Acute Treatment Effects on GFR in Randomized Clinical Trials of Kidney Disease Progression

CKD-EPI Clinical Trials; Neuen, Brendon L.; Tighiouart, Hocine; Heerspink, Hiddo J.L.; Vonesh, Edward F.; Chaudhari, Juhi; Miao, Shiyuan; Chan, Tak Mao; Fervenza, Fernando C.; Floege, Jurgen

Published in:
Journal of the American Society of Nephrology

DOI:
10.1681/ASN.2021070948

Publication date:
2022

Acute Treatment Effects on GFR in Randomized Clinical Trials of Kidney Disease Progression

Brendon L. Neuen,[1] Hocine Tighiouart,[2,3] Hiddo J.L. Heerspink,[4] Edward F. Vonesh,[5] Juhi Chaudhari,[6] Shiyuan Miao,[6] Tak Mao Chan,[7] Fernando C. Fervenza,[8] Jürgen Floege,[9] Marian Goicoechea,[10] William G. Herrington,[11] Enyu Imai,[12] Tazeen H. Jafar,[13,14] Julia B. Lewis,[15] Philip Kam-Tao Li,[16] Francesco Locatelli,[17] Bart D. Maes,[18] Ronald D. Perrone,[6] Manuel Praga,[19] Annalisa Perna,[20] Francesco P. Schena,[21] Christoph Wanner,[22] Jack F.M. Wetzels,[23] Mark Woodward,[1,24] Di Xie,[25] Tom Greene,[26] and Lesley A. Inker[6] on behalf of CKD-EPI Clinical Trials*

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Acute changes in GFR can occur after initiation of interventions targeting progression of CKD. These acute changes complicate the interpretation of long-term treatment effects.

Methods To assess the magnitude and consistency of acute effects in randomized clinical trials and explore factors that might affect them, we performed a meta-analysis of 53 randomized clinical trials for CKD progression, enrolling 56,413 participants with at least one estimated GFR measurement by 6 months after randomization. We defined acute treatment effects as the mean difference in GFR slope from baseline to 3 months between randomized groups. We performed univariable and multivariable metaregression to assess the effect of intervention type, disease state, baseline GFR, and albuminuria on the magnitude of acute effects.

Results The mean acute effect across all studies was −0.21 ml/min per 1.73 m^2 (95% confidence interval, −0.63 to 0.22) over 3 months, with substantial heterogeneity across interventions (95% coverage interval across studies, −2.50 to +2.08 ml/min per 1.73 m^2). We observed negative average acute effects in renin angiotensin system blockade, BP lowering, and sodium-glucose cotransporter 2 inhibitor trials, and positive acute effects in trials of immunosuppressive agents. Larger negative acute effects were observed in trials with a higher mean baseline GFR.

Conclusion The magnitude and consistency of acute GFR effects vary across different interventions, and are larger at higher baseline GFR. Understanding the nature and magnitude of acute effects can help inform the optimal design of randomized clinical trials evaluating disease progression in CKD.

JASN 33: 291–303, 2022. doi: https://doi.org/10.1681/ASN.2021070948

A key challenge in the design and conduct of randomized controlled trials (RCTs) of CKD is that kidney failure typically develops over a long period of time, thus studies seeking to detect effects on this outcome require substantial follow-up time. As a result, there has been substantial effort from investigators, regulatory authorities, and sponsors toward identifying robust alternative endpoints for kidney failure, particularly for the early stages of CKD and for early-phase trials.[1–6]

A 2018 scientific workshop convened by the National Kidney Foundation, United States Food and Drug Administration, and European Medicines Agency evaluated the evidence for rate of change in GFR (*i.e.*, GFR slope) as an alternative endpoint for kidney disease progression in RCTs.[7] On the basis of two separate meta-analyses of observational cohorts and RCTs, the workshop concluded that treatment effects on GFR slope accurately predicted treatment effects

on clinical outcomes, indicating GFR slope may be a viable alternative endpoint for kidney disease progression. On the basis of these data, some ongoing studies are using GFR slope as an endpoint.[8–14] Interventions that affect CKD progression often produce early, short-term effects on GFR (referred to hereon in as acute effects) that differ from their long-term treatment effects (referred to hereon in as chronic slope), as, for example, are seen with agents that block the renin-angiotensin system (RAS) and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[15–18] The presence of acute effects may complicate the design and interpretation of RCTs in which GFR slope is the primary outcome. For example, negative acute effects may increase risk of falsely concluding no benefit, whereas positive acute effects may increase the risk of falsely concluding treatment benefit.

Although such acute effects are common, there is little understanding of them. We sought to describe the nature and magnitude of acute treatment effects on GFR in RCTs in which kidney disease progression was assessed, and evaluate the consistency of these effects across key study level characteristics, including intervention type, GFR, and albuminuria.

Significance Statement

GFR slope has been proposed as a surrogate endpoint for progression to kidney failure in clinical trials studying patients with CKD. Acute or immediate effects on GFR after treatment initiation may complicate the interpretation of long-term treatment effects. In this large meta-analysis of 53 randomized clinical studies of CKD progression, the authors found the magnitude and nature of acute effects are variable across different interventions and may be larger at a higher baseline GFR. Negative acute effects (such as an acute reduction in GFR) were observed in trials of renin-angiotensin system blockade and BP lowering, whereas positive acute effects were more common in trials of immunosuppressive therapies. Such information can inform the optimal design and analysis plan for randomized clinical trials in CKD.

METHODS

Datasets

As part of our previous work, we developed a pooled database of RCTs by performing a systematic literature search to identify relevant trials and obtaining individual participant data for these studies.[1,19–61] A complete list of search terms used is provided in Supplemental Table 1 and the study inclusion criteria are listed in Supplemental Table 2. Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration[62] (Supplemental Figure 1). As we have done previously, we included a separate randomized treatment comparison for each independent treatment versus control comparison for trials that evaluated more than one intervention, but unlike in our prior work, we did not pool small trials that had <100 participants if the disease and intervention were the same.[1,34,42–44,48,49,51–54,63–65] For this analysis, we excluded four RCTs that did not have at least one follow-up study visit at or before 6 months postrandomization.[63–66] The study was approved by Tufts Medical Center Institutional Review Board.

GFR

GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation.[67] Creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison, or was reduced by 5%, as has previously been described.[68]

Estimation of Acute Effects

Our primary definition of the acute treatment effect was the mean difference in the change in GFR from baseline to

Received July 14, 2021. Accepted October 28, 2021.

*The CKD-EPI Clinical Trials CKD-EPI investigators/collaborators are: AASK: Tom Greene; ABCD: Robert W. Schrier, Raymond O. Estacio; ADVANCE: Mark Woodward, John Chalmers, Min Jun; AIPRI (Maschio): Giuseppe Maschio, Francesco Locatelli; ALTITUDE: Hans-Henrik Parving, Hiddo JL Heerspink; Bari (Schena): Francesco Paolo Schena, Manno Carlo; Bologna (Zucchelli): Pietro Zucchelli, Tazeen H Jafar; Boston (Brenner): Barry M. Brenner; canPREVENT: Brendan Barrett; Copenhagen (Kamper): Anne-Lise Kamper, Svend Strandgaard; CSG (Lewis 1992, 1993): Julia B. Lewis, Edmund Lewis; EMPA-REG OUTCOME: Christoph Wanner, Maximilian von Eynatten; Groningen (van Essen): Paul E. de Jong, GG van Essen, Dick de Zeeuw; Guangzhou (Hou): Fan Fan Hou, Di Xie; HALT-PKD: Arlene Chapman, Vicente Torres, Alan Yu, Godela Brosnahan; HKVIN: Philip KT Li, Kai-Ming Chow, Cheuk-Chun Szeto, Chi-Bon Leung; IDNT: Edmund Lewis, Lawrence G. Hunsicker, Julia B. Lewis; Lecco (Pozzi): Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi, Donatella Casartelli; Leuven (Maes): Bart Maes; Madrid (Goicoechea): Marian Goicoechea, Eduardo Verde, Ursula Verdalles, David Arroyo; Madrid (Praga): Fernando Caravaca-Fontán, Hernando Trujillo, Teresa Cavero, Angel Sevillano; MASTERPLAN: Jack FM Wetzels, Jan van den Brand, Peter J Blankestijn, Arjan van Zuilen; MDRD Study: Gerald Beck, Tom Greene, John Kusek, Garabed Eknoyan; Milan (Ponticelli): Claudio Ponticelli, Giuseppe Montagnino, Patrizia Passerini, Gabriella Moroni; ORIENT: Fumiaki Kobayashi, Hirofumi Makino, Sadayoshi Ito, Juliana CN Chan; Hong Kong Lupus Nephritis (Chan): Tak Mao Chan; REIN: Giuseppe Remuzzi, Piero Ruggenenti, Aneliya Parvanova, Norberto Perico; RENAAL: Dick De Zeeuw, Hiddo JL Heerspink, Barry M. Brenner, William Keane; ROAD: Fan Fan Hou, Di Xie; Rochester (Donadio): James Donadio, Fernando C. Fervenz; SHARP: Colin Baigent, Martin Landray, William Herrington, Natalie Staplin; STOP-IgAN: Jürgen Floege, Thomas Rauen, Claudia Seikrit, Stefanie Wied; Strasbourg (Hannedouche): Thierry P. Hannedouche; SUN-MACRO: Julia B. Lewis, Jamie Dwyer, Edmund Lewis; Texas (Toto): Robert D. Toto; Victoria (Ihle): Gavin J. Becker, Benno U. Ihle, Priscilla S. Kincaid-Smith.

Published online ahead of print. Publication date available at www.jasn.org.

B.L.N. and H.T. are co-first authors.

Correspondence: Dr. Lesley A. Inker, Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02474. Email: LInker@Tuftsmedicalcenter.org

3 months between the treatment and control arms. The primary analysis used analysis of covariance to estimate the acute effect while adjusting for baseline GFR as a covariate. This analysis was restricted to studies with baseline GFR and at least one planned measurement of GFR between month 3 and month 6. For patients who had measurements at 4, 5, or 6 months, the acute effect was computed at that time. As we have previously performed, we categorized the observed mean acute effect (ml/min per 1.73 m^2) as very large negative (≤ -2.5), moderate-to-large negative (>-2.5 to <-1.25), small negative (-1.25 to <0), small positive (>0 to <1.25), moderate-to-large positive (1.25 to <2.5), and very large positive (≥ 2.5).[69] In a sensitivity analysis, we fitted a linear mixed effects model to GFR between months 3 and 24 of follow-up, with covariate adjustment for the baseline GFR level. This model includes fixed effects for treatment assignment, baseline GFR and the interactions of these factors with time, and random slopes and intercepts for characterizing variation in GFR trajectories across patients. For studies that had follow-up longer than 24 months, the follow-up time was truncated at 24 months to ensure the long-term trajectory did not overly influence the estimation of the acute effect. This sensitivity analysis was able to formally evaluate mean GFR change to 3 months, even if the initial GFR follow-up assessment occurred later than month 3, on the basis of the assumption of linear mean decline between months 3 and 24. With the exception of the analyses that related the size of the acute effects to baseline GFR and urinary albumin-creatinine ratio (UACR) levels (see below), acute effects were estimated on the basis of change in GFR on the linear (raw) scale and expressed in units of ml/min per 1.73 m^2.

Meta-analyses

We performed separate random effects meta-analyses to model the distribution of "true" treatment effects on the acute GFR change to 3 months across all studies, and then separately for subgroups of studies on the basis of intervention type. Our random effects models assumed the acute effects were normally distributed across studies. We used these models to obtain the mean acute effect across the studies included in each analysis, with a 95% confidence interval. In addition, to assess heterogeneity of acute effects between studies, we computed 95% coverage intervals from the mean and the between-study SD of the acute effects from the random-effects meta-analysis. The coverage interval provides lower and upper limits that included 95% of the acute effects across the studies, under the assumption that the acute effects are normally distributed.

We performed separate univariable metaregression analyses to explore the effect of mean baseline GFR and median baseline UACR on the magnitude of the acute effects across studies. For these analyses, we analyzed the longitudinal GFR measurements for estimation of the acute effect on both on the linear scale and natural log scale. When the longitudinal GFR measurements were expressed on the linear scale, the acute effect is expressed in absolute units of ml/min per 1.73 m^2. When the longitudinal GFR measurements were expressed on the natural log scale, the acute effect is expressed as a relative effect and expressed as a ratio of geometric mean GFR levels between the treatment and control groups. Median baseline UACR was log transformed in these analyses irrespective of whether the longitudinal GFR measurements were expressed on the raw scale or natural log scale. Baseline GFR was expressed on the linear scale when the longitudinal GFR measurements were expressed on the linear scale and on the natural log scale when the longitudinal GFR measurements were log transformed. In addition, to consider whether standard of care at the time of the study affected the magnitude of the acute effects, we also performed separate univariable metaregression analyses by year of publication.

We also performed multivariable metaregression to further assess the effect of baseline mean GFR and median UACR on acute effects after adjusting for intervention type, and diabetes status. In additional sensitivity analyses, we analyzed acute effects by quartiles of baseline GFR within individual studies to compare associations observed at the study and individual participant levels.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R 3.16.1 (R Project for Statistical Computing, www.r-project.org).

RESULTS

We included 53 randomized studies enrolling 56,413 participants that had at least one visit by 6 months after randomization. Aggregate characteristics of included studies stratified by intervention are summarized in Table 1, Supplemental Table 3 (stratified by disease), and Supplemental Table 4. The median baseline UACR was higher in trials with lower mean baseline GFR, except for immunosuppression studies (Supplemental Figure 2).

Acute Effects Overall and by Intervention

Across all studies, the mean acute effect (difference in GFR between randomized groups) was -0.21 ml/min per 1.73 m^2 over the first 3 months (95% confidence interval, –0.63 to 0.22). There was substantial heterogeneity across studies; the 95% coverage interval for the acute effect across studies ranged from –2.50 to +2.08 ml/min per 1.73 m^2 (Figure 1, Supplemental Table 5, Supplemental Figure 3, and Supplemental Figure 4). Results were similar in sensitivity analyses using the simple linear mixed models (Supplemental Table 5 and Supplemental Figure 5). For specific intervention types, there is evidence that RAS blockade versus calcium channel blockers (CCB), RAS blockade versus control,

Table 1. Clinical characteristics of the population overall and stratified by intervention

	N studies	*N* participants	Age	Female	Black	Diabetes	GFR	ACR
Overall	53	56413	61.5 (11.2)	22514 (37.4)	4601 (7.6)	45342 (75.3)	61.8 (26.3)	59 (13, 539)
Intervention								
RASB versus control	19	25157	61.7 (11.1)	9964 (37.9)	1720 (6.5)	22650 (86.1)	64.0 (23.8)	83 (14, 691)
RASB versus CCB	4	1884	57.6 (9.1)	832 (36.3)	862 (37.6)	1520 (66.3)	52.1 (20.5)	836 (105, 1983)
BP[a]	5	2438	51.0 (12.8)	1157 (40.4)	1235 (43.1)	435 (15.2)	55.9 (26.3)	68 (24, 393)
Diet[b]	2	731	51.8 (12.4)	332 (39.6)	66 (7.9)	43 (5.1)	34.5 (13.5)	192 (42, 904)
IS[a]	15	1039	41.7 (12.9)	407 (33.0)	19 (1.5)	4 (0.3)	72.1 (29.2)	1557 (898, 2814)
Other	8	25164	64.0 (9.1)	9822 (36.8)	699 (2.6)	20690 (77.4)	61.4 (28.3)	30 (9, 186)

Values for age and GFR are presented as mean (SD) and for ACR as median (25th, 75th percentile). Values for other characteristics are presented as number (%).The *N* participants presented here are for the primary analysis (analysis of covariance). RASB, renin angiotensin system blockers.
[a]BP, low versus usual BP control.
[b]Diet, low versus high protein diet.
[c]IS, various immunosuppression treatment versus control studies.

SGLT2 inhibitors versus placebo, and intensive BP lowering led to negative average acute effects, and that immunosuppressive agents led to a positive average acute effect (Figure 1, Supplemental Table 5, and Supplemental Figure 4), although in most cases statistical significance was not reached. The substantial variation in acute effects across different trials persisted within the individual treatment comparison classes (Supplemental Table 5 and Supplemental Figure 4), and by year of publication (Supplemental Figure 6). Heterogeneity was greatest among immunosuppression (95% coverage interval across studies, −2.34–6.29 ml/min per 1.73 m^2) and renin-angiotensin receptor blockers versus CCB trials (95% coverage interval across studies, −4.28–1.07 ml/min per 1.73 m^2).

Supplemental Table 6 shows the categories of large, moderate, or small observed mean acute effects overall and by intervention. Overall, moderate to large (>−2.5 to ≤−1.25 ml/min per 1.73 m^2) or very large (≤−2.5 ml/min per 1.73 m^2) negative acute effects were observed in 13 trials, moderate to large (≥1.25 to <2.5 ml/min per 1.73 m^2) or very large (≥2.5 ml/min per 1.73 m^2) positive acute effects were observed in 13 trials, and small positive or negative acute effects were observed in the remaining studies. Reflecting a combination of true variation in acute effects and random sampling error, which predominates in smaller trials, in these descriptive analyses negative acute effects were observed in four out of four studies comparing RAS blockade with CCBs, in 13 out of 23 studies comparing RAS blockade to control, in one trial comparing SGLT2 inhibitors to control, and four out of five trials of immunosuppressive agents. Positive acute effects were observed in 11 of the 15 trials of immunosuppressive agents (Supplemental Table 6).

Acute Effects by Baseline GFR

Larger negative acute effects (expressed in units of ml/min per 1.73 m^2) tended to be observed in studies with higher levels of mean baseline GFR (P=0.02; Figure 2). The association between the acute effect and baseline GFR remained mostly consistent after adjustment for intervention and diabetic status at the study level (Supplemental Table 7). For trials of RAS blockade versus control, the mean acute effect (SE) varied from 0.24 (0.36) when the mean baseline GFR was 20 ml/min per 1.73 m^2 compared with −1.57 (0.42), when mean baseline GFR was 80 ml/min per 1.73 m^2 (Figure 3). For trials comparing low versus usual BP

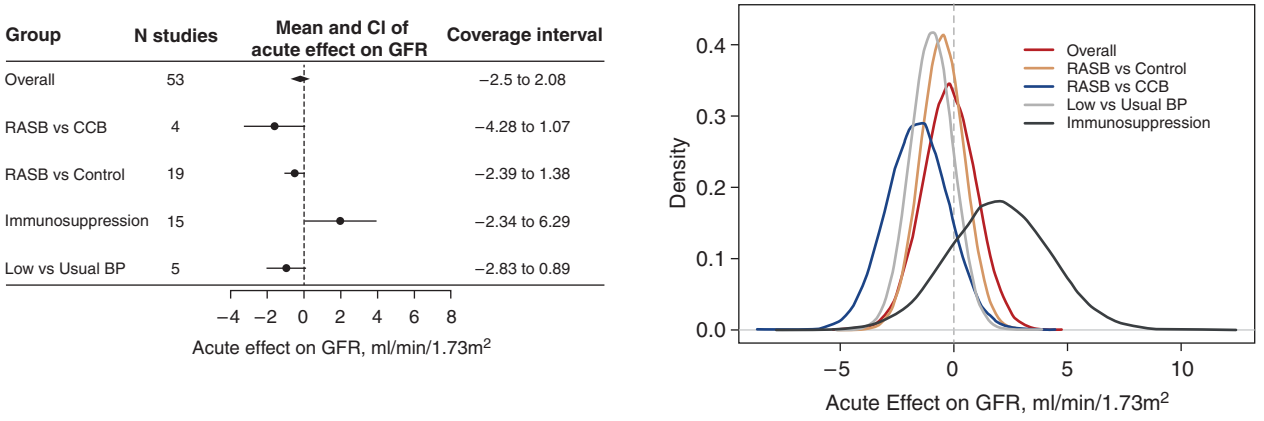


Figure 1. Distribution and estimated mean acute effect on GFR by intervention. Coverage interval refers to the interval under which 95% of the studies fall. 95% CI, 95% confidence interval; RASB, renin-angiotensin receptor blockers.

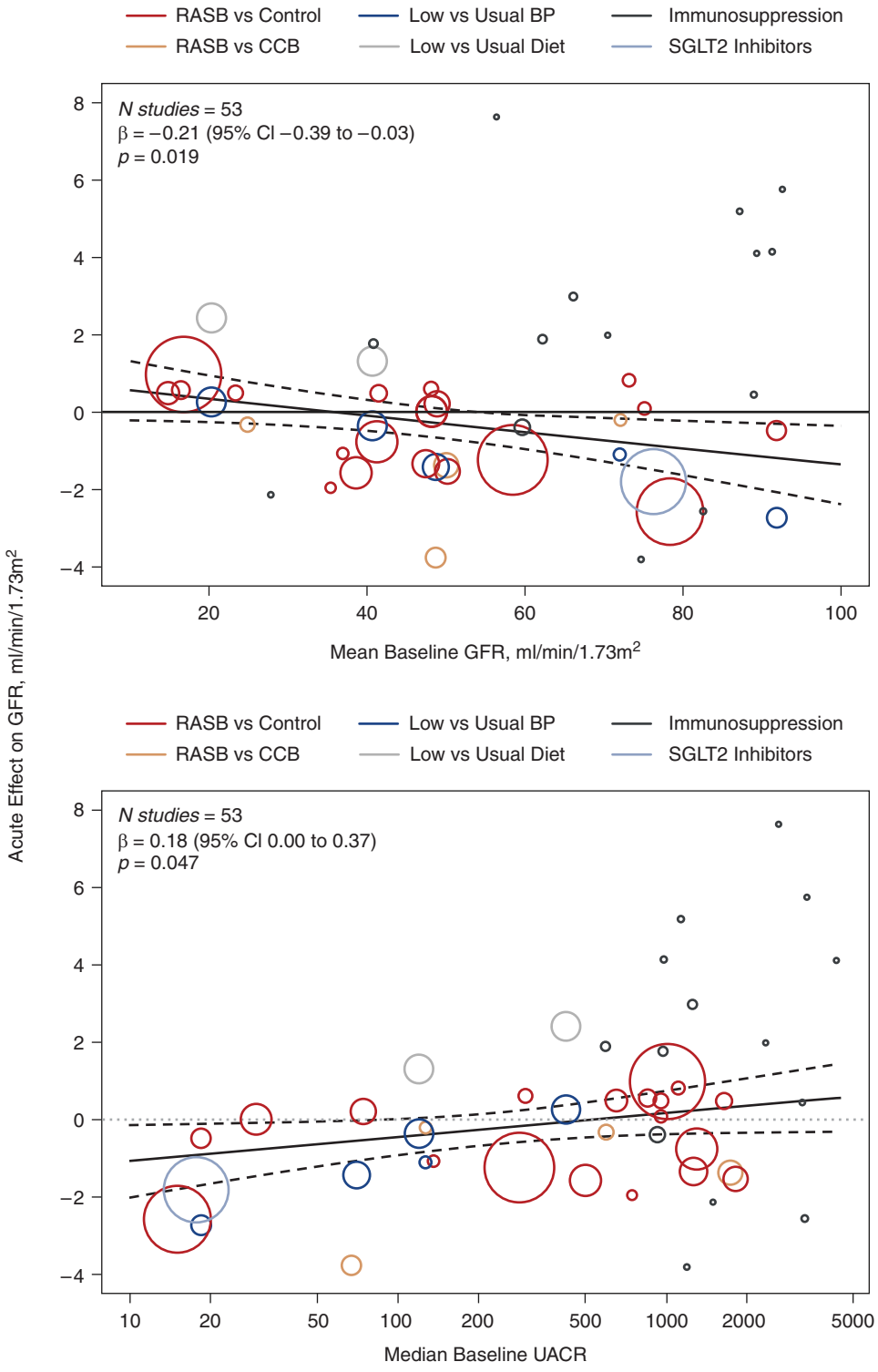


Figure 2. Meta regression of acute treatment effect on GFR by baseline GFR (top panel) and UACR (bottom panel). β refers to the coefficient for the slope through the meta-regression of the association of acute effects by mean baseline level of GFR in each study and is expressed per 10 ml/min per 1.73 m^2 higher levels of GFR. RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; SGLT2, sodium-glucose cotransporter-2; UACR, urine albumin: creatinine ratio.

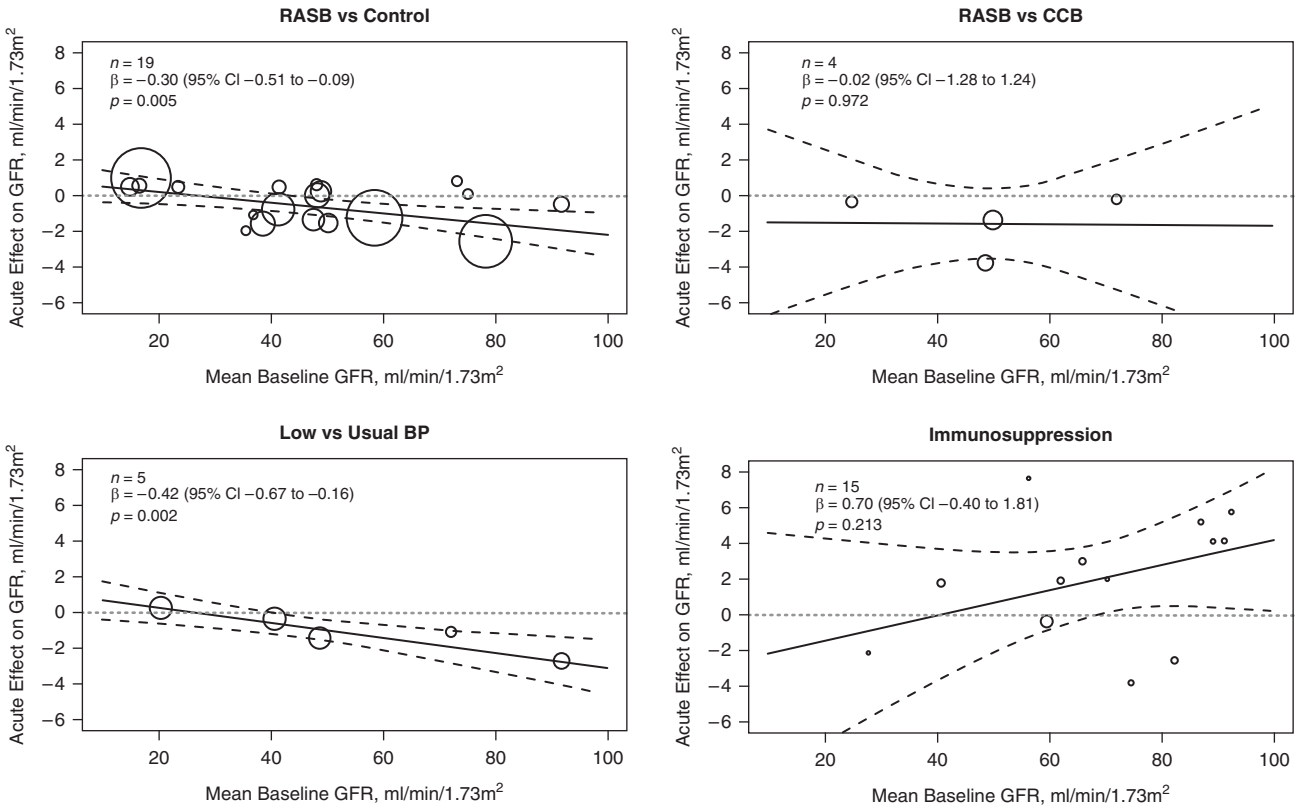


Figure 3. Meta regression plot of variation in acute effect on GFR according to baseline GFR by intervention. β refers to the coefficient for the slope through the meta-regression of the association of acute effects by mean baseline level of GFR in each study and is expressed per 10 ml/min per 1.73 m^2 higher levels of GFR. RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers.

control the mean acute effect varied from 0.24 (0.43) when mean baseline GFR was 20 ml/min per 1.73 m^2 compared with −2.25 (0.55) when mean baseline GFR was 80 ml/min per 1.73 m^2 (Figure 3). There was no clear association between the acute effect and mean baseline GFR for RAS blockade versus CCB or for immunosuppression trials (Figure 3), although the wide confidence bands indicate low statistical power for these analyses. The association between the acute effect and baseline GFR did not substantively change after removing trials of immunosuppressive agents (data not shown). The effect persisted when GFR was log transformed (Supplemental Figure 7 and Supplemental Figure 8). For RAS blockade versus control, there was a similar relationship between the acute effect and baseline GFR when participants were categorized by GFR quartiles within individual studies (Supplemental Figure 9).

Acute Effects by Baseline UACR

Acute effects were also somewhat more negative for studies with lower baseline UACR (Figure 2), although there was an attenuation of the effect after adjustment for baseline GFR (Supplemental Table 7). When stratified by intervention type, the association between the acute effect and baseline UACR was only observed in studies evaluating low versus usual BP targets, with no association observed between baseline UACR and the magnitude of acute effects for other interventions (Figure 4). Results were similar in sensitivity analyses when the acute effect was estimated on the basis of log transformed GFR (Supplemental Figure 7 and Supplemental Figure 8).

DISCUSSION

We provide a comprehensive assessment of the magnitude and consistency of acute treatment effects on GFR, across a range of interventions and disease states in 53 RCTs evaluating treatments for CKD progression. Negative acute effects were observed in the majority of RAS blockade, BP lowering, and SGLT2 inhibitor trials, whereas positive acute effects were observed in immunosuppression trials. However, even within interventions there was substantial variability in the observed acute effects. These findings have important implications for the design of clinical trials assessing kidney disease progression, and highlight the importance of understanding the nature and magnitude of acute effects for specific interventions in early-phase trials to inform the

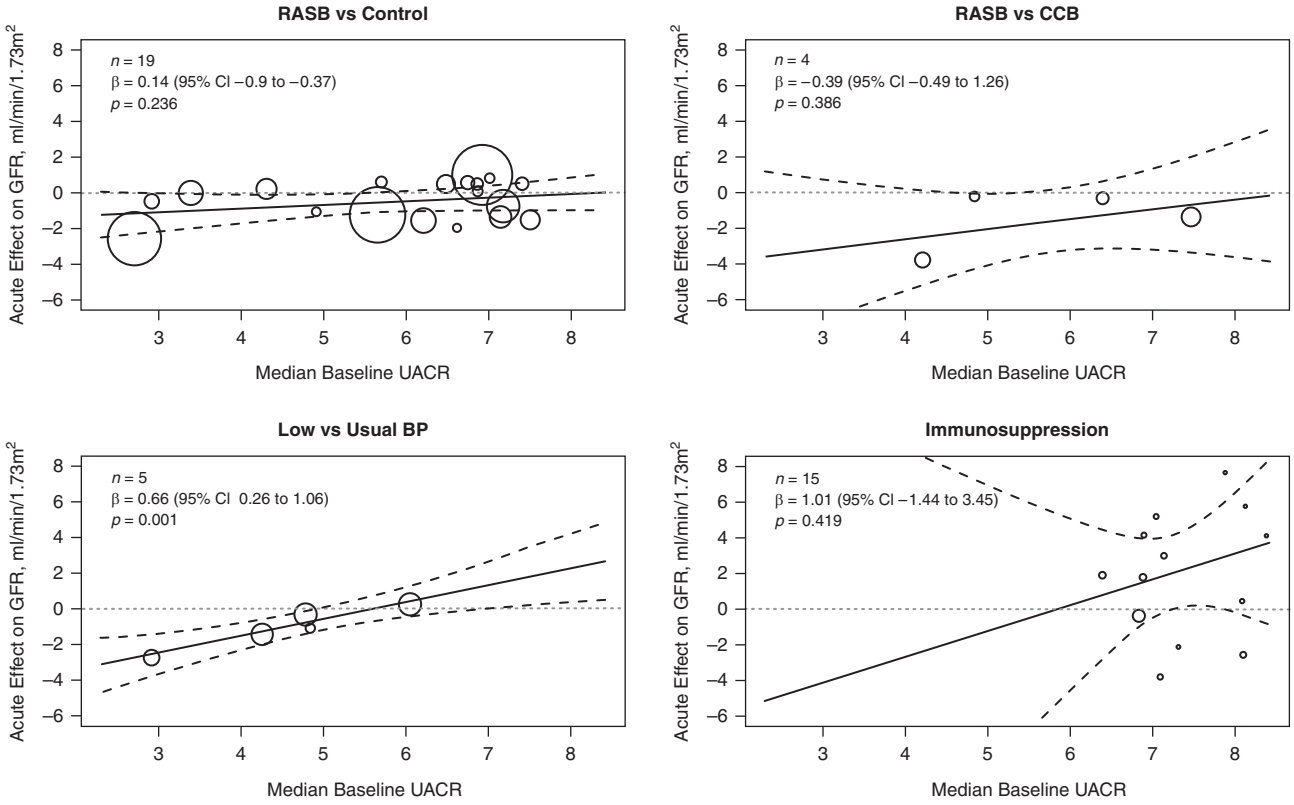


Figure 4. Meta regression plot of variation in acute effect on GFR according to UACR by intervention. β refers to the coefficient for the slope through the meta-regression of the association of acute effects by mean baseline level of GFR in each study and is expressed per 10 ml/min per 1.73 m^2 higher levels of GFR. RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; UACR, urine albumin: creatinine ratio.

design and analysis of longer-term studies, specifically, the decision to use a slope-based outcome or a clinical endpoint.

Negative acute effects are known to be common in interventions for CKD progression. For example, RAS blockade, SGLT2 inhibitors, and BP lowering all lead to hemodynamic changes in GFR, which are thought to differ from the long-term protective effect on the kidney. These hemodynamic effects influence the function of individual nephrons, not the number of nephrons, and are reversible on treatment discontinuation. Negative acute effects may also be a result of changes in non-GFR determinants of creatinine, as in, for example, decreased creatinine secretion by the tubules. Regardless of the mechanism, negative acute effects can increase the risk of false negative conclusions about the treatment benefit. Negative acute effects may also reduce the utility of slope-based analyses or time-to-event analyses, with endpoints defined by 30% or 40% GFR declines by eliminating power advantages of total GFR slope, or time to lesser GFR decline compared with the clinical endpoint.[69–71] In a *post-hoc* analysis of the CANVAS Program assessing the effect of the SGLT2 inhibitor canagliflozin on different GFR decline thresholds (*i.e.*, 50%, 40%, and 30% declines in GFR), the power advantage of using lesser declines in GFR was only observed after excluding the negative acute hemodynamic effect of canagliflozin.[72]

One potential solution to overcome negative acute effects and utilize slope as an endpoint is to use chronic (rather than total) GFR slope, which computes the change in GFR slope after the acute phase. However, this approach may introduce bias from attenuation of the acute effect over time or early discontinuation of the study treatment.[69,73,74] Another potential strategy is to assess GFR slope from baseline to off-treatment measures, when it is anticipated that acute and reversible hemodynamic effects will no longer be present. Ongoing trials of sparsentan and atrasentan in people with FSGS and IgA nephropathy plan to account for anticipated negative acute effects by employing both approaches: excluding the acute effect from baseline to week 6 and by assessing slope from baseline to 4 weeks off treatment.[9,10] A third approach would be to leverage an active run-in period to assign different baseline GFRs to the active and control arms. In the Efficacy and Safety of Selonsertib in Participants with Moderate to Advanced DKD (MOSAIC, NCT04026165) trial, testing the effects of selonsertib (which causes a negative acute effect by inhibiting creatinine secretion) in people with diabetic kidney disease, the GFR at the beginning of the run-in

period is taken as the baseline measure for placebo-treated participants, whereas the GFR at randomization is used as the baseline measure in the active treatment arm.[14] Finally, artificial censoring of GFR values after treatment discontinuation while using weighting or imputation to reduce the risk of selection bias may limit bias due to reversal of acute effects after treatment discontinuation.[69] As we have previously shown, if negative acute effects are relatively small (*e.g.*, <-1.5 ml/min 1.73 m^2), adequate statistical power can be achieved to detect treatment effects using total slope if there is sufficient follow-up relative to the mean rate of progression in the study population.[69]

We observed positive acute effects primarily in studies of immunosuppressive agents. The cause is not well understood, but it may be related to the early anti-inflammatory action of immunosuppressive agents in glomerular diseases, or the positive hemodynamic effect of steroids.[75] If an intervention has a positive acute effect but leads to harm on the longer-term chronic slope, then positive acute effects could lead to false conclusions about treatment benefits if assessment of the treatment effect is performed on the total GFR slope. Bardoxolone produces an early increase in GFR, which has been hypothesized to be due to an increase in mesangial surface area in addition to its longer-term effect on reducing inflammation.[76] Trials evaluating bardoxolone have computed change in GFR using off-treatment GFR values to help determine whether the positive acute effect is a false conclusion or a lasting effect of the drug on the kidney. This underscores the importance of understanding the mechanisms for earlier versus longer-term changes and designing trials accordingly.

The use of GFR slope to assess kidney disease progression may be particularly relevant to trials conducted in the early stages of CKD. The association between larger negative acute effects and higher baseline mean GFR remained significant after adjustment for intervention and diabetes status. Thus, studies seeking to use GFR slope should carefully consider the mechanism of action of an intervention, study design and population characteristics (for example, the proportions of participants recruited with different levels of GFR), to ensure efficiency, and protect against the risk of a falsely positive or negative conclusion. Additionally, trials using GFR slope as an outcome must also ensure sufficient information on safety, given the timeframes over which individuals with CKD are treated.

We observed a high degree of heterogeneity in the magnitude of acute effects, even within interventions where the nature and magnitude of the acute effect is anticipated due to well-understood mechanisms of action. The reason for this observation is unclear. Possible variation in study quality may be one explanation of the heterogeneity; indeed, there was greater heterogeneity among immunosuppressive studies, which in general were smaller, and of lower quality. Because the acute effect was defined as the difference in change in GFR between treatment and control arms, differences in the care in the control arm (*i.e.*, placebo versus active treatment) across different trials may have also contributed to the observed heterogeneity, although accounting for year of publication did not affect the results. Future work including newer studies with more consistent standard medical care in the control arm may help to evaluate this hypothesis. In addition, as we previously demonstrated, combined assessment of changes in GFR and albuminuria may predict treatment effects and outcomes better than either alone.[7] Further work will assess the utility of combined assessments of treatment effects on GFR slope and change in albuminuria that could overcome the challenges from acute effects.

This study has a number of strengths, including a systematic literature search, inclusion of a large number of studies with a diverse range of interventions, analyses of individual participant data, and the use of multiple methods to estimate acute GFR effects. However, a number of limitations should be considered when interpreting our findings. First, we estimated the acute effect at 3 months, but not all studies had measurements at this time point. For some studies, the acute effect might have occurred over a different time period and might not be linear. For example, the negative acute effect with SGLT2 inhibition calculated at 3 months is less than previously reported at 1 month, possibly due to an attenuation of the acute effect over time.[77,78] The timing of an acute effect is important to appreciate due to its implications for study power; as the timing of the acute effect increases, power to detect treatment effects on total slope decreases. Second, acute effects were calculated on the basis of estimated GFR rather than measured GFR; although potentially important at an individual level, this is less likely to affect our conclusions at a population level. Third, although these analyses examined the effect of intervention type, GFR and UACR individually on the observed acute effects, effects might be multifactorial and variation in acute effects could be due to other factors not captured. We also had relatively few studies for some interventions, including trials of SGLT2 inhibitors, and had no studies with pediatric participants. Finally, despite the large number of studies and participants overall, there were an insufficient number of trials to evaluate the magnitude of acute effects for individual classes of immunosuppressive agents with different mechanisms of action and to assess more granular subgroups, which could have explained the causes of the observed heterogeneity within these groups.

In summary, the magnitude and consistency of acute effects is variable across different interventions and may be larger at higher baseline GFR. Future work will involve understanding the timing of the acute effect and the associations of the acute effects with subsequent outcomes and longer-term treatments effects. Understanding the magnitude, timing and nature of the acute effect for a specific intervention and population can help inform the optimal design of randomized trials in CKD.

DISCLOSURES

B.L. Neuen reports having consultancy agreements with and receiving personal fees for advisory boards, scientific presentations, steering committee roles, and travel support from AstraZeneca, Bayer, and Janssen, all paid to institution. C. Wanner reports receiving personal fees from Boehringer-Ingelheim during the conduct of the study, and reports receiving personal fees from Astellas, AstraZeneca, Bayer, Chiesi, Eli-Lilly, Fresenius Medical Care, Merck Sharp & Dohme Corp., Sanofi-Genzyme, and Shire-Takeda outside the submitted work; reports having consultancy agreements with Akebia, Bayer, Boehringer-Ingelheim, Gilead, GlaxoSmothKline, Merck Sharp & Dohme Corp., Sanofi-Genzyme, Triceda, and Vifor; reports receiving research funding from Idorsia and Sanofi-Genzyme, grant to institution; and reports having other interests/relationships with the European Renal Association–European Dialysis and Transplant Association. D. Xie reports having other interests/relationships as an International Society of Nephrology member. E.F. Vonesh reports serving as a paid biostatistics consultant for the National Kidney Foundation for the express purpose of developing statistical models for use in the estimation and comparison of GFR slopes as a surrogate endpoint in CKD RCTs; reports serving as a biostatistics consultant to Prometic and Tricida, Inc., in which some of the work entailed consulting on the design and analysis of clinical trials in patients with CKD; and reports having consultancy agreements with Fresenius-Kabi, and Sarepta Therapeutics, Inc.; and reports other interests/relationships with the National Kidney Foundation. E. Imai reports receiving honoraria fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Daiichi Sankyo, and Eli-Lilly; and reports receiving research funding from AstraZeneca, Boehringer Ingelheim, and Tanabe Mitsubishi. F. Fervenza reports having consultancies with Alexion, Alnylam, BioCryst, GlaxoSmithKline Morphosys, Novartis, Otsuka, and Takeda; reports receiving research funding from Chemocentryx, Genentech, Janssen Pharmaceutical, Questcor/Mallinckrodt, and Retrophin; reports receiving honoraria from UpToDate; reports being a scientific advisor or member of Journal of the American Society of Nephrology, Kidney International, Nephrology, Nephrology Dialysis and Transplantation, and Up-To-Date. F. Locatelli reports receiving personal fees from Amgen, Astellas, Bayer, Baxter, Norgine, Otzuka, Roche, and Vifor Fresenius Pharma outside of the submitted work; reports having consultancy agreements with Amgen and Baxter; reports being a scientific advisor or member of Accelsior, Amgen, Astellas, AstraZeneca, GlaxoSmithKline, Norgine, Otsuca Roche, Travere, and Vifor Pharma; reports speakers bureau from Amgen, Astellas, and Roche; and reports having other interests/relationships with European Renal Association, Italian Society of Nephrology, Dialysis Outcomes and Practice Patterns Study, and Kidney Disease: Improving Global Outcomes. F.P. Schena reports receiving a grant from the University of Bari. H.J L. Heerspink reports having consultancy agreements with AbbVie, AstraZeneca, Bayer, Boehringer-Ingelheim, CSL Pharma, Chinook, Dimerix Fresenius, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, NovoNordisk, and Travere Pharmaceuticals; reports receiving research funding from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen (grant funding directed to employer); and reports speakers bureau from AstraZeneca. J.B. Lewis reports being a principal investigator in the study that contributed data to this analysis; reports current consulting fees from BIOVIE and CSL Behring; and reports being a scientific advisor or member of treasurer and board member of the Collaborative Study Group for a not-for-profit academic research organization. J. Floege reports receiving consultancy honoraria and/or speaker fees from Alnylam, Amgen, Astellas, AstraZeneca, Bayer, Calliditas, Fresenius, Omeros, Novo Nordisk, Travere, Visterra, and Vifor; and reports being a scientific advisor or member of Calliditas, Omeros, and Travere. J. Wetzels reports receiving grants from Amgen, Pfizer, and Sanofi; reports receiving other from Achillion, Shire, and Vifor Fresenius; reports having consultancy agreements with Novartis and Travere; reports receiving research funding from Alexion and Chemocentryx; reports receiving honoraria from Travere and UptoDate; reports being a scientific advisor or member of Kidney International; reports speakers bureau from Novartis; and reports having other interests/relationships with an Advisor Patient organization in the Netherlands. L.A. Inker reports receiving funding to institute for research and contracts with the National Institutes of Health, National Kidney Foundation, Reata Pharmaceuticals, Retrophin, Omeros, and Travere; reports having consulting agreements with Diamtrix, Omeros Corp., and Tricida Inc.; reports being a scientific advisor or member of Alport's Foundation, Diametrix, and Goldfinch; reports having other interests/relationships as a member of the American Society of Nephrology, National Kidney Disease Education Program, and National Kidney Foundation. M. Goicoechea reports receiving consultancy honorary and/or speaker fees from Alexion, Amgen, Astellas, AstraZeneca, Genzyme, Menarini, Novo-Nordisk, and Vifor. M. Praga reports receiving consultancy honoraria and/or speaker fees from Alexion, AstraZeneca, Novartis, Silence, and Travere; and reports receiving research funding from Amgen, Astellas, and Novartis. M. Woodward reports receiving personal fees from Amgen, Freeline, and Kyowa Kirin. P.K.T. Li reports receiving speaker honorarium (personal fees) from AstraZeneca, Baxter, and FibroGen; reports having consultancy agreements with (2019) Fibrogen, Co-Chair of advisory board Treatment of Anemia in Peritoneal, Dialysis Patients What is the Asia Pacific Experience; reports being a scientific advisor or member of Kidney International, Peritoneal Dialysis International, Co-Chair for Fibrogen Advisory Board Meeting on Anemia in Peritoneal Dialysis Patients (2019); and reports having other interests/relationships as Immediate Past President of Asian Pacific Society of Nephrology, President of International Association of Chinese Nephrologists, and President of Hong Kong College of Physicians. R.D. Perrone reports receiving personal fees from KluwersWolter, Otsuka, Palladiobio, Sanofi-Genzyme, and UpToDate; reports receiving research funding from Kadmon, Otsuka, Palladiobio, Reata, and Sanofi-Genzyme outside of the submitted work; reports having consultancy agreements with Caraway, Navitor, Otsuka, Palladiobio, Reata, and Sanofi-Genzyme; reports being a scientific advisor or member of Otsuka, PalladioBio, Sanofi-Genzyme, and Up-to-Date; and reports having other interests/relationships with the Polycystic Kidney Disease Foundation and UpToDate. T. Greene reports receiving grants from the National Kidney Foundation during the conduct of the study; reports receiving personal fees from DURECT Corporation, Janssen Pharmaceuticals, and Pfizer Inc. outside the submitted work; reports having consultancy agreements with AstraZeneca, Invokana, Janssen Pharmaceuticals, Pfizer Inc., and Novartis; and reports receiving research funding from AstraZeneca, Boehringer-Ingelheim, CSL, and Vertex. T.M. Chan reports receiving grants from Astellas, Baxter, and Kyowa Kirin; and reports having consultancy agreements with GSK, Novartis, and Visterra. W. Herrington reports being supported by a Medical Research Council Kidney Research UK Professor David Kerr Clinician Scientist Award, and reports receiving institutional grants from Boehringer-Ingelheim, British Heart Foundation, Eli-Lilly, and Health Data Research (UK); reports adhering to a department policy not to accept honoraria or other payments from the pharmaceutical industry, expect for the reimbursement of costs to participate in scientific meetings; and reports being a scientific advisor or member of Clinical Kidney Journal subject editor and the Nephrology Dialysis and Transplantation. All remaining authors have nothing to disclose.

FUNDING

The study was funded by the National Kidney Foundation.

ACKNOWLEDGMENTS

T. Greene, H. Heerspink, L. Inker, and E. Vonesh conceived of the study and design; T.M. Chan, F. C. Fervenza, J. Floege, M. Goicoechea, W.

Herrington, E. Imai, T. Jafar, J. Lewis, P. Li, F. Locatelli, B. Maes, R. Perrone, M. Praga, A. Perna, F. Schena, C. Wanner, J. Wetzels, M. Woodward, and D. Xie and their collaborators acquired the data; J. Chaudhari, T. Greene, S. Miao, H. Tighiouart, and E. Vonesh analyzed the data; all authors took part in the interpretation of the data; T. Greene, L. Inker, and B. Neuen drafted the manuscript; all authors provided critical revisions of the manuscript for important intellectual content; all collaborators who shared data were given the opportunity to comment on the manuscript; T. Greene, H. Heerspink, and L. Inker obtained funding for CKD-EPI, and the individual cohort support is listed in Supplemental Appendix 1. We thank all investigators, study teams, and patients for participating in the studies included in the meta-analysis. Study acronyms are listed in Supplemental Appendix 2 along with other abbreviations. A variety of sources have supported the RCTs included in the CKD-EPI Clinical Trials. These fundingsources include government agencies, such as the National Institutes of Health and medical research councils, and foundations and industry sponsors listed in Supplemental Appendix 1.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021070948/-/DCSupplemental.

Supplemental Appendix 1. Abbreviations, units, and terms.

Supplemental Appendix 2. Study funding sources.

Supplemental Table 1. Search terms.

Supplemental Table 2. Study inclusion criteria.

Supplemental Table 3. Clinical characteristics of the population overall and stratified by disease.

Supplemental Table 4. Patient characteristics by study.

Supplemental Table 5. Estimated acute effects using different methods to compute the acute effect on GFR, overall, and by intervention and disease.

Supplemental Table 6. Magnitude of acute effects on GFR, by intervention.

Supplemental Table 7. Multivariable metaregression of acute effects on GFR, both for GFR and ACR.

Supplemental Figure 1. Evaluation of bias in studies included in meta-analysis.

Supplemental Figure 2. Mean baseline GFR and median baseline UACR across studies.

Supplemental Figure 3. Distribution and estimated mean acute effect on GFR by disease.

Supplemental Figure 4. Forest plot of acute effect on GFR by intervention, all studies, ANCOVA method.

Supplemental Figure 5. Forest plot of acute effects on GFR by intervention, all studies, sensitivity analysis using the linear mixed model.

Supplemental Figure 6. Variation in acute effect on GFR by year of study publication.

Supplemental Figure 7. Meta regression plot of variation in acute effect by (A) baseline natural log-transformed eGFR and (B) natural log acute effect by UACR.

Supplemental Figure 8. Meta regression plot of variation in acute effect by intervention by (A) baseline natural log-transformed eGFR and (B) natural log acute effect by UACR.

Supplemental Figure 9. Variation in acute effect on GFR by within-study GFR quartiles, by intervention .

Supplemental References.

REFERENCES

1. Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, et al.: GFR slope as a surrogate end point for kidney disease progression in clinical trials: A meta-analysis of treatment effects of randomized controlled trials. *J Am Soc Nephrol* 30: 1735–1745, 2019
2. Grams ME, Sang Y, Ballew SH, Matsushita K, Astor BC, Carrero JJ, et al.: Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: An individual participant meta-analysis of observational data. *J Am Soc Nephrol* 30: 1746–1755, 2019
3. Heerspink HJL, Greene T, Tighiouart H, Gansevoort RT, Coresh J, Simon AL, et al.; Chronic Kidney Disease Epidemiology Collaboration: Change in albuminuria as a surrogate endpoint for progression of kidney disease: A meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol* 7: 128–139, 2019
4. Coresh J, Heerspink HJL, Sang Y, Matsushita K, Arnlov J, Astor BC, et al.; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration: Change in albuminuria and subsequent risk of end-stage kidney disease: An individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol* 7: 115–127, 2019
5. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al.: Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 311: 2518–2531, 2014
6. Levey AS, Inker LA, Matsushita K, Greene T, Willis K, Lewis E, et al.: GFR decline as an end point for clinical trials in CKD: A scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis* 64: 821–835, 2014
7. Levey AS, Gansevoort RT, Coresh J, Inker LA, Heerspink HL, Grams ME, et al.: Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: A scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis* 75: 84–104, 2020
8. Thompson A, Smith K, Lawrence J: Change in estimated GFR and albuminuria as end points in clinical trials: A viewpoint from the FDA. *Am J Kidney Dis* 75: 4–5, 2020
9. Barratt J, Rovin B, Diva U, Mercer A, Komers R; PROTECT Study Design Group: Implementing the Kidney Health Initiative surrogate efficacy endpoint in patients with IgA Nephropathy (the PROTECT Trial). *Kidney Int Rep* 4: 1633–1637, 2019
10. Komers R, Diva U, Inrig JK, Loewen A, Trachtman H, Rote WE: Study Design of the Phase 3 Sparsentan Versus Irbesartan (DUPLEX) study in patients with focal segmental glomerulosclerosis. *Kidney Int Rep* 5: 494–502, 2020
11. US National Library of Medicine: ClinicalTrials.gov. *Dabigatran vs Warfarin in AF Patients With T2D and CKD (RE-ELECT).* Available at: https://clinicaltrials.gov/ct2/show/NCT03789695. Accessed May 27, 2020
12. US National Library of Medicine: ClinicalTrials.gov. *Metformin vs Tolvaptan for Treatment of Autosomal Dominant Polycystic Kidney Disease (METROPOLIS).* Available at: https://clinicaltrials.gov/ct2/show/NCT03764605. Accessed May 27, 2020
13. Meijer E, Drenth JP, d'Agnolo H, Casteleijn NF, de Fijter JW, Gevers TJ, et al.; DIPAK Consortium: Rationale and design of the DIPAK 1 study: A randomized controlled clinical trial assessing the efficacy of lanreotide to Halt disease progression in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 63: 446–455, 2014
14. US National Library of Medicine: ClinicalTrials.gov. *Efficacy and Safety of Selonsertib in Participants with Moderate to Advanced Diabetic Kidney Disease (MOSAIC).* Available at: https://clinicaltrials.gov/ct2/show/NCT04026165. Accessed May 27, 2020
15. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, et al.: An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* 80: 282–287, 2011
16. Ohkuma T, Jun M, Rodgers A, Cooper ME, Glasziou P, Hamet P, et al.; ADVANCE Collaborative Group: Acute increases in serum

creatinine after starting angiotensin-converting enzyme inhibitor-based therapy and effects of its continuation on major clinical outcomes in Type 2 diabetes mellitus: The ADVANCE Trial. *Hypertension* 73: 84–91, 2019
17. Kraus BJ, Weir MR, Bakris GL, Mattheus M, Cherney DZI, Sattar N, et al.: Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int* 99: 750–762, 2021
18. Oshima M, Jardine MJ, Agarwal R, Bakris G, Cannon CP, Charytan DM, et al.: Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice. *Kidney Int* 99: 999–1009, 2021
19. Kamper AL, Strandgaard S, Leyssac PP: Effect of enalapril on the progression of chronic renal failure: A randomized controlled trial. *Am J Hypertens* 5: 423–430, 1992
20. Ihle BU, Whitworth JA, Shahinfar S, Cnaan A, Kincaid-Smith PS, Becker GJ: Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: A controlled double-blind trial. *Am J Kidney Dis* 27: 489–495, 1996
21. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al.: Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 354: 131–140, 2006
22. Hannedouche T, Landais P, Goldfarb B, el Esper N, Fournier A, Godin M, et al.: Randomised controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. *BMJ* 309: 833–837, 1994
23. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al.: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: A meta-analysis of patient-level data. *Ann Intern Med* 135: 73–87, 2001
24. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al.; The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334: 939–945, 1996
25. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al.: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 354: 359–364, 1999
26. van Essen GG, Apperloo AJ, Rensma PL, Stegeman CA, Sluiter WJ, de Zeeuw D, et al.: Are angiotensin converting enzyme inhibitors superior to beta blockers in retarding progressive renal function decline? *Kidney Int Suppl* 63: S58–S62, 1997
27. Wright JT, Jr., Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al.: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 288: 2421–2431, 2002
28. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al.; RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
29. Imai E, Chan JC, Ito S, Yamasaki T, Kobayashi F, Haneda M, et al.; ORIENT study investigators: Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. *Diabetologia* 54: 2978–2986, 2011
30. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al.; Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
31. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM; The Lupus Nephritis Collaborative Study Group: A controlled trial of plasmapheresis therapy in severe lupus nephritis. *N Engl J Med* 326: 1373–1379, 1992
32. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
33. Packham DK, Wolfe R, Reutens AT, Berl T, Heerspink HL, Rohde R, et al.; Collaborative Study Group: Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy. *J Am Soc Nephrol* 23: 123–130, 2012
34. Li PK, Leung CB, Chow KM, Cheng YL, Fung SK, Mak SK, et al.; HKVIN Study Group: Hong Kong study using valsartan in IgA nephropathy (HKVIN): A double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 47: 751–760, 2006
35. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, et al.; HALT-PKD Trial Investigators: Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med* 371: 2267–2276, 2014
36. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al.; HALT-PKD Trial Investigators: Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 371: 2255–2266, 2014
37. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al.; ALTITUDE Investigators: Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 367: 2204–2213, 2012
38. Patel A, MacMahon S, Chalmers J, MacMahon S, Chalmers J, Neal B, et al.: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New Eng J Med* 358: 2560–2572, 2008
39. Zucchelli P, Zuccalà A, Borghi M, Fusaroli M, Sasdelli M, Stallone C, et al.: Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 42: 452–458, 1992
40. Estacio RO, Jeffers BW, Gifford N, Schrier RW: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23[Suppl 2]: B54–B64, 2000
41. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al.; Modification of Diet in Renal Disease Study Group: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 330: 877–884, 1994
42. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al.: Corticosteroid effectiveness in IgA nephropathy: Long-term results of a randomized, controlled trial. *J Am Soc Nephrol* 15: 157–163, 2004
43. Pozzi C, Andrulli S, Pani A, Scaini P, Del Vecchio L, Fogazzi G, et al.; Multicenter Study Randomized Controlled Trial: Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. *J Am Soc Nephrol* 21: 1783–1790, 2010
44. Pozzi C, Andrulli S, Pani A, Scaini P, Roccatello D, Fogazzi G, et al.: IgA nephropathy with severe chronic renal failure: A randomized controlled trial of corticosteroids and azathioprine. *J Nephrol* 26: 86–93, 2013
45. Donadio JV Jr, Grande JP, Bergstralh EJ, Dart RA, Larson TS, Spencer DC; Mayo Nephrology Collaborative Group: The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. *J Am Soc Nephrol* 10: 1772–1777, 1999
46. Donadio JV Jr, Larson TS, Bergstralh EJ, Grande JP: A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. *J Am Soc Nephrol* 12: 791–799, 2001
47. Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al.; STOP-IgAN Investigators: Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med* 373: 2225–2236, 2015
48. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, et al.: Mycophenolate mofetil in IgA nephropathy: Results of a 3-year prospective placebo-controlled randomized study. *Kidney Int* 65: 1842–1849, 2004

49. Manno C, Torres DD, Rossini M, Pesce F, Schena FP: Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial Transplant* 24: 3694–3701, 2009
50. Chan TM, Tse KC, Tang CS, Mok MY, Li FK; Hong Kong Nephrology Study Group: Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 16: 1076–1084, 2005
51. Ponticelli C, Zucchelli P, Passerini P, Cagnoli L, Cesana B, Pozzi C, et al.: A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 320: 8–13, 1989
52. Ponticelli C, Zucchelli P, Passerini P, Cesana B; The Italian Idiopathic Membranous Nephropathy Treatment Study Group: Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. *N Engl J Med* 327: 599–603, 1992
53. Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, et al.: A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol* 9: 444–450, 1998
54. Ponticelli C, Passerini P, Salvadori M, Manno C, Viola BF, Pasquali S, et al.: A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. *Am J Kidney Dis* 47: 233–240, 2006
55. Praga M, Barrio V, Juárez GF, Luño J; Grupo Español de Estudio de la Nefropatía Membranosa: Tacrolimus monotherapy in membranous nephropathy: A randomized controlled trial. *Kidney Int* 71: 924–930, 2007
56. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al.; EMPA-REG OUTCOME Investigators: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373: 2117–2128, 2015
57. Goicoechea M, Garcia de Vinuesa S, Verdalles U, Verde E, Macias N, Santos A, et al.: Allopurinol and progression of CKD and cardiovascular events: Long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 65: 543–549, 2015
58. Hou FF, Xie D, Zhang X, Liang M, Guo ZJ, Jiang PJ: Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: A randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol* 18: 1889–1898, 2007
59. Peeters MJ, van Zuilen AD, van den Brand JA, Bots ML, van Buren M, Ten Dam MA, et al.: Nurse practitioner care improves renal outcome in patients with CKD. *J Am Soc Nephrol* 25: 390–398, 2014
60. Barrett BJ, Garg AX, Goeree R, Levin A, Molzahn A, Rigatto C, et al.: A nurse-coordinated model of care versus usual care for stage 3/4 chronic kidney disease in the community: A randomized controlled trial. *Clin J Am Soc Nephrol* 6: 1241–1247, 2011
61. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al.; SHARP Investigators: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet* 377: 2181–2192, 2011
62. Higgins J, Green S: *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed July 14, 2021
63. Praga M, Gutiérrez E, González E, Morales E, Hernández E: Treatment of IgA nephropathy with ACE inhibitors: A randomized and controlled trial. *J Am Soc Nephrol* 14: 1578–1583, 2003
64. Frisch G, Lin J, Rosenstock J, Markowitz G, D'Agati V, Radhakrishnan J, et al.: Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: A double-blind randomized controlled trial. *Nephrol Dial Transplant* 20: 2139–2145, 2005
65. Katafuchi R, Ikeda K, Mizumasa T, Tanaka H, Ando T, Yanase T, et al.: Controlled, prospective trial of steroid treatment in IgA nephropathy: A limitation of low-dose prednisolone therapy. *Am J Kidney Dis* 41: 972–983, 2003
66. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, et al.; REIN-2 Study Group: Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): Multicentre, randomised controlled trial. *Lancet* 365: 939–946, 2005
67. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
68. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD: Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. *Am Heart J* 162: 548–554, 2011
69. Greene T, Ying J, Vonesh EF, Tighiouart H, Levey AS, Coresh J, et al.: Performance of GFR slope as a surrogate end point for kidney disease progression in clinical trials: A statistical simulation. *J Am Soc Nephrol* 30: 1756–1769, 2019 10.1681/asn.2019010009
70. Greene T, Teng CC, Inker LA, Redd A, Ying J, Woodward M, et al.: Utility and validity of estimated GFR-based surrogate time-to-event end points in CKD: A simulation study. *Am J Kidney Dis* 64: 867–879, 2014 10.1053/j.ajkd.2014.08.019
71. Inker LA, Heerspink HJL, Vonesh EF, Greene T: Letter by Inker et al. Regarding Article, "Pitfalls in Using Estimated Glomerular Filtration Rate Slope as a Surrogate for the Effect of Drugs on the Risk of Serious Adverse Renal Outcomes in Clinical Trials of Patients With Heart Failure". *Circ Heart Fail* 2022 10.1161/CIRCHEARTFAILURE.121.008983
72. Oshima M, Neal B, Toyama T, Ohkuma T, Li Q, de Zeeuw D, et al.: Different eGFR decline thresholds and renal effects of canagliflozin: Data from the CANVAS Program. *J Am Soc Nephrol* 31: 2446–2456, 2020
73. McCausland Finnian R, Lefkowitz Martin P, Claggett B, Anavekar NS, Senni M, Gori M, et al.: Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation* 142: 1236–1245, 2020
74. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, et al.: Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction. *Circulation* 143: 298–309, 2021
75. Baylis C, Handa RK, Sorkin M: Glucocorticoids and control of glomerular filtration rate. *Semin Nephrol* 10: 320–329, 1990
76. Baigent C, Lennon R: Should we increase GFR with bardoxolone in Alport Syndrome? *J Am Soc Nephrol* 29: 357–359, 2018
77. Wanner C, Heerspink HJL, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, et al.; EMPA-REG OUTCOME Investigators: Empagliflozin and kidney function decline in patients with type 2 diabetes: A slope analysis from the EMPA-REG OUTCOME trial. *J Am Soc Nephrol* 29: 2755–2769, 2018
78. Neuen BL, Weldegiorgis M, Herrington WG, Ohkuma T, Smith M, Woodward M: Changes in GFR and albuminuria in routine clinical practice and the risk of kidney disease progression. *Am J Kidney Dis* 78: 350–360.e1, 2021

AFFILIATIONS

[1]The George Institute for Global Health, University of New South Wales, Sydney, Australia
[2]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts
[3]Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts
[4]Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, Netherlands
[5]Department of Preventive Medicine, Northwestern University, Chicago, Illinois
[6]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts
[7]Department of Medicine, University of Hong Kong, Pokfulam, Hong Kong
[8]Division of Nephrology and Hypertension and Department of Medicine, Mayo Clinic Rochester, Minnesota
[9]Division of Nephrology, RWTH Aachen University, Aachen, Germany
[10]Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[11]Medical Research Council Population Health Research Unit at the University of Oxford Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
[12]Nakayamadera Imai Clinic, Takarazuka, Japan
[13]Program in Health Services and Systems Research, Duke-NUS Medical School, Singapore, Singapore
[14]Duke Global Health Institute, Duke University, Durham, North Carolina
[15]Division of Nephrology, Vanderbilt University, Nashville, Tennessee
[16]Division of Nephrology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong
[17]Department of Nephrology, Alessandro Manzoni Hospital, ASST Lecco, Italy
[18]Department of Nephrology, AZ Delta, Roeselare, Belgium
[19]Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain
[20]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy
[21]Renal, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy
[22]Division of Nephrology, University Hospital of Würzburg, Würzburg, Germany
[23]Department of Nephrology, Radboud Institute for Health Sciences, Nijmegen, The Netherlands
[24]The George Institute for Global Health, Imperial College London, United Kingdom
[25]Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China
[26]Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, Utah

Acute treatment effects on GFR in randomized clinical trials of kidney disease progression

Supplementary tables and figures

Table of Contents

Appendix 1: Study funding sources

Study Name	Funding
AASK[1]	Supported by grants to each clinical center and the coordinating center from the National Institute of Diabetes and Digestive and Kidney Diseases. In addition, AASK was supported by the Office of Research in Minority Health (now the National Center on Minority Health and Health Disparities, NCMHD) and the following institutional grants from the National Institutes of Health: M01 RR-00080, M01 RR-00071, M0100032, P20-RR11145, M01 RR00827, M01 RR00052, 2P20 RR11104, RR029887, and DK 2818-02. King Pharmaceuticals provided monetary support and antihypertensive medications to each clinical center. Pfizer Inc., AstraZeneca Pharmaceuticals, Glaxo Smith Kline, Forest Laboratories, Pharmacia and Upjohn also donated antihypertensive medications.
ABCD[2]	Supported by Bayer and the National Institute of Diabetes, Digestive, and Kidney Diseases (DK50298-02)
ADVANCE[3]	ADVANCE was funded by grants from Servier and the National Health and Medical Research Council of Australia
ALTITUDE[4]	Supported by Novartis
Brenner[5]	Supported by Merck & Co.
CanPREVENT[6]	Supported by the Memorial University of Newfoundland
Chan[7]	Supported by the Wai Hung Charitable Foundation and the Mr & Mrs Tam Wing Fan Edmund Renal Research Fund
Donadio 2001[8]	Supported by research grants from Pronova Biocare a.s. (Oslo, Norway) and Mayo Foundation (Rochester, MN)
EMPA-REG OUTCOME[9]	Supported by Boehringer Ingelheim (BI) and Eli Lilly
Goicoechea[10]	Supported by REDINREN RD016/0019 FEDER funds
HALT-PKD A[11] and B[12]	Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK62410 to Dr. Torres, DK62408 to Dr. Chapman, DK62402 to Dr. Schrier, DK082230 to Dr. Moore, DK62411 to Dr. Perrone, and DK62401 to Washington University at St. Louis) and the National Center for Research Resources General Clinical Research Centers (RR000039 to Emory University, RR000585 to the Mayo Clinic, RR000054 to Tufts Medical Center, RR000051 to the University of Colorado, RR023940 to the University of Kansas Medical Center, and RR001032 to Beth Israel Deaconess Medical Center), National Center for Advancing Translational Sciences Clinical and Translational Science Awards (RR025008 and TR000454 to Emory University, RR024150 and TR00135 to the Mayo Clinic, RR025752 and TR001064 to Tufts University, RR025780 and TR001082 to the University of Colorado, RR025758 and TR001102 to Beth Israel Deaconess Medical Center, RR033179 and TR000001 to the University of Kansas Medical Center, and RR024989 and TR000439 to Cleveland Clinic), by funding from the Zell Family Foundation (to the University of Colorado), and by a grant from the PKD Foundation.
Hannedouche[13]	Supported by Merck Sharp & Dohme
HKVIN[14]	Supported by Novartis Pharmaceuticals (Hong Kong) Ltd by providing the study medication and placebo
Hou[15]	Supported by a National Nature and Sciences Grant for Major Projects (30330300) and a People's Liberation Army Grant for Major Clinical Research (to Dr. Hou) and in part by Novartis
IDNT[16]	Supported by the Bristol-Myers Squibb Institute for Medical Research and Sanofi–Synthelabo
Ihle/Kincaid[17]	Supported in part by Merck & Co, Inc., West Point, PA
Kamper[18]	Supported by Merck Sharp & Dohme
Lewis 1992[19]	Supported by grants (R01-AM-27769 and R01-AM-27770) from the Public Health Service
Lewis 1993[20]	Supported by grants from the Public Health Service (5 R01-DK 39908, 5 R01-DK 39826, MO1-RR00030, MO1-RR00034, MO1-RR00036, MO1-RR00051, MO1-RR00058, MO1-RR00059,

	and MO1-RR00425) and by the Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, N.J.).
Maes[21]	The study medication was kindly provided by Hoffmann-LaRoche, Basel, Switzerland
MASTERPLAN[22]	Supported by the Dutch Kidney Foundation, grant number PV-01, and the Netherlands Heart Foundation, grant number 2003B261. Unrestricted grants were providedby Amgen, Genzyme, Pfizer and Sanofi-Aventis
MDRD Study A[23] and B[23]	Supported by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK UO1 DK35073 and K23 DK67303, K23 DK02904). Funding for the MDRD Study included the formerly named Health Care and Financing Administration (HCFA); now the Center for Medicare and Medicaid Services.
ORIENT[24]	Supported by a research grant from Daiichi Sankyo
Ponticelli 1989[25]	Supported in part by a grant (82.01308.04) from the Consiglio Nazionale delle Ricerche.
Ponticelli 1998[26]	Supported in part by a grant from Ospedabc Maggiore di Milano
Ponticelli 2006[27]	This was a spontaneous clinical trial sponsored by the grant “Project Glomerulonephritis”
Pozzi 2004[28]	The authors did not receive any financial support
Pozzi 2010[29]	The authors did not receive any financial support
Pozzi 2012[30]	The authors did not receive any financial support
Praga 2007[31]	This study was partially supported by Astellas
REIN[32]	Supported in part by a grant from Aventis Pharma SA, Antony, France.
RENAAL[33]	Supported by Merck & Co.
ROAD[34]	Supported by a National Nature and Sciences Grant for Major Projects (30330300), a People's Liberation Army Grant for Major Clinical Research (2000), and National 11th Five-Years Plan Foundation (to F.F.H.)
Schena[35]	Supported in part by a grant of University of Bari
SHARP[36]	Funded by Merck & Co. and Schering Plough Corporation, which merged in 2009. Additional support was provided from the Australian National Health Medical Research Council, the British Heart Foundation and the Medical Research Council.
STOP- IgAN[37]	Supported by a grant (GFVT01044604) from the German Federal Ministry of Education and Research.
SUN- MACRO[38]	Sponsored by Keryx Biopharmaceuticals, Inc.
Toto[5]	By grant RO1 DK53869A from the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Levey); grant RO1 HS 10064 from the Agency for Healthcare Research and Quality (Dr. Schmid); a grant from Dialysis Clinic, Inc., Paul Teschan Research Fund 1097-5 (Dr. Jafar); New England Medical Center St. Elizabeth’s Hospital Clinical Research Fellowship, Boston, Massachusetts (Dr. Jafar); and an unrestricted grant from Merck Research Laboratories, West Point, Pennsylvania (Dr. Levey).
Van Essen[39]	Supported by Merck Sharp & Dohme, Haarlem, The Netherlands
Zucchelli[40]	None

Appendix 2: Abbreviations, units, and terms

AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints
ANCOVA	ANalysis of COVariance
BP	blood pressure
CanPREVENT	Canadian Prevention of Renal and Cardiovascular Endpoints Trial
CCB	calcium channel blockers
CKD	chronic kidney disease
Diet	low protein diet
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (referred to as EMPA-REG here on in)
ESKD	end-stage kidney disease
GFR	glomerular filtration rate (mL/min/1.73 m^2)
HALT-PKD	Halt Progression of Polycystic Kidney Disease study
HKVIN	Hong Kong study using Valsartan in IgA Nephropathy
IDNT	Irbesartan Diabetic Nephropathy Trial
IgA	immunoglobulin A nephropathy
Interv	intervention
IS	immunosuppresion
MASTERPLAN	Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners study
MDRD Study	Modification of Diet in Renal Disease study
N	sample size
NKF	National Kidney Foundation
ORIENT	Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial
RASB	renin-angiotensin system blockade
RCT	randomized controlled trial
REIN	Ramipril Efficacy In Nephropathy study
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
ROAD	Renoprotection of Optimal Antiproteinuric Doses study
SCr	serum creatinine (mg/dL)
SD	standard deviation
SE	standard error
SGLT2	Sodium-glucose co-transporter-2
SHARP	Study of Heart and Renal Protection
STOP-IgAN	Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy trial
SUN-MACRO	Sulodexide Macroalbuminuria trial
UACR	Urine albumin to creatinine ratio

Table S1. Search terms

Database: Ovid MEDLINE(R)

Search Strategy:

1 kidney disease$.mp. (112999)
2 chronic renal insufficiency.mp. (4302)
3 chronic kidney disease.mp. (21120)
4 renal disease.mp. (41875)
5 IgA nephropathy.mp. (4903)
6 lupus nephritis.mp. (6931)
7 diabetic nephropathy.mp. (12605)
8 glomerular disease.mp. (2168)
9 polycystic kidney disease.mp. (5535)
10 focal sclerosis.mp. (118)
11 membranous nephropathy.mp. (2402)
12 CKD.mp. (12820)
13 Hypertension/ and (renal or kidney).mp. (36281)
14 albuminuria.mp. (15383)
15 proteinuria.mp. (38350)
16 or/1-15 (222355)
17 randomized controlled trial.pt. (403784)
18 controlled clinical trial.pt. (89947)
19 randomized controlled trials/ (100110)
20 Random Allocation/ (85054)
21 Double-blind Method/ (132413)
22 Single-Blind Method/ (21138)
23 clinical trial.pt. (495584)
24 Clinical Trials.mp. or exp Clinical Trial/ (939562)
25 (clinic$ adj25 trial$).tw. (271601)
26 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (129554)
27 placebo$.tw. (159277)
28 Placebos/ (32953)
29 random$.tw. (710194)
30 trial$.tw. (636501)
31 (latin adj square).tw. (3512)
32 or/17-31 (1577197)
33 16 and 32 (23308)
34 limit 33 to (guideline or meta analysis or practice guideline or "review") (5907)
35 33 not 34 (17401)
36 limit 35 to comment and (letter or editorial).pt. (187)
37 limit 35 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index) (501)
38 35 not (36 or 37) (16778)
39 limit 38 to animals/ (2192)
40 38 not 39 (14586)
41 limit 40 to humans (14553)
42 limit 40 to english language (13398)
43 limit 42 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (11047)
44 limit 43 to yr="2007 -Current" (5299)
45 remove duplicates from 44 (5257)

Table S2. Study inclusion criteria

1. Randomized controlled trial
2. Article published in English
3. Human subjects
4. Adults
5. Follow up > 12 months after first follow up measurement of UP or GFR
6. Quantifiable albuminuria/proteinuria (i.e. not dipstick)
7. Glomerular filtration rate > 15 mL/min/1.73 m^2
8. First follow up albuminuria/proteinuria or serum creatinine latest at 12 months
9. Number of events (differ by disease)*
   a. Glomerular disease : >10 events
   b. Kidney disease, diabetes, hypertension, polycystic kidney disease, non-specified or other: follow-up > 500 person years and > 30 events
   c. High risk population (diabetes, hypertension, cardiovascular disease, heart failure not selected for having kidney disease): follow-up > 1000 person years and > 30 events

*Events - (end-stage kidney disease, doubling of serum creatinine, 40% or 30% decline in glomerular filtration rate)

Table S3. Clinical characteristics of the population overall and stratified by disease

	N Studies	N participants	Age	Female	Black	Diabetes	GFR	ACR
Overall	53	56413	61.5 (11.2)	22514 (37.4)	4601 (7.6)	45342 (75.3)	61.8 (26.3)	59 (13, 539)
Disease								
CKD	25	13516	56.2 (13.9)	6055 (39.3)	3098 (20.1)	1854 (12.0)	38.3 (22.2)	140 (35, 700)
Diabetes	12	41752	64.0 (8.5)	15973 (36.7)	1484 (3.4)	43481 (100.0)	69.8 (22.2)	35 (9, 361)
Glomerular	16	1145	41.6 (12.7)	486 (36.2)	19 (1.4)	7 (0.5)	72.4 (29.2)	1497 (898, 2695)

Values for age and GFR are presented as mean (standard deviation) and for ACR as median (25^{th}, 75^{th} percentile). Values for other characteristics are presented as number (percentage). N, sample size; GFR, estimated glomerular filtration rate (mL/min/1.73m^2); ACR, albumin: creatinine ratio (mg/g); RASB, renin angiotensin system blockers; CB, calcium channel blockers; BP, low vs usual blood pressure control; Diet, low vs high protein diet; IS, immunosuppression; CKD, chronic kidney disease.
Note: The N participants presented here are for the primary analysis (ANCOVA).

Table S4. Patient characteristics by study

Intervention	Disease	Study	N participants	Age	Female	Black	Diabetes	eGFR	ACR
RASB v Control	CKD (CNS)	Kamper	55	49.8 (11.7)	28 (50.9)	0 (0.0)	0 (0.0)	14.8 (9.0)	654 (264, 1558)
	CKD (CNS)	Ihle/Kincaid	67	45.5 (12.8)	34 (50.7)	0 (0.0)	0 (0.0)	16.5 (6.7)	856 (449, 1766)
	CKD (CNS)	Hou	224	44.7 (15.4)	113 (50.4)	0 (0.0)	0 (0.0)	16.8 (4.4)	1012 (635, 1338)
	CKD (CNS)	Hannedouche	98	51.2 (14.1)	47 (48.0)	0 (0.0)	0 (0.0)	23.4 (7.8)	958 (359, 1916)
	CKD (CNS)	Brenner	106	46.7 (13.2)	38 (35.8)	37 (34.9)	0 (0.0)	35.4 (17.2)	747 (154, 1883)
	CKD (CNS)	Toto	122	52.4 (11.6)	44 (36.1)	74 (60.7)	0 (0.0)	37.0 (17.5)	136 (60, 585)
	CKD (CNS)	AIPRI	562	50.9 (12.5)	157 (27.9)	0 (0.0)	0 (0.0)	38.6 (11.6)	500 (78, 1473)
	CKD (CNS)	REIN	322	48.8 (13.6)	73 (22.7)	2 (0.6)	0 (0.0)	41.5 (18.8)	1646 (916, 2599)
	CKD (CNS)	Van Essen	103	50.6 (12.9)	35 (34.0)	1 (1.0)	0 (0.0)	48.1 (19.3)	299 (60, 1497)
	CKD (HTN)	AASK	876	54.6 (10.7)	339 (38.7)	876 (100.0)	0 (0.0)	48.9 (15.8)	74 (26, 364)
	CKD (PKD)	HALT-PKD B	462	48.8 (8.2)	238 (51.5)	12 (2.6)	0 (0.0)	48.2 (11.8)	30 (17, 76)
	CKD (PKD)	HALT-PKD A	542	36.6 (8.3)	270 (49.8)	13 (2.4)	0 (0.0)	91.9 (17.7)	18 (12, 33)
	Diabetes	ALTITUDE	8150	64.4 (9.7)	2572 (31.6)	267 (3.3)	8150 (100.0)	58.4 (21.2)	284 (57, 881)
	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	15 (7, 40)
	Diabetes (CKD)	RENAAL	1513	60.2 (7.4)	557 (36.8)	230 (15.2)	1513 (100.0)	41.3 (13.2)	1307 (616, 2732)
	Diabetes (CKD)	ORIENT	566	59.2 (8.1)	175 (30.9)	0 (0.0)	566 (100.0)	47.5 (12.1)	1270 (617, 2285)
	Diabetes (CKD)	IDNT	1135	58.8 (7.7)	363 (32.0)	139 (12.2)	1135 (100.0)	50.2 (19.5)	1816 (1051, 3234)
	Diabetes (CKD)	Lewis 1993	407	34.5 (7.6)	191 (46.9)	32 (7.9)	407 (100.0)	73.2 (25.3)	1111 (605, 2299)
	Glom (IgAN)	HKVIN	109	40.5 (9.5)	79 (72.5)	0 (0.0)	3 (2.8)	75.1 (29.0)	958 (629, 1560)
RASB v CCB	CKD (CNS)	Zucchelli	121	55.4 (10.9)	47 (38.8)	0 (0.0)	0 (0.0)	24.9 (10.1)	599 (251, 1557)
	CKD (HTN)	AASK	652	54.4 (10.8)	255 (39.1)	652 (100.0)	0 (0.0)	48.7 (15.8)	67 (25, 343)
	Diabetes	ABCD	392	59.0 (8.2)	130 (33.2)	63 (16.1)	392 (100.0)	72.1 (18.7)	127 (56, 661)
	Diabetes (CKD)	IDNT	1128	59.2 (7.5)	400 (35.5)	147 (13.0)	1128 (100.0)	50.1 (18.7)	1740 (1009, 3059)
Low v Usual BP	CKD (CNS)	MDRD Study B	255	50.8 (12.8)	104 (40.8)	13 (5.1)	13 (5.1)	20.3 (5.8)	425 (102, 1222)
	CKD (CNS)	MDRD Study A	584	52.2 (12.2)	228 (39.0)	53 (9.1)	30 (5.1)	40.7 (11.0)	120 (33, 668)
	CKD (HTN)	AASK	1093	54.6 (10.7)	425 (38.9)	1093 (100.0)	0 (0.0)	48.7 (15.7)	70 (25, 349)
	CKD (PKD)	HALT-PKD A	542	36.6 (8.3)	270 (49.8)	13 (2.4)	0 (0.0)	91.9 (17.7)	18 (12, 33)
	Diabetes	ABCD	392	59.0 (8.2)	130 (33.2)	63 (16.1)	392 (100.0)	72.1 (18.7)	127 (56, 661)
Low v Usual Diet	CKD (CNS)	MDRD Study B	255	50.8 (12.8)	104 (40.8)	13 (5.1)	13 (5.1)	20.3 (5.8)	425 (102, 1222)
	CKD (CNS)	MDRD Study A	584	52.2 (12.2)	228 (39.0)	53 (9.1)	30 (5.1)	40.7 (11.0)	120 (33, 668)
Immuno-suppression	Glom (IgAN)	Pozzi 2012	46	42.0 (11.5)	9 (19.6)	0 (0.0)	0 (0.0)	27.8 (7.0)	1497 (898, 2395)
	Glom (IgAN)	Donadio 2001	72	46.3 (13.1)	13 (18.1)	2 (2.8)	0 (0.0)	40.8 (14.4)	971 (441, 1886)
	Glom (IgAN)	STOP-IgAN	151	44.2 (12.4)	34 (22.5)	0 (0.0)	0 (0.0)	59.7 (27.6)	928 (641, 1229)
	Glom (IgAN)	Maes	34	44.8 (11.3)	10 (29.4)	0 (0.0)	0 (0.0)	62.2 (18.9)	596 (353, 1599)
	Glom (IgAN)	Donadio 1999	96	38.5 (13.4)	26 (27.1)	0 (0.0)	0 (0.0)	66.1 (22.5)	1257 (719, 2066)

Intervention	Disease	Study	N participants	Age	Female	Black	Diabetes	eGFR	ACR
	Glom (IgAN)	Pozzi 2010	197	39.2 (12.6)	55 (27.9)	0 (0.0)	0 (0.0)	74.7 (25.5)	1198 (898, 1617)
	Glom (IgAN)	Pozzi 2004	83	38.6 (11.7)	25 (30.1)	0 (0.0)	0 (0.0)	87.2 (21.6)	1138 (838, 1437)
	Glom (IgAN)	Schena	95	33.7 (11.1)	29 (30.5)	0 (0.0)	2 (2.1)	91.3 (23.7)	982 (790, 1497)
	Glom (Lupus)	Lewis 1992	79	32.6 (12.0)	66 (83.5)	17 (21.5)	0 (0.0)	56.4 (36.3)	2635 (1165, 4905)
	Glom (Lupus)	Chan	61	40.1 (9.9)	51 (83.6)	0 (0.0)	2 (3.3)	70.4 (26.3)	2359 (1557, 4216)
	Glom (Membran)	Ponticelli 1998	91	49.9 (10.7)	28 (30.8)	0 (0.0)	0 (0.0)	82.5 (19.9)	3293 (2395, 5210)
	Glom (Membran)	Ponticelli 1989	75	44.4 (10.9)	15 (20.0)	0 (0.0)	0 (0.0)	87.7 (23.0)	2874 (2275, 4731)
	Glom (Membran)	Ponticelli 1992	76	46.7 (13.3)	26 (34.2)	0 (0.0)	0 (0.0)	89.0 (25.1)	3234 (2455, 4641)
	Glom (Membran)	Praga 2007	48	46.6 (12.5)	8 (16.7)	0 (0.0)	0 (0.0)	89.3 (20.2)	4338 (2640, 5828)
	Glom (Membran)	Ponticelli 2006	31	49.3 (10.5)	12 (38.7)	0 (0.0)	0 (0.0)	92.6 (22.2)	3353 (2395, 4850)
SGLT2 inhibitors	Diabetes	EMPA-REG	6936	63.2 (8.6)	1977 (28.5)	354 (5.1)	6936 (100.0)	76.2 (19.9)	18 (7, 72)
Others	CKD (CNS)	Goicoechea	113	71.8 (8.7)	40 (35.4)	0 (0.0)	42 (37.2)	40.5 (12.4)	35 (15, 362)
	CKD (CNS)	ROAD	339	50.9 (13.7)	126 (37.2)	0 (0.0)	0 (0.0)	29.0 (13.4)	958 (641, 1599)
	CKD (CNS)	MASTERPLAN	640	60.5 (12.5)	199 (31.1)	49 (7.7)	156 (24.4)	36.7 (15.4)	147 (51, 449)
	CKD (CNS)	CanPREVENT	458	65.1 (7.5)	250 (54.6)	25 (5.5)	144 (31.4)	47.6 (9.9)	72 (48, 115)
	CKD (CNS)	SHARP	6245	62.9 (11.7)	2363 (37.8)	119 (1.9)	1426 (22.8)	26.2 (12.3)	206 (44, 762)
	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	15 (7, 40)
	Diabetes (CKD)	SUN-MACRO	1110	63.5 (9.3)	256 (23.1)	115 (10.4)	1110 (100.0)	33.7 (9.7)	1075 (569, 1798)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean (standard deviation) except ACR which is shown as median (25^{th}, 75^{th} percentile). Participants with missing data on age, race, sex, serum creatinine, urine albumin were excluded.

Table S5. Estimated acute effects using different methods to compute the acute effect on GFR, overall and by intervention and disease

Subgroup	N Studies	ANCOVA		Linear mixed model	
		Mean (95% CI)	Coverage interval	Mean (95% CI)	Coverage interval
Overall	53	-0.21 (-0.63, 0.22)	(-2.50, 2.08)	-0.15 (-0.54, 0.25)	(-2.31, 2.01)
Intervention					
RASB v CCB	4	-1.60 (-3.25, 0.05)	(-4.28, 1.07)	-1.39 (-3.10, 0.32)	(-4.30, 1.52)
RASB vs Control	19	-0.51 (-1.06, 0.04)	(-2.39, 1.38)	-0.30 (-0.83, 0.23)	(-2.16, 1.56)
Immunosuppression	15	1.97 (0.01, 3.93)	(-2.34, 6.29)	0.96 (-0.64, 2.56)	(-2.03, 3.95)
Low v Usual BP	5	-0.97 (-2.02, 0.09)	(-2.83, 0.89)	-0.91 (-2.02, 0.20)	(-2.97, 1.16)
SGLT2 inhibitors	1	-1.81 (-2.25, -1.36)	(-1.81, -1.81)	-1.43 (-1.92, -0.94)	(-1.43, -1.43)
Disease					
CKD	25	-0.02 (-0.56, 0.53)	(-2.30, 2.27)	0.10 (-0.42, 0.62)	(-2.14, 2.34)
Diabetes	12	-1.01 (-1.62, -0.40)	(-2.78, 0.76)	-0.88 (-1.43, -0.33)	(-2.46, 0.69)
Glomerular	16	1.55 (-0.08, 3.18)	(-1.72, 4.83)	0.55 (-0.73, 1.83)	(-1.10, 2.20)

ANCOVA, Analysis of covariance method; N, number of studies; CI, confidence interval; RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, sodium-glucose co-transporter-2; CKD, chronic kidney disease.

Table S6. Magnitude of acute effects on GFR, by intervention

Subgroup	Very Large Negative <=-2.5	Moderate-to-Large Negative >-2.5 & <=-1.25	Small Negative >-1.25 & <0	No Acute Effect 0	Small Positive >0 & <1.25	Moderate-to-Large Positive >=1.25 & <2.5	Very Large Positive >=2.5
Overall	5	8	10	0	17	5	8
RASB vs CCB	1	1	2	0	0	0	0
RASB vs Control	1	4	4	0	10	0	0
Immunosuppression	2	1	1	0	1	3	7
Low vs Usual BP	1	1	2	0	1	0	0
SGLT2 inhibitors	0	1	0	0	0	0	0

Values displayed are the number of studies in each magnitude category.
RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, sodium-glucose co-transporter-2.

Table S7. Multivariable meta-regression of acute effects on GFR, both for GFR and ACR

A. GFR

Model	Variable	Estimate (95% CI)	P-value
GFR	GFR	-0.21 (-0.39, -0.03)	0.019
GFR+Interv	GFR	-0.25 (-0.40, -0.10)	0.001
	RASB vs control	-0.74 (-1.22, -0.25)	0.003
GFR+Interv+Diab	GFR	-0.19 (-0.37, -0.02)	0.033
	RASB vs control	-0.48 (-1.10, 0.14)	0.132
	Diabetes	-0.26 (-0.66, 0.14)	0.199

B. ACR

Model	Variable	Estimate (95% CI)	P-value
ACR	ACR	0.18 (0.00, 0.37)	0.047
ACR+Interv	ACR	0.18 (0.02, 0.35)	0.029
	RASB vs control	-0.46 (-0.98, 0.07)	0.088
ACR+Interv+Diab	ACR	0.18 (0.03, 0.33)	0.019
	RASB vs control	-0.10 (-0.66, 0.45)	0.720
	Diabetes	-0.46 (-0.81, -0.10)	0.011
ACR+GFR	ACR	0.12 (-0.08, 0.32)	0.260
	GFR	-0.14 (-0.35, 0.08)	0.210

CI, confidence interval; GFR, glomerular filtration rate; interv, intervention; Diab, diabetes; ACR, albumin: creatinine ratio; RASB, renin-angiotensin receptor blocker

Note: Estimates for GFR are denoted in 10 unit increases in ml/min/1.73m^2

Figure S1. Evaluation of bias in studies included in meta-analysis

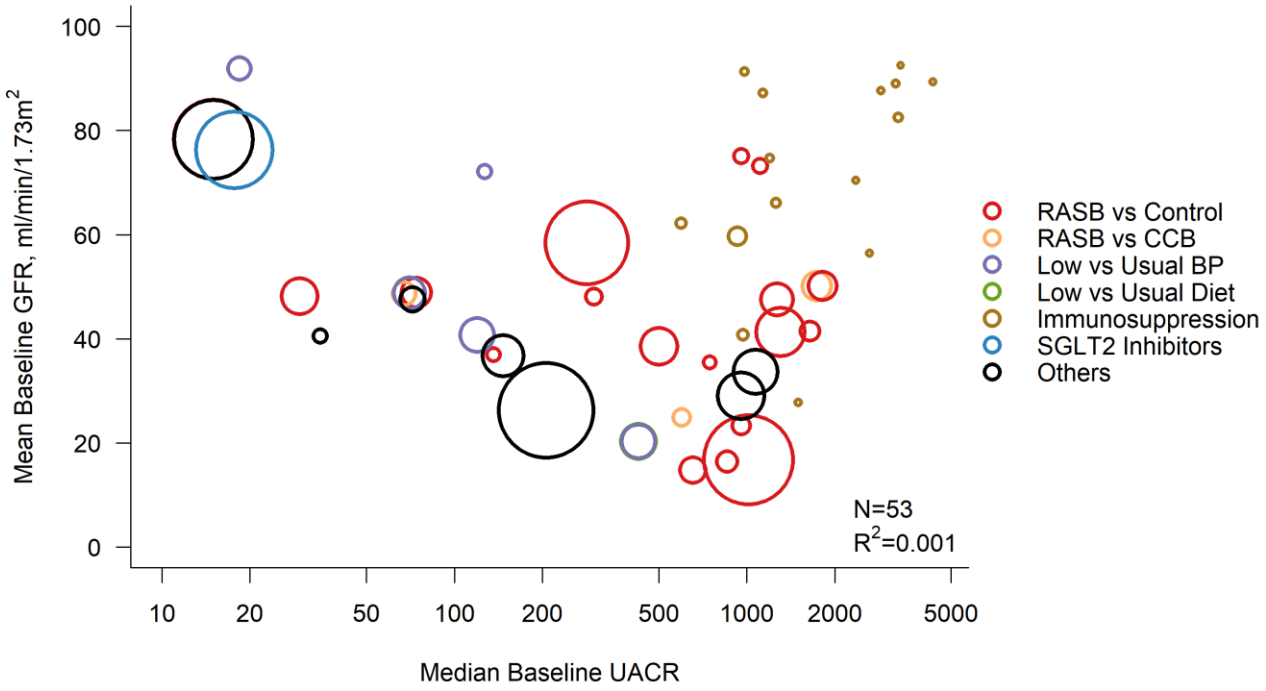
	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Kamper	+	+	-	+	?	+
Ihle/Kincaid	?	?	+	+	+	+
Hou	+	+	+	+	+	+
Hannedouche	+	?	-	+	?	+
Brenner	+	?	+	+	-	+
Toto	?	?	?	?	+	+
AIPRI	?	?	+	+	+	+
REIN	?	?	+	+	+	+
Van Essen	?	?	+	+	+	+
AASK	?	?	+	+	+	+
HALT-PKD B	+	?	+	+	+	+
HALT-PKD A	+	+	+	+	+	+
ALTITUDE	+	+	+	+	+	+
ADVANCE	+	+	+	+	+	+
RENAAL	+	+	+	+	+	+
ORIENT	?	?	+	+	?	+
IDNT	+	?	+	+	+	+
Lewis 1993	+	?	+	+	+	+
HKVIN	+	+	+	+	+	+
Zucchelli	?	?	?	+	+	+
ABCD	?	?	+	+	+	+
MDRD Study	+	+	-	+	?	+
Pozzi 2012	?	?	-	+	+	+
Donadio 2001	-	-	-	+	+	+
STOP-IgAN	+	?	-	+	+	+
Maes	?	?	?	+	+	+
Donadio 1999	?	?	-	+	?	+
Pozzi 2010	+	?	-	+	?	+
Pozzi 2004	+	?	-	+	+	+
Schena	+	+	-	+	+	+
Lewis 1992	+	+	?	?	+	+
Chan	+	?	-	+	+	+
Ponticelli 1998	+	?	-	+	+	+
Ponticelli 1989	+	+	-	+	+	+
Ponticelli 1992	?	?	?	+	+	+
Praga 2007	+	+	-	+	+	+
Ponticelli 2006	+	+	?	?	+	+
ROAD	+	+	-	+	+	+
SUN-MACRO	+	?	+	+	+	+
EMPA-REG OUTCOME	+	?	+	+	+	+
Goicoechea	+	?	?	+	+	+
MASTERPLAN	+	?	?	-	?	+
CanPREVENT	-	+	-	+	?	+
SHARP	+	+	+	+	+	+

(Legend on the following page)

Key: Green and + indicates low risk of bias; red and – indicates high risk of bias; yellow and ? indicates unclear risk of bias.

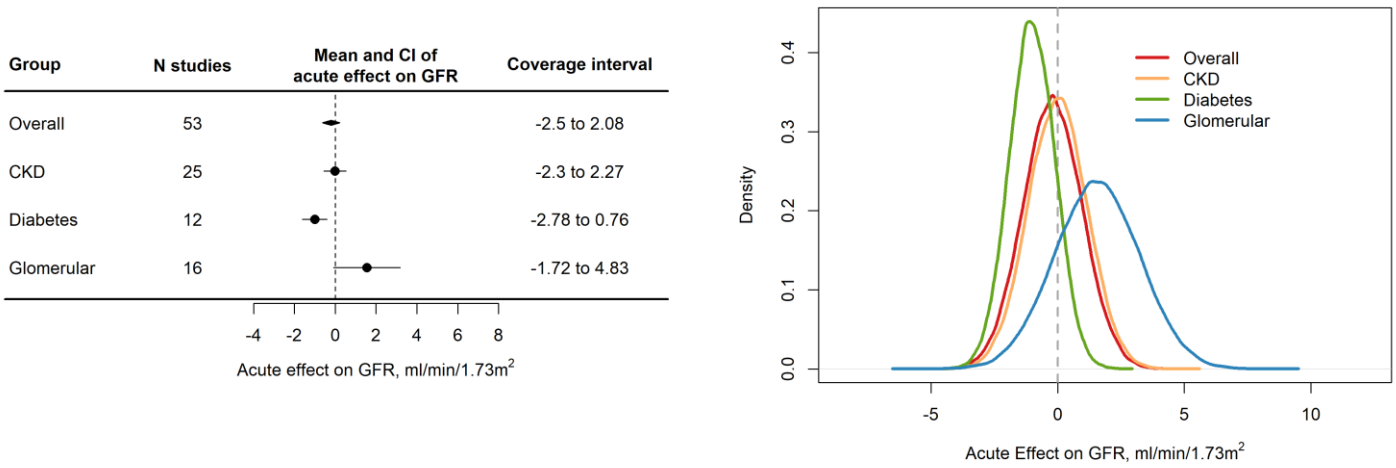
Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration. The tool includes these components: sequence generation (i.e. computer-generated random number, use of random number table or other truly random process); allocation concealment (i.e. web-based or telephone central randomization or consecutively numbered sealed opaque envelopes); blinding of participants, study personnel and outcome assessors; incomplete outcome data; selective outcome reporting. Each item of potential bias was scored as low, high or unclear based on criteria specified by the Cochrane Handbook1.

Figure S2. Mean baseline GFR and median baseline UACR across studies



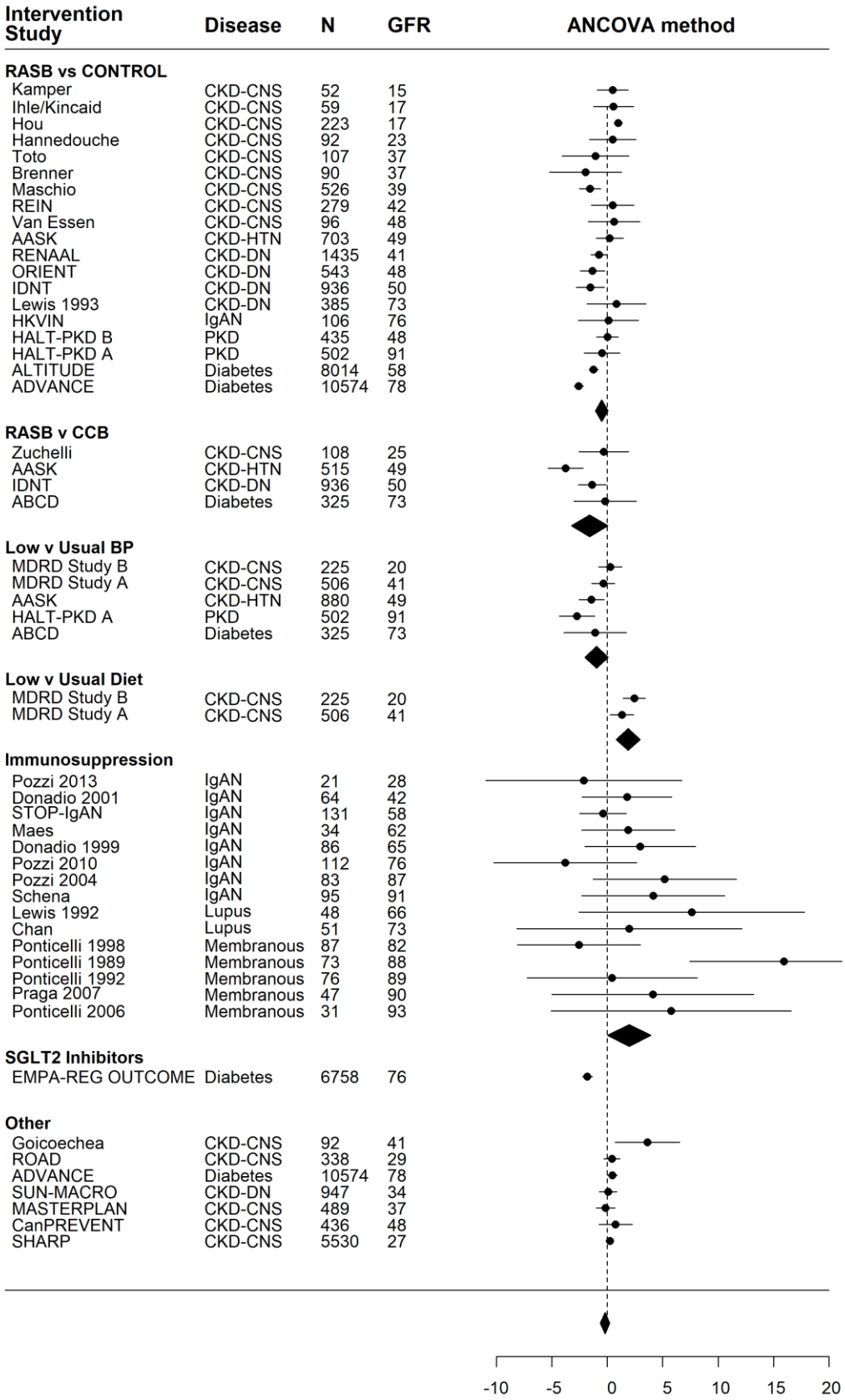
GFR, glomerular filtration rate; UACR, urine albumin creatinine ratio; RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, Sodium-glucose Cotransporter-2; N, number of studies.

Figure S3. Distribution and estimated mean acute effect on GFR by disease



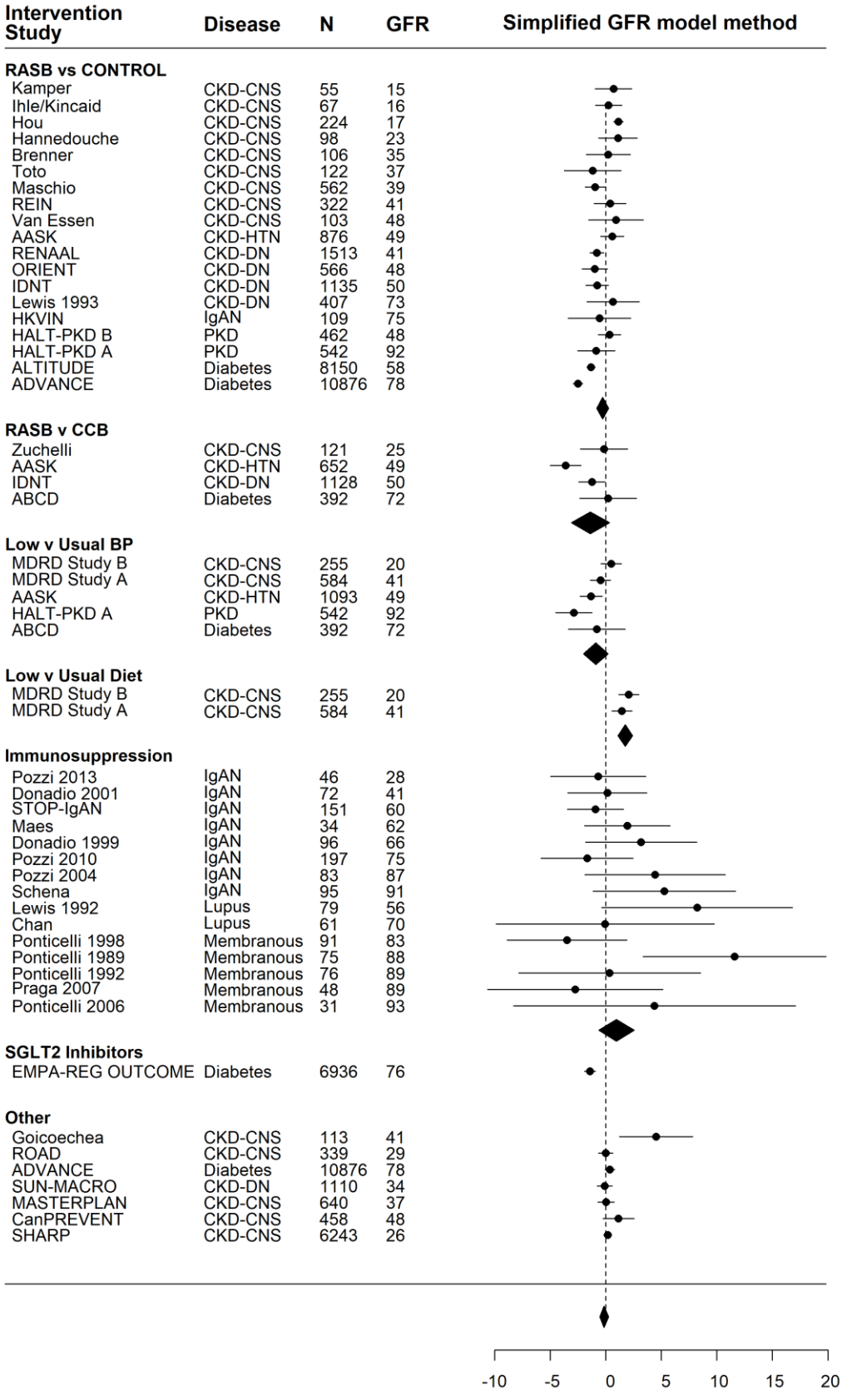
CI, confidence intervals; CKD, chronic kidney disease. Coverage interval refers to the interval under which 95% of the studies fall; N, sample size.

Figure S4: Forest plot of acute effect on GFR by intervention, all studies, ANCOVA method



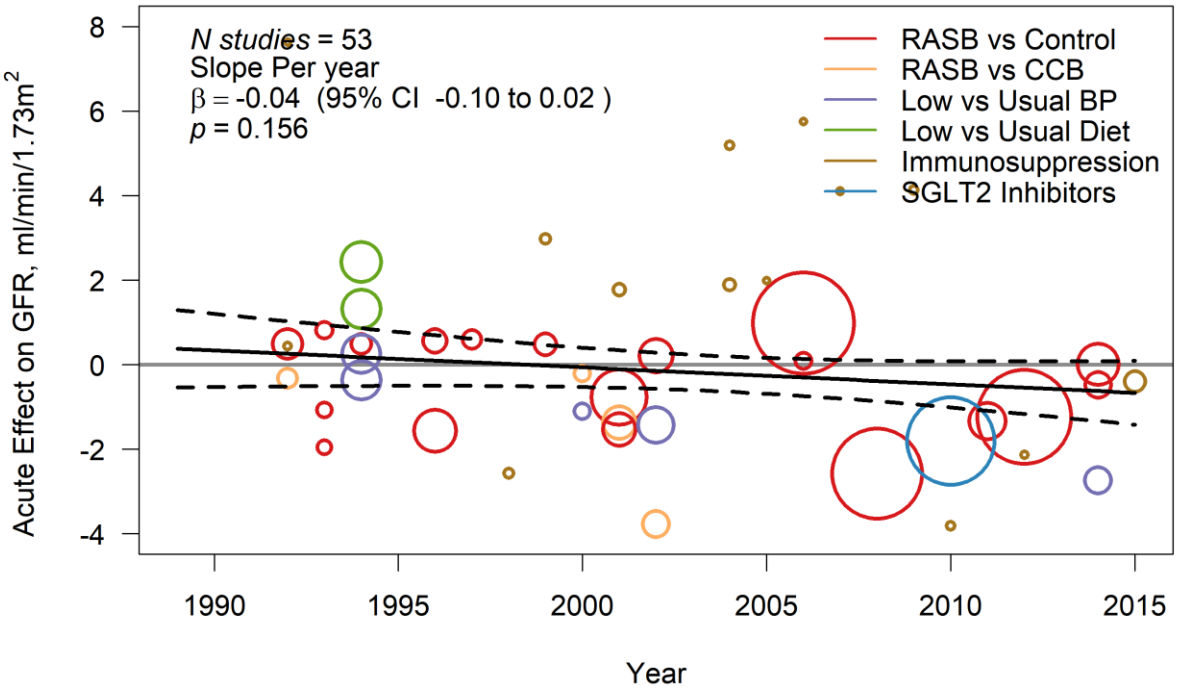
RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, sodium-glucose cotransporter-2; GFR, glomerular filtration rate; N, sample size (participants).

Figure S5: Forest plot of acute effects on GFR by intervention, all studies, sensitivity analysis using the linear mixed model



RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, sodium-glucose cotransporter-2; GFR, glomerular filtration rate; N, sample size (participants).

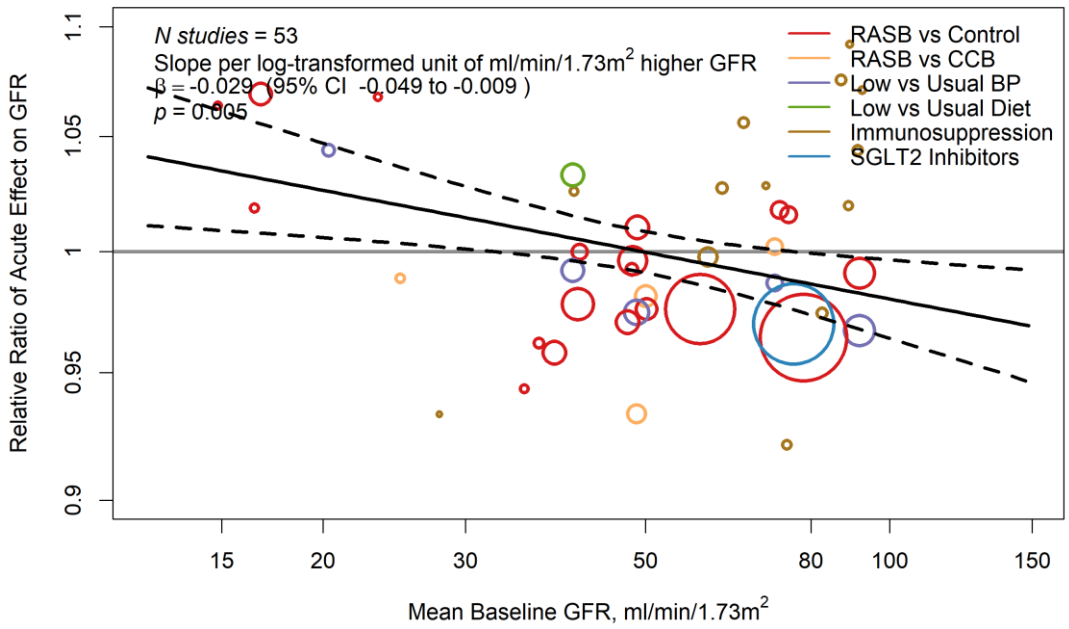
Figure S6: Variation in acute effect on GFR by year of study publication



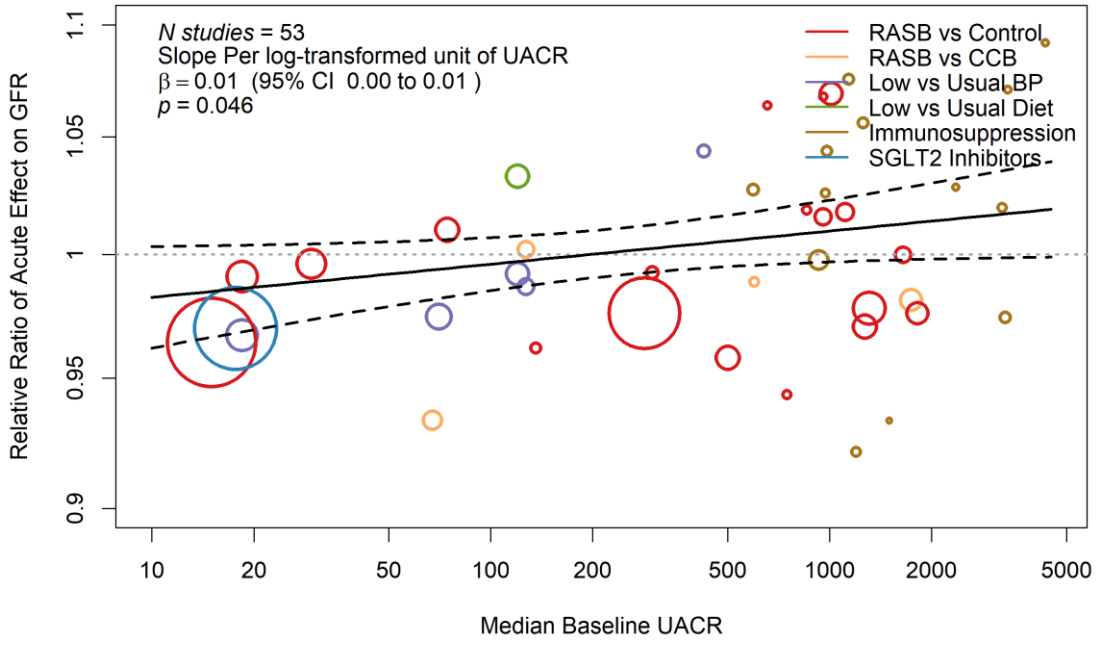
RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, sodium-glucose cotransporter-2; GFR, glomerular filtration rate; CI, confidence interval; β, slope; N, sample size.

Figure S7: Meta regression plot of variation in acute effect by (A) baseline natural log-transformed eGFR and (B) natural log acute effect by UACR

(A)



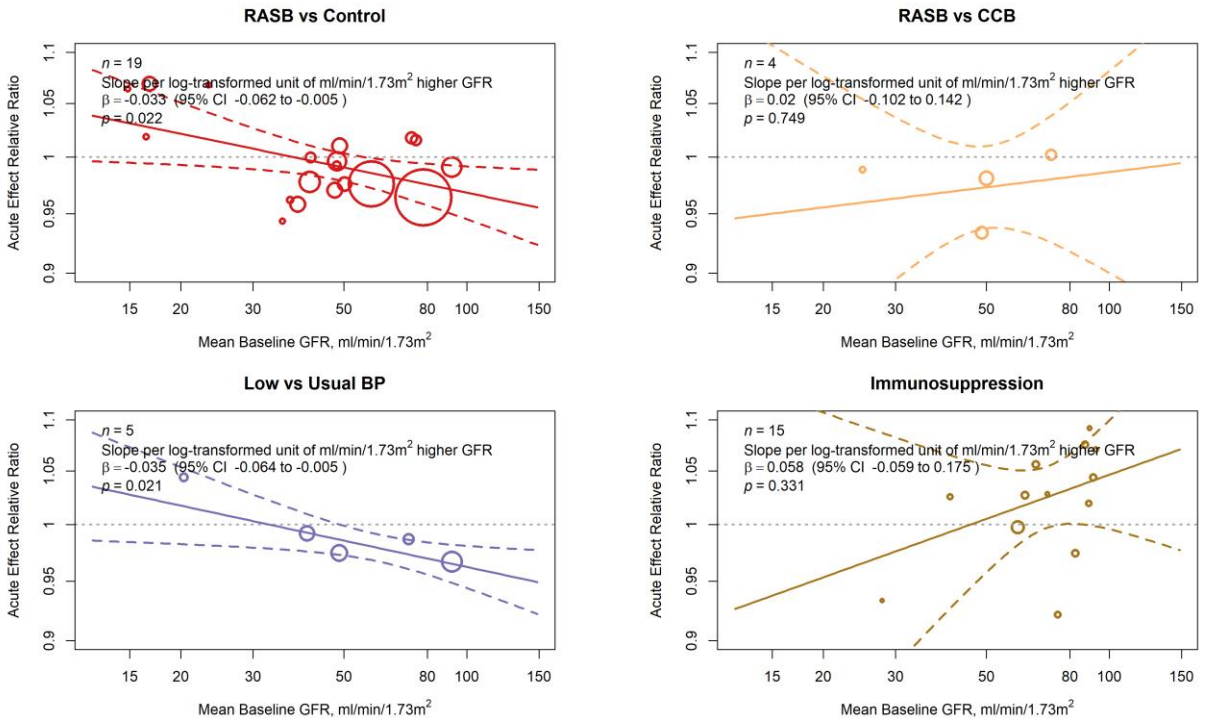
(B)



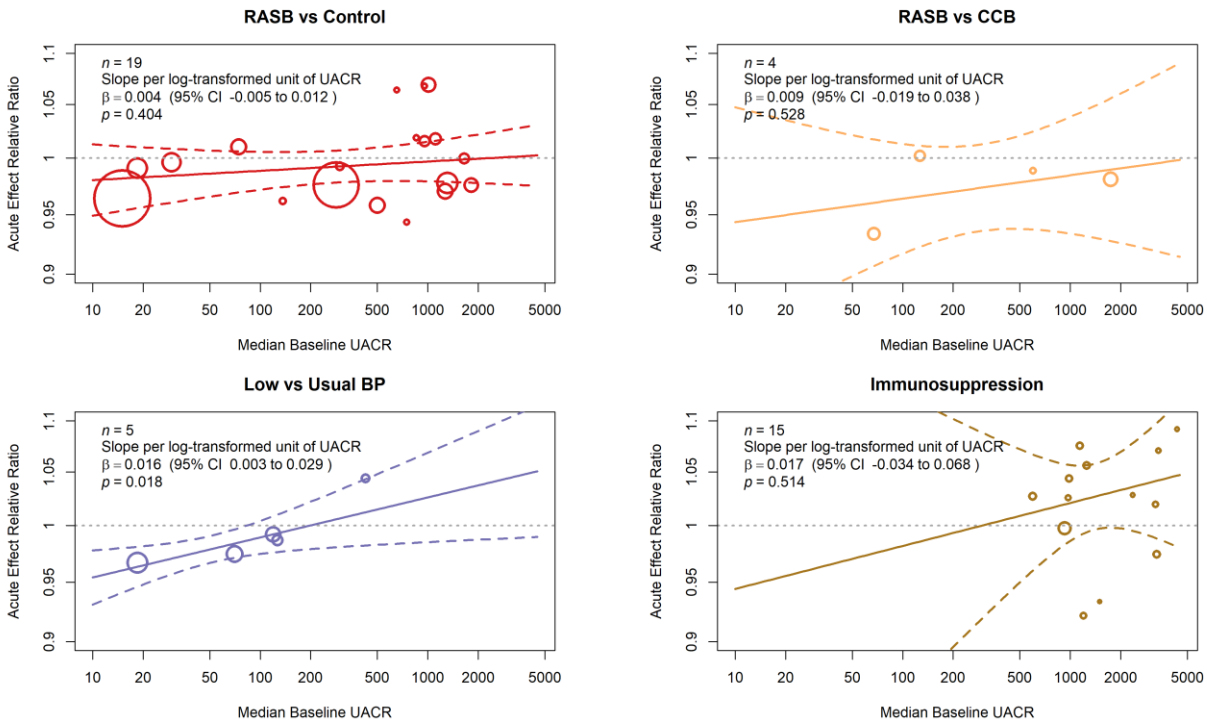
RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; SGLT2, Sodium-glucose Cotransporter-2; GFR, glomerular filtration rate.

Figure S8: Meta regression plot of variation in acute effect by intervention by (A) baseline natural log-transformed eGFR and (B) natural log acute effect by UACR

(A)

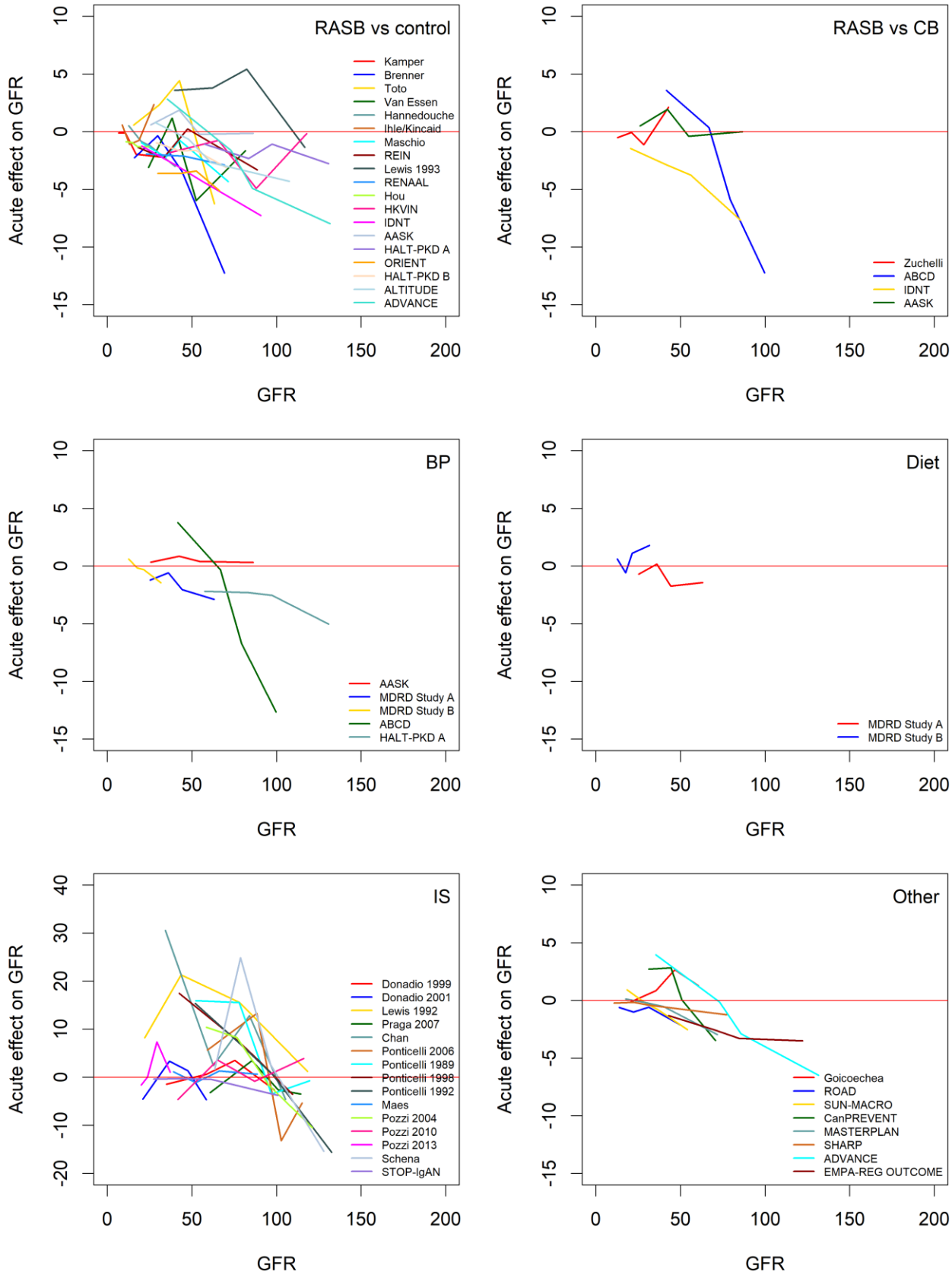


(B)



RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; UACR, urine albumin: creatinine ratio; GFR, glomerular filtration rate.

Figure S9: Variation in acute effect on GFR by within-study GFR quartiles, by intervention



RASB, renin-angiotensin receptor blockers; CCB, calcium channel blockers; BP, blood pressure; IS, immunosuppression; GFR, glomerular filtration rate

References

1. Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288(19):2421-31.
2. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes care 2000;23 Suppl 2:B54-64.
3. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New England Journal Medicine 2008;358(24):2560-72.
4. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. The New England journal of medicine 2012;367(23):2204-13.
5. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Annals of internal medicine 2003;139(4):244-52.
6. Barrett BJ, Garg AX, Goeree R, et al. A nurse-coordinated model of care versus usual care for stage 3/4 chronic kidney disease in the community: a randomized controlled trial. Clinical journal of the American Society of Nephrology : CJASN 2011;6(6):1241-7.
7. Chan TM, Tse KC, Tang CS, Mok MY, Li FK. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005;16(4):1076-84.
8. Donadio JV, Jr., Larson TS, Bergstralh EJ, Grande JP. A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. J Am Soc Nephrol 2001;12(4):791-9.
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 2015;373(22):2117-28.
10. Goicoechea M, Garcia de Vinuesa S, Verdalles U, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. Am J Kidney Dis 2015;65(4):543-9.
11. Schrier RW, Abebe KZ, Perrone RD, et al. Blood pressure in early autosomal dominant polycystic kidney disease. New England Journal of Medicine 2014;371(24):2255-66.
12. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. New England Journal of Medicine 2014;371(24):2267-76.
13. Hannedouche T, Landais P, Goldfarb B, et al. Randomised controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. BMJ 1994;309(6958):833-7.
14. Li PK, Leung CB, Chow KM, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. Am J Kidney Dis 2006;47(5):751-60.
15. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. The New England journal of medicine 2006;354(2):131-40.
16. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. The New England journal of medicine 2001;345(12):851-60.
17. Ihle BU, Whitworth JA, Shahinfar S, Cnaan A, Kincaid-Smith PS, Becker GJ. Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: a controlled double-blind trial. Am J Kidney Dis 1996;27(4):489-95.
18. Kamper AL, Strandgaard S, Leyssac PP. Effect of enalapril on the progression of chronic renal failure. A randomized controlled trial. American journal of hypertension 1992;5(7):423-30.
19. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. The New England journal of medicine 1992;326(21):1373-9.
20. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. The New England journal of medicine 1993;329(20):1456-62.

21. Maes BD, Oyen R, Claes K, et al. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. Kidney international 2004;65(5):1842-9.
22. Peeters MJ, van Zuilen AD, van den Brand JA, et al. Nurse practitioner care improves renal outcome in patients with CKD. J Am Soc Nephrol 2014;25(2):390-8.
23. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. The New England journal of medicine 1994;330(13):877-84.
24. Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia 2011;54(12):2978-86.
25. Ponticelli C, Zucchelli P, Passerini P, et al. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. The New England journal of medicine 1989;320(1):8-13.
26. Ponticelli C, Altieri P, Scolari F, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol 1998;9(3):444-50.
27. Ponticelli C, Passerini P, Salvadori M, et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. Am J Kidney Dis 2006;47(2):233-40.
28. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol 2004;15(1):157-63.
29. Pozzi C, Andrulli S, Pani A, et al. Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. J Am Soc Nephrol 2010;21(10):1783-90.
30. Pozzi C, Andrulli S, Pani A, et al. IgA nephropathy with severe chronic renal failure: a randomized controlled trial of corticosteroids and azathioprine. Journal of nephrology 2013;26(1):86-93.
31. Praga M, Barrio V, Juarez GF, Luno J. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. Kidney international 2007;71(9):924-30.
32. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999;354(9176):359-64.
33. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. The New England journal of medicine 2001;345(12):861-9.
34. Hou FF, Xie D, Zhang X, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol 2007;18(6):1889-98.
35. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2009;24(12):3694-701.
36. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377(9784):2181-92.
37. Rauen T, Eitner F, Fitzner C, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. New England Journal of Medicine 2015;373(23):2225-2236.
38. Packham DK, Wolfe R, Reutens AT, et al. Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy. J Am Soc Nephrol 2012;23(1):123-30.
39. van Essen GG, Apperloo AJ, Rensma PL, et al. Are angiotensin converting enzyme inhibitors superior to beta blockers in retarding progressive renal function decline? Kidney Int Suppl 1997;63:S58-62.
40. Zucchelli P, Zuccala A, Borghi M, et al. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. Kidney international 1992;42(2):452-8.