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PHARMACODYNAMICS

Variability in response to albuminuria-lowering drugs: true or random?

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Keywords albuminuria, drug response, personalized medicine, precision medicine

AIMS

Albuminuria-lowering drugs have shown different effect size in different individuals. Since urine albumin levels are known to vary considerably from day-to-day, we questioned whether the between-individual variability in albuminuria response after therapy initiation reflects a random variability or a true response variation to treatment. In addition, we questioned whether the response variability is drug dependent.

METHODS

To determine whether the response to treatment is random or a true drug response, we correlated in six clinical trials the change in albuminuria during placebo or active treatment (on-treatment) with the change in albuminuria during wash-out (off-treatment). If these responses correlate during active treatment, it suggests that at least part of the response variability can be attributed to drug response variability. We tested this for enalapril, losartan, aliskiren, atrasentan and paricalcitol.

RESULTS

No correlation between the on- and off-treatment albuminuria change was observed in the placebo arm of all clinical trials ($R^2 < 0.01$). However, we observed significant associations between the on- and off-treatment response (R^2 0.14 to 0.57; all $P < 0.015$) for different albuminuria lowering drugs. Additionally, the albuminuria responses strongly correlated when the same individual was re-exposed to the same drug at the same dose: lisinopril 10 mg day^{-1} (R^2 = 53%; $P < 0.01$), losartan 50 mg day^{-1} (R^2 = 63%; $P < 0.01$).

CONCLUSION

The degree of albuminuria lowering with antialbuminuric drugs varies between patients. This variability in response appears drug-class independent. Identifying which factors determine this initial short-term variation in drug response appears important since the degree of albuminuria lowering is related to subsequent long-term renoprotection.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Individual patients show a wide range of responses to albuminuria-lowering drugs. Since albuminuria varies considerably from day-to-day we questioned whether this variability in response reflects a random variability or a true drug response.

WHAT THIS STUDY ADDS

- This study showed that the variable changes in albuminuria after start of albuminuria-lowering drugs can be separated from day-to-day fluctuations in albuminuria, indicating that individual drug responses can be adequately quantified in clinical trial settings. These data support further research into the factors that determine drug response in order to develop measures to overcome therapy resistance to albuminuria-lowering drugs. This is relevant since the initial effect of a drug on albuminuria is related to its long-term renal protective effect.

Tables of Links

TARGETS	
GPCRs [2]	**Enzymes** [4]
AT2 receptor	Angiotensin converting enzyme
Endothelin receptor	Renin
Nuclear hormone receptors [3]	
Vitamin D receptor	

LIGANDS	
Aliskiren	Irbesartan
Atrasentan	Losartan
Enalapril	Paricalcitol
Fosinopril	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2–4].

Introduction

Intervention in the renin–angiotensin system (RAS) is the cornerstone of treatment to delay progression of renal disease in both diabetic and nondiabetic chronic kidney disease. The effects of RAS intervention on slowing renal function decline vary to a considerable extent between patients, ranging from a complete arrest of renal function loss to no effect [5]. This between-patient response variability on renal outcome is also observed in the short-term response in the renal risk markers including albuminuria and blood pressure. In fact, the initial change in albuminuria is in many cases a good indicator for the ultimate renal protective effect of the drug [6, 7].

Changes in albuminuria over time, however, can also be the result of other factors not related to drug intervention. It is well known that albuminuria shows a substantial within-individual day-to-day variability that can be attributed to physical activity [8, 9], analytical factors, measurement variability [10], posture [11, 12] or fever [13]. These daily fluctuations hamper the accuracy of drug efficacy monitoring. It has been suggested that short-term changes in risk markers can be largely attributed to background variability in the risk marker rather than individual drug response variability thereby limiting the value of these measures in individual drug response monitoring [14]. However, this suggestion is based on secondary analyses of large multicentre trials and the conclusions may be biased by many factors such as changes in background medication over time, suboptimal drug adherence, and laboratory drift and variability over time.

To obtain more insight as to whether changes in albuminuria can be used to assess individual drug responsiveness unrelated to other factors, we analysed a series of clinical trials that tested the effects of different interventions on albuminuria. We first assessed the within-individual day-to-day variability in albuminuria in placebo arms of randomized controlled trials. Secondly, we determined whether the change in albuminuria following treatment initiation correlates with the change in albuminuria following treatment discontinuation in active and placebo groups of randomized controlled trials. We postulate that if these changes in albuminuria correlate in the active treatment group but not in the placebo group, variable drug response is real. Thirdly, we measured albuminuria changes in patients who were rechallenged to the same drug at the same dose, to validate a true drug response variation. Finally, we tested whether these findings are consistent when different albuminuria lowering drugs were used.

Methods

Data sources

Day-to-day variability in albuminuria. To assess the day-to-day variability in albuminuria we calculated the intraindividual coefficient of variation in the placebo arms of PREVEND-IT, BENEDICT, IRMA-2, and RENAAL clinical trials [15–18]. The characteristics of the included populations are described elsewhere. In brief, the trials included patients with type 2 diabetes and nondiabetes

with either normo-, micro- or macroalbuminuria. First morning voided urines were collected in all trials, except PREVEND-IT in which 24-h urine samples were collected, for assessment of albuminuria at baseline and every 6 months thereafter except in PREVEND-IT, in which albuminuria was measured at yearly intervals.

Between-individual drug response variability in albuminuria. To assess drug response variability in albuminuria we assessed the association in change of albuminuria directly after the initiation and cessation of drug treatment. To this end, we used the individual patient data of clinical trials that measured albuminuria in the first weeks after study treatment and drug discontinuation in six clinical studies. [15, 17, 19–22]. A systematic review of the literature was also conducted to identify additional studies. The search strategy and study flow diagram are described in supplement 1. Although a couple of additional studies were identified, we were unable to obtain the individual patient data. The study protocols of all included studies were approved by independent ethics committees. All participating patients signed informed consent before any study specific procedure commenced. Four studies tested the effect of RAS intervention, one the effect of an endothelin receptor antagonist, and another a vitamin D receptor antagonist. Four studies had a parallel design and two studies a cross-over design. Four studies had a follow-up ranging between 4 and 24 weeks, whereas follow-up was 2 and 4 years in two other studies. Albuminuria was the primary surrogate end point in all trials. Albuminuria was measured 4 weeks after treatment discontinuation in all studies except in one study in which it was measured 12 weeks after treatment discontinuation. Albuminuria or proteinuria was measured in 24-h urine collections in three studies, and in the remaining four studies the albumin to creatinine ratio was measured in first morning void urine collections.

We identified one clinical study to investigate the consistency in drug response exposing the same patient twice to the same dose of the same intervention. In that crossover study, nondiabetic proteinuric patients were exposed twice to 6-week treatments to either losartan 50 mg day^{-1} or lisinopril 10 mg day^{-1} [23].

Statistical analysis. Continuous variables are described as mean and standard deviation, or median and 25^{th} to 75^{th} percentile. Categorical variables are presented as proportions or ratios. Albuminuria was log-transformed before analysis to take into account its nonparametric distribution and reported as geometric mean change. The within-individual coefficient of variation over time was calculated per individual as the standard deviation of three measurements divided by their geometric mean value. Kruskal–Wallis was used with Dunn's *posthoc* test to determine statistical significance in the coefficient of variation in patients with normo-, micro- or macroalbuminuria. Deming regression was applied to assess the association between individual changes in albuminuria after treatment initiation and discontinuation. To determine what proportion of the variability in albuminuria could be attributed to response variability, Deming regression was used to assess the correlation in albuminuria responses when the same individual was exposed twice to the same drug at the same dose. In addition, we calculated the positive predictive value, negative predictive value and area under the receiver operator characteristic for a 40% and 50% reduction in albuminuria during the second treatment period using the responses in albuminuria during the first treatment period with the same drug–dose combination as predictor. The 40% and 50% thresholds were chosen since albuminuria decreased by 40–50% in this study. All analyses were conducted using StataSE version 13 for Windows. In all analyses, a *P*-value of <0.05 was used to reject the null hypothesis.

Results

Within-individual variability in albuminuria over time

To assess the day-to-day within-individual variability in albuminuria (without any drug intervention), we firstly calculated the within-individual coefficient of variation (CV) in

Table 1

Within-individual coefficient of variation of albuminuria at different time-intervals in the placebo arms of trials in nondiabetic and diabetic patients with high normo-, micro- or macroalbuminuria

Trial	*n*	Baseline albuminuria (mg g^{-1})	Time-interval (months)	CV(25^{th} – 75^{th} Percentile) (%)
PREVEND-IT	127	23	0–12-24	26.9 [16.2–45.5]
			24–36-48	25.0 [16.3–40.0]
BENEDICT	120	5.8	0–6-12	22.2 [13.6–39.6]
			12–18-24	20.0 [14.1–32.4]
			24–30-36	24.0 [17.6–43.3]
IRMA-2	125	53	0–6-12	35.7 [22.8–56.5]
			12–18-24	37.7 [26.5–57.5]
RENAAL	205	1013	0–6-12	34.9 [20.6–54.0]
			12–18-24	33.4 [20.5–50.4]
			24–30-36	35.5 [22.7–56.6]

albuminuria using all samples over the full length of the placebo arm in four different trials. In the overall population, the median within-individual CV in albuminuria was 31.8% over a 12-month time period (range between trials 20.0 to 37.7%, Table 1). The within-individual CV was consistent regardless of the period during which it was assessed. The within-individual CV was somewhat higher in patients with micro- or macroalbuminuria at baseline compared to those with normoalbuminuria (Table 1 and Figure 1).

Correlation between the initial and post-treatment albuminuria change

Secondly, to assess whether the change in albuminuria after drug initiation correlates with the change after drug discontinuation, we analyzed six randomized placebo-controlled trials that assessed the effects of various drugs on albuminuria. The baseline characteristics of the trials are reported in Table 2. In all trials active treatment significantly decreased albuminuria with mean reductions ranging from 19% to 59% (Table 3). Across all trials, the mean decrease in albuminuria after treatment initiation significantly correlated with the mean increase following treatment discontinuation (R^2 = 0.907; $P < 0.01$; Figure 2). Additionally, within each trial, the change in albuminuria following treatment initiation significantly correlated with the change in albuminuria after treatment discontinuation in the active treatment arms of each study except in the case of paricalcitol treatment (Table 3). These correlations remained statistically significant after adjustment for baseline blood pressure or changes in blood pressure. There was no statistically significant correlation in the placebo arms of all trials. In two additional trials in which patients with high normo- or microalbuminuria were followed for 2 and 4 years before treatment was discontinued, [15, 17] we also found that the initial albuminuria response significantly correlated with the response after drug discontinuation, although the correlation was weaker compared to the studies with shorter follow-up.

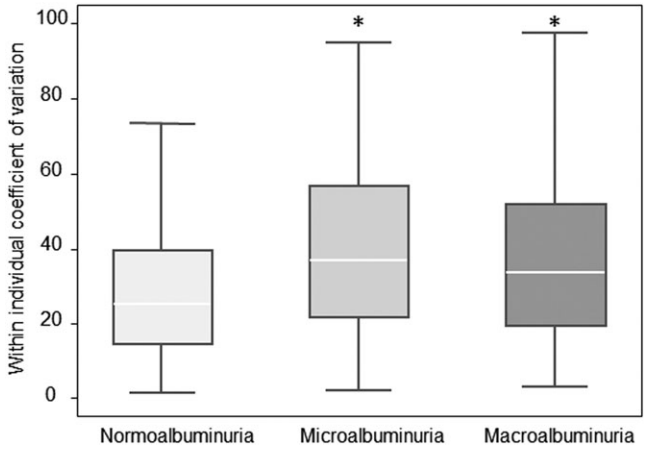

Figure 1

Within individual coefficient of variation higher in patients with micro- or macroalbuminuria compared to normoalbuminuria. * $P < 0.01$

Correlation in response after re-exposure

Thirdly, to further explore if the between-individual variability in response is related or unrelated to drug treatment, we analyzed a cross-over study in which 17 patients were exposed twice to the same intervention and calculated how much of the between patient variability at second exposure could be explained by the first exposure. [23] We observed that 53% and 63% of the between-individual variability in albuminuria following the second exposure to lisinopril 10 mg day^{-1} or losartan 50 mg day^{-1} was explained by the first exposure to these agents, respectively (Figure 3). The positive and negative predictive values of the first albuminuria response to predict a 40% reduction in albuminuria to losartan or lisinopril during the second exposure were 72.7% and

Table 2

Study characteristics

	Gansevoort (*n* = 11)	Persson (*n* = 19)	RADAR (*n* = 174)	VITAL (*n* = 140)	IRMA-2 (*n* = 73)	PREVEND-IT (*n* = 655)
Age, years	42.2 (12)	64.3 (7)	64.7 (9)	64.4 (10)	56.1 (9)	51.2 (11)
Female, *n* (%)	2 (18.2)	1 (5)	42 (24)	46 (33)	20 (27.4)	216 (33)
Albuminuria	4.6[a]	553 [180–746]	827 [465–1516]	567 [261–1114]	50 [30–80]	23 [16–43]
(e)GFR (ml min^{-1} 1.73m^{-2})	70.7 (17)	80.4 (23)	49.4 (14)	42.0 (18)	75.3 (13)	75.7 (12)
Systolic BP (mmHg)	153 (11)	136.6 (10)	136.5 (14)	140.9 (16)	151 (12)	130.2 (17)
Diabetes, *n* (%)	0 (0)	19 (100)	174 (100)	140 (100)	73 (100)	0 (0)
Intervention	ACEi / ARB(Enalapril 20 mg / Losartan 100 mg)	DRI (Aliskiren 150, 300, 600 mg)	ERA (Atrasentan 0.75, 1.25 mg)	VDRA (Paricalcitol 2 μg)	ARB (Irbesartan 150/300 mg)	ACEi (Fosinopril 20 mg)
Follow-up duration	4 weeks	4 weeks	12 weeks	24 weeks	2 years	4 years

[a]Proteinuria in 24-h urine collection; (e)GFR, (estimated) glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker, ERA, endothelin receptor antagonist; VDRA, vitamin D receptor antagonist; ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor

Table 3

Albuminuria response after start of treatment (on-drug response), albuminuria response after drug discontinuation (off-drug response), and correlation between on-drug and off-drug response within each trial

		Mean drug response after start and discontinuation						Correlation between on-and off-drug response			
Studies	***n***	**On-drug albuminuria response (%)**	**P25[a]**	**P75**	**Off-drug albuminuria response (%)**	**P25**	**P75**	**Regression coefficient**	***P*-value**	r^2	***r***
Macroalbuminuria: Gansevoort											
Losartan 100 mg	11	–49.2	–61.5	–20.9	39.3	31.1	47.4	–0.47	**0.015**	0.465	0.682
Enalapril 20 mg	11	–56.8	–69.2	–29.0	47.5	17.5	71.4	–0.79	**0.007**	0.569	0.754
Macroalbuminuria: Persson											
Placebo	19	–8.8	–44.6	32.9	–0.4	–40.0	19.3	–0.35	0.111	0.143	0.377
Aliskiren 150 mg	19	–42.7	–61.9	–28.4	36.9	12.0	56.5	–0.10	0.675	0.011	0.103
Aliskiren 300 mg	19	–54.6	–73.1	–7.1	50.0	14.0	68.5	–0.49	**0.005**	0.375	0.612
Aliskiren 600 mg	19	–59.4	–79.5	–21.4	55.4	35.6	77.8	–0.55	**0.001**	0.472	0.687
Macroalbuminuria: RADAR											
Placebo	46	2.8	–18.2	29.6	–4.5	–26.6	16.1	–0.08	0.514	0.009	0.095
Atrasentan 0.75 mg	64	–35.9	–51.2	–4.0	40.4	14.2	58.4	–0.44	<**0.001**	0.268	0.518
Atrasentan 1.25 mg	64	–40.7	–56.4	–15.9	36.6	10.9	49.1	–0.38	<**0.001**	0.142	0.377
Macroalbuminuria: VITAL											
Placebo	71	–7.1	–37.0	38.2	–9.1	–44.3	21.5	–0.03	0.77	0.001	0.035
Paricalcitol 2 μg	64	–18.8	–49.4	17.2	13.3	–19.7	40.5	–0.04	0.69	0.002	0.049
Normo/Microalbuminuira: PREVEND–IT											
Placebo	325	0.1	–21.0	29.0	1.2	–34.6	24.6	–0.04	0.574	0.001	0.032
Fosinopril 20 mg	330	–24.3	–45.7	2.0	23.5	–15.7	46.0	–0.13	**0.025**	0.015	0.122
Microalbuminuria: IRMA–2											
Placebo	29	20.2	0.0	60.8	11.8	–16.7	39.6	0.25	0.217	0.056	0.236
Irbesartan 150/300 mg	47	–37.3	–56.0	0.0	30.5	0.0	59.5	–0.47	**0.046**	0.085	0.292

[a]P25/P75 denotes the first and third quartile of the on-drug and off-drug response

71.4%, and the area under the receiver operating characteristic curve was 0.84. The positive predictive value, negative predictive value and area under the receiver operating characteristic curve to predict a 50% albuminuria reduction during re-exposure were 83.3%, 75.0%, and 0.78, respectively.

Finally, the correlation between the initial and post-treatment albuminuria change, as well as the correlation in response after re-exposure were consistent regardless of which drugs were used.

Discussion

Individual patients show a large variability in their albuminuria response after the initiation of treatment. Whether this variability represents a true response variability or a random variability unrelated to treatment was not previously studied. In this analysis of multiple trials determining the albuminuria-lowering effects of different classes of drugs in patients with and without diabetes we can detect a true marked response variation in albuminuria lowering to varying drugs between patients, despite within-individual fluctuations in albuminuria over time of around 25%. This variation is true as supported by several results: first, 50–60% of the variation after re-exposure to the same drug in the same patient can be explained by the variation during the first exposure. Second, the initial degree of albuminuria response appears to correlate with the change in albuminuria after drug discontinuation; even after several years, albuminuria returns to baseline values.

Two previous rotation studies have drawn similar conclusions using blood pressure instead of albuminuria data: blood pressure measurements fluctuate within an individual, blood pressure responses to antihypertensive drugs vary consistently between individuals, as evidenced by the finding that re-exposure to antihypertensive medication results in a similar blood pressure response at re-exposure [24–26]. An additional finding in these rotation studies was that patients who responded well to one class of drug responded poorly

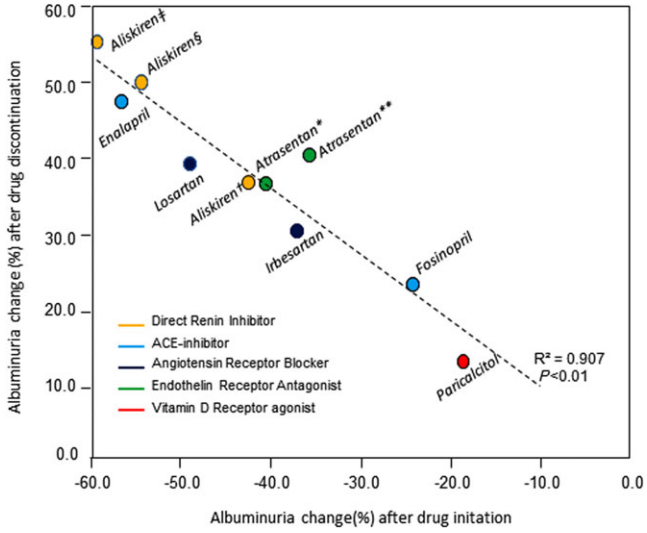

Figure 2

Correlation between the initial albuminuria response and response after drug discontinuation across trials. *Atrasentan 0.75 mg; **Atrasentan 1.25 mg; †Aliskiren 150 mg; ‡Aliskiren 300 mg; §Aliskiren 600 mg

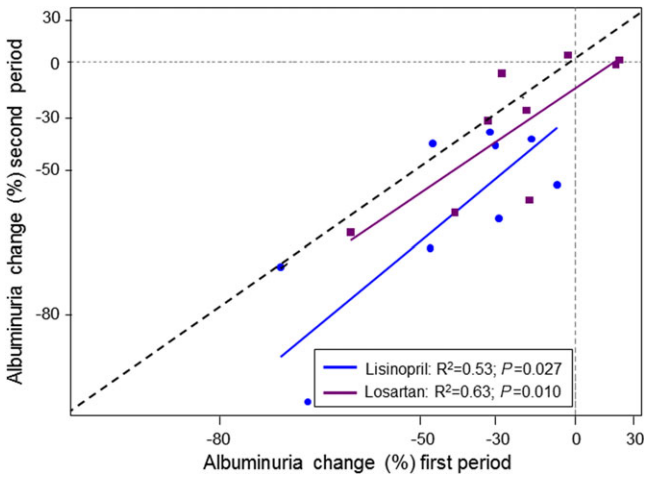

Figure 3

Albuminuria responses when the same individual is exposed twice to the same drug at the same dose

to another class of drug. This led to the Cambridge AB/CD rule for optimization of antihypertensive drugs because the individual responses to ACE-inhibitors and β-blockers correlated with each other and so did the responses to calcium antagonist and diuretics. We did see a clear difference in the average albuminuria lowering response to the different drugs tested in our different studies. However, since we did not expose each patient to multiple of these drugs, we cannot conclude whether there is an optimal drug for each patient.

A recent meta-analysis concluded that the evidence of between patient variability in blood pressure responses to ACE-inhibitors is weak [14]. This meta-analysis included multinational trials not designed to analyze between-individual drug response variability in contrast to prior prospectively designed rotation blood pressure trials [24]. Various factors such as therapy adherence, changes in background medication, and disease progression influence individual drug response. These factors may have biased the conclusion that most of the response variation to antihypertensive medication is due to within-individual day-to-day fluctuations in blood pressure.

What could explain the individual drug response variability? It is possible that the individual response in albuminuria is explained by individual blood pressure responses. However, this possibility is unlikely since previous studies have shown that the blood pressure and albuminuria response to RAS intervention within an individual are dissociated [27, 28]. In other words, some patients show a reduction in both blood pressure and albuminuria, but in other patients only blood pressure or albuminuria is reduced. Indeed, adjustment for individual changes in blood pressure in the current study did not alter our findings. Various other factors may be involved in individual differences in responsiveness to RAS-intervention, such as genetic factors [29], extracellular volume status [30] or the type and severity of renal disease. Using novel 'omic' and systems medicine network approaches provide new opportunities to understand the underlying determinants of drug response variability [31]. Additionally, imaging techniques to better characterize and visualize drug disposition *in vivo* may also provide new avenues to study determinants of drug response variability.

Prior studies have already shown that albuminuria shows substantial day-to-day variability [32]. We confirmed these findings and also showed in a large cohort that the individual day-to-day variability is consistent over time. In addition, we showed that the variability depends on the baseline albuminuria level such that the largest intraindividual albuminuria variability over time is observed in patients with microalbuminuria, while within-individual variations in albuminuria are smaller in the low or high albuminuria range.

The practical implication of our study is that clinicians should measure and monitor the initial response of each individual to albuminuria lowering intervention. The alternative of taking the average drug response observed in clinical trials is not recommended since a substantial part of the total between-individual variability in response could be attributed to drug response variability. If the reduction in albuminuria following intervention is insufficient, up-titrating the dose of the drug, moderation of dietary sodium intake or adding diuretic treatment to the therapeutic regimen may further lower albuminuria and potentially improve prognosis [33–35].

This study has limitations. First of all, we used data from several trials that were not designed to address our research question. Secondly, we were unable to include all clinical studies with an albuminuria treatment response and recovery period in our analysis due to inaccessibility of individual patient data. In addition, only one trial could be included that exposed the same individual twice to the same drug to assess whether individual drug responses on albuminuria are consistent. An ongoing trial (IMPROVE; Dutch trial registry NTR4439) is designed to prospectively study between-individual variability in drug response in albuminuria by multiple exposures. Another limitation is that plasma drug

levels were not available in four studies to verify that patients adhered to study medication.

In conclusion, the variable changes in albuminuria following drug initiation can be separated from the day-to-day within-individual variability in albuminuria, indicating that individual drug responses can be adequately quantified in a clinical trial setting. Monitoring for albuminuria responses is thus feasible and recommended in practice. The factors that determine drug response should be investigated in future studies, in order to develop measures to improve drug response in nonresponsive patients. This is of particular relevance since the initial effect of a drug on albuminuria is related to its long-term renal protective effect.

Competing Interests

S.P. reports no conflicts of interest. D.d.Z. is consultant for and received honoraria (to employer) from AbbVie, Astellas, Eli-Lilly, Chemocentryx, Fresenius, and Janssen. F.P. and P.R. are employed at Steno Diabetes Center, Gentofte, Denmark. Steno Diabetes Center is an independent academic institution owned by Novo Nordisk and The Novo Nordisk Foundation. F.P. reports having received research grants from Astra Zeneca, lecture fees from Astra Zeneca, MSD, Janssen, Lily, Boehringer Ingelheim, Novo Nordisk, Novartis and being consultant/advisory board member for Astra Zeneca and MSD. P.R. received lecture fees from Novartis and Boehringer Ingelheim, and research grant from Novartis, Astra Zeneca, Novo Nordisk and has served as a consultant for Merck, Astra Zeneca, Boehringer Ingelheim, MSD, AbbVie, Novo Nordisk and having equity interest in Novo Nordisk. R.T.G. is consultant and/or received honoraria (to employer) from Abbvie, Bayer, Genzyme, Ipsen, and Otsuka. H.J.L.H. is consultant for and received honoraria (to employer) from AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Janssen, Merck, and ZS-Pharma.

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Search strategy and selection criteria

We conducted a systematic review of the available literature to identify potential additional studies for inclusion in our analysis. Relevant studies were identified by searching Medline via Pubmed from 1950 up to November 2016). A literature search was conducted in the Medline database from 1966 to 8 November 2016. The search included medical subject headings as described below. The search was restricted to clinical trials. Reference lists of identified studies were manually scanned to identify any other relevant studies.

Medical subject headings

("Albuminuria/drug therapy"[Majr:noexp] OR "Proteinuria/drug therapy"[Majr:noexp]) AND ("Angiotensin Receptor Antagonists"[Mesh:noexp] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh:noexp] OR "Mineralocorticoid Receptor Antagonists"[Mesh:noexp] OR "aliskiren" [Supplementary Concept] OR "Endothelin Receptor Antagonists"[Mesh:NoExp] OR "Ergocalciferols/drug therapy"[Majr:NoExp] OR "Canagliflozin"[Majr:NoExp] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR "empagliflozin" [Supplementary Concept] OR "Receptors, CCR2/antagonists and inhibitors"[Majr:NoExp] OR "Receptors, CCR2/drug effects"[Majr:NoExp] OR "Phosphodiesterase 5 Inhibitors"[Mesh:NoExp] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh:NoExp]) AND "Clinical Trial" [Publication Type].

Study flow and selection

Figure S1 shows the study flow. We identified 230 potential studies through our search supplemented by three studies from other sources. We reviewed 26 full articles and obtained the individual patient data from six studies. We were unable to obtain the individual patient data from the other identified studies either because the investigators did not have the data anymore, or did not respond to our request to participate in our study.

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Appendix S1 Systematic review
Figure S1 Study flow