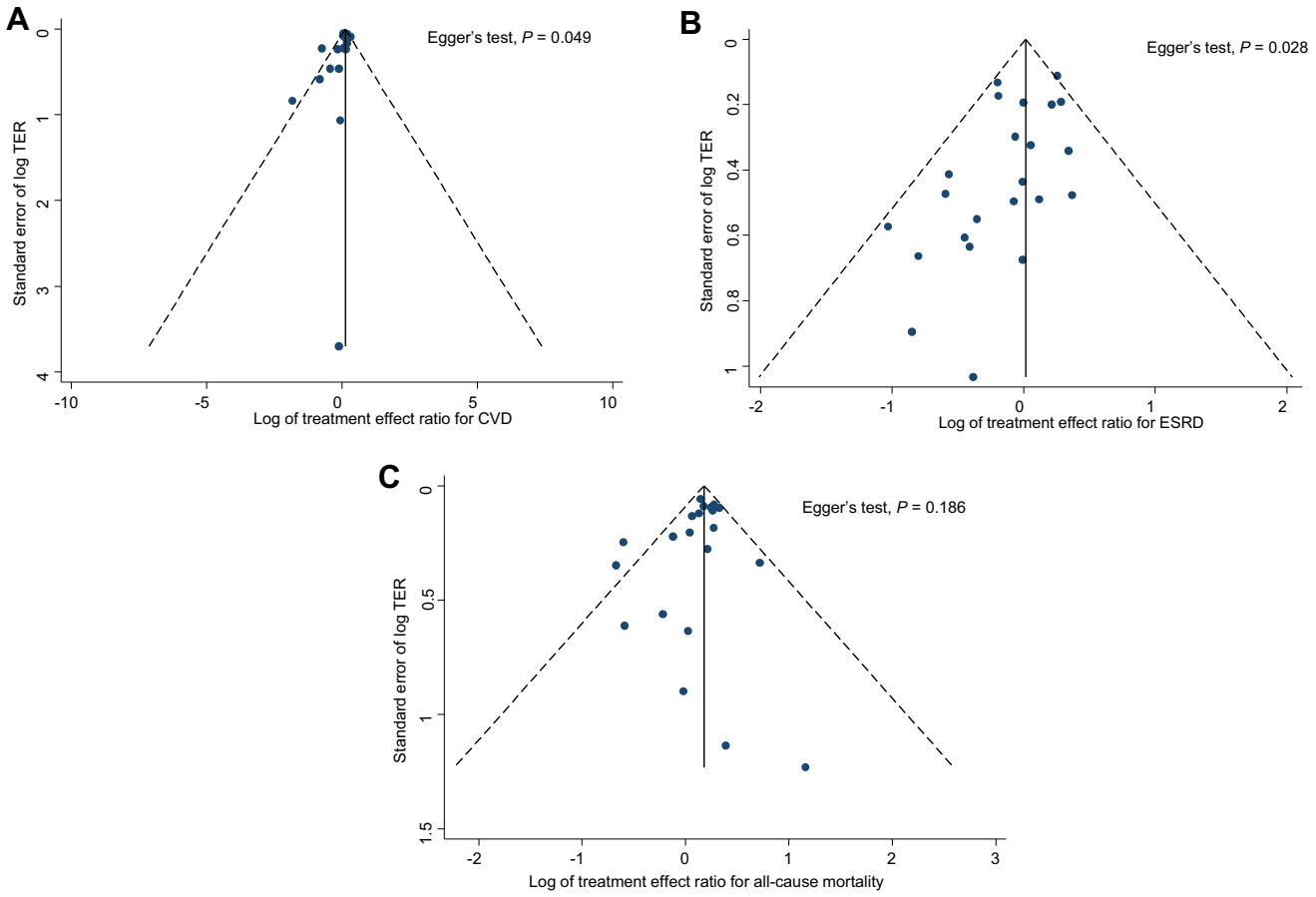


Figure 4. Assessment of publication bias for cardiovascular events, end-stage renal disease, and all-cause mortality outcomes. Publication bias was assessed using funnel plot analysis for (**A**) cardiovascular events, (**B**) end-stage renal disease (ESRD) events, and (**C**) mortality events. The Egger test was completed to assess for significance of publication bias. CVD, cardiovascular disease; TER, treatment effect ratio.

surrogacy of change in albuminuria for CV and mortality outcomes.

As part of outcome surrogacy validation there must be biological plausibility that the surrogate outcome is associated with the intended clinical outcome, which appears to be the case for proteinuria.[59] The widely accepted Steno hypothesis suggests that proteinuria as a marker of subclinical renal disease represents systemic endothelial dysfunction.[60,61] Changes in proteinuria have also been linked with high sensitivity troponin T, a marker of myocardial ischemia and necrosis.[62] Proteinuria has been linked to endothelial prothrombotic molecules, which are postulated to increase coronary thrombosis risk.[63-66] Additionally, experimental research has shown that proteinuria contributes significantly to tubulointerstitial injury and parenchymal fibrosis, which leads to progressive renal decline and ESRD, supporting the surrogacy of proteinuria.[67] In addition, the degree of proteinuria or albuminuria reduction has been suggested in some disease settings (type 2 diabetes, vascular disease) to correlate with reduced renal events and CV events,[1,68] although not in all populations.

Nonetheless, whereas proteinuria has been shown to be independently associated with adverse CV and renal outcomes,[9] the prognostic utility of measuring its change remains controversial. Three studies (secondary analyses of RCT data) have reported linear relationships between change in albuminuria and CV events (ie, decreased albuminuria predicted decreased risk of CV events and vice-versa).[1,69,70] For example, observational analysis of the **On**going **T**elmisartan **A**lone and in combination with **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET) and **T**elmisartan **R**andomised **A**ssessme**n**t **S**tudy in A**CE** I**n**tolerant Subjects With Cardiovascular **D**isease (TRANSCEND) trials suggested that a twofold or greater increase in albuminuria was associated with approximately 50% higher rate of mortality, increased CV events, and need for dialysis.[1] In contrast, a recent post hoc analysis of the **D**iabetes **C**ontrol and **C**omplications **T**rial/**E**pidemiology of **D**iabetes **I**nterventions and **C**omplications (DCCT/EDIC) study in type 1 diabetes reported that progression of albuminuria was associated with increased risk of CV events, but there was still an increase in risk of CV events when albuminuria remitted.[42] Similarly, in a post hoc observational analysis of the **Al**iskiren **T**rial **i**n **T**ype 2 Diabetes **U**sing Car**d**iorenal **E**ndpoints (ALTITUDE) trial, which examined the additional use of aliskiren with renin-angiotensin system blockade in diabetic patients with CKD or CV disease, reduction in albuminuria was associated with significantly reduced risk of ESRD but not CV events, whereas increasing albuminuria was associated with an increased risk of ESRD.[71] It is with these often conflicting

results that there is interest in investigating the controversial role of changing proteinuria as a surrogate outcome in clinical trials for often distant outcomes like CV events, progression to ESRD, and mortality, as we have investigated in this study.[72-77]

Although previous evidence supports the potential utility of change in proteinuria or albuminuria as a surrogate for CV events, our data suggest that further validation is required. Previous meta-analyses[6,7] have not assessed the association between change in proteinuria or albuminuria and CV events. Further, our subgroup analyses for CV events revealed significant heterogeneity in trials according to average age at baseline, suggesting that change in proteinuria or albuminuria might not be a useful surrogate for CV events in older adults, in whom it might overestimate the change in CV event incidence. Certainly, the progression of endothelial dysfunction and atherosclerotic vascular disease responsible for CV events is a chronic process. Vascular disease in older patients might be more advanced and less modifiable in conjunction with reductions in albuminuria alone. Additionally, our subgroup analysis suggests that in non-hypertensive populations the treatment effect of change in proteinuria or albuminuria on CV events might be overestimated. Recent literature has provided an example in support of this hypothesis, in that reductions in albuminuria were associated with an increase in CV events in a relatively young, normotensive population.[42] This evidence supports some arguments that in certain populations, targeting albuminuria might be deleterious to patient health.[76,77] Taken together, the absence of consistent treatment effects across all subgroups suggests that treatment effects on proteinuria or albuminuria alone might not uniformly predict subsequent risk of CV events. Further research might still be warranted to identify subpopulations or specific interventions in which proteinuria or albuminuria change could be valid surrogates for long-term CV events.

The surrogacy of change in proteinuria or albuminuria and ESRD outcomes has been explored in several recent systematic reviews and meta-analyses. Similar to our results, Heerspink et al. reported that short-term reduction in albuminuria by a drug-based intervention could be used as a surrogate for future development of ESRD in clinical trials.[7] A subsequent meta-analysis completed by Jun et al. assessed the validity of the potential surrogate outcomes of doubling of serum creatinine and change in albuminuria.[6] Although doubling of serum creatinine was deemed to be a good surrogate for ESRD, data on change in albuminuria was promising but limited by the critical paucity of trials reporting on this outcome. Palmer et al. completed a meta-analysis of 22 trials of blood pressure-lowering therapies, to examine the surrogacy of drug effects on proteinuria or albuminuria and drug effects on ESRD outcome. Their results did not suggest that drug effects on proteinuria or albuminuria would be good surrogates for ESRD, but were limited by a paucity of studies because of the inclusion of only blood pressure-lowering interventions, and unclear risk of bias.[10] Our current meta-analysis adds to the available evidence by including 17 new trials that assessed the ESRD outcome. With the breadth of included trials, our study had minimal heterogeneity and a pooled TER close to 1. Among recent meta-analyses, our study was unique by not restricting intervention type, and by including clinical outcomes other than progression to ESRD, including CV events and mortality.

Finally, we also found that treatment effects on proteinuria and albuminuria overestimated treatment effects on all-cause mortality. If we hypothesize that change in these urinary measures are acceptable surrogates for mortality, this result might represent a survival bias in the included trials, whereby the outcome of change in proteinuria or albuminuria for obvious reasons happens much earlier than death. Alternatively, change in proteinuria and albuminuria might not be a suitable surrogate outcome for mortality. This is the most plausible explanation, because the etiology of death can be diverse, and it is difficult to speculate that changing urinary proteins have a direct role (as a surrogate) in all cases.

There are limitations to our study. The inclusion criteria were intentionally broad, which led to inclusion of trials for which a change in proteinuria or albuminuria was not identified, and might have contributed to underestimation of the surrogacy. For example, this might be the case if an intervention was not directed at lowering proteinuria or albuminuria but the outcome was still reported (hence, no urinary protein change). It is also key to recognize, as shown by our subgroup analyses, that surrogacy of biomarkers is more clinically relevant when it is determined for specific interventions or populations. For example, there is more convincing biological plausibility that progression of proteinuria in hypertensive or diabetic kidney disease might be more predictive and causative in the development of clinical outcomes such as CV disease or ESRD.[60-62] In contrast to this, progression of proteinuria in kidney disease related to amyloidosis would not be as plausible as a biologically causative factor in CV events or mortality, for which outcomes are related to amyloid deposition in myocardial tissue.[78] Similarly, because most of the trials were not conducted specifically among people with CKD, we were unable conduct additional subgroup analyses according to primary cause of CKD. The method of urinary protein or albumin quantification is also a limiting factor. As per previous studies,[6,7,10] measures of urinary protein or albumin were transformed into 24-hour proteinuria to allow for comparison between studies. However, recent literature suggests that spot urine samples do not correlate strongly with 24-hour urine measures,[79] suggesting that there should be standardization of methods to measure proteinuria among trials that report this outcome. Finally, although the pooling of TERs is a useful method when assessing the surrogacy of an outcome across different interventions (as per previous studies),[6,80] its clinical utility might be limited, because the magnitude of difference in TERs (from 1) that reflect substantial disagreement has not been well established.

Conclusions

Overall, our meta-analysis raises concern for the prospect of using changing proteinuria or albuminuria levels as a clinical surrogate for CV events and mortality. There are several biological and clinical evidence-based limitations as identified in this current review, and further investigation into this possible relationship is needed. However, our systematic review and meta-analysis is congruent with and expands on previous work, and suggests that changing

proteinuria or albuminuria levels are a suitable surrogate outcome for ESRD.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.10.014.