Performance of Estimated GFR Slope as a Surrogate Endpoint for Kidney Disease Progression in Clinical Trials: A Statistical Simulation

Supplemental Materials

Supplemental Appendix 1: Abbreviations, units, and terms

AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes trial
ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin to creatinine ratio
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AIPRI	The Angiotensin-converting-enzyme Inhibition on Progressive Renal Insufficiency trial
Alb Protocol	albuminuria targeted protocol
Alternative clinical endpoint	ESKD, 40% GFR decline and GFR < 15 mL/min per 1.73 m^2
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints
Aus	Australia
AZA	azathioprine
BP	blood pressure
CanPREVENT	Canadian Prevention of Renal and Cardiovascular Endpoints Trial
Clinical endpoint	ESKD, doubling of serum creatinine and GFR < 15 mL/min per 1.73 m^2
CI	confidence interval
CKD	chronic kidney disease
CNS	cause not specified
CSG	Collaborative Study Group
DIET	low protein diet
EMA	European Medicines Association
EMPA	Empagliflozin
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
Est	estimate
Eur	Europe
F/U	follow-up time (months)
FDA	Food and Drug Administration
GFR	glomerular filtration rate(mL/min/1.73 m^2)
Glom	glomerular disease
GLUC	intensive glucose
GMR	geometric mean ratio
HALT-PKD	Halt Progression of Polycystic Kidney Disease study
HKVIN	Hong Kong study using Valsartan in IgA Nephropathy
HR	hazard ratio
HTN	hypertension
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

Mem or Mebran	membranous
MMF	mycophenolate mofetil
N	sample size
NA	North America
NKF	National Kidney Foundation
ORIENT	Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial
POM model	power of the mean model
PPV	positive predictive value
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
SHARP	Study of Heart and Renal Protection
Simva/Eze	simvastatin+ezetimibe
STOP-IgAN	Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy trial
SUN-MACRO	Sulodexide Macroalbuminuria trial

Supplemental Appendix 2: Protocol summary

Background and rationale

Chronic kidney disease (CKD) is a significant global public health problem, but the progression of CKD is often slow and there are few specific symptoms until the stage of kidney failure has been reached. There is general agreement that biomarkers will be needed to approve new drugs to slow the progression of kidney disease. The two most widely studied biomarkers are glomerular filtration rate (GFR) and albuminuria - maximizing the information on both is desired.

The National Kidney Foundation (NKF) in collaboration with the Food and Drug Administration (FDA) held a Scientific Workshop in December 2012, "GFR Decline as an End Point in Clinical Trials in CKD". The results of the analyses performed for the workshop showed strong relationships between change in GFR and kidney failure and mortality in observational studies and based on analyses from past clinical trials and simulations proposed that a 30 or 40% decline in GFR would be an acceptable alternative endpoint in clinical trials in some circumstances[1-5]. Application of this endpoint is limited at higher baseline GFR and for agents that cause an "acute effect" on GFR. As such, these alternative endpoints are less applicable in drug development for drugs targeted at earlier stages of kidney disease and for many drugs with potential hemodynamic effects. Strategies to overcome these limitations include assessing changes in albuminuria (or proteinuria) as an earlier marker of kidney disease progression, alternative approaches to assessing GFR decline, and combinations of both strategies.

At higher GFR, a trial designed to compare mean slopes of GFR decline vs. time between randomized groups may have greater statistical power than comparison of time to a designated GFR decline from baseline such as 30% or 40%. However, acute effects are often greater at higher GFR levels, so they can in some cases pose a more serious problem at higher GFR. Design and analytic strategies proposed to overcome these limitations include evaluation of a "chronic" slope evaluated during the portion of follow-up after acute effects are expected to occur, rather than "total slope from randomization", and evaluation of reversal of acute effects following discontinuation of treatment, or both. However, there is no generally accepted method, and there is substantial controversy.

In March 2018, the NKF, in collaboration with the FDA and European Medicines Agency (EMA), sponsored a scientific workshop "Change in Albuminuria and GFR as Endpoints for Clinical Trials in Early Stages of Chronic Kidney Disease" to evaluate surrogate endpoints for trials of kidney disease progression and improve understanding of change in albuminuria and GFR as measures of kidney disease progression. The Workshop was chaired by Andrew S Levey, MD and Ron Gansevoort, MD and was supported by the planning committee and operations committee. Planning and operations committee members consisted of Andrew Levey (Chair), Ron Gansevoort, Josef Coresh, Dick de Zeeuw, Kai-Uwe Eckardt, Hrefna Gudmundsdottir, Adeera Levin, Romaldas Maciulaitis, Tom Manley, Vlado Perkovic, Kimberly Smith, Norman Stockbridge, Aliza Thompson, Thorsten Vetter, Kerry Willis, and Luxia Zhang. Prior to the workshop, the protocol was reviewed by the planning committee, analytical committee and stakeholder advisory group and was available at https://www.kidney.org/CKDEndpoints.

For this workshop, analyses were performed to support the validity of albumin to creatinine ratio (ACR) change and GFR slope as surrogate endpoints. Here we report the results of a statistical simulation study designed to determine the conditions in which analyses based on the chronic and total GFR slope provide substantial increases in statistical power compared to analyses of the clinical endpoint without incurring an inflated risk of false positive conclusions of benefit or false negative conclusions of harm.

Dataset development

For our prior work investigating surrogate endpoints, we had performed a systematic search of the literature and developed a pooled database from January 1 1946 to May 15 2007.[2,6] To update this dataset for the current analysis, we repeated our systematic search beginning May 16 2007 when the initial search had been completed and ending in December 15, 2016. In addition, we reviewed references of published meta-analyses of RCTs including the REASSURE study.[7,8] **Supplemental Table 1** lists all of the inclusion criteria. Our goal was to include all studies where there was sufficient progression of kidney failure for analyses and to include studies of rarer diseases. We therefore varied the number of events required for inclusion based on disease state. For studies of glomerular disease, we required 10 events whereas for studies of other kinds of CKD, we required 30 events as well as 500-person years of follow-up and for studies of high-risk populations, we required 30 events and 1000 person years of follow-up.

We were able to identify, obtain agreement and obtain access to 49 studies that had sufficient data. We were not able to obtain data or data was not sufficient in 12 studies. For trials that evaluated more than one intervention, we included a separate group for each independent treatment comparison, such that some participants were included in more than one analytical comparison[9-13]. We then pooled small studies that had less than 100 participants if the disease and intervention was the same[14-26] (**Supplemental Table 2**). This process resulted in 47 distinct randomized treatment group comparisons, which are described in **Supplemental Table 3**.

Supplemental statistical methods

Part 1: Simulation of GFR trajectories and ESKD and death events.

The purpose of the statistical simulations is to provide accurate comparisons of the performance of analyses of alternative slope and time-to-event endpoints when these analyses are performed on the same data set. This assures that the simulations provide comparisons of performance between analyses of different endpoints that are calibrated to the same data and to the same underlying treatment effects. By contrast, standard power calculations for slope and time-to-event endpoints express required sample sizes in terms of different metrics of effect size which are not directly comparable. For example, in a given study, a 25% difference in mean slope may translate to a hazard reduction for time to event outcomes based on ESKD and GFR change which may either be substantially greater or substantially smaller than 25%, depending on the characteristics of the study population and the study design. Hence, if standard power calculations were used, differences in required sample sizes between different endpoints would largely reflect differences in the way treatment effects are calibrated between methods as opposed to true differences in statistical power between the different endpoints.

Step 1: Simulation of GFR-trajectories prior to the active treatment intervention. The simulations used a growth curve model in which each subject's GFR measurements vary randomly about a subject-specific linear trajectory defined by random intercepts and slopes[27]. We generated the subject-specific slopes according to a generalized log-gamma distribution which approximates a normal distribution but has a slight negative skewness to account for fast progressors with steeper than normal GFR slopes[28]. We generated GFR measurements to be normally distributed around these trajectories. The standard deviations of the GFR measurements were assumed to be proportional to the square root of the predicted GFR based on each the trajectories defined by each patient's random intercept and slope to account for greater variability of GFR measurements at higher GFR levels[1]. After this first step, the distribution of the GFR trajectories was the same in the active treatment and control groups. Steps 2 and 3 below modified these GFR trajectories to account for the long and short-term treatment effects for patients in the active treatment group.

Step 2: Simulation of long-term treatment effects on GFR-slope. We simulated three types of long-term treatment effects on the chronic slope: a) a uniform effect, in which the same treatment effect is assumed for all patients, irrespective of their rate of progression, b) a proportional effect, in which the treatment effect is proportional to the rate of GFR decline among patients with negative slopes but the treatment has no effect among patients whose slopes would have been greater than 0 without the treatment, c) an intermediate model halfway between the uniform and proportional effect models (see Table 1 footnote).

Under the uniform effect model, long-term GFR slopes for patients in the treatment group were simulated by adding a constant to the slopes that would have been observed without treatment. Note that the uniform long-term treatment effect implies that some patients who would have had positive or only slightly negative GFR slopes without treatment will have their slopes shifted to larger positive slopes with treatment.

Under the proportional effect model, the distribution of the long-term GFR slopes in the treatment group were generated by simulating the slope of the ith patient as $\beta_i \times \{(1-k)1[\beta_i < 0] + 1[\beta_i \geq 0]\}$, where β_i denotes the slope the patient would have had without the treatment, k is the proportional reduction due to the treatment among patients whose GFR would have declined without the treatment, and $1[\beta_i < 0]$ and $1[\beta_i \geq 0]$ are 0-1 indicator variables for negative and zero or positive slopes, respectively. Thus the

proportional effect model assumes the treatment reduces the magnate of the slope by 100 x k percent among patients whose slope would have been negative without the treatment but has no effect on patients whose slope would have been greater than or equal to 0 without the treatment.

Under the intermediate treatment effect model, the chronic slopes in the treatment group were generated as $[\beta_i - (k/2) \times \text{mean}(\beta_i)] + [\beta_i \times \{(1-(k/2))1[\beta_i < 0] + 1[\beta_i \geq 0]\}]$.

We note that the type of long term treatment effect, whether it be uniform, proportional, or intermediate, is a property of the full distribution of GFR slopes across the study population. The implications of the type of long-term treatment effect differ for different types of analysis. In particular, analyses of mean slope are best adapted to uniform or intermediate treatment effects since the analysis averages results over all patients, irrespective their rate of GFR decline. On the other hand, treatment effects on time-to-event outcomes based on designated declines in GFR or ESKD are most strongly influenced by the subset of fast progressors with steep GFR decline. Hence, time-to-event analyses, especially those based on very large GFR declines of 50% or more, are best adapted to intermediate or proportional treatment effects, and less so to uniform effects.

Step 3: Simulation of the acute effect. As described in the methods section of the manuscript, we simulated acute effects of the treatment by adding $(K + \varepsilon_i) \times (GFR_i(t) - 15 \text{ mL/min/1.73m}^2)$ to each treated patient's GFR level at all follow-up times $t \geq 3$ months, where $GFR_i(t)$ represents the patient's GFR at follow-up time t after incorporating the long term treatment effect but prior to adding the acute effect, and K is defined so that $K \times (42.5 \text{ mL/min/1.73m}^2 - 15 \text{ mL/min/1.73m}^2)$ is equal either to -2.50, -1.25, 0, +1.25, or +2.50 mL/min/1.73m^2. Under this formulation, the acute effect of the treatment is 0 when $GFR_i(t) = 15$ mL/min/1.73m^2. Our formulation assumes that acute effects of the treatment occur fully by 3 months follow-up, and that the mean GFR slope is constant throughout the chronic phase of the study, which is assumed to start by the 3-month follow-up visit.

The ε_i were simulated as a normal random variable with mean 0 and standard deviation 1 to account for random variation in the acute effect between patients.

Step 4: Simulation of Relationships of GFR with kidney failure and death. The mortality hazard rate was assumed to be linearly related to the patients' underlying predicted GFR, with higher death rates at lower GFR. Specifically, we first simulated each patient's projected GFR at the start of each 6-month time interval *t* during the follow-up period after accounting for the long-term treatment effect and the acute effect (denoted as $E(GFR_i(t))$, and during that 6 month period mortality was assumed to be exponentially distributed with hazard rate equal to $0.03375 - 0.00025 \times E(GFR_i(t))$. ESKD was assumed to occur when either the GFR trajectory first declined below a patient-specific uniformly distributed random threshold between 6 and 15 mL/min/1.73m^2.

Step 5: *Simulation of missing data*. All GFR measurements obtained after exponentially distributed loss-to-follow-up times were set to missing. The rate of loss-to-follow-up was set to 0.02 per patient-year. To account for intermittent missing GFRs, post-baseline GFR measurements prior to the end of follow-up were randomly set to missing according to independent Bernoulli random variables with probability of intermittent missingness equal to 0.05.

We note that while the simulations assume the GFR follow-up terminates at ESKD and death, the simulations assume that the timing of intermittent missing GFR measurements and of other types of premature loss-to-follow-up occur independently of the patient's GFR level. It is also of interest to

consider scenarios in which these types of missingness are related to GFR level; however, we defer this problem to subsequent research.

An important limitation of the simulations used for this manuscript is that they did not consider medication dropouts distinct from missing data. It is possible that such dropouts could lead to reversal of acute effects in these patients, leading to biases in analyses of the chronic slope. Due to the complexity of this issue, it will be evaluated in detail in a later publication.

We note that the magnitude of the treatment effects are not always directly comparable between different scenarios. For example, a 25% treatment effect has a different meaning for uniform and proportional effects. Thus, while comparisons of required sample size between methods can be made without qualification for any specific scenario, comparisons of required sample size between different scenarios need to account for differences in the interpretation of effect sizes between those scenarios.

Part 2: Analysis of simulated data.

For each set of input parameters, we simulated 800 independent data sets, each with 500 subjects (250 assigned to the treatment and 250 to control). We then performed analyses of GFR slope based on mixed effects models and of the time-to-event outcomes using Cox proportional hazards regression for each simulated data set.

To estimate treatment effects on GFR slope, we fit a mixed effects shared parameter informative censoring model in which the patients' GFR declines after 3 months follow-up follow linear trajectories with normally distributed residuals whose standard deviations depend on the GFR level according to a power of the mean model[29,30]. The model included baseline GFR, treatment group, follow-up time, and interactions of follow-up time with baseline GFR and treatment group as fixed effects, and patient-specific intercepts and slopes as bivariate normally distributed random effects. To account for informative censoring, the composite endpoint of kidney failure or death was assumed to follow a Weibull distribution whose log-transformed rate parameter depends linearly on the random intercepts and slopes. For scenarios in which the mean number of ESKD or death events was smaller than 25 per 500 patients, the shared parameter component of the mixed effects model was dropped.
Cox proportional hazard regression was used to estimate hazard ratios for the effect of treatment on each of the time-to-event endpoints while censoring death.

Note that the statistical models for the slope and time-to-event outcomes incorporate several simplifying assumptions which led to deviations from the actual simulated data. The key simplifications included the assumption of normally distributed slopes in both the treatment and control groups and Weibull distributions for ESKD or death conditional on the underlying GFR slopes and intercepts for the GFR slope analyses, and the implicit assumption of proportional hazards for the time-to-event analyses. These simplifications in the analytic models relative to the simulated data are intended to reflect real-world applications, where it is widely understand that parametric or semi-parametric statistical models invoke simplifying assumptions relative to complexities of real data.

Part 3. Estimation of required sample sizes and relative efficiencies.

For each scenario, averages and standard deviations of the estimated treatment effects on each endpoint were obtained for the 800 simulated data sets. We obtained standard errors for sample sizes N that differed from 500 as SE(N) = SE(500) $\sqrt{500/N}$, where SE(500) is the standard deviation of the

estimated treatment effects across the 800 simulated data sets with *N* = 500. The means and standard errors for treatment effects from the simulations were used to estimate and compare the total sample sizes (counting patients in both the treatment and control groups combined) required to detect 25% treatment effects with 90% power and 2-sided α=0.05 based on each outcome (chronic and total slope, confirmed 30%, 40% and 57% GFR decline) for simulated scenarios with a benefit of the treatment on time to ESKD, and to compare bias and risk of a false conclusions of treatment benefit or harm for scenarios with no effect of the treatment on time to ESKD.

We compared the efficiency of the analyses based on the different outcomes by presenting the ratios of the total sample sizes required to achieve 90% power when using the clinical endpoint vs. the sample sizes required when using each of the other outcomes. These relative efficiencies were computed between the slope or the confirmed 30% and 40% GFR decline endpoints over either 2, 2.5-4, or 4-6 years vs. the clinical endpoint over 4-6 years in order to evaluate if the alternative endpoints can be used to simultaneously reduce follow-up duration and reduce sample size. We note that relative efficiencies greater than 1 indicate superior statistical power for the alternative endpoints vs. the clinical endpoint.

An important limitation of the simulations used for this manuscript is that they did not consider medication dropouts distinct from missing data. It is possible that such dropouts could lead to reversal of acute effects in these patients, leading to biases in analyses of the chronic slope. Due to the complexity of this issue, it will be evaluated in detail in a later publication.

Our results contain some random error because they are based on statistical simulation rather than theoretical calculation. We estimated the standard errors of the relative efficiencies obtained by the simulations by dividing the standard deviations of the relative efficiencies across the independent simulated data sets by the square root of the number of the 800 simulations for which convergence was obtained. We present the standard errors for the relative efficiency calculations in **Supplemental Table 6**.

Supplemental Table 1. Study inclusion criteria

1. RCT
2. Articles 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 (ie not dipstick)
7. GFR > 15
8. First follow up albuminuria/proteinuria or Scr latest at 12 months
9. Number of events (differ by disease)*

    a. Glomerular disease : >10 events

    b. Kidney disease DM, HTN, PKD, nonspecified or other: follow-up > 500 person years and > 30 events*

    c. High risk population (diabetes, HTN, CVD, heart failure not selected for having kidney disease): follow-up > 1000 person years and > 30 events*

*Events - (ESKD, 2X Scr, 40% or 30% decline)

Abbreviations: RCT randomized controlled trial; UP urine protein excretion; GFR glomerular filtration rate; Scr serum creatinine; DM diabetes mellitus; HTN hypertension; PKD polycystic kidney disease; CVD cardiovascular disease, ESKD end stage kidney disease.

Supplemental Table 2. Studies pooled by intervention

Study	Pooled group
Pozzi 2004[22]	Steroid
Katafuchi[25]	
Schena[26]	
Praga 2003[14]	IgA-ACEI
HKVIN[15]	
Maes[20]	IgA-MMF
Appel[21]	
Pozzi 2010[23]	IgA-AZA
Pozzi 2012[24]	
Ponticelli 1989[17]	Mem-Ponticelli
Ponticelli 1992[19]	
Ponticelli 1998[18]	
Ponticelli 2006[16]	

Supplemental Table 3. Description of studies

Intervention	Disease	Study Name	Collaborators	Year	Region	Creatinine calibration required*
RASB v Control	CKD (CNS)	Kamper[31]	Anne Lise Kamper, Svend Strandgaard	1992	NA, Eur, Aus	Yes
	CKD (CNS)	Ihle/Kincaid[32]	Gavin .J. Becker, Benno Ihle, Priscilla S. Kincaid-Smith	1996	NA, Eur, Aus	Yes
	CKD (CNS)	Hou[33]	Fan Fan Hou	2006	Asia	Yes
	CKD (CNS)	Hannedouche[34]	Thierry P. Hannedouche	1994	NA, Eur, Aus	Yes
	CKD (CNS)	Brenner[35]	Barry M. Brenner	1993	NA, Eur, Aus	Yes
	CKD (CNS)	Toto[36]	Robert Toto	1993	NA, Eur, Aus	Yes
	CKD (CNS)	AIPRI[37]	Guiseppe Maschio, Francesco Locatelli	1996	NA, Eur, Aus	Yes
	CKD (CNS)	REIN[38]	Giuseppe Remuzzi, Piero Ruggenenti	1999	NA, Eur, Aus	Yes
	CKD (CNS)	Van Essen[39]	Paul E. de Jong, GG van Essen	1997	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes
	CKD (PKD)	HALT-PKD A[40]	Ronald D. Perrone, Vicente Torres, Arlene Chapman, Godela Brosnahan	2014	NA	No
	CKD (PKD)	HALT-PKD B[13]	Ronald D. Perrone, Vicente Torres, Arlene Chapman, Godela Brosnahan	2014	NA	No
	Diabetes	ADVANCE	Vlado Perkovic	2008	International	Yes
	Diabetes	ALTITUDE[41]	Hans-Henrik Parving	2012	International	No
	Diabetes (CKD)	RENAAL[42]	Dick De Zeeuw, Hiddo J Lambers Heerspink ,Barry M. Brenner, William Keane	2001	International	Yes
	Diabetes (CKD)	ORIENT[43]	Enyu Imai, Fumiaki Kobayashi, Hirofumi Makino, Sadayoshi Ito	2011	Asia	Yes
	Diabetes (CKD)	IDNT[9]	Ed Lewis, Lawrence G. Hunsicker	2001	International	Yes
	Diabetes (CKD)	Lewis 1993[44]	Julia B. Lewis, Jamie P. Dwyer, Edmund J. Lewis, John M. Lachin	1993	NA	Yes
	Glom (IgAN)	HKVIN[15]	Philip Kam-Tao Li, CB Leung, CC Szeto, KM Chow	2006	Asia	Yes
	Glom (IgAN)	Praga 2003[14]	Manuel Praga, Fernando Caravaca, Eduardo Gutierrez, Angel Sevillano	2003	Eur	Yes
RASB v CCB	CKD (CNS)	Zucchelli[45]	Pietro Zucchelli	1992	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes
	Diabetes	ABCD[12]	Robert W. Schrier, Raymond O. Estacio	2000	NA, Eur, Aus	Yes
	Diabetes (CKD)	IDNT[9]	Julia B. Lewis, Jamie P. Dwyer, Edmund J. Lewis, Lawrence G. Hunsicker	2001	International	Yes
Intensive BP	CKD (CNS)	MDRD Study B[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	CKD (CNS)	REIN 2[46]	Giuseppe Remuzzi, Piero Ruggenenti	2005	NA, Eur, Aus	Yes
	CKD (CNS)	MDRD Study A[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes
	CKD (PKD)	HALT-PKD A[40]	Ronald D. Perrone, Kaleab Z. Abebe	2014	NA	No
	Diabetes	ABCD[12]	Robert W. Schrier, Raymond O. Estacio	2000	NA, Eur, Aus	Yes
Low Protein Diet	CKD (CNS)	MDRD Study A[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	CKD (CNS)	MDRD Study B[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
Immuno-suppresion	Glom (IgAN)	Pozzi 2012[24]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2012	NA, Eur, Aus	No
	Glom (IgAN)	Donadio 2001[47]	James Donadio, Fernando Fervenza	2001	NA, Eur, Aus	Yes
	Glom (IgAN)	Appel[21]	Gerald B. Appel, Gershon Frisch	2005	NA, Eur, Aus	Yes

Interven-tion	Disease	Study Name	Collaborators	Year	Region	Creatinine calibration required*
	Glom (IgAN)	STOP-IgAN[48]	Jürgen Floege, Thomas Rauen, Christina Fitzner; Ralf-Dieter Hilgers	2015	Eur	No
	Glom (IgAN)	Maes[20]	Bart Maes	2004	Eur	Yes
	Glom (IgAN)	Donadio 1999[49]	James Donadio, Fernando Fervenza	1999	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2010[23]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2010	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2004[22]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2004	NA, Eur, Aus	Yes
	Glom (IgAN)	Schena[26]	Francesco Paolo Schena, Manno Carlo	2009	Eur	No
	Glom (IgAN)	Katafuchi[25]	Ritsuko Katafuchi	2003	Asia	Yes
	Glom (Lupus)	Lewis 1992[50]	Edmund Lewis, Roger A. Rodby, Richard D. Rohde, Julia B. Lewis	1992	NA, Eur, Aus	Yes
	Glom (Lupus)	Chan[51]	Tak-Mao Chan	2005	Asia	Yes
	Glom (Membran)	Ponticelli 1998[18]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1998	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 1989[17]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1989	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 1992[19]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1992	NA, Eur, Aus	Yes
	Glom (Membran)	Praga 2007[52]	Manuel Praga, Fernando Caravaca, Eduardo Gutierrez, Angel Sevillano	2007	Eur	Yes
	Glom (Membran)	Ponticelli 2006[16]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	2006	NA, Eur, Aus	Yes
Alb Protocol	CKD (CNS)	ROAD[53]	Fan Fan Hou	2007	Asia	Yes
Sulodexide	Diabetes (CKD)	SUN-MACRO[54]	Julia B. Lewis, Jamie P. Dwyer, Edmund J. Lewis	2012	International	Yes
EMPA	Diabetes	EMPA-REG OUTCOME[55]	Christoph Wanner, Maximilian von Eynatten	2010	International	Yes
Allopurinol	CKD (CNS)	Goicoechea[56]	Marian Goicoechea, Eduardo Verde, Ursula Verdalles, Jose Luño	2015	NA, Eur, Aus	Yes
GLUC	Diabetes	ADVANCE[57]	Vlado Perkovic	2008	International	Yes
Nurse Care	CKD (CNS)	MASTERPLAN[58]	Jack F.M. Wetzels, Peter J Blankestijn, Arjan D. van Zuilen, Jan van den Brand	2014	Eur	Yes
	CKD (CNS)	CanPREVENT[59]	Brendan Barret	2011	NA, Eur, Aus	No
Simva/Eze	CKD (CNS)	SHARP	Martin Landray, Will Herrington, Natalie Staplin, Colin Baigent	2011	NA, Eur, Aus	No

*If calibration required, creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison or were reduced by 5% as has previously been described.[60]

Supplemental Appendix 3: Analyses of previous studies

Patient characteristics
The patient characteristics are summarized across the 47 randomized treatment group comparisons in **Supplemental Table 4**.

Meta-analyses of key input parameters for the simulations.
We carried out meta-analyses or meta-regressions for the 47 randomized treatment group comparisons to establish ranges for evaluation for three key input parameters of the simulations: 1) The mean chronic slope in the control group; 2) The standard deviation of the chronic slope in the control group; 3) The mean acute effect of the treatment. The meta-analyses were applied to the results of analyses of GFR slope carried out separate for each randomized group comparison as described in the Inker *et al* paper.[61] Briefly, to maintain a consistent method of analysis across studies, these analyses were performed using a simplified linear mixed effects model based on a single slope starting at three months post randomization adjusted for baseline GFR. Under this model, the differences between the randomized groups in the mean intercepts (at 3 months follow-up), the mean slopes after 3 months, and the estimated mean changes from baseline to either 1, 2, 3 or 4 years follow-up factored by the follow-up duration represented the treatment effects on the acute, chronic, and total slopes. We accounted for between-subject variability in GFR trajectories with use of random slopes and intercepts; for greater variation in individual GFR measurements at higher GFR levels with the use of a power of the mean (POM) model; and for non-uniform effects in which treatments may have larger effects for patients with faster GFR decline than for patients with slower GFR decline by allowing different between-patient slope variances in the treatment and control groups.[61] In studies in which at least 15 subjects died or reached ESKD, we accounted for informative censoring resulting from these events by nesting the mixed model for the GFR measurements within a shared parameter model that also includes the event times.[26,27] Simplified models were used in cases where convergence could not be obtained with the full model. The full shared parameter mixed effects models were fit using the SAS (version 9.4) nonlinear mixed-effects regression procedure, NLMIXED.

After obtaining the results of the mixed effects analyses described above for each study, we then carried out mixed effects meta-analyses to estimate the mean and the standard deviation across studies in the mean and standard deviation of the chronic slope in the control group and the mean acute effect across the 47 randomized treatment comparisons. The results of these meta-analyses are provided in **Supplemental Table 5**.

Meta-regression to evaluate the nature of the long-term treatment effect.
The potential gain in statistical power for GFR slope endpoints vs. the clinical endpoint is dependent on the nature of the long-term effects of the treatment on the chronic slope. If the treatment effect is uniform, leading to the same change in slope irrespective of the patients' underlying progression rate, statistical power for slope endpoints can be expected to be relative high compared to time-to-event endpoints since the analyses of mean slope incorporates data from all patients, including those with slow progression rates. By contrast, analyses of time-to-event endpoints censor those patients with relatively slow progression who do not reach events, and therefore do not account for information

provided by different rates of progression among patients not reaching events. On the other hand, if the effect of the treatment is proportional to the rate of GFR decline that would have occurred without the treatment, the size of the treatment effect will be larger in faster progressing patients than in more slowly progressing patients. In this case, the effect size for time-to-event outcomes tends to be amplified compared to the effect size for analyses of mean slope. This is because the effect size for the analysis of mean slope is attenuated by small effects on slowly progressing patients, whereas these patients are censored and thus do not contribute to the effect size for time-to-event outcomes.

By definition, proportional effects, but not uniform effects, attenuate the standard deviation (SD) as well as the mean of the GFR slopes. Hence, to evaluate if treatment effects are proportional or uniform, we applied a meta-regression analysis to relate the ratio of the chronic slope standard deviations to the ratio of mean chronic slopes between treatment and control groups across the 47 randomized treatment comparisons. The ratios of the means and standard deviations of the chronic slopes and their associated standard errors were first estimated within each study using the mixed effects models described above. We assumed that the sampling errors for the mean slopes and the standard deviations of the slopes were statistical independent within each study.

The results of the meta-regression are reported in **Supplemental Figure 1**. The figure shows that treatments that reduce the mean chronic slope also often reduce the slope SD, indicating that effective treatments tend to slow progression more in faster than in slower progressors. The intercept of the meta-regression line is approximately 0 and the slope of the meta-regression line is 0.45 ± 0.13, about half way between 0 (corresponding to uniform effects) and 1 (corresponding to proportional effects), suggesting treatment effects are usually roughly intermediate between uniform and proportional.

Supplemental Table 4. Patient characteristics by study

Intervention	Disease	Study	N	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)
	Glom (IgAN)	Praga 2003	44	31.6 (11.5)	17 (38.6)	0 (0.0)	0 (0.0)	98.1 (26.5)	1018 (659, 1437)
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)
Intensive 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)	REIN 2	330	54.2 (14.9)	82 (24.8)	0 (0.0)	17 (5.2)	32.3 (18.1)	1429 (906, 2194)
	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 Protein	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)
Diet	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)
	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)

Immunosuppr	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)
ession	Glom (IgAN)	Appel	29	37.9 (12.3)	5 (17.2)	0 (0.0)	0 (0.0)	42.2 (26.6)	1371 (982, 1976)
	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)
	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 (IgAN)	Katafuchi	81	35.6 (11.2)	48 (59.3)	0 (0.0)	0 (0.0)	98.8 (21.4)	797 (563, 1543)
	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)
Alb Protocol	CKD (CNS)	ROAD	339	50.9 (13.7)	126 (37.2)	0 (0.0)	0 (0.0)	29.0 (13.4)	958 (641, 1599)
Sulodexide	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)
EMPA	Diabetes	EMPA-REG	6936	63.2 (8.6)	1977 (28.5)	354 (5.1)	6936 (100.0)	76.2 (19.9)	18 (7, 72)
Allopurinol	CKD (CNS)	Goicoechea	113	71.8 (8.7)	40 (35.4)	0 (0.0)	42 (37.2)	40.5 (12.4)	35 (15, 362)
GLUC	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	15 (7, 40)
Nurse Care	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)
Simva/Eze	CKD (CNS)	SHARP	6245	62.9 (11.7)	2363 (37.8)	119 (1.9)	1426 (22.8)	26.2 (12.3)	206 (44, 762)
Pooled studies	Glom (IgAN)	IgAN-ACEI	153	37.9 (10.8)	96 (62.7)	0 (0.0)	3 (2.0)	81.7 (30.1)	958 (659, 1497)
	Glom (IgAN)	IgAN-MMF	63	41.6 (12.2)	15 (23.8)	0 (0.0)	0 (0.0)	53.0 (24.7)	1078 (497, 1946)
	Glom (IgAN)	IgAN-AZA	243	39.8 (12.4)	64 (26.3)	0 (0.0)	0 (0.0)	65.8 (29.5)	1198 (898, 1737)
	Glom (IgAN)	IgAN-steroid	259	35.9 (11.5)	102 (39.4)	0 (0.0)	2 (0.8)	92.3 (22.7)	1018 (726, 1497)
	Glom (Membran)	Mem-Ponticelli	273	47.4 (11.7)	81 (29.7)	0 (0.0)	0 (0.0)	86.9 (22.7)	3174 (2395, 4790)

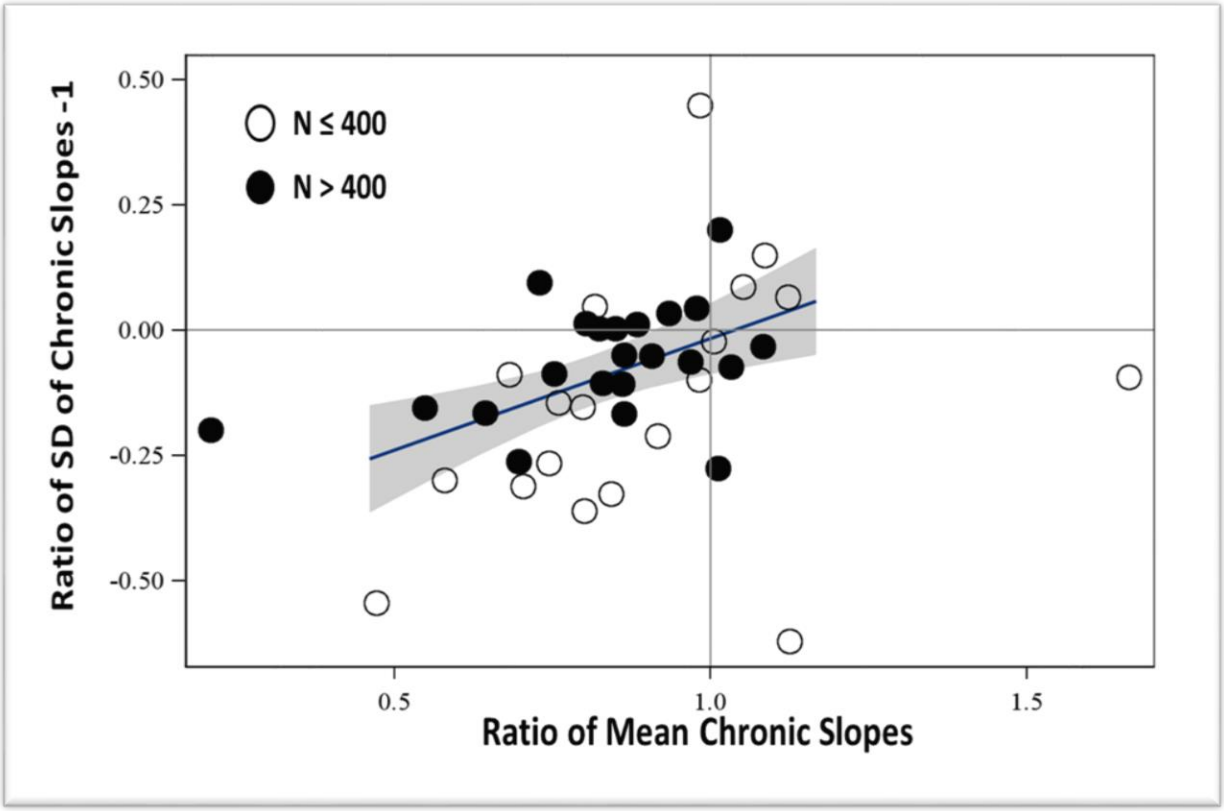
Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean (standard deviation). The number of participants refers to those included in the GFR analysis. Participants with missing data on age, race, sex, serum creatinine, urine albumin were excluded.

Supplemental Table 5: Distribution of key input parameters for statistical simulations

Parameter	Mean (SE)	SD (SE)
Acute Effect (mL/min/1.73m^2)	0.19 (0.23)	1.27 (0.19)
Acute Effect Normed to a GFR of 42.5 mL/min/1.73m^2*	0.15 (0.18)	1.01 (0.15)
Standard Deviation of Chronic GFR Slope (mL/min/1.73m^2/year)	3.89 (0.22)	1.43 (0.18)
Mean GFR Slope in Control Group (mL/min/1.73m^2/year)	-3.54 (0.26)	1.73 (0.20)

* Normalized acute effects were expressed relative to a GFR of 42.5 mL/min/1.73m^2 assuming acute effects are linearly related to the GFR level and attenuate to 0 when GFR is ≤ 15 mL/min/1.73m^2.

Supplemental Figure 1. Meta-regression relating ratios of slope standard deviations to ratios of mean chronic slopes between treatment and control groups



The vertical axis indicates the difference between the ratio between treatment and control groups in the standard deviations of the chronic slopes and 1 and the horizontal axis indicates the ratio of mean chronic slopes between the treatment and control groups. This data points represent individual randomized treatment comparisons across different trials, with closed circles representing trials with greater than 400 subjects and open circles representing smaller trials. The meta-regression line relating these variables across the 47 randomized treatment comparisons is displayed with it 95% pointwise confidence band. The slope (and standard error) of the meta-regression line is 0.45 (0.13). This indicates and a reduction of the ratio of mean chronic slopes by 0.10 is associated with a reduction in the ratio of standard deviations by 0.045 (0.013).

Supplemental Table 6A: Gains in efficiency (with simulation standard errors in parentheses) for the total slope compared to the clinical outcome when the long-term treatment effect is intermediate between uniform and proportional and there is no acute effect

Mean Baseline GFR (mL/min/ 1.73m^2)	Mean Slope (mL/min/ 1.73m^2/year)	No Acute Effect			
		Relative Efficiency of the Total Slope vs. the Clinical Endpoint			Required N for Clinical Outcome in a 4-6 Year RCT
		Total Slope in 2 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Total Slope in 2.5-4 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Total Slope in 4-6 Year RCT vs. Clinical Outcome in 4-6 Year RCT	
27.5	-1.5	1.14 (0.016)	1.16 (0.014)	1.07 (0.015)	4,980
	-3.25	1.51 (0.016)	1.64 (0.016)	1.58 (0.016)	2,170
	-5	1.24 (0.016)	1.29 (0.017)	1.40 (0.025)	870
42.5	-1.5	0.71 (0.021)	1.20 (0.014)	1.11 (0.014)	4,130
	-3.25	1.41 (0.019)	1.39 (0.014)	1.71 (0.013)	1,750
	-5	1.17 (0.018)	1.56 (0.014)	1.61 (0.014)	830
67.5	-1.5	1.06 (0.018)	1.66 (0.015)	1.83 (0.013)	6,090
	-3.25	1.28 (0.018)	2.07 (0.016)	2.16 (0.015)	2,480
	-5	1.63 (0.017)	2.34 (0.016)	2.42 (0.014)	1,310

All calculations assume a 25% intermediate long term effect.
Relative efficiencies are given by the ratio of sample size (N) for the clinical endpoint over 4-6 years vs. the slope analysis over the indicated follow-up period. Relative efficiencies > 1 indicate that a smaller sample size is required to achieve the same statistical power with the slope outcome over the indicated follow-up period compared to the clinical endpoint over 4-6 years.

Supplemental Table 6B: Gains in efficiency (with simulation standard errors in parentheses) for total slope and chronic slope compared to the clinical outcome when the long-term treatment effect is intermediate between uniform and proportional and there is a moderate negative acute effect

Mean Baseline GFR (mL/min/ 1.73m^2)	Mean Slope (mL/min/ 1.73m^2/year)	Relative Efficiency of the Total Slope vs. the Clinical Endpoint			Relative Efficiency of the Chronic Slope vs. the Clinical Endpoint			Required N for Clinical Outcome in a 4-6 Year RCT
		Total Slope in 2 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Total Slope in 2.5-4 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Total Slope in 4-6 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Chronic Slope in 2 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Chronic Slope in 2.5-4 Year RCT vs. Clinical Outcome in 4-6 Year RCT	Chronic Slope in 4-6 Year RCT vs. Clinical Outcome in 4-6 Year RCT	
27.5	-1.5	0.37 (0.017)	0.84 (0.014)	0.41 (0.022)	1.27 (0.018)	1.62 (0.015)	0.76 (0.022)	7,140
	-3.25	0.82 (0.016)	1.33 (0.015)	1.49 (0.016)	1.29 (0.018)	1.69 (0.016)	1.81 (0.017)	2,190
	-5	1.13 (0.016)	1.25 (0.017)	1.53 (0.024)	1.32 (0.018)	1.40 (0.018)	1.77 (0.024)	960
42.5	-1.5	0.28 (0.020)	0.15 (0.014)	0.39 (0.013)	0.71 (0.022)	1.38 (0.015)	1.68 (0.013)	5,010
	-3.25	0.26 (0.020)	0.73 (0.014)	1.23 (0.013)	1.13 (0.023)	1.70 (0.015)	2.32 (0.013)	1,940
	-5	0.64 (0.017)	1.05 (0.014)	1.59 (0.014)	1.26 (0.020)	1.77 (0.015)	2.33 (0.014)	930
67.5	-1.5	0.46 (0.017)	0.46 (0.016)	0.46 (0.013)	1.18 (0.020)	2.09 (0.017)	2.83 (0.013)	8,240
	-3.25	0.16 (0.018)	0.17 (0.016)	0.69 (0.013)	1.42 (0.021)	2.41 (0.017)	3.65 (0.013)	2,940
	-5	0.09 (0.017)	0.70 (0.016)	1.25 (0.013)	1.36 (0.020)	2.64 (0.016)	3.29 (0.013)	1,260

All calculations assume a 25% intermediate long term effect.

Relative efficiencies are given by the ratio of sample size (N) for the clinical endpoint over 4-6 years vs. the slope analysis over the indicated follow-up period. Relative efficiencies > 1 indicate that a smaller sample size is required to achieve the same statistical power with the slope outcome over the indicated follow-up period compared to the clinical endpoint over 4-6 years.

Use of the chronic slope may incur an inflated risk of a false positive conclusion when the acute effect is negative.

Supplemental Appendix 4: Legends for supplemental figures

Supplemental Figure 2. Relationship of relative efficiency of alternative endpoints vs. type of long-term treatment effect when there is no acute effect and mean GFR decline is fast

Shown are the relative efficiencies of the alternative endpoints compared to the clinical endpoint when the mean GFR slope in the control group is fast (-5 mL/min/1.73m^2/year). Relative efficiencies greater than 1 indicate higher power for the alternative endpoint than the clinical endpoint. Within each panel, relative efficiencies are provided for uniform, intermediate and proportional long-term treatment effects. The panels correspond to trials in which the mean baseline GFR is low (27.5 mL/min/1.73m^2; top panels), intermediate (42.5 mL/min/1.73m^2; middle panels), or high (67.5 mL/min/1.73m^2; bottom panels), with either short (2 years; left panels), medium (2.5-4 years; middle panels), or long (4-6 years, right panels) follow-up. Relative efficiencies could not be accurately computed for trials with high baseline GFR and 2 years of follow-up due to insufficient events for the clinical endpoint.

Supplemental Figure 3. Required total sample size of alternative endpoints when the long-term treatment effect is fully proportional and there is no acute effect

Shown are the total sample sizes in both the treatment and control groups combined required to obtain 90% power with 2-sided α=0.05 to detect a 25% reduction in the rate of ESKD when the analysis is based on the indicated endpoints and the long term treatment effect is fully proportional. Within each panel, the required sample sizes are provided for slow (-1.5 mL/min/1.73m^2/year), intermediate (-3.25 mL/min/1.73m^2/year) or fast (-5.0 mL/min/1.73m^2/ year) mean rates of GFR decline. The panels correspond to trials in which the mean baseline GFR is low (27.5 mL/min/1.73m^2; top panels), intermediate (42.5 mL/min/1.73m^2; middle panels), or high (67.5 mL/min/1.73m^2; bottom panels), with either short (2 years; left panels), medium (2.5-4 years; middle panels), or long (4-6 years, right panels) follow-up. Required sample sizes greater than 12,800 are indicated by open circles. All required sample sizes assume there is no acute effect.

Supplemental Figure 4: Required total sample size of alternative endpoints when the long-term treatment effect is intermediate between proportional and uniform and there is moderate negative acute effect which attenuates

Shown are the total sample sizes in both the treatment and control groups combined required to obtain 90% power with 2-sided α=0.05 to detect a 25% reduction in the rate of ESKD when the analysis is based on the indicated endpoints and the long term treatment effect is intermediate between proportional and uniform and there is moderate negative acute effect which attenuates. The size of the negative acute effect is assumed to be greater at higher levels of GFR such that the acute effect fully attenuates by the time GFR declines to 15 mL/min/1.73m^2. Within each panel, the required sample sizes are provided for slow (-1.5 mL/min/1.73m^2/year), intermediate (-3.25 mL/min/1.73m^2/year) or fast (-5.0 mL/min/1.73m^2/ year) mean rates of GFR decline. The panels correspond to trials in which the mean baseline GFR is low (27.5 mL/min/1.73m^2; top panels), intermediate (42.5 mL/min/1.73m^2; middle panels), or high (67.5 mL/min/1.73m^2; bottom panels), with either short (2 years; left panels), medium

(2.5-4 years; middle panels), or long (4-6 years, right panels) follow-up. Required sample sizes greater than 12,800 are indicated by open circles.

Supplemental Figure 5: Required total sample size of alternative endpoints when the long-term treatment effect is intermediate between proportional and uniform and there is moderate negative acute effect which does not attenuate

Shown are the total sample sizes in both the treatment and control groups combined required to obtain 90% power with 2-sided α=0.05 to detect a 25% reduction in the rate of ESKD when the analysis is based on the indicated endpoints and the long term treatment effect is intermediate between proportional and uniform and there is moderate negative acute effect which attenuates. The size of the negative acute effect is assumed to be the same at all GFR levels so that the acute effect does not attenuate as GFR declines. Within each panel, the required sample sizes are provided for slow (-1.5 mL/min/1.73m^2/year), intermediate (-3.25 mL/min/1.73m^2/year) or fast (-5.0 mL/min/1.73m^2/ year) mean rates of GFR decline. The panels correspond to trials in which the mean baseline GFR is low (27.5 mL/min/1.73m^2; top panels), intermediate (42.5 mL/min/1.73m^2; middle panels), or high (67.5 mL/min/1.73m^2; bottom panels), with either short (2 years; left panels), medium (2.5-4 years; middle panels), or long (4-6 years, right panels) follow-up. Required sample sizes greater than 12,800 are indicated by open circles.

Supplemental Figure 6. Relationship of relative efficiency of alternative endpoints vs. standard deviation of GFR slopes when there is no acute effect and the long-term treatment effect is intermediate between proportional and uniform

Shown are the relative efficiencies of the alternative endpoints compared to the clinical endpoint when the mean GFR slope in the control group is moderate (-3.25 mL/min/1.73m^2/year) and the long-term treatment effect is intermediate between proportional and uniform. Relative efficiencies greater than 1 indicate higher power for the alternative endpoint than the clinical endpoint. Within each panel, the standard deviation of the chronic slopes is plotted on the x-axis. The panels correspond to trials in which the mean baseline GFR is low (27.5 mL/min/1.73m^2; top panels), intermediate (42.5 mL/min/1.73m^2; middle panels), or high (67.5 mL/min/1.73m^2; bottom panels), with either short (2 years; left panels), medium (2.5-4 years; middle panels), or long (4-6 years, right panels) follow-up.

Supplemental Figure 7. Bias and risk of false positive and false negative conclusions when there is no long-term treatment effect and follow-up time is short

The top panels display the effects of the treatment on the mean total slope to 2 years (left) and the mean chronic slope (right) as a function of the acute effect on the horizontal axis when the acute effect is assumed to increase linearly from 0 at 15 mL/min/1.73m^2 to the values indicated on the horizontal axis at a GFR of 42.5 mL/min/1.73m^2 and follow-up is short (2 years). The acute effects are then assumed to attenuate linearly as GFR declines during subsequent follow-up, with complete attenuation reached at a GFR of 15 mL/min/1.73m^2. Because there is no effect of the treatment on the time to ESKD or death, any non-zero effects represent a bias relative to the treatment effect on the clinical endpoint. The bottom panels indicate the implications of these biases for the risk of false conclusions of treatment

benefit or of treatment harm. The mean baseline GFR was assumed to be intermediate (42.5 mL/min/1.73m^2).

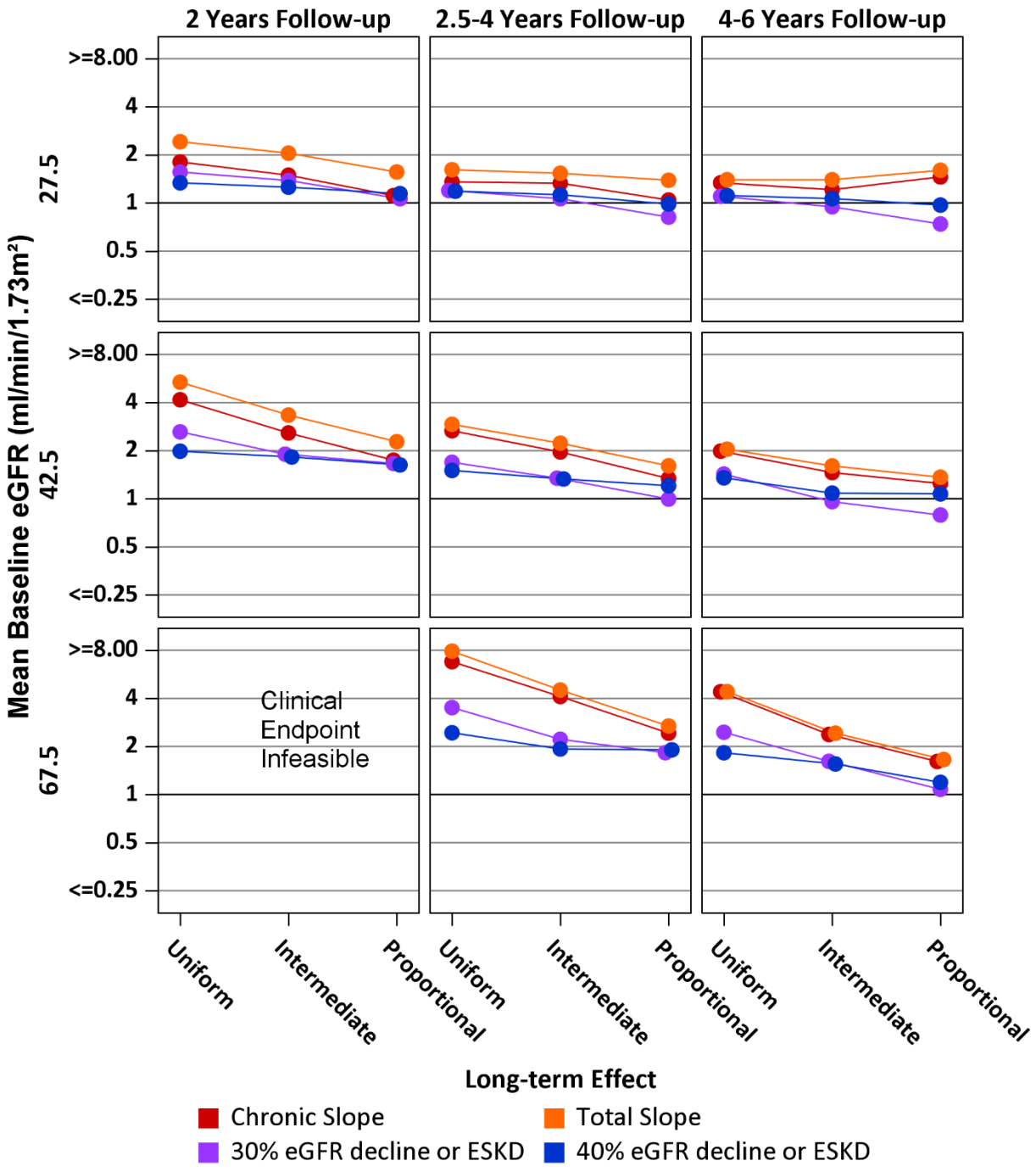
Supplemental Figure 8. Bias and risk of false positive and false negative conclusions when there is no long-term treatment effect and follow-up time is long

The top panels display the effects of the treatment on the mean total slope to 4 years (left) and the mean chronic slope (right) as a function of the acute effect on the horizontal axis when the acute effect is assumed to increase linearly from 0 at 15 mL/min/1.73m^2 to the values indicated on the horizontal axis at a GFR of 42.5 mL/min/1.73m^2 and follow-up is long (4-6 years). The acute effects are then assumed to attenuate linearly as GFR declines during subsequent follow-up, with complete attenuation reached at a GFR of 15 mL/min/1.73m^2. Because there is no effect of the treatment on the time to ESKD or death, any non-zero effects represent a bias relative to the treatment effect on the clinical endpoint. The bottom panels indicate the implications of these biases for the risk of false conclusions of treatment benefit or of treatment harm. The mean baseline GFR was assumed to be intermediate (42.5 mL/min/1.73m^2).

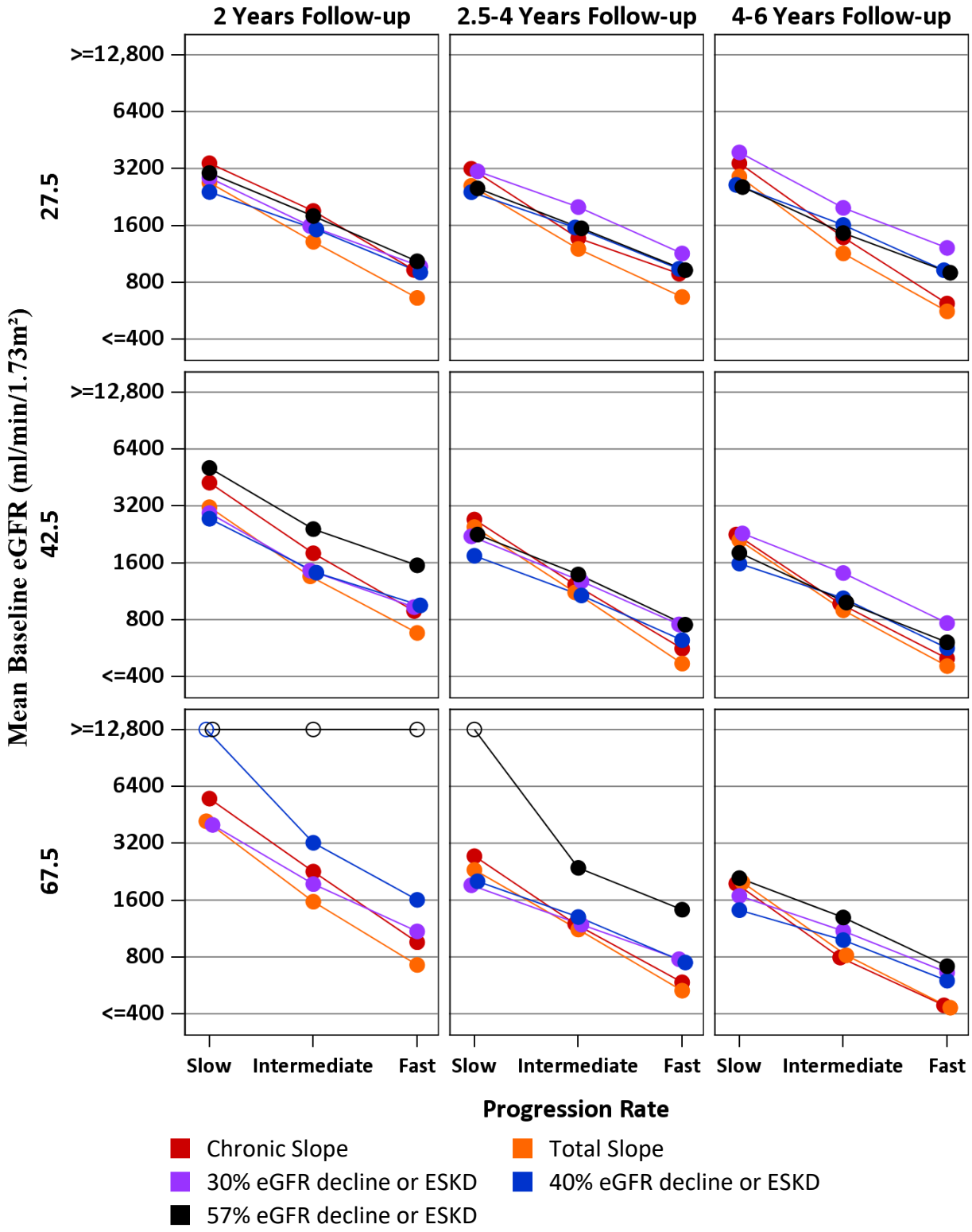
Supplemental Figure 9: Estimated treatment effects on the chronic and total slopes when there is no long-term treatment effect and follow-up time is intermediate, and the acute effect does not attenuate

The top panels display the effects of the treatment on the mean total slope to 3 years (left) and the mean chronic slope (right) as a function of the acute effect on the horizontal axis when the acute effect does not attenuate and follow-up is medium (2.5 - 4 years). The acute effect is assumed to be the same irrespective of the GFR level. No long-term effect of the treatment is assumed. In this setting, the acute effect does not attenuate, and treatment effects on the total slope represent true benefit or harm even though there is no treatment effect on the chronic slope. The bottom level panel shows the probabilities that an analysis of the total slope would infer benefit or harm when the total sample size is 1,000. The bottom right panel shows that the chronic slope as a probability of 0.025 of inferring either benefit or harm in this situation, corresponding to half the 2-sided α-level.

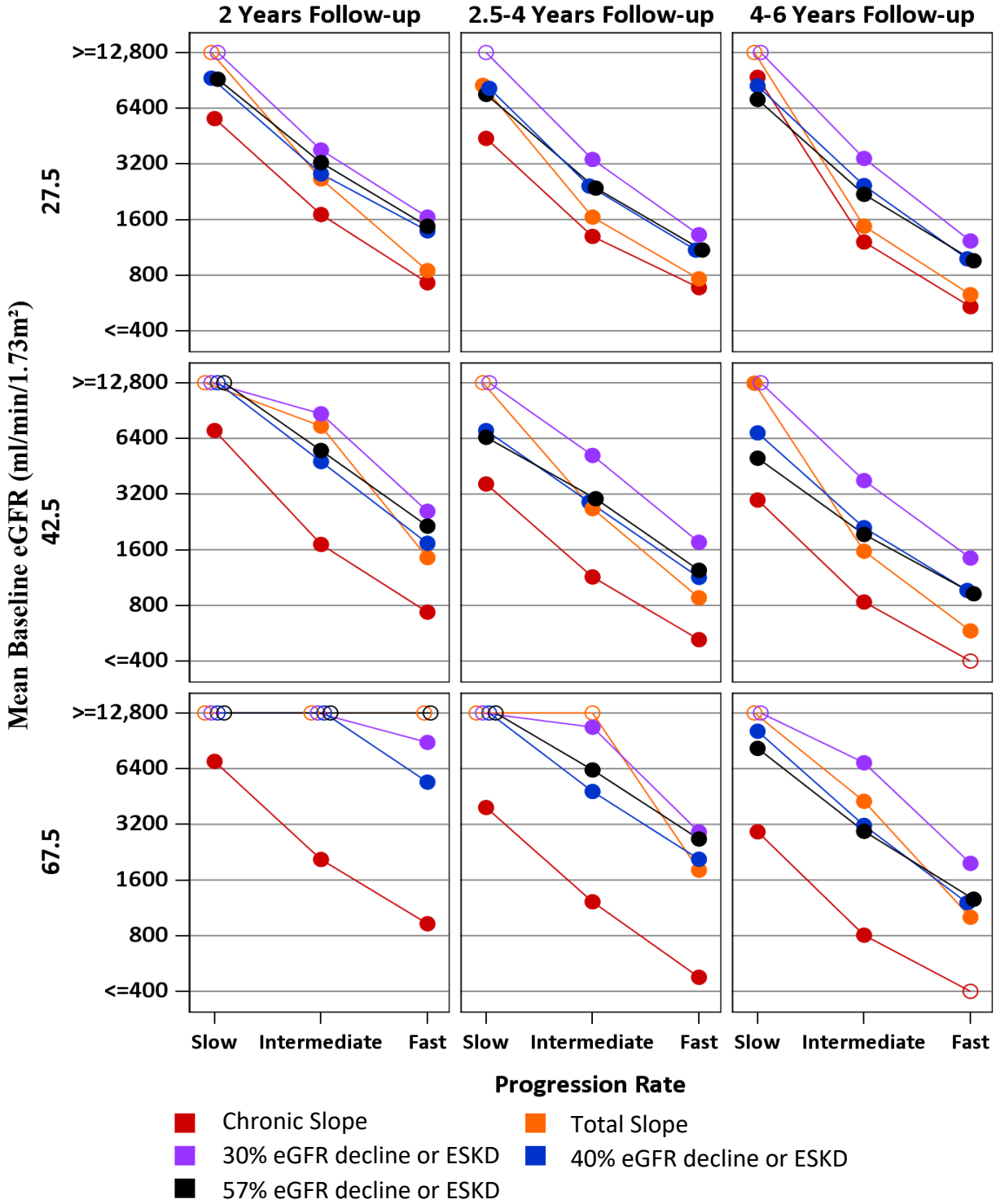
Supplemental Figure 2: Relationship of relative efficiency of alternative endpoints vs. type of long-term treatment effect when there is no acute effect and progression is fast



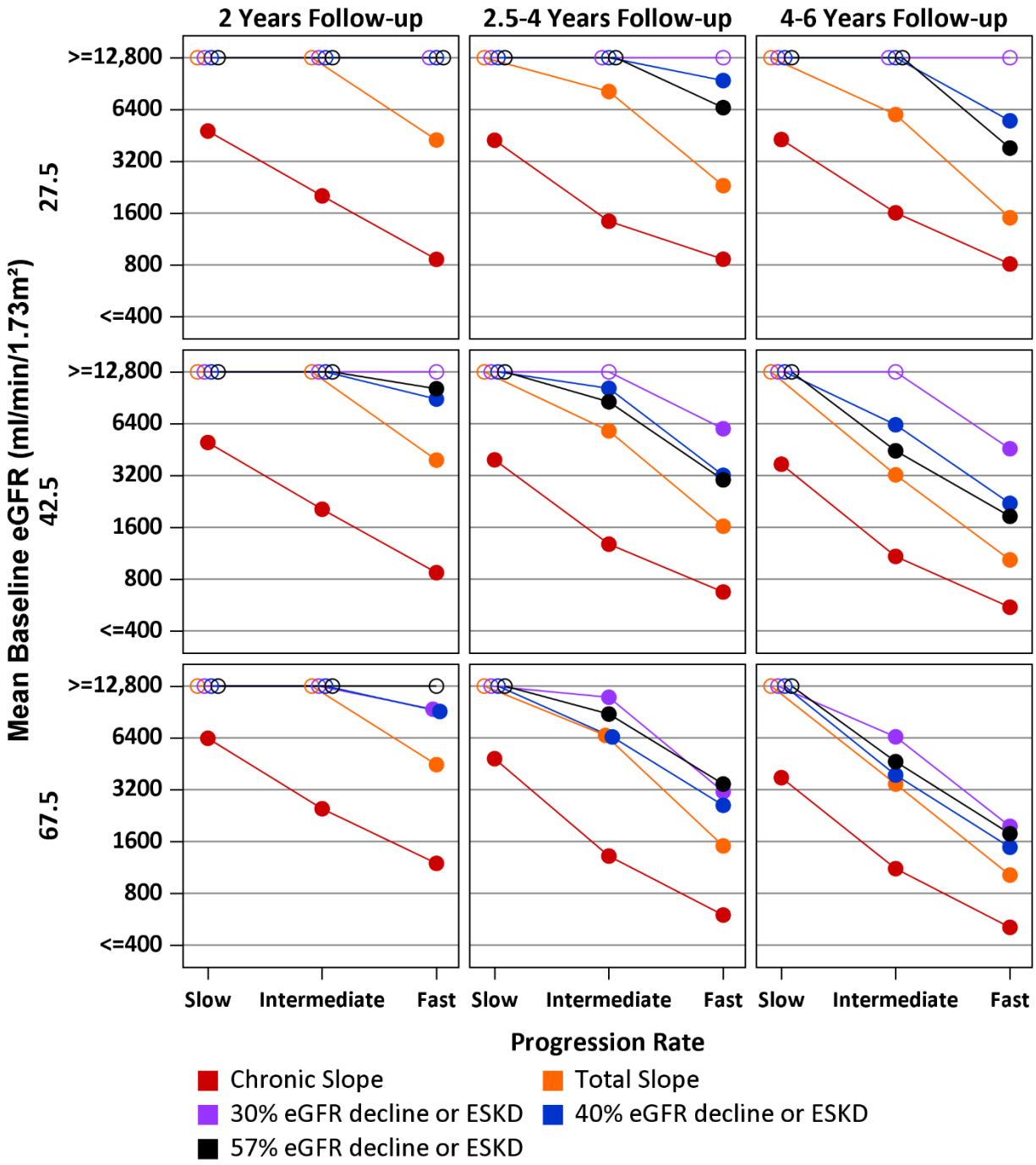
Supplemental Figure 3: Required total sample size of alternative endpoints when the long-term treatment effect is fully proportional and there is no acute effect



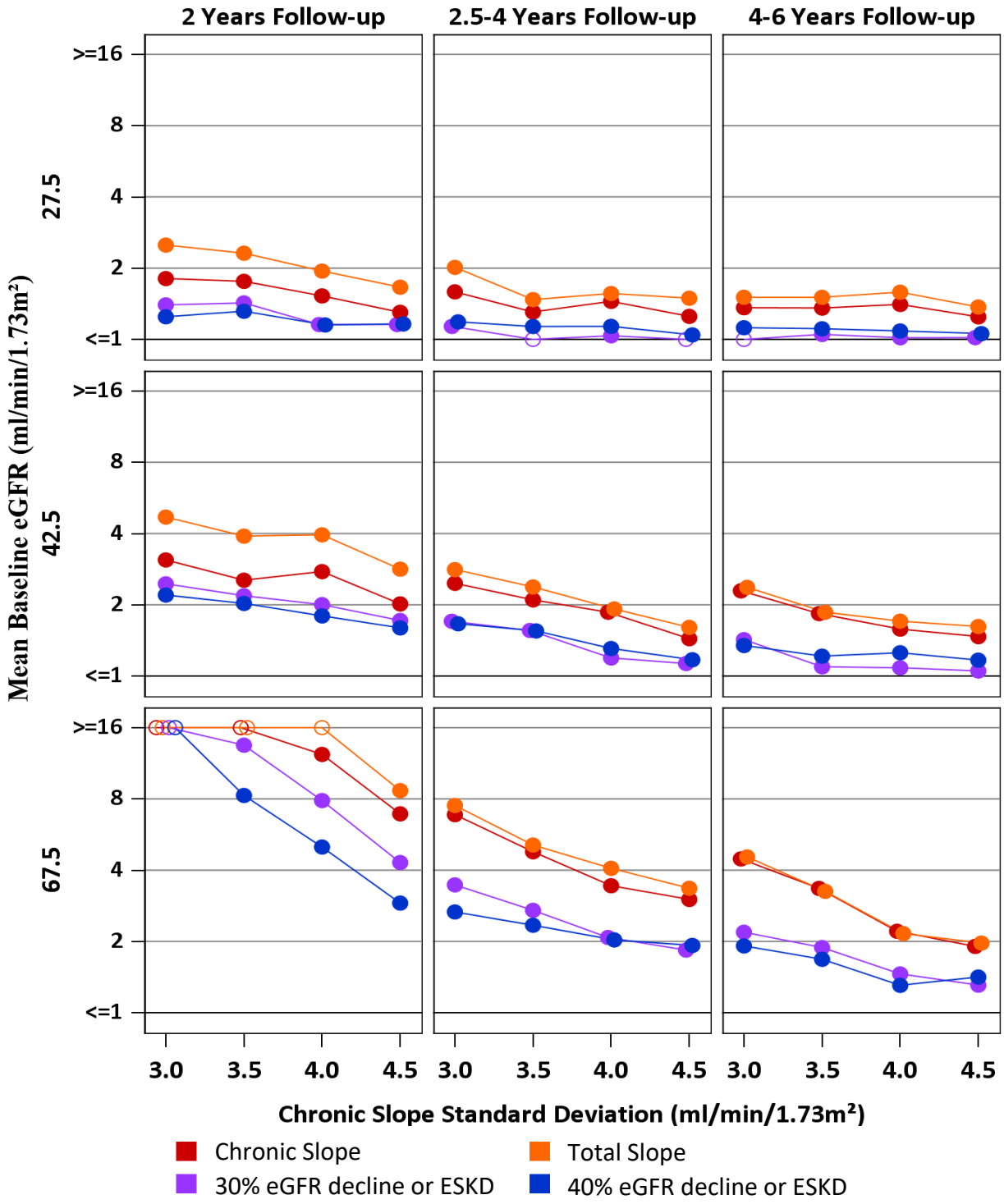
Supplemental Figure 4: Required total sample size of alternative endpoints when the long-term treatment effect is intermediate between proportional and uniform and there is moderate negative acute effect which attenuates



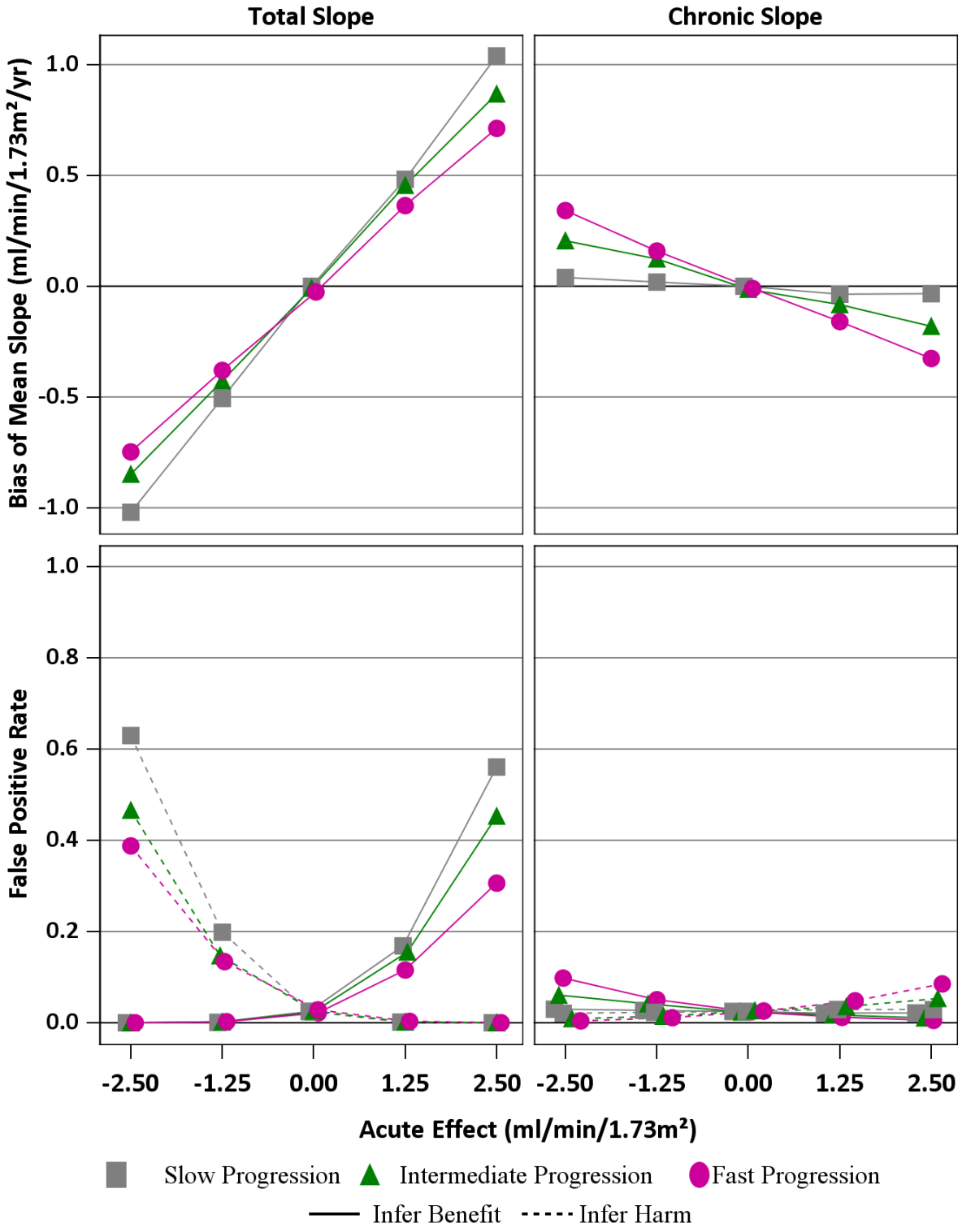
Supplemental Figure 5: Required total sample size of alternative endpoints when the long-term treatment effect is intermediate between proportional and uniform and there is moderate negative acute effect which does not attenuate



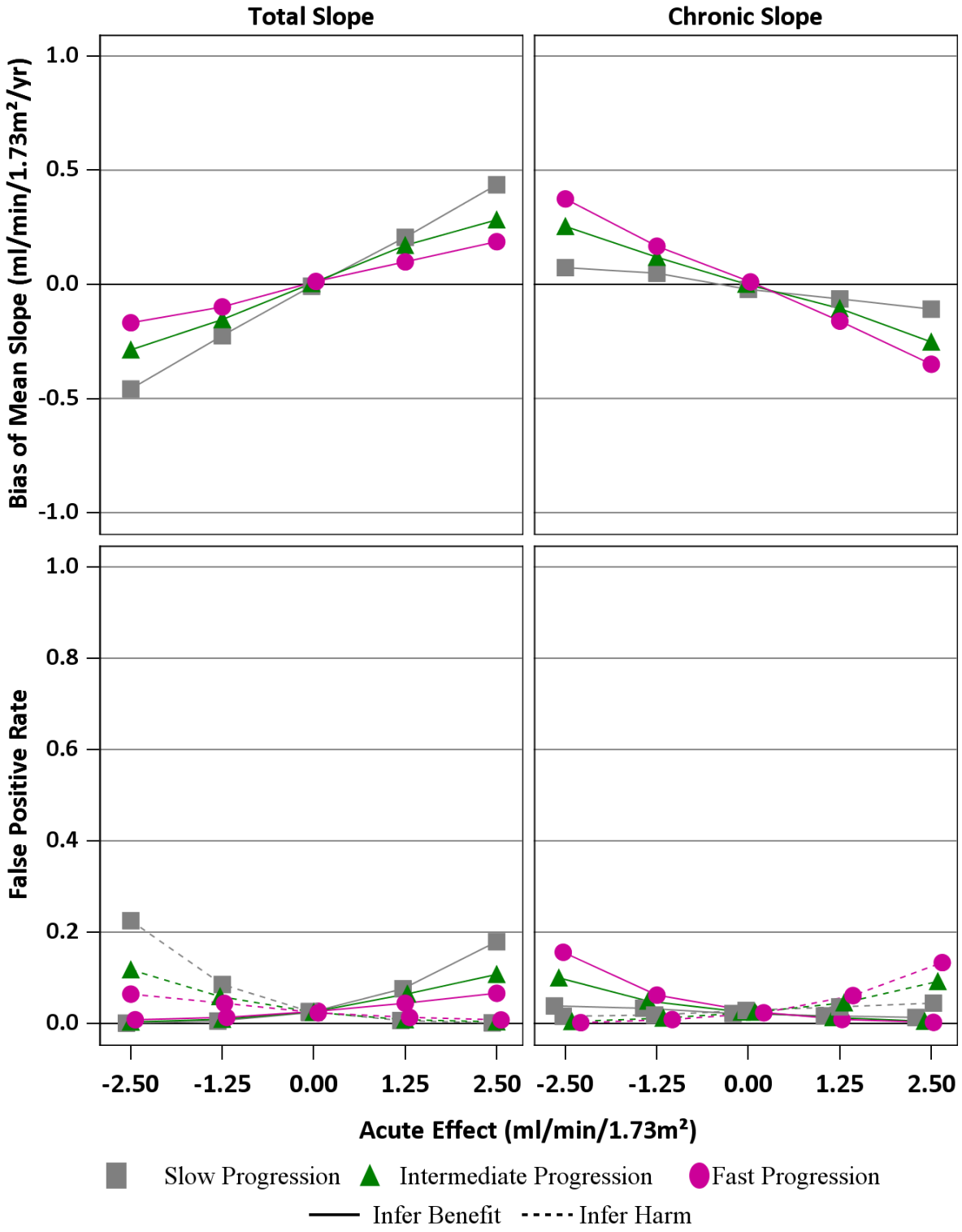
Supplemental Figure 6: Relationship of relative efficiency of alternative endpoints vs. standard deviation of GFR slopes when there is no acute effect and the long-term treatment effect is intermediate between proportional and uniform



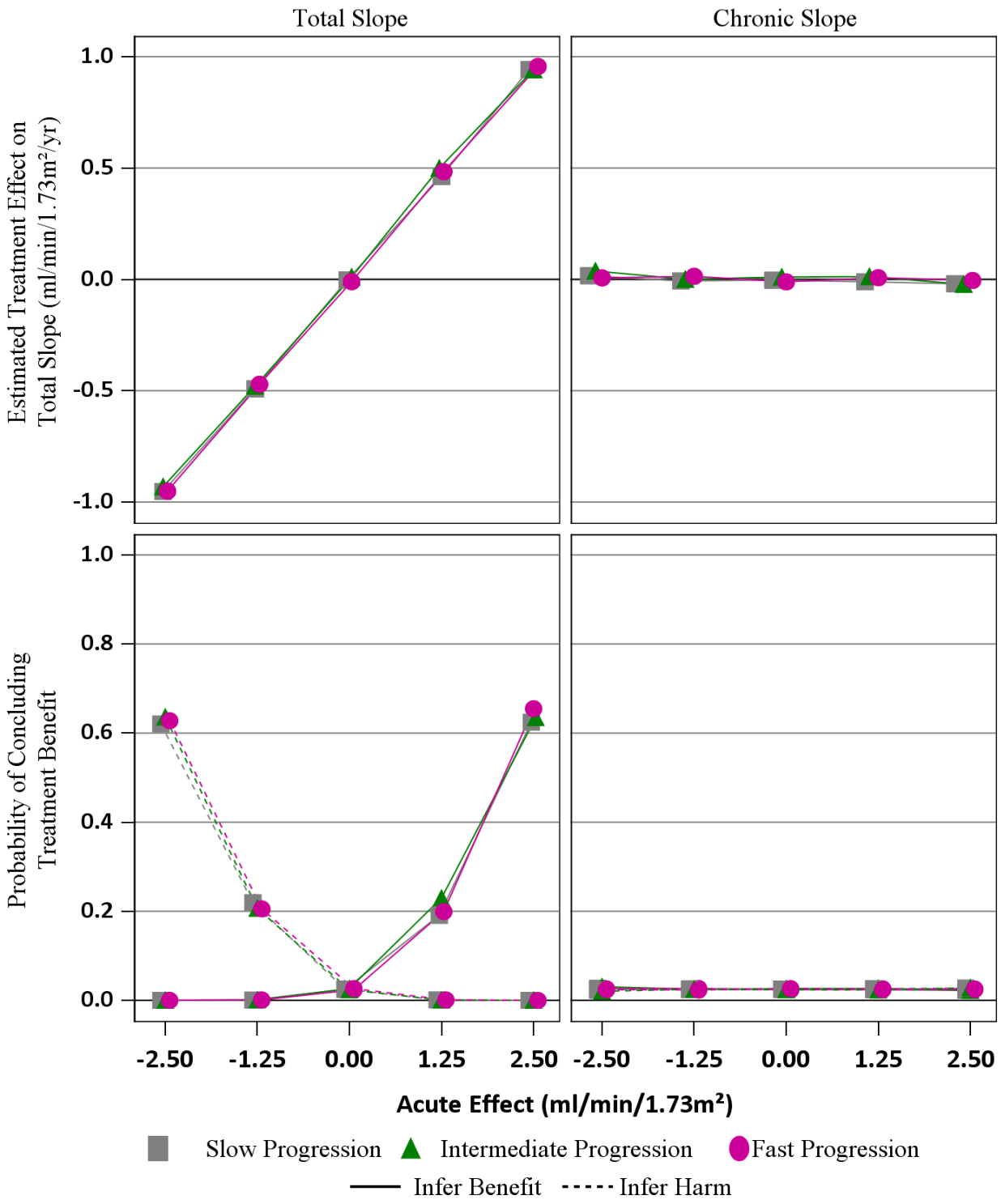
Supplemental Figure 7: Bias and risk of false positive and false negative conclusions when there is no long term treatment effect and follow-up time is short



Supplemental Figure 8: Bias and risk of false positive and false negative conclusions when there is no long term treatment effect and follow-up time is long



Supplemental Figure 9: Estimated treatment effects on the chronic and total slopes when there is no long-term treatment effect and follow-up time is intermediate, and the acute effect does not attenuate



Supplemental Appendix 5: Guide to Excel Spread Sheet with Expanded Results

The file Exel Spreadsheet Expanded Results.xlsx includes 4 different sheets which provide the required total sample size, the relative efficiency vs. the clinical endpoint, and the standard error of the relative efficiency for the chronic slope, total slope, confirmed 30% GFR decline, and the confirmed 40% GFR decline for a total of 342 different scenarios. These scenarios for each of the 4 sheets are defined as below. Some entries are left blank due to insufficient precision, primarily due to insufficient events for the clinical endpoint for accurate analysis. All the scenarios presented in the Spreadsheet have long-term treatment effects which are intermediate between uniform and proportional.

Part I: Full Attenuation of Acute Effects and Base-Case Scenarios for Slope and GFR Variability (Total of 135 rows)

Column Heading	Mean Intercept	Mean Slope	Follow-up Period	Slope SD	Residual GFR SD Around Trajectories	Long-Term Model	Acute Effect
Units	mL/min/1.73m^2	mL/min/1.73m^2 /yr	years	mL/min/1.73m^2/yr	mL/min/1.73m^2	-	mL/min/1.73m^2
Scenarios Included	27.5, 42.5, 67.5	-1.5, -3.25, -5.0	2, 2.5-4, 4-6	4	Sqrt(0.817 x GFR)	Intermediate	-2.5, -1.25, 0, 1.25, 2.5

Part II: No Attenuation of Acute Effects and Base-Case Scenarios for Slope and GFR Variability (Total of 81 rows)

Column Heading	Mean Intercept	Mean Slope	Follow-up Period	Slope SD	Residual GFR SD Around Trajectories	Long-Term Model	Acute Effect
Units	mL/min/1.73m^2	mL/min/1.73m^2 /yr	years	mL/min/1.73m^2/yr	mL/min/1.73m^2	-	mL/min/1.73m^2
Scenarios Included	27.5, 42.5, 67.5	-1.5, -3.25, -5.0	2, 2.5-4, 4-6	4	Sqrt(0.817 x GFR)	Intermediate	-1.25, 0, 1.25

Part III: No Acute Effect, Alternative Scenarios for Slope Variability (Total of 45 rows)

Column Heading	Mean Intercept	Mean Slope	Follow-up Period	Slope SD	Residual GFR SD Around Trajectories	Long-Term Model	Acute Effect
Units	mL/min/1.73m^2	mL/min/1.73m^2 /yr	years	mL/min/1.73m^2/yr	mL/min/1.73m^2	-	mL/min/1.73m^2
Scenarios Included	27.5, 42.5, 67.5	-3.25	2, 2.5-4, 4-6	2.5, 3, 3.5, 4, 4.5	Sqrt(0.817 x GFR)	Intermediate	0

Part IV: Low Residual GFR Variability
(Total of 81 rows)

Column Heading	Mean Intercept	Mean Slope	Follow-up Period	Slope SD	Residual GFR SD Around Trajectories	Long-Term Model	Acute Effect
Units	mL/min/1.73m^2	mL/min/1.73m^2 /yr	years	mL/min/1.73m^2/yr	mL/min/1.73m^2	-	mL/min/1.73m^2
Scenarios Included	27.5, 42.5, 67.5	-1.5, -3.25, -5.0	2, 2.5-4, 4-6	4	Sqrt(0.67 x GFR)	Intermediate	-1.25, 0, 1.25

Supplemental Appendix 6: Study funding sources

Study name	Funding
AASK	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	Supported by Bayer and the National Institute of Diabetes, Digestive, and Kidney Diseases (DK50298-02)
ADVANCE	ADVANCE was funded by grants from Servier and the National Health and Medical Research Council of Australia
AIPRI	Supported by a grant from Ciba–Geigy
ALTITUDE	Supported by Novartis
Appel	This study was supported in part by Roche Pharmaceuticals and the Glomerular Center at Columbia University as an investigator-initiated study (J.L. and G.A.), the NKF of NY/NJ under the Fred C. Trump Fellowship (J.L.), a KUFA fellowship (J.R.) and the Kidney Foundation of Canada (G.F.).
Brenner	Supported by Merck & Co.
CanPREVENT	Supported by the Memorial University of Newfoundland
Chan	Supported by the Wai Hung Charity Foundation and the Lee Wing Tat Renal Research Fund
Donadio 2001	Supported by research grants from Pronova Biocare a.s. (Oslo, Norway) and Mayo Foundation (Rochester, MN)
EMPA-REG OUTCOME	Supported by Boehringer Ingelheim (BI) and Eli Lilly
Goicoechea	Supported by REDINREN RD016/0019 FEDER funds
HALT-PKD	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	Supported by Merck Sharp & Dohme

HKVIN	Supported by Novartis Pharmaceuticals (Hong Kong) Ltd by providing the study medication and placebo
Hou	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	Supported by the Bristol-Myers Squibb Institute for Medical Research and Sanofi–Synthelabo
Ihle/Kincaid	Supported in part by Merck & Co, Inc., West Point, PA
Kamper	Supported by Merck Sharp & Dohme
Lewis 1992	Supported by grants (R01-AM-27769 and R01-AM-27770) from the Public Health Service
Lewis 1993	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	The study medication was kindly provided by Hoffmann-LaRoche, Basel, Switzerland
MASTERPLAN	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	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	Supported by a research grant from Daiichi Sankyo
Ponticelli 1989	Supported in part by a grant (82.01308.04) from the Consiglio Nazionale delle Ricerche.
Ponticelli 1998	Supported in part by a grant from Ospedabc Maggiore di Milano
Ponticelli 2006	This was a spontaneous clinical trial sponsored by the grant “Project Glomerulonephritis”
Pozzi 2004	The authors did not receive any financial support
Pozzi 2010	The authors did not receive any financial support
Pozzi 2012	The authors did not receive any financial support
Praga 2007	This study was partially supported by Astellas
REIN	Supported in part by a grant from Aventis Pharma SA, Antony, France.
REIN 2	REIN2 was an independent, academic study, where Aventis Pharma SA, Antony (France) and SIMESA SpA (Italy) only provided study medication (ramipril and felodipine, respectively).
RENAAL	Supported by Merck & Co.
ROAD	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	Supported in part by a grant of University of Bari
SHARP	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	Supported by a grant (GFVT01044604) from the German Federal Ministry of Education and Research.
SUN-MACRO	Sponsored by Keryx Biopharmaceuticals, Inc.

Toto	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	Supported by Merck Sharp & Dohme, Haarlem, The Netherlands

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