Request for Qualification Opinion	
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Request for CHMP Qualification Opinion

Acceptance of GFR Slope as a Validated Surrogate Endpoint for Chronic Kidney Disease Progression in Clinical Trials for Standard Marketing Authorization and Indication Extension Approvals

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this briefing document.

Abbreviation or special term	Explanation
ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
ARB	Angiotensin receptor blocker
BCI	Bayesian credible interval
BP	Blood pressure
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-EPI CT	CKD-EPI Clinical Trials
CKD-PC	Chronic Kidney Disease Prognosis Consortium
CNS	Cause not specified
CV	Cardiovascular
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESKD	End-stage kidney disease (also known as kidney failure with replacement therapy)
FDA	Food and Drug Administration
GFR	Glomerular filtration rate (mL/min/1.73 m^2)
HR	Hazard ratio
IgA	Immunoglobulin A
KFRT	Kidney failure with replacement therapy (also known as end-stage renal disease or end-stage kidney disease)
Meta-regression	Analysis that uses regression models to synthesize findings from multiple studies
MRA	Mineralocorticoid receptor antagonist
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NKF	National Kidney Foundation
PPV	Positive predictive value

Abbreviation or special term	Explanation
RAAS	Renin-angiotensin-aldosterone system
RASB	Renin-angiotensin system blocker
RCT	Randomized, controlled trial
RMSE	Root mean square error
SD	Standard deviation
SGLT-2	Sodium-glucose cotransporter 2
SNGFR	Single nephron

2. EXECUTIVE SUMMARY

The objective of this request is to seek a qualification opinion on the use of glomerular filtration rate (GFR) slope, i.e., the mean rate of change in GFR, as a validated surrogate endpoint for chronic kidney disease (CKD) progression in clinical trials for standard marketing authorization and indication extension approvals.

Statement of need for an impact of proposed novel methodology

Chronic kidney disease and its related complications represent a major public health burden globally, with an estimated 850 million people worldwide living with some form of kidney disease. Despite the disease prevalence and some progress made in identifying agents that can slow progression to kidney failure with replacement therapy (KFRT), there remains residual risk and an unmet need for additional therapies to slow or prevent CKD progression. This is reflected in the very small number of randomized, controlled trials (RCTs) in nephrology compared with other disease areas. An important factor contributing to the slow pace of development of interventions in CKD is that the clinical endpoints approved by regulators to support drug approval or marketing authorization, i.e., KFRT or doubling of serum creatinine, are late manifestations of progression of CKD. Such studies usually require long follow-up periods, very large sample sizes, or must focus on patients in later stages of disease to achieve sufficient statistical power to detect a significant treatment effect.

Validated surrogate endpoints are needed to reduce the time and patient numbers required to assess whether treatments are effective to prevent CKD progression and KFRT and to consequently support market authorization of such treatments. The acceptance of validated surrogate endpoints for use in the broad population of patients with CKD would increase efficiency of drug development to slow CKD progression across a spectrum disease types and would enhance feasibility of studies of interventions for patients earlier in the disease process or who have slower progressing disease. This could incentivise product developers to increase their engagement to develop new treatments for patients with CKD, a patient population who continues to have a high medical need despite some recent advances. Importantly, acceptance of GFR slope as a validated surrogate endpoint is likely to be meaningful for patients, as a greater variety of effective medicines would be available more quickly and across more CKD settings (Damron et al 2022, Friedman 2022).

This application provides empirical data that treatment effects on GFR slope predict treatment effects on clinical endpoint for CKD progression in studies conducted across a range of patient populations and intervention types. GFR slope is therefore proposed as a validated surrogate endpoint in trials for full regulatory approval and label claim acceptance with broad applicability.

Context of use for GFR slope as a validated surrogate endpoint

- **General setting**: The proposed novel method is intended to be used as a validated surrogate endpoint in confirmatory RCTs of therapeutic interventions for CKD progression, i.e., to evaluate treatment response in trials intended to form an adequate

basis for standard marketing authorizations for new medicines and indication extensions for already approved medicines

Target population: Broad population of patients with CKD or at high risk of CKD, including early disease and subgroups by GFR and causal disease of CKD. Characteristics of the proposed methodology

The key criteria for establishing the validity of a surrogate endpoint are:

1. **Biological plausibility**: There must be strong support from cellular, molecular, animal, and human studies that the endpoint can plausibly be expected to predict the clinical outcome of interest.
2. **Individual level associations:** There should be epidemiologic data demonstrating a strong and consistent relationship between the surrogate endpoint and outcome of interest.
3. **Trial level analyses** It must be possible to predict the treatment effect on the clinical endpoint based on the treatment effect on the surrogate.

The CKD Epidemiology Collaboration (CKD-EPI) (co-applicant with the National Kidney Foundation [NKF]), and a component collaboration CKD-EPI Clinical Trials (CKD-EPI CT), was first formed in 2003 to evaluate one potential surrogate endpoint in CKD (proteinuria), as well as other key challenges in CKD epidemiology at the time. Work has been conducted over the past two decades, facilitated by milestone scientific workshops held in conjunction with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2008, 2012, and 2018. These investigations led to the conclusion that GFR slope fulfils the criteria for surrogacy for use as an endpoint in clinical trials for CKD progression under certain conditions. The work presented in this qualification request expand on the earlier findings and strongly support the use of GFR slope as a validated surrogate endpoint for CKD progression across a broad range of patient populations and therapeutic interventions.

Sources of data and major findings

1. **Biologic plausibility:** GFR is overall the best method to assess kidney function. Regardless of cause, reduced GFR is a criterion for the definition and classification of CKD, and changes in GFR are used to define progression of CKD. Decline in GFR is on the causal pathway to kidney failure; patients cannot have kidney failure without having changes in GFR. **Therefore, GFR has biologic plausibility as a valid surrogate, the first criterion for a surrogate endpoint listed above.**

2. **Individual level associations:** Meta-analysis of observational cohorts demonstrated a strong relationship between percent changes in GFR over 30% to 40% (Coresh et al 2014) and GFR slope over 1 to 3 years (Grams et al 2019) and clinical endpoint (KFRT) in cohort data and provides epidemiological support for GFR decline as a surrogate endpoint. In these analysis, **GFR decline is a strong risk predictor for all complications of kidney disease, including progression to kidney failure, cardiovascular disease (CVD) and mortality, thus meeting the second criterion listed above**. The analysis evaluating GFR slope specifically is summarized in in Section 6 of this request.

3. **Trial level analyses**: We performed meta-analysis of 37 randomized treatment comparisons published in 2014 that demonstrated strong associations between treatment effects on time to 30% and 40% decline in GFR and treatment effects on the clinical endpoint (defined as doubling of serum creatinine, GFR <15 ml/min per 1.73 m^2, or KFRT). Based on these analyses, 40% decline in GFR was accepted as a validated surrogate endpoint (FDA 21CFR.510, EMA/CHMP/500825/2016). However, these endpoints are still only able to capture CKD progression in participants who have relatively fast progression of their disease and are not able to incorporate information on participants who had the event subsequent to study closure. We then turned to investigate GFR slope which overcomes these limitations.

Analysis of GFR slope first required development of analytical methods to compute slope across a broad set of studies. The slope model developed used mixed models that incorporated informative censoring and heterogeneity within and across subjects (Vonesh et al 2019). Because many of the prior RCT evaluated interventions that produce initial GFR changes that differ from their long-term effects, GFR decline was computed as the total slope (defined as the mean slope from randomization to study end, operationally computed as the change from baseline to specified time point) and on the chronic slope (defined as the mean slope starting after the initial phase, operationally computed after 3 months after randomization, until the study end).

A meta-analysis of 47 randomized treatment comparisons published in 2019 evaluated the relationship between treatment effects on GFR slope and treatments effects on the clinical endpoint. The studies, identified from systematic review of the literature, had a wide range of interventions, cause of disease, estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) values at baseline. Bayesian analyses were used to evaluate the strength of the association between treatment effects on GFR slope with treatment effects on the clinical endpoint. The output of the Bayesian analyses is a meta-regression model which is used to predict the clinical endpoint for applications in future trials. Across all 47 studies, there was strong agreement between the treatment effects on the total slope computed at 3 years and the chronic slope with treatment effects on the clinical endpoint R^2 0.97 (Bayesian credible interval [BCI] 0.78, 1.00) and 0.96 (BCI 0.63, 1.00), respectively. For future trials, the meta regression predicted that with sufficient sample size, an observed treatment effect of 0.75 mL/min per 1.73 m^2/year or greater on GFR slope confers probabilities of at least 96% for clinical benefit on CKD progression.

A high level of heterogeneity in interventions and disease subclasses across well powered RCTs included in a trial-level analysis is critical for the value of the analyses to achieve a broad scope of applicability. Since these prior analyses were conducted, several large well powered trials were published. To provide improved precision to the results of the trial level analyses, the Applicant ascertained 19 additional studies and updated the analyses for the purpose of this qualification procedure. The new analyses now include data from 66 randomized treatment comparisons that tested 17 interventions in 187,323 participants across 4 broad disease groups (CKD not stated otherwise, diabetes, glomerular disease, and CVD. The new set of studies have an even wider range of mean eGFR and ACR values at baseline. Bayesian mixed effects regression analyses were again used. The inclusion of the additional studies increased the number of well-powered trials with at least 300 events for the clinical endpoint from 4 to 10 and

expanded the scope of the previous analyses by increasing the number of SGLT-2 inhibitor trials from 1 to 4 and added additional inventions such as dipeptidyl peptidase 4 (DPP-4), non-steroidal mineralocorticoid receptor antagonists (MRAs), endothelin receptor antagonist, and glucagon-like peptide 1 (GLP-1).

Across all 66 studies, there was strong agreement between the treatment effects on the total slope computed at 3 years with treatment effects on the clinical endpoint (R^2 0.98 [95% BCI, 0.85 to 1.00]). The output of the slope of the meta-regression line was significant and indicated that each 0.75 ml/min per 1.73 m^2/year greater treatment effect on the total GFR slope was associated with an average 23% lower hazard for the clinical end point. The intercept of the regression line was non-significant, with a 95% BCI of (-0.09 to +0.01), indicating that when the treatment had no effect on the total GFR slope over 3 years, there was a low probability of having a substantial treatment effect on the clinical endpoints. The results were consistent across all diseases, and across all subgroups defined by baseline GFR, baseline ACR, or rate of progression as indicated by chronic slope in the control arm.

For chronic slope, the trial-level analysis showed moderate agreement between treatment effects on chronic GFR slope and those on the clinical endpoint (R^2 0.56 [95% BCI 0.25, 0.78]). The association with chronic slope was less strong than the results of our prior investigations. Almost half of the reduction in R^2 appears to be explained by the addition of 2 large studies with large acute effects and larger treatment effects on the chronic slope; thus, results of chronic slope are more dependent on specific studies.

The results of these trial-level analyses show that GFR slope can reliably predict the treatment effect on the clinical outcomes, meeting the third and most critical criterion for a surrogate endpoint listed above. For example, using the meta-regression model, for a moderate sized trial of size 800, a treatment effect of total slope of 0.75 ml/min per 1.73 m^2/year or greater predicts a clinical benefit on CKD progression with at least 98% probability. These results are presented in Section 7 of this request.

Considerations for use of GFR slope

A number of factors have been identified that affect the predictive accuracy of GFR slope and must be considered when assessing the utility of GFR slope for a particular trial design. These include (but are not limited to):

1. The nature and magnitude of acute effects of the intervention
2. Rate of progression
3. Level of baseline GFR
4. Possible differences in sampling times or other design features in a shorter duration trial versus longer trials with clinical endpoints

These factors can help to select among available endpoints (clinical endpoint, time to GFR decline, total slope and its duration or chronic slope). The simulations and other analyses that have helped to delineate these factors are presented in Section 8 of this request.

Conclusion

In conclusion, validated surrogate endpoints to support standard marketing authorization and indication extension approval are needed to increase the pace of development of interventions for delaying CKD progression by improving the feasibility and efficiency of conducting trials for CKD interventions.

The mean difference in the rate of change in GFR between treatment groups meets the key criteria for an endpoint in CKD RCTs. This surrogate endpoint is biologically plausible, as GFR decline is on the causal path to kidney failure and has a strong established epidemiological relationship with the clinical endpoint. In work that substantially expands prior analyses published in 2019, an updated Bayesian individual patient meta-analysis of 66 RCTs of 17 randomized treatment comparisons including 187,323 participants support the use of GFR slope as a validated surrogate endpoint for CKD progression in pivotal clinical trials in broad CKD populations, supporting regulatory decision making for full marketing authorization of therapeutic interventions. Decisions about use of GFR slope versus other endpoints and the nature and timing of the slope are dependent upon the population, intervention and study design parameters.

Use of GFR slope as a validated surrogate endpoint for pivotal trials in CKD program across broad populations can provide earlier access to efficacious medications for this population with unmet need.

3. BACKGROUND

3.1 Chronic kidney disease

3.1.1 Natural history and burden of disease

Chronic kidney disease is a heterogeneous group of conditions defined by abnormalities of kidney structure or function, present for >3 months, with implications for health (KDIGO 2012). CKD has a major public health impact worldwide, with an estimated 850 million people worldwide living with some form of kidney disease (Cockwell and Fisher 2020). CKD is listed as number 12 of the 20 most common global causes of death in 2017 (GBD Chronic Kidney Disease Collaboration 2020). The global prevalence of CKD has been estimated at approximately 9%, and CKD resulted in an estimated 1.21 million deaths in 2017 (GBD Chronic Kidney Disease Collaboration 2020). Prevalence has been increasing in recent decades, in part due to the increasing prevalence of diabetes mellitus and hypertension, which the two leading causes of CKD, as discussed further in Section 3.1.4 (GBD Chronic Kidney Disease Collaboration 2020). In 2017, CKD resulted in an estimated 28.5 million years of life lost and 35.8 disability-adjusted life-years globally (GBD Chronic Kidney Disease Collaboration 2020).

Patients with CKD are at increased risk of adverse outcomes due to progression of kidney disease and complications in organ systems other than the kidneys, which lead to elevated risk of hospitalization and mortality (Go et al 2018). The most common and visible manifestations of CKD include kidney failure with replacement therapy (KFRT) (Gansevoort et al 2011, Webster

et al 2017), all-cause mortality (Go et al 2004, Turin et al 2012b), and vascular disease, including coronary artery disease, heart failure, peripheral vascular disease, and cerebrovascular disease(GBD Chronic Kidney Disease Collaboration 2020, Go et al 2004, Dhingra et al 2011). Decreased GFR leads to metabolic and endocrine abnormalities such as acidosis, hyperkalaemia, anaemia and abnormalities of bone and mineral metabolism (Inker et al 2019b). Patients with CKD are also highly vulnerable to infection and infectious complications, and bone and coagulation disorders, particularly patients with KFRT (Chang et al 2020, Yan et al 2021). For all of these complications, the risk increases as GFR declines, providing support for use of endpoints that capture CKD progression prior to onset of kidney failure (KDIGO 2012).

The personal and economic impact of CKD and KFRT is very large (Kelly et al 2021, GBD Chronic Kidney Disease Collaboration 2020). CKD costs have been estimated at a global median of 6.5% of the gross domestic product (GDP) and as high as 12% of the GDP of Western European countries (Kelly et al 2021). Even in early-stage disease, CKD is associated with cardiovascular (CV) morbidity and mortality (Shabaka et al 2021), and a perceived negative impact on health-related quality of life (Nguyen et al 2018, Kefale et al 2019).

3.1.2 Definition and staging of chronic kidney disease

Criteria for diagnosis include decreased GFR <60 ml/min/1.73 m^2 or at least one marker of kidney damage, e.g., albuminuria (albumin excretion rate ≥30 mg/24 hours; urinary ACR ≥30 mg/g [≥3 mg/mmol]) and other abnormalities as described in the clinical guidelines (KDIGO 2012). These categorizations have been reiterated in the recent National Institute for Health and Care Excellence guidelines (NICE Guidelines 2021).

Staging of CKD is based on GFR category and albuminuria category, as shown in Figure 1, and also cause of CKD (KDIGO 2012, Inker et al 2014a). Both GFR and albuminuria are widely accepted as criteria for kidney disease and function and are both key independent risk predictors for progression to kidney failure, CVD, and mortality. CKD prognosis and risk factors for rapid progression to clinical outcomes are further discussed in Section 3.1.3.

Figure 1 Staging of CKD and risk assessment by GFR and albuminuria

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

A, Albuminuria category; CKD, Chronic kidney disease; G, GFR category; GFR, Glomerular filtration rate. Reproduced with permission from KDIGO 2012.

In most settings, GFR is typically evaluated as measurement of serum creatinine levels for determination of eGFR (Inker and Titan 2021, Levey et al 2015).

3.1.3 Prognosis and risk factors for progression of CKD

It is important to understand the risk factors for progression to guide patient management, helping to identify those who will benefit most from an intervention, with particular focus on patients in the early course of disease. This will help to inform clinical trial design, including the selection of appropriate study populations.

Risk factors for progression can be assessed as the association between outcomes and baseline characteristics at a single measure in time, or between changes in kidney measures, such as eGFR and ACR, over time.

Across multiple patient populations, including those with and without diabetes as the underlying causal disease, the presence of albuminuria or proteinuria and, lower baseline eGFR have been

found to be among the strongest predictors of fast progression of CKD (Koye et al 2018, Go et al 2018, Zoppini et al 2012, Roscioni et al 2014, Turin et al 2012a). Other independent predictors include presence of diabetes, older age, hypertension, anemia, and heart failure, (Zoppini et al 2012, Garlo et al 2011).

Changes in eGFR have been shown to predict subsequent progression to clinical endpoints, supporting evaluation of its potential use as an accepted surrogate endpoint in RCTs. This is further discussed in Section 3.4.

3.1.4 Pathophysiology of CKD development and progression

Progression of kidney disease refers to declining GFR. The mechanisms of CKD development and progression can be viewed in different phases: the nature of initial damage and the pathophysiologic processes that follow the initial initiating factors.

The initial damage can be caused by diabetic nephropathy, hypertensive nephropathy, infectious glomerulonepthritis, autoimmune diseases, genetic abnormalities, renal vasculitis, and other CKD causal diseases. These diseases lead to specific factors that cause damage (e.g., hyperglycemia, mechanical damage, immune-mediated destruction, etc). This damage initiates hemodynamic changes, inflammation, kidney remodeling, and fibrosis (López-Novoa et al 2010, Kanwar et al 2011). A cycle of damage/progression ensues that is ultimately irreversible, even if the underlying disease resolves (Shabaka et al 2021).

Regardless of the underlying disease and mechanisms of initial kidney damage, loss of nephrons leads to decreased GFR. The remaining functional glomeruli increase filtration rate to compensate for the loss, causing further damage and resulting in decreased GFR. When the GFR decreases below a critical level, the loss of a critical number of nephrons facilitates further nephron loss through adaptive pathophysiologic mechanisms which causes a cycle of further damage. Later in the course of disease, GFR decline is associated with common cellular and biochemical pathophysiologic processes, i.e., inflammation and cytokine imbalance, fibrosis, tubular degeneration and scarring, and vascular contraction (López-Novoa et al 2010), irrespective of the causal disease.

Thus, decreased GFR is on the causal pathway of CKD progression, irrespective of the underlying causal disease. GFR is therefore the most important risk marker for kidney disease progression irrespective of damage status for many forms of kidney disease.

3.1.5 Management of CKD

Management of progression of CKD is based on the underlying cause of disease, and the stage of CKD based on GFR and ACR (KDIGO 2012, NICE Guidelines 2021).

Non-specific interventions include non-pharmacologic therapies, such as diet and lifestyle changes, i.e., dietary sodium restriction, avoidance of high protein diets, and exercise/physical activity compatible with health status, weight control, and smoking cessation (KDIGO 2012, NICE Guidelines 2021).

Standard of medical care for pharmacologic therapy in patients with and without diabetes includes blood pressure (BP) control and use of blockade of renin angiotensin-aldosterone systems (RAAS), combined with general CV risk management, and glycemic control as necessary (Inker et al 2014a, KDIGO 2012, Heerspink and de Zeeuw 2013). Newer agents such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors and MRA antagonists have supporting data and are incorporated into recent guidelines (ADA CKD Guidelines 2022, KDIGO 2020).

Cause-specific interventions may also include immunosuppressive medications for glomerular or autoimmune diseases.

Currently, only a limited number of therapeutic options have been shown in clinical trials to delay disease progression in CKD patients. These include agents that target the RAAS, i.e., angiotensin-converting enzyme inhibitors (ACEi) (Lewis et al 1993) and angiotensin receptor blockers (ARBs) (RENAAL; Brenner et al 2001, IDNT; Lewis et al 2001, Ruggenenti et al 2005), and more recently, agents that inhibit sodium glucose co-transporter 2 (SGLT-2) (Perkovic et al 2019, Heerspink et al 2020, McMurray et al 2021) or the nonsteroidal MRA (Bakris et al 2020, Pitt et al 2021).

In a meta-analysis of 119 randomized controlled trials of CKD (with or without diabetes) (Xie et al 2016), ACE inhibitors and ARBs were found to reduce the odds of kidney failure by 39% and 30%, respectively, compared to placebo. SGLT-2 inhibitors and the nonsteroidal MRA antagonist finerenone, when added to RAAS blockers, led to additional reductions in risk of the composite clinical endpoint(s) (Perkovic et al 2019, Heerspink et al 2020,Bakris et al 2020, Pitt et al 2021).

Despite availability of these agents that can slow CKD progression when added to RAAS blockers or other standards of care, there is residual risk of kidney disease progression in patients with CKD with or without type 2 diabetes. For example, in a recent meta-analysis of 27 studies conducted in patients with type 2 diabetes and CKD, SGLT-2 inhibitor treatment resulted in a 29% reduction in risk of the composite renal outcomes compared with standard of care. In addition, patients with CKD are at risk for complications, in particular, CVD; prevention progression of CKD will decrease risk for these other complications. Although this represents excellent progress, residual risk remains in this population as well as others with CKD from other causal disease.

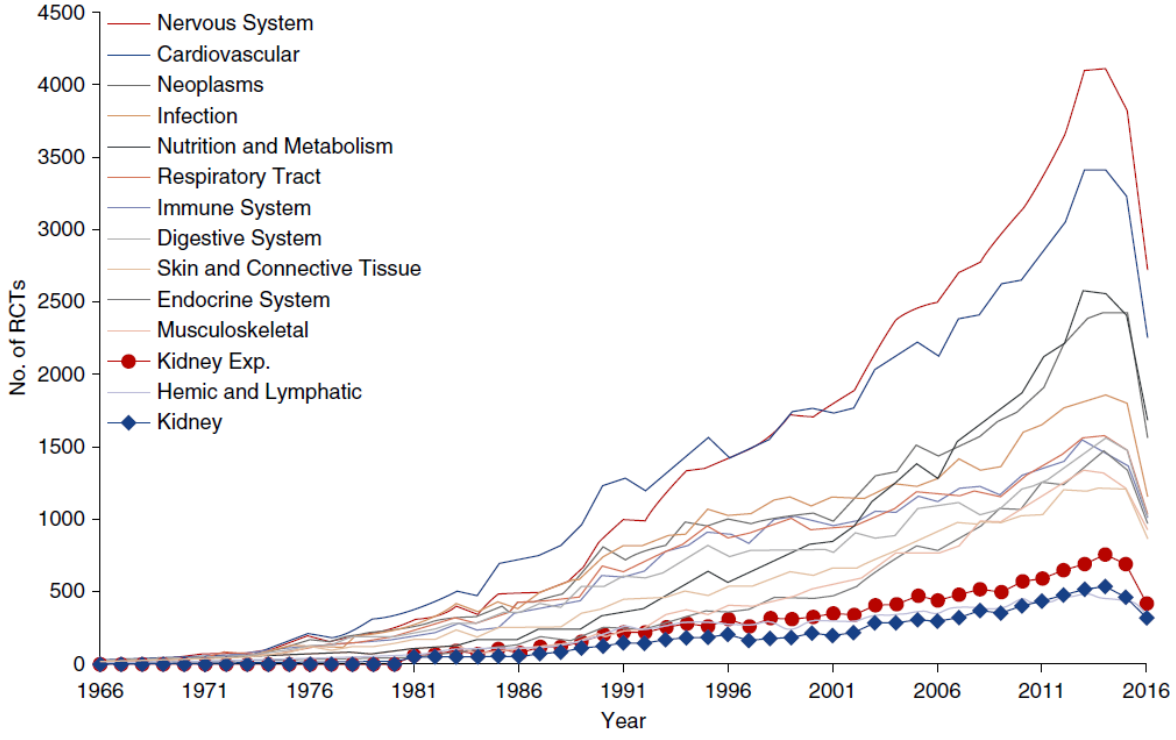
Moreover, the reduced risk that has been attained on top of current standard of care over the past 3 years has made new trials aimed at addressing the remaining unmet need even more difficult with respect to the time and sample sizes needed to accrue sufficient events within the typical 3 years' duration of a phase 3 clinical trial. Thus, there remains a strong unmet need to well powered, high quality RCTs to investigate new interventions that can slow or arrest progression across different populations both early and later in the disease course.

3.1.6 Unmet need for more treatments in CKD and need for alternative approach to defining endpoints for kidney disease progression

Despite the disease prevalence and some progress made in identifying agents that can slow progression to KFRT, there remains residual risk and an unmet need for additional therapies slow or prevent CKD progression, particularly in early-stage CKD. For example, in the DAPA-CKD trial of SGLT-2 inhibitor dapagliflozin conducted in a broad CKD population with and without diabetes, there was a significant relative risk reduction for the primary composite outcome of sustained decline in eGFR of at least 50%, end-stage kidney disease, or kidney-related or CV death) (hazard ratio [HR] 0.64, 95% CI 0.52, 0.79). However, 274 of 2152 patients in the treatment arm (12%) experienced KFRT, nonfatal myocardial infarction, nonfatal stroke, unplanned HF hospitalization or died during follow-up (McMurray et al 2021). This indicates considerable residual risk of highly clinically relevant events even in the context of an efficacious intervention.

The small number of available interventions is a reflection of a very small number of RCTs for CKD interventions compared with those for other disease areas (Kyriakos et al 2019).

Figure 2 Number of randomized controlled trials in kidney disease compared with other domains in the Cochrane database



Nephrology ("Kidney") is represented by the MeSH term "kidney diseases." Expanded (Exp.) nephrology ("Kidney Exp.") also covers the MeSH term "RRT" (subterms included "renal dialysis," "peritoneal dialysis," and "kidney transplantation"). Refer to Kyriakos et al 2019 for additional information on methods.
Reproduced with permission from Kyriakos et al 2019.

Pivotal CKD RCTs traditionally use KFRT, eGFR <15 ml/min per 1.73 m^2, or doubling of serum creatinine as clinical endpoints. These are late events in the course of disease and progression to KFRT can be slow in some patients or groups. Therefore, CKD trials based on kidney failure events require long follow-up periods, very large patient numbers, and/or need to be restricted to later-stage patients or those with disease associated with rapid GFR decline to achieve sufficient numbers of clinical events to have adequate power to determine a significant treatment effect of therapeutic interventions. Additionally, some interventions may provide greater long-term benefits if initiated earlier in the disease process. Patients with earlier disease are particularly infeasible to study due to the lack of later clinical outcomes within the time frame of the study.

Therefore, there is an unmet need to approve new drugs that can slow or prevent disease progression earlier in the process, before irreversible damage occurs. There is also an unmet need for valid endpoints accepted by regulatory agencies that can be used to indicate efficacious treatments after a reasonable length trial. These advances would provide value from the patient and societal perspectives and drug development standpoint.

3.2 The development of validated surrogates may also be critical to the development of progressive CKD treatments, particularly treatments that are effective in the earlier stages of CKD

3.2.1 Definition of surrogates

A clinically meaningful endpoint directly measures how a patient feels, functions, or how long a patient survives, and is the definitive measure for phase III clinical trials. Therapeutic interventions should have an impact on such endpoints to be considered for regulatory approval. A surrogate endpoint is intended to substitute for a desired clinical endpoint. Typically, surrogate endpoints are biomarkers, but may also be other clinical outcomes. The key is that a surrogate endpoint can be measured earlier, more easily, more frequently, and/or with higher precision than the target clinical endpoint (Stevens et al 2006, Inker and Chaudhari 2020). A goal of the use of a surrogate endpoint is to reduce sample size requirements and enable faster decision-making during the drug development and approval process (Stevens et al 2006).

Intermediate endpoints are special case of surrogate endpoints. An intermediate endpoint is a specific type of surrogate endpoint on the causal pathway between an intervention and the clinical endpoint and has stronger biological connections than a surrogate.

Table 1 summarizes terminology related clinical, surrogate, and intermediate endpoints in clinical trials, with examples from within the kidney and non-kidney domains. Table 1 also provides information on the current view from EMA and the FDA on surrogate endpoints in CKD trials. The regulatory authority view on surrogate endpoints in CKD trials is discussed further in Section 3.4.

Table 1 Biomarker terminology and examples in kidney and other domains

Endpoint	Definition	Examples from non-kidney domain	Examples from Kidney domain	
			Marker	Position of regulators on use as primary endpoint in pivotal clinical trials
Endpoint	Precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question.	-	-	-
Clinical Endpoint	Characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.	MI, stroke, AIDS related infections, diabetes complications, fracture rate, survival	Kidney failure (GFR <15 ml/min per 1.73 m^2 or the initiation of dialysis or transplantation. Doubling of serum creatinine is considered a part of the definition.) (Levin et al 2020)	Accepted (FDA 21CFR, EMA/CHMP/500825/2016, Thompson et al 2014)
Biomarker	Defined characteristic that objectively indicates normal biologic or pathogenic processes, or biologic responses to an exposure or therapeutic intervention.	BP, lipid levels, HIV-RNA load reduction, uric acid, HbA1c, glycemia [c]	Urine albumin[a] Measured or eGFR	
Surrogate Endpoint	Biomarker intended to substitute for a clinical endpoint benefit, harm, or lack thereof. Surrogates can be validated, reasonably likely, or candidate [b]	Reduction in BP or lipid levels (stroke, MI), or viral load (AIDS), FEV_1 (COPD, asthma)[c]	Change in Urine albumin[a]	Under consideration ; Accepted for accelerated approval for IgA nephropathy (Thompson et al 2020)
			Complete remission of nephrotic syndrome	Accepted for membranous nephropathy (Thompson et al 2015)
			Total kidney volume	Accepted as a prognostic enrichment marker in ADPKD (EMA/CHMP/SAWP/473433/2015)
Intermediate Endpoint	Characteristic intermediate on the causal pathway	Ejection fraction, exercise	Percent GFR decline	Accepted (FDA 21CFR, EMA/CHMP/500825/2016, Thompson et al 2020)

Table 1 Biomarker terminology and examples in kidney and other domains

Endpoint	Definition	Examples from non-kidney domain	Examples from Kidney domain	
			Marker	**Position of regulators on use as primary endpoint in pivotal clinical trials**
	between an intervention and the clinical endpoint. Stronger biological connections than a surrogate In a regulatory context, an endpoint measuring a clinical outcome that can be measured earlier than an effect on irreversible morbidity or mortality	tolerance (heart failure)	GFR slope	Accepted by FDA for rare chronic kidney diseases and being considered for use in trials in more common diseases (Thompson et al 2020) Primary or secondary outcome in several ongoing phase III trials of IgA nephropathy approved in EU[e] Objective of this qualification request

[a] Urine albumin or total protein.
[b] Surrogate endpoint, can be classified by the level of clinical validation as either a "validated, reasonably likely or candidate based on the level of scientific evidence.
[c] All are validated surrogate endpoints. Other examples can be found here: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure;
[d] Accelerated approval is a mechanism used by the FDA to provide marketing authorization for drugs that treat serious conditions where there is an unmet medical. They generally require a post-marketing confirmatory trial (FDA Guidance for Industry 2014, FDA 21CFR314, Subpart H). Surrogates that meet the criteria as "Reasonably likely", can be used in this context. European Union pharmaceutical legislation does not have a parallel process and the type of endpoint for efficacy demonstration per se is not a guiding principle for the type of marketing authorization. Use of reasonably likely validated surrogates can lead to full marketing authorization by the EMA, potentially requiring certain post-authorization commitments (EMA/CHMP/500825/2016). In some situations, a conditional approval can be granted in the EU, provided post-approval commitments/specific obligations.
[e] ALIGN (EUDRA CT 2020-003084-26), PROTECT (EUDRA CT 2017-004605-41), APPLAUSE (EUDRA CT 2020-001049-38), NEFIGARD (EUDRA CT 2017-004902-16), OMS721 (EUDRA CT 2018-000075-33).
AIDS, Acquired immunodeficiency syndrome; BP, Blood pressure; COPD, Chronic obstructive pulmonary disease; eGFR, Estimated glomerular filtration rate; FEV1, Forced expiratory volume in one second; Hg A1C, Hemoglobin A1C; HIV-RNA, Human immunodeficiency virus ribonucleic acid; MI, Myocardial infarction; IgA, Immunoglobulin A; ADPKD, Autosomal dominant polycystic kidney disease.
Adapted from Inker and Chaudhari 2020 and BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK338448/

3.2.2 Criteria for the adoption of a surrogate endpoint

The key criteria for validity of surrogates are:

- **Biological plausibility**: There must be strong support from cellular, molecular, animal, and human studies that the endpoint can plausibly be expected to predict the clinical outcome of interest.

- **Individual level associations**: There should be epidemiologic data demonstrating a strong and consistent relationship between the surrogate endpoint and outcome of interest.

- **Trial level analyses**: It is possible to predict the effect of the treatment on the clinical endpoint on the basis of the effect of the treatment on the surrogate (Stevens et al 2006, Levey et al 2020). This is the most difficult criterion to establish because an analysis across multiple randomized clinical trials is required to demonstrate a relationship between a causal effect of a treatment on the surrogate endpoint and a causal effect of a treatment on the clinical endpoint (Inker and Chaudhari 2020). Heterogeneity of treatment effects for both the clinical endpoints and the surrogate endpoints are required for analysis. This is now widely regarded as the most important criterion for demonstrating the validity of a surrogate endpoint.

Once a surrogate has been deemed valid, simulations can be helpful to assess trial conditions and patient characteristics that are favorable or unfavorable for use of the surrogate endpoint. Key goals of simulations are to determined conditions for increasing power compared with clinical outcomes to demonstrate a positive treatment effect without increasing the probability of Type 1 errors for the surrogate endpoint relative to clinical outcome in scenarios with null treatment effects.

3.2.3 Potential surrogates for CKD

The two most widely studied biomarkers in CKD are GFR and albuminuria.

Both albuminuria and GFR are measures of glomerular function. Albuminuria is primarily a measure of the permeability of the glomerular capillary wall to macromolecules. Albuminuria occurs earlier than GFR decline in the course of many causal diseases, such as glomerulonephritis. Impaired uptake of proteins from tubular fluid may also cause increased albuminuria, and increased concentrations of macromolecules in the tubule can cause direct damage. Thus, albuminuria which occurs as a consequence of glomerular damage or tubular impairment may result in variable associations with kidney disease progression, based on causal disease. Thus, the relationship between change in albuminuria and clinical kidney outcomes may vary among different causes of kidney disease. It is therefore possible that an increase in albuminuria may not be on the path to kidney failure for all causes of kidney disease.

In contrast, GFR is generally considered the most useful overall measure of kidney function in health and disease, and the decline in other kidney functions often mirrors the decline in GFR across all diseases. A severe reduction in GFR is defined as kidney failure; hence, by definition, GFR decline is on the path of progression to kidney failure for all kidney diseases, and it is more strongly related to development of kidney failure and its complication than increased albuminuria. Because kidney failure occurs specifically when GFR declines to a narrow range, of approximately 7 to 15 ml/min/1.73 m^2 (Astor et al 2011, Matsushita et al 2010, Gansevoort et al 2011, Inker et al 2019b), GFR slope and other GFR-based surrogate endpoints are linked to the target clinical endpoint through an objective mathematical relationship which is stronger than for many surrogate endpoints

Both albuminuria and GFR have been evaluated as potential surrogates. Section 3.4.2 briefly summarizes the work done on albuminuria, since this is not a focus for the qualification document, it is only briefly mentioned. In the section below, some of the considerations and challenges of use of GFR as an endpoint are described. Results of our prior work on the evaluation of GFR slope as an endpoint are summarized in Section 3.4.4.

3.3 GFR decline

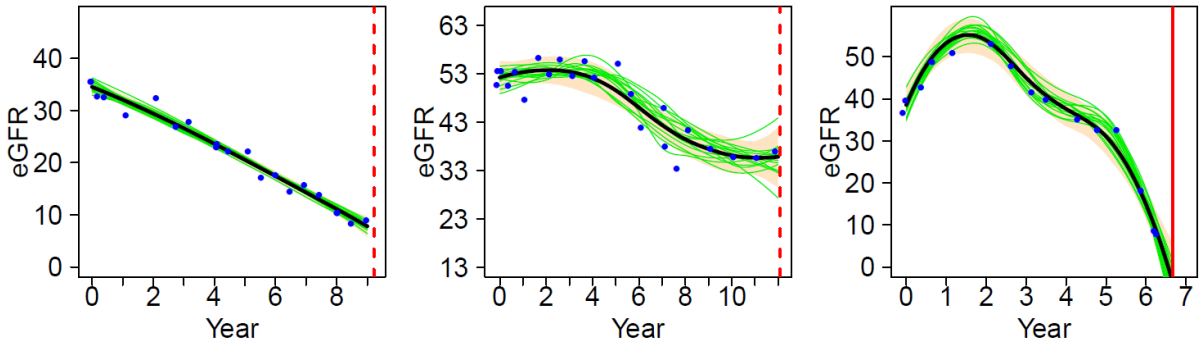
3.3.1 GFR

GFR is determined by filtration pressure, surface area of the glomerular capillary wall, and its permeability to small solutes and water. The normal value is approximately 125 ml/min/1.73 m^2. The total GFR is related to the overall number of nephrons (N) multiplied by the function of each single nephron (SNGFR). CKD progression is related to the decline in N but changes over the shorter term can reflect either change in N or SNGFR. Severe GFR reduction (<15 ml/min/1.73 m^2) defines kidney failure; thus, GFR declines are on the causal path to kidney failure.

3.3.2 Individual trajectories of GFR decline

Within individuals, a variety of trajectories of eGFR decline have been noted, including both linear trajectories and nonlinear trajectories. Figure 3 shows 3 sample patients from the African American Study of Kidney Disease (AASK) (Li et al 2012).

Figure 3 GFR trajectories for individual patients in the AASK Study



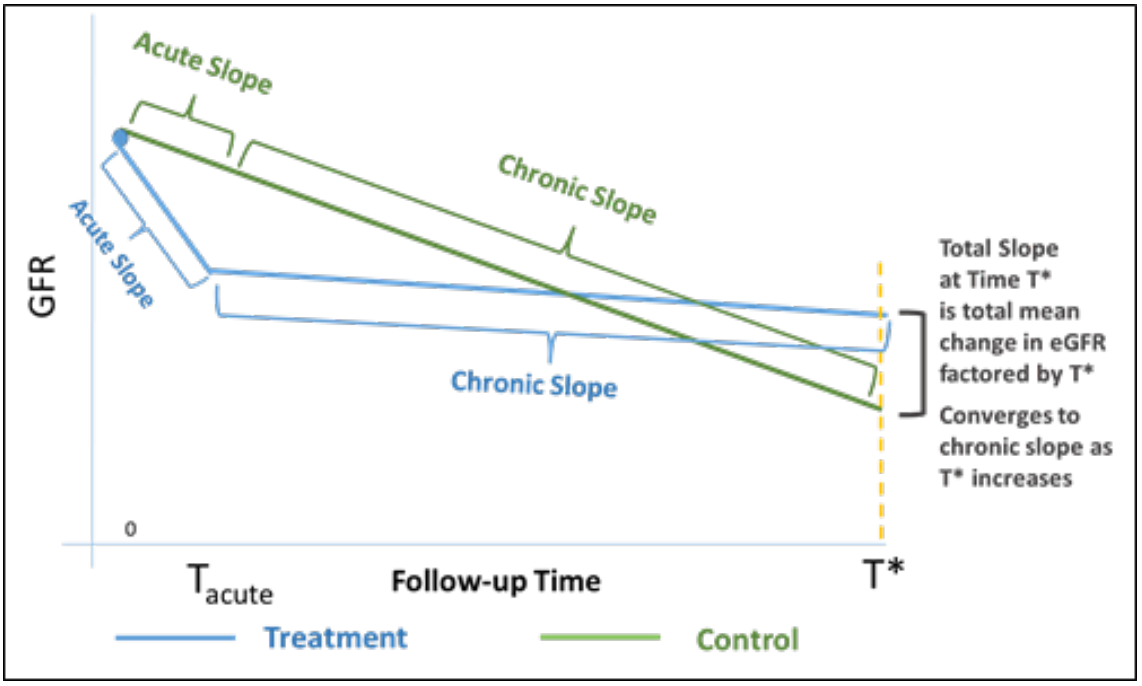
Three example GFR trajectories with varying deviations from linear decline. On each trajectory plot, the horizontal axis is year since randomization, and the vertical axis is eGFR (mL/min/1.73 m^2). The blue dots are eGFR data, the black smooth curve is the estimated trajectory, and the bisque color band is the pointwise 95% Bayesian confidence interval. The red vertical line represents time of either censoring (dashed) or dialysis (solid). Fifteen of 3,000 Monte Carlo trajectories sampled under the Bayesian model are randomly selected and plotted for illustration (green curves).
eGFR, Estimated glomerular filtration rate; GFR, Glomerular filtration rate.
Reproduced with permission from Li et al 2012.

3.3.3 Group changes in GFR in clinical trials

When averaged across all individuals randomized to a particular treatment group in a RCT, the

deviations from linearity in individual GFR trajectories often smooth out so that the average GFR level exhibits a decline that can be approximated by a 2-slope linear spline model. This is depicted in Figure 4. The reason for application of a 2-slope model is that some therapeutic interventions can have an acute, or immediate, treatment effect on GFR that is unrelated to potential long-term renal protective effects. In some cases, the acute effects are thought to be primarily related to reversible effects, resulting from short-term hemodynamic effects at the level of the individual nephron versus longer-term effects on the number of nephrons.

Figure 4 Hypothetical depiction of GFR decline in treatment and control arms in RCT where the treatment leads to acute decline in GFR followed by shallower slope in the chronic phase



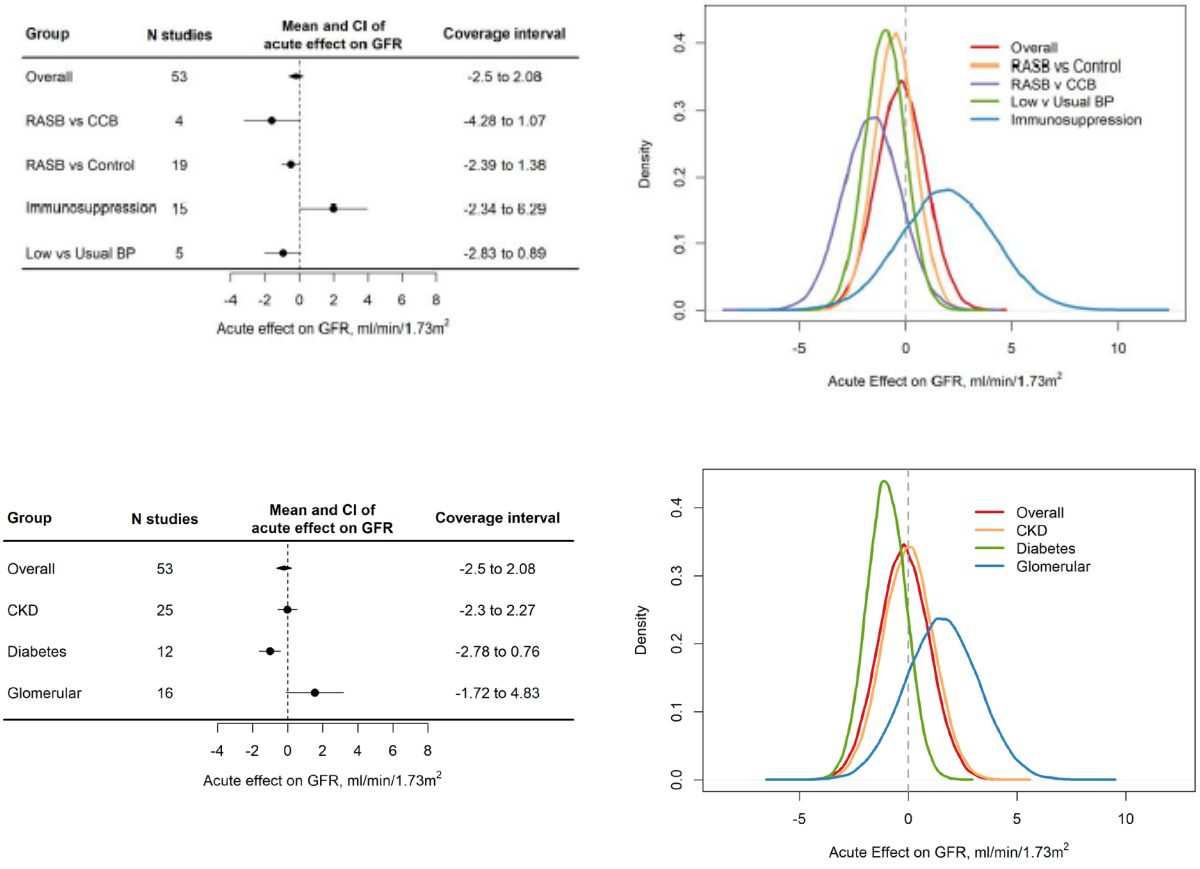
eGFR, Estimated glomerular filtration rate; GFR, Glomerular filtration rate; RCT, Randomized controlled trial; T, Time.

These acute effects can be negative or positive and can complicate the interpretation of treatment effects on CKD progression. For many past studies, the acute effect has more commonly been negative and related to hemodynamic changes. Therefore, the magnitude and consistency of acute effects on GFR slope was investigated in a meta-analysis of 53 CKD RCTs enrolling 56,413 patients. This work has been previously published (see Neuen et al 2022 in Appendix C). As shown in Figure 5, a moderate-to-large negative mean acute effect was observed in a combined analysis of all studies (-0.21 ml/min per 1.73 m^2 [95% CI -0.63 to 0.22]) with substantial heterogeneity across the studies, as indicated by the 95% coverage interval for acute effect across the studies ranged from -2.50 to 2.08 ml/min per 1.73 m^2. As expected, negative mean acute effects were observed across most trials of renin-angiotensin system blockers

(RASB) or intensive BP lowering, while positive mean acute effects were observed across most trials of immunosuppressive therapies, although with heterogeneity among all interventions.

The early and late mean GFR slopes may also differ from each other due to regression to the mean if the entry criteria for the treatment depend on the GFR level. For treatments without an acute effect and where regression to the mean is not a major issue, the average GFR trajectories within treatment groups can be characterized by a single mean slope which can be compared between randomized groups to assess the effect of the interventions on the mean GFR slope. When two-slope models are necessary, ambiguity can arise as to whether it is more meaningful to compare the mean chronic slopes or the mean "total slopes" which incorporate both the acute and chronic phases of the study.

Figure 5 Distribution and estimated mean acute effect on GFR by intervention and disease, ANCOVA



Top panel, by intervention, bottom panel, by disease.
Coverage interval refers to the interval under which 95% of the studies fall.
BP, Blood pressure; CCB, Calcium channel blockers; CI, Confidence interval; CKD, Chronic kidney disease; GFR, Glomerular filtration rate; N, Number; RASB, Renin-angiotensin receptor blocker.
Reproduced with permission from: Neuen et al 2022.

Other challenges in the consideration of GFR slope are informative censoring by KFRT and death, and heterogeneity in the variability of GFR between subjects with different GFR levels and treatment arms. For this reason, time to changes in GFR have been initially used (in the form of doubling of serum creatinine) and then evaluated in the form of 30% and 40% decline in GFR. However, all of these are not sufficient for use in higher levels of GFR and time to 30% is still very susceptible to acute changes in GFR. Thus, as described in Section 7.2, the Applicant embarked on development of methods to estimate GFR slope that overcome these challenges.

3.3.4 Benefits of slope as endpoint

GFR slope must be viewed as a surrogate endpoint since its analysis characterizes a mean rate of change in a biomarker rather than a clinical event. In contrast to albuminuria, which effects only a subset of diseases and interventions, GFR decline is appropriate for all causes In comparison to clinical endpoints based on KFRT or large GFR declines, GFR slope may provide advantages in statistical power (Section 8.3) and interpretational advantages. In particular, treatment effects of analyses of clinical endpoints reflect only the effect of the treatment on the subgroup of rapidly progressing patients who reach the endpoint during the trial. By contrast, comparisons of mean GFR slope represent comparisons of GFR decline for all study patients, including those who may potentially progress to the clinical endpoint subsequent to the period of the trial.

To overcome the challenges described above, but take advantage of the potential benefits, these challenges were approached with slope analyses, by evaluating both the chronic slope and the total slope as surrogate endpoints and empirically evaluating their performance in trial level analyses that relate treatment effects on each slope endpoint to treatment effects on the clinical endpoint.

3.4 Prior work by CKD-EPI on evaluation of surrogate endpoints for progression of CKD: Project history and regulatory interaction

The CKD-EPI Collaboration and NKF are co-applicants for this request. See Appendix B for information on the organizational structure, collaborators, and funding sources for this work.

3.4.1 Overview

As discussed above, there has long been agreement that that there is a need for biomarkers and/or surrogate endpoints to facilitate the development of new drugs to slow the progression of CKD. The following outlines the steps taken thus far in assessment of surrogate endpoints. Section 3.4 describes the key output in greater detail.

- **2002: Proteinuria and Other Markers of CKD** The NKF and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) co-sponsored a Scientific Workshop “Proteinuria and Other Markers of Chronic Kidney Disease,” which produced recommendations to standardize measurement and monitoring of proteinuria in CKD and conduct research on the potential use of proteinuria as a surrogate endpoint for progression (Eknoyan et al 2003).

- **2003: Establishment of CKD-EPI** KUH of the NIDDK included assessment of treatment effects on proteinuria as part of a newly formed consortium to address this and other key challenges addressing CKD epidemiology at the time (U01 funding mechanisms).

  The CKD-EPI Collaboration led by Andrew S, Levey MS as a research group was subsequently formed. In addition to evaluation of surrogate endpoints, the CKD-EPI (https://www.tuftsmedicalcenter.org/Research-Clinical-Trials/Institutes-Centers-Labs/Chronic-Kidney-Disease-Epidemiology-Collaboration/Overview) has major interests in measurement and estimation of GFR (CKD-EPI GFR) (see Appendix B for a description of the organization and list of CKD-EPI collaborators and funding sources).

  CKD-EPI Clinical Trials (CKD-EPI CT) is the component of the larger research group that analyses of RCTs and other studies for the purposes of evaluation of surrogate endpoints for CKD clinical trials.

- **May 2008: Proteinuria as a Surrogate Outcome in CKD** The US FDA approached NKF to organize a scientific workshop on the question of use of proteinuria as a surrogate endpoint for CKD trials. At that time, it was concluded that there was sufficient evidence to recommend changes in proteinuria as a surrogate endpoint for CKD progression only in selected circumstances, given that proteinuria is not necessarily on the causal path to kidney failure (Levey et al 2009a). Results from meta-analyses were not available at the time. Future research was recommended to further characterize the context in which albuminuria could be used as a surrogate endpoint.

- **December 2012: GFR Decline as an Endpoint in Clinical Trials in CKD** The FDA again approached the NKF to organize a scientific workshop on the utility of lesser GFR declines (compared to doubling of serum creatinine) as surrogate endpoints. The NKF turned to the CKD-EPI and another collaborative group, CKD Prognosis Consortium (CKD-PC) (https://www.ckdpc.org/) who together were in a position to conduct analyses to explore this question. The analyses showed strong relationships between change in eGFR and kidney failure and mortality in observational studies; and strong associations between treatment effects on 30% and 40% decline in GFR and the clinical endpoint in past trials (Coresh et al 2014 Heerspink et al 2014, Inker et al 2014b). 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 (Levey et al 2014, Inker et al 2014b, Greene et al 2014). See Section 3.4.3 for a brief summary of the key evaluations and conclusions on this work.

- **March 2018: Change in Albuminuria and GFR as Endpoints for Clinical Trials in Early Stages of CKD** The NKF, in collaboration with the FDA and EMA, sponsored a scientific workshop to further evaluate surrogate endpoints for trials of kidney disease progression and improve understanding of change in albuminuria and GFR as measures of kidney disease progression (Levey et al 2020). For the 2018 workshop, analyses were performed by the CKD-EPI and CKD-PC groups to support the validity of ACR change and GFR slope as surrogate endpoints. Based on the work presented at this workshop, it

was concluded that early change in albuminuria and GFR slope both fulfil criteria for surrogacy for use as endpoints in clinical trials for CKD progression under certain conditions. In was concluded that the data supported use of GFR slope as a valid surrogate endpoint for CKD progression (Levey et al 2020).

Following this workshop, the FDA (Thompson et al 2020) stated that they *"accepted eGFR slope as an end point and basis for full approval of therapies for rare chronic kidney diseases"* with the caveat that acute effects should be considered, also pointing out that the *"analyses provide an important foundation for further discussions with the nephrology community about eGFR slope as an end point for registration trials for common chronic kidney diseases such as diabetic kidney disease."* The FDA further stated that *"these data provide reassurance that the treatment effect on kidney function that is seen in a trial, an effect that is likely to be small in absolute terms, will translate into a clinically relevant effect on progression to kidney failure."*

Similarly, EMA (Holtkamp et al 2020) stated: *"GFR slope offers promising potential for a surrogate endpoint in the confirmatory phase of a specific clinical program."*

Section 3.4.2 includes a summary of the key evaluations and conclusions on albuminuria as a surrogate endpoint.

As outlined in Section 4 and the remainder of this document, the objective of this application is to seek a positive qualification opinion by CHMP/EMA on the use of GFR slope as a surrogate endpoint in confirmatory CKD RCTs to form an adequate basis for full regulatory approval in support of specific labeling claims. The evidence to support this opinion is:

- The epidemiologic data demonstrates strong and consistent relationship between GFR slope and clinical endpoints, thus meeting the second criterion outlined in Section 3.2.2. The data are presented in Section 6 is a summary of published information previously presented at the 2018 workshop.

- The trial-level analysis demonstrates that GFR slope can predict the treatment effect on the clinical endpoint based on the treatment effect on the surrogate GFR slope, thus meeting the third and most critical criterion listed in Section 3.2.2. The previously published results are summarized briefly in Section 3.4.4 and the updated analyses are presented in Section 7.

3.4.2 Change in proteinuria as a surrogate endpoint

CKD-EPI has investigated change in proteinuria as a potential surrogate endpoint because it has with biologic plausibility as a widely accepted biomarker of kidney damage; is related to the diagnosis and classification of CKD; and is considered to be a key risk predictor for progression to KFRT (Levey et al 2020). Key findings and conclusions include the following:

In an epidemiologic cohort meta-analysis of individual patient-level data of 41 treatment comparisons across 28 studies including 696,816 individuals conducted by CKD-PC and CKD-EPI (Coresh et al 2019), a 30% reduction in urinary ACR over 2 years was associated with

decreased risk of subsequent KFRT (adjusted HR of 0.83 [95% CI 0.74, 0.94], and a 43% increase in ACR over 2 years was associated with an increased risk of subsequent KFRT (HR 1.16 [95% CI 1.03, 1.31]). A trial-level meta-analysis of change in albuminuria as a surrogate endpoint was conducted 41 treatment comparisons in 29,979 RCT participants (Heerspink et al 2019). Over a median follow-up of 3.4 years, each 30% decrease in geometric mean urinary ACR by the treatment relative to the control, measured over a 2-year baseline period, was associated with an average 27% lower hazard for the clinical endpoint (95% BCI 5%, 45%; R^2 0.47, 95% BCI 0.02, 0.96). The association was stronger analyses were restricted to patients with baseline ACR >30 mg/g (R^2 0.72 [95% BCI, 0.05, 0.99]).

In conclusion, this work demonstrated that early albuminuria change can be a valid surrogate endpoint in certain circumstances, i.e., in participants with high baseline ACR and in instances of relatively large treatment effects. Based on these data, Levey et al 2020 concluded *"The threshold of 20% to 30% reduction in geometric mean UACR could be used to evaluate results of phase 2 trials to determine which interventions have greatest promise to bring into phase 3 trials"* (Levey et al 2020).

3.4.3 GFR decline as time-to-event surrogate endpoint in CKD clinical trials

CKD-EPI investigated lesser declines in GFR (e.g., 30% or 40% declines) because GFR decline has biologic plausibility as a widely accepted biomarker of kidney function; is related to the diagnosis and classification of CKD; and is on the causal path of for progression to KFRT across all kidney diseases (Inker et al 2019a).

This work was presented in a workshop co-sponsored by the FDA and the NKF in December 2012 (Levey et al 2014). Key findings and conclusions include the following:

- In an epidemiologic cohort analysis of 9,488 participants in 37 randomized controlled trials in CKD, a strong linear association was observed between eGFR declines of 30% or 40% measured over a period of 12 months and subsequent established clinical endpoints (e.g., eGFR <15 ml/min per 1.73 m^2, KFRT, or doubling of serum creatinine level) (Heerspink et al 2014). HRs for the established endpoint for 30% and 40% decreases in eGFR compared to a 0% decline were 9.6 (95% CI 7.3, 12.6) and 20.3 (95% CI 14.1, 29.3), respectively. The associations were consistent regardless of baseline eGFR, causes of disease, interventions, and proteinuria.

- Trial-level meta-analyses were conducted including 9,488 participants from 37 randomized controlled trials of CKD progression across 5 intervention types (Inker et al 2014b). The time-to-event endpoints evaluated included 20%, 30%, 40%, and 57% change in eGFR from baseline throughout study duration and to 12, 18, and 24 months. These alternative endpoints were compared to the established clinical endpoint (composite of KFRT, untreated kidney failure defined as GFR <15 ml/min/1.73m^2, or doubling of serum creatinine level. Over the full median follow-up duration of 3.6 years, the ratios (95% credible interval) of the HR for the alternative to established endpoints across the interventions evaluated ranged from 0.91 (0.64, 1.43) to 1.12 (0.89, 1.40) for a 40% eGFR decline and from 0.88 (0.63, 1.39) to 1.15 (0.88, 1.54) for a 30% eGFR

decline. Similar results were obtained over a 24-month follow-up period when using a 40% decline, but point estimates for ratios for the 30% decline were greater than 1.0 during the shorter follow-up interval, indicating an attenuation of the treatment effect for this alternative endpoint. Overall, the analyses provided support for a 30% or 40% decline as a valid surrogate endpoint, but evidence was stronger in support of a 40% decline in certain situations.

In guidance adopted in 2016, EMA recommends as a primary endpoint in CKD RCTs *"clinically meaningful and stable GFR loss rate (measured either via slope or time to event analyses)"* (EMA/CHMP/500825/2016) and has indicated that a 40% decline is acceptable as a surrogate endpoint (Holtkamp et al 2020).

The US FDA also accepted 40% decline as a surrogate endpoint based on this work and considered that a 30% decline might be acceptable under certain circumstances (Thompson et al 2014).

3.4.4 GFR slope as surrogate endpoint in CKD clinical trials: prior work

The results of previously reported trial-levels analyses (Inker et al 2019a), which utilized data from 47 RCTs, are presented in Table 2. The treatment effect on total slope computed at 3 years and on chronic slope (starting at 3 months after study randomization) strongly predicted the treatment effect on the clinical endpoint, with median R^2 (95% BCI) of 0.97 (0.78, 1.00) and 0.96 (0.63, 1.00), respectively.

Table 2 Prior trial level association between GFR slope and clinical endpoint

	N Studies (N Interv)	N patients (N events)	Meta-Regression Slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Total slope 3 years	47 (12)	60620 (7115)	-0.42 (-0.55, -0.30)	-0.05 (-0.14, 0.02)	0.97 (0.78, 1.00)	0.06 (0.02, 0.14)
Total slope 2 years	47 (12)	60620 (7115)	-0.30 (-0.42, -0.19)	-0.14 (-0.22, -0.06)	0.83 (0.48, 0.97)	0.12 (0.06, 0.21)
Chronic slope	47 (12)	60620 (7115)	-0.46 (-0.62, -0.29)	0.02 (-0.09, 0.12)	0.96 (0.63, 1.00)	0.06 (0.01, 0.16)

BCI, Bayesian credible interval; GFR, Glomerular filtration rate; Interv, Intervention; RMSE, Root mean square error.
Adapted from: Inker et al 2019a.

Based on this analysis, it was determined that with a sufficient sample size, a treatment effect of 0.75 ml/min per 1.73 m^2/year or greater on total slope computed at 3 years or chronic slope predicts a clinical benefit on CKD progress with at least 96% probability. These data supported the potential utility of GFR slope as a valid surrogate endpoint and led to the substantially expanded evaluation presented in this briefing package.

Table 3 Predicted treatment effect on clinical end point and PPVs for total GFR slope over 3 years and chronic slope

	Observed treatment effect on change in GFR slope	Large RCT		Modest RCT	
		Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV
Total GFR slope over 3 years	0.75	0.69 (0.52, 0.89)	1.00	0.69 (0.47, 1.00)	0.98
	1.0	0.62 (0.47, 0.80)	1.00	0.62 (0.42, 0.90)	1.00
Chronic slope	0.75	0.72 (0.54, 0.94)	0.99	0.72 (0.48, 1.05)	0.96
	1.0	0.65 (0.48, 0.85)	1.00	0.65 (0.42, 0.94)	0.99

Units of GFR are mL/min per 1.73 m^2. Treatment effect on GFR slope is expressed as mean difference and in units of mL/min per 1.73 m^2/year. Treatment effect on the clinical endpoint is expressed as HR. PPVs are defined as the 97.5% probabilities for clinical benefit, defined as HR <1 for an infinite, large- or modest-sized RCT. A large RCT was defined as one in which the treatment effect on GFR slope can be estimated to within a SE of 0.25, corresponding to a total sample size (N) of about 1900 for RCTs whose average follow-up accorded with the RCTs in the analysis. A modest RCT was defined as having SE of 0.4 (N roughly 720).
GFR, glomerular filtration rate; HR, Hazard ratio; PPV, Positive predictive value; RCT, Randomized controlled trial; SE, standard error.
Adapted from: Inker et al 2019a.

4. CURRENT QUALIFICATION REQUEST: GFR SLOPE AS A SURROGATE ENDPOINT IN CKD CLINICAL TRIALS

The objective of this request is to seek a qualification opinion on the use of GFR slope, i.e., the mean rate of change in GFR, as a validated surrogate endpoint for CKD progression in clinical trials for standard marketing authorization and indication extension approvals.

This request is based on the 3 key areas of investigation that were initially presented in the March 2018 conference, along with updated analyses for the second of the three areas, as described below:

1. Evidence from the meta-analysis of observational cohorts participating in the CKD-PC was presented at the March 2018 workshop and subsequently published (Grams et al 2019). This work demonstrates a strong relationship between the surrogate endpoint GFR slope and the clinical endpoint KFRT in cohort data and provides strong epidemiological support for GFR as a surrogate endpoint. **This work is summarized in Section 6**, and meets the second criterion for a valid surrogate endpoint described in Section 3.2.2.
2. Trial-level analyses with Bayesian methodology was used to examine the agreement between treatment effects on GFR slope and treatment effects on the clinical endpoint, and provide predictions for future trials. Initial results of trial-level analyses were presented as part of the 2018 workshop and published (Inker et al 2019a). Section 3.4.4 has a brief summary of this work. These analyses have now been updated to include

several more recent and larger high-quality, high powered RCTs evaluating additional interventions, to better characterize the meta-regression**, with the new results presented in Sections 7.** Based on these results, GFR slope is demonstrated to be a valid surrogate endpoint. As discussed in Section 3.2.2, trial-level analyses are considered the most important criterion for acceptance of a surrogate endpoint.

3. Statistical simulations of trial-level data, which were presented at the 2018 workshop and subsequently published (Greene et al 2019), identified the RCT scenarios where GFR slope improves statistical power as a surrogate endpoint compared with endpoints based on a 30% or 40% GFR decline and the clinical endpoint of KFRT (i.e., scenarios that permit the reductions in sample size or trial durations relative to time-to-event endpoints, while preserving a low risk of bias and type 1 error). This work provides information regarding when to consider slope versus other endpoints but does not empirically define the extent to which slope has met the conditions of a valid surrogate in previous clinical trials. **It is summarized in Section 8.1.**

4.1 Regulatory interaction

On 10 May 2021, a telephone conference was held between CKD-EPI investigators (Lesley Inker and Hiddo Heerspink) with EMA (Peter Mol, Thorsten Vetter, Romaldus Macialitus, and Frank Holtkamp) to discuss the value of GFR slope as a surrogate endpoint in RCTs of CKD. EMA expressed an interest in reviewing a package in support of a request for qualification opinion on GFR slope as a surrogate endpoint for clinical trials in CKD in support of regulatory approval for specific labelling claims, based on the analyses already published in the Journal of American Society of Nephrology 2019, based on the March 2018 workshop (Section 3.4.1), updated for some of the key trials in CKD published since then. There was general agreement with EMA that a broad context of use with respect to patient populations and different causal diseases could be proposed if supported by the data.

5. CONTEXT OF USE STATEMENT

General setting: The proposed novel method, GFR slope, is intended to be used as a validated surrogate endpoint for CKD in clinical trials for standard marketing authorization and indication extension approvals.

- **Target population**: Broad population of patients with CKD or at risk for CKD, including early disease and subgroups by kidney function and causal disease of CKD.

6. PREVIOUSLY CONDUCTED AND PUBLISHED EPIDEMIOLOGIC COHORT ANALYSIS OF RELATIONSHIP BETWEEN GFR SLOPE AND KFRT

6.1 Cohort analysis methods

As described above, an important criterion to support a potential surrogate endpoint is to establish that there is a relationship between the surrogate endpoint and the clinical endpoint of KFRT in epidemiologic cohort data. CKD-PC in collaboration with CKD-EPI for the purpose of the March 2018 workshop, as described in Section 3.4.1 conducted and published a meta-analysis of individual participant data. The methods and results from this work described below.

Data from observational cohorts participating in the CKD-PC to quantify the magnitude of association between GFR slope over 1, 2, and 3 years with long-term risk of reaching the clinical endpoint of KFRT (Grams et al 2019). The magnitude of the relationship was assessed across patient subgroups, including those with baseline eGFR < or ≥60 mL/min per 1.73 m^2, and subgroups defined by age, sex, and causal disease (diabetes, hypertension, and CV). All participants were aged ≥18 years and did not have KFRT diagnosed before or during the baseline period (defined as the 1, 2, or 3 year periods over which GFR slope was calculated).

A total of 14 cohorts were included in the analyses, from an initial 70 cohorts with data on eGFR, albuminuria, and clinical outcomes, based on their agreement to participate, availability of the data, and whether the following criteria were met:

- Could provide data for all of the 1-, 2-, and 3-year baseline periods and had subsequent longitudinal follow-up for KFRT and all-cause mortality
- GFR slope during the baseline period could be estimated for all participants with at least two eGFR measures separated by the desired time window, which was defined as 1, 2, or 3 years ±33%

Separate meta-analyses were conducted for individuals with eGFR < or ≥60 mL/min per 1.73 m^2, and a given cohort could be included in both analyses if there were sufficient numbers of individuals who developed KFRT (≥10 events) within each subgroup.

GFR was estimated from serum creatinine level, expressed as mL/min/1.73 m^2 body surface area, using the CKD-EPI equation.

GFR slope was computed using linear regression over 1, 2, and 3 years and accounting for variance from unreliable estimates using mixed models.

The primary outcome was KFRT, which was defined as the initiation of kidney replacement therapy. The secondary outcome was all-cause mortality. Time at risk for both outcomes began on the date of the last creatinine used in the eGFR slope estimate.

The primary focus of this analyses was on slope computed over 2 years of exposure; analyses over 1 and 3 years were supportive.

6.2 Cohort analysis results

Across the 14 cohorts, there were 3,353,210 individuals included in the 1-year eGFR slope analysis, 3,881,215 in the 2-year analysis, and 3,943,212 in the 3-year analysis. There were 12 cohorts in the eGFR <60 ml/min per 1.73 m^2 analyses (N=122,664) and 7 in the eGFR ≥60 ml/min per 1.73 m^2 analyses (N=3,881,215) (with 5 cohorts contributing patients to both analyses).

Baseline characteristics by cohort and by cohort subtotal in each of the 2 GFR subgroups are described in Grams et al 2019. The GFR <60 ml/min per 1.73 m^2 subgroup had a mean age of 71 years, was 56% women, and 3% black. Mean GFR was 47 ml/min per 1.73 m^2, ranging from 35 to 49 across the cohorts, and 28% had diabetes. The GFR ≥60 ml/min per 1.73 m^2 subgroup had a mean age of 66 years, was 25% women, and 11% black. Mean GFR was 87 ml/min per 1.73 m^2, ranging from 83 to 101 across the cohorts, and 21% had diabetes. The characteristics of the cohorts in the 1- and 3-year observation periods were similar.

Subsequent to the 2-year baseline period, there were 6083 KFRT events and 44,135 deaths over a mean follow-up of 3.3 years in the eGFR <60 ml/min per 1.73 m^2 cohorts and 6552 KFRT events and 520,061 deaths over 4.2 years in the eGFR ≥60 ml/min per 1.73 m^2 cohorts (see Supplemental Table 3 in Grams et al 2019 in Appendix C).

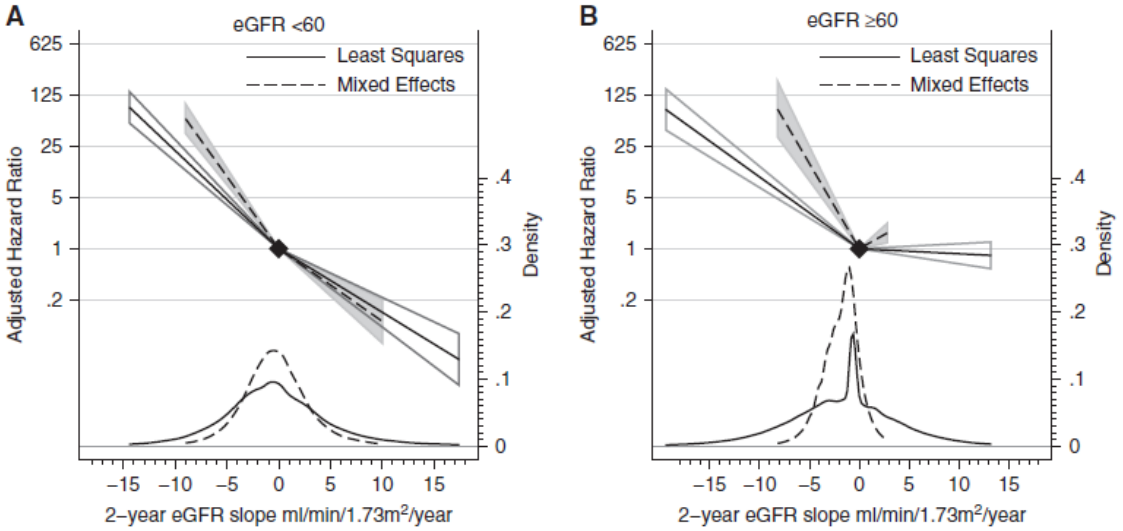
The 2-year mixed model mean slope ranged from -4.92 to 0.27 ml/min per 1.73 m^2 per year and from -3.71 to -1.06 ml/min per 1.73 m^2 per year across the eGFR <60 and ≥60 ml/min per 1.73 m^2 cohorts, respectively (see Supplemental Table 6 in Grams et al 2019 in Appendix C). The standard deviations (SDs) of eGFR slopes were smaller and mean slopes were generally more modest with longer observation periods.

Shown in Figure 8, a steeper eGFR decline over a 2-year observation period was associated with higher risk of subsequent KFRT, using either a mixed effects model or linear regression model to estimate slope. This association was statistically significant in the meta-analysis within both strata of eGFR and over the 1-, 2-, and 3-year observation periods.

A similar association between eGFR decline and risk of KFRT was observed within each eGFR cohort across strata of baseline age (<65/≥65 years), sex (male/female), presence of diabetes, hypertension, or history of CVD, or when adjusted for baseline use of ACEi/ARB (see Supplemental Figures 2 to 7 in Grams et al 2019 in Appendix C).

A lesser eGFR decline by 0.75 ml/min per 1.73 m^2 per year was also associated with lower risk of subsequent mortality, although the magnitude of this association was small compared with the association with KFRT and was not statistically significant in every cohort (see Supplemental Table 8 in Grams et al 2019 in Appendix C).

Figure 6 Analysis in cohorts: association of eGFR slope with subsequent KFRT for the 2-year observation period



Meta-analyzed adjusted hazard ratios show a strong association between 2-year eGFR decline and subsequent ESKD in participants with eGFR <60 ml/min per 1.73 m^2 (A) and ≥60 ml/min per 1.73 m^2 (B), with stronger associations when using mixed effects models to estimate slope. Mixed effects indicates the best linear unbiased prediction from linear mixed models; the least squares is the β coefficient from linear regression of eGFR on time. The distribution of slopes is shown in the kernel density plot in the bottom half of the graph, demonstrating the substantial shrinkage, particularly in the higher eGFR group.
eGFR, Estimated glomerular filtration rate; KFRT, Kidney failure with replacement therapy.
Reproduced with permission from: Grams et al 2019 Figure 1.

The absolute risk reduction of KFRT for an individual assuming a difference in eGFR slope of 0.75 ml/min per 1.73 m^2 per year was estimated by applying HRs from the mixed model slopes to baseline sub-hazard of KFRT risk. Table 4 summarizes the HRs for KFRT associated with a 0.75 ml/min per 1.73 m^2 per year change in eGFR over time, by the 1- 2- and 3-year observation periods, stratified by baseline eGFR (<60 ml/min per 1.73 m^2 and ≥60 ml/min per 1.73 m^2). This magnitude of slope reduction over 1, 2, and 3 years was protective for KFRT in both eGFR cohorts in the meta-analysis across the cohorts (Table 4) and each of the individual cohorts (see Grams et al 2019 Supplemental Table 7 in Appendix C). As can be seen in Table 4, the relationship between the decline in slope and protection for KFRT was strongest with the 3-year slope. Based on the 3-year observation period, the HR for KFRT associated with a 0.75 ml/min per 1.73 m^2 per year change using the mixed model was 0.63 (95% CI 0.60, 0.67) in the <60 ml/min per 1.73 m^2 cohort and 0.71 (95% CI 0.68, 0.73) in the ≥60 ml/min per 1.73 m^2 cohort. Results based on the 2-year observation period also showed a strong association between a 0.75 ml/min per 1.73 m^2 per year change and the HR for KFRT (Table 4)

Table 4 Hazard ratios for KFRT associated with a 0.75 ml/min per 1.73 m^2 per year change in eGFR over time for the 1-, 2-, and 3-year observation periods in meta-analysis of cohorts

eGFR subgroup Observation period	Linear mixed models regression	Least squares mean regression
<60 ml/min per 1.73 m^2		
1 year	0.79 (0.76, 0.83)	0.88 (0.86, 0.91)
2 years	0.71 (0.68, 0.74)	0.79 (0.77, 0.81)
3 years	0.63 (0.60, 0.67)	0.71 (0.68, 0.73)
≥60 ml/min per 1.73 m^2		
1 year	0.74 (0.69, 0.80)	0.93 (0.92, 0.94)
2 years	0.70 (0.68, 0.72)	0.84 (0.82, 0.87)
3 years	0.66 (0.64, 0.68)	0.77 (0.74, 0.80)

Mixed effects indicates the best linear unbiased prediction from linear mixed models; the least squares is the beta coefficient from linear regression of eGFR on time. All eGFR values within a given observation period (1-, 2-, 3-years +/- 30%) were used to estimate slope coefficient.
eGFR, Estimated glomerular filtration rate; KFRT, Kidney failure with replacement therapy.
Adapted from: Grams et al 2019 Supplemental Table 7 in Appendix C.

The association between eGFR slope and KFRT is strongest in those at highest risk for rapid progression. For hypothetical populations with mean (SD) eGFR slope of -5 (4) (fast progressor) or -1 (4), an intervention that reduced eGFR decline by 0.75 ml/min per 1.73 m^2 per year would be expected to reduce the 5-year KFRT from 8.3% to 6.7% for the fast progressors and from 0.58% to 0.45% for the slow progressors (Grams et al 2019).

In conclusion, results from the cohort analyses conducted by Grams in collaboration with CKD-EPI CT and CKD-PC (Grams et al 2019) provide strong epidemiologic evidence in support of GFR slope as a surrogate endpoint for KFRT in clinical trials. Slower decline in eGFR over a 1-, 2-, or 3-year baseline observational period was associated with lower risk of subsequent KFRT, even in participants with eGFR ≥60 ml/min per 1.73 m^2 at baseline.

7. TRIAL-LEVEL ANALYSES OF GFR SLOPE AS SURROGATE ENDPOINT

As discussed in Section 3.2.2, the most difficult and important criterion for establishing the validity of a surrogate is to demonstrate a relationship between a causal effect of a treatment on the surrogate and a causal effect of a treatment on the clinical endpoint.

A high level of heterogeneity in interventions and disease subclasses across well powered RCTs included in a trial-level analysis is critical for the value of the analyses to achieve a broad scope of applicability. As such, the analyses have been updated from the previously published work

(Inker et al 2019a) to include data from an additional 19 RCTs, including additional causal diseases and interventions. The inclusion of the additional studies increased the number of very large trials with at least 300 events for the clinical endpoint from 4 to 10, and expanded the scope of the previous analyses by increasing the number of SGLT-2 inhibitor trials from 1 to 4 and added additional inventions such as DPP-4 inhibitors, mineral receptor antagonists, endothelin receptor antagonists, and GLP-1 agonists. The methods and results of the trial-level analyses presented in this section form the key support for this qualification request.

7.1 Dataset development for clinical trial evaluations

7.1.1 Datasets and analytical groups

The general approach to dataset development was described in the supplemental materials in Inker et al 2019 in Appendix C (Protocol).

A systematic literature search was performed to develop a pooled database from January 1946 to April 2020 to identify relevant RCTs of CKD intervention in which there was sufficient progression of kidney failure for analyses and to include studies of rarer diseases. Table A-1 lists the search terms. Table A-2 lists all of the study inclusion criteria for the meta-analysis.

The number of events required for inclusion was varied based on disease state. For studies of glomerular disease, 10 events were required, whereas for studies of more common kinds of CKD, 30 events were required, as well as 500-person years of follow-up. For studies of high-risk populations (i.e., diabetes mellitus, history of CVD, or hypertension, with or without diagnosis of CKD), 30 events and 1000 person-years of follow-up were required. Of 137 potential RCTs identified, a total of 79 studies were identified that met the inclusion criteria and had sufficient data, for which the Applicant was able to obtain agreement to participation and obtained access to the data. Of these, 8 studies were disqualified due to problems with the data. For trials that evaluated more than one intervention, a separate group for each independent treatment comparison was included, such that some participants were included in more than one analytical comparison. Thus, 81 treatment comparisons were derived. Table A-4 summarizes the individual treatment comparisons. Seven treatment comparisons had insufficient endpoints for estimation of treatment effects of the clinical endpoint. Small studies that had less than 100 participants were pooled if the disease and intervention was the same (see Table A-3 for a list of these studies). Therefore, the main analyses presented in this submission included 66 randomized treatment comparisons. A flow chart of the RCTs evaluated and included in the analyses is presented in Figure A-1.

Risks of bias for each study included was assessed using the risk-of-bias tool of the Cochrane collaboration (Higgins and Green 2011) (Figure A-2) which demonstrated that there is not likely to be differential bias on the clinical endpoint and surrogate endpoint. For trials that evaluated more than one intervention, separate groups for each independent treatment comparison were included, such that some participants were included in more than one analytical comparison (Lewis et al 2001, Wright et al 2002, Klahr et al 1994, Estacio et al 2000, Torres et al 2014).

7.1.2 Data management

For each study included in the analysis, the active treatment was defined as the treatment hypothesized to produce the greater reduction in the risk of the clinical endpoint.

The studies were categorized by intervention type: RASB versus control, RASB versus calcium channel blocker (CCB), RASB plus CCB versus placebo, immunosuppressive therapy (including steroid, azathioprine, tacrolimus, fish oil, plasmapheresis), intensive BP control, SGLT-2 inhibitor, antiplatelet therapy, DPP-4 inhibitor, allopurinol, GLP-1 agonist, low protein diet, MRA, nurse-coordinated care, albuminuria targeted protocol, endothelin receptor antagonist, intensive glucose-lowering protocol, and cholesterol-lowering (statin + ezetimibe).

The underlying causal diseases were categorized as: diabetes (including studies of patients with diabetes not restricted to CKD and studies of patients with diabetes with established CKD), glomerular disease (immunoglobulin A [IgA] nephropathy, focal segmental glomerulosclerosis [FSGS], membranous nephropathy), CVD (high CV risk [with or without established CKD, or heart failure]) and CKD (such as cause not specified [CNS], CKD-hypertension, and polycystic kidney disease [PKD]) (Table A-5).

If the study-defined censoring dates were not available, study-level administrative data were approximated by using information on the length of follow-up across the participants in the study. The administrative censoring date was defined as the time from randomization to the final recorded visit date in the data provided plus 6 months plus the study-specific 90th percentile of the average interval between visits with serum creatinine. The purpose of adding 6 months to the estimated right censoring date was to retain a higher proportion of clinical outcome events that occurred following the patient's final study visit. This has been the method utilized in all our prior work. Events were included that occurred up to 1 month following administrative censoring time as often study centers do not learn about kidney failure or death events until close out time. Patients who had events but no visits were included if event occurred within 12 months from baseline.

7.1.3 Clinical endpoints

Clinical endpoints were defined as treated kidney failure (KFRT, defined as initiation of treatment with dialysis or transplantation); untreated kidney failure, defined as GFR <15 ml/min/1.73 m^2 in those with GFR >25 ml/min per 1.73 m^2 at baseline that was confirmed or observed at the last visit; or doubling of serum creatinine that occurred over the full study duration. Table A-8 summarizes the endpoints used for each study in the trial level analysis.

7.1.4 Estimated GFR

GFR was estimated using the CKD-EPI 2009 creatinine equation (Levey et al 2009b). Creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison or was reduced by 5% as has previously been described (Inker et al 2019a) (Table A-4 lists which studies were calibrated).

7.2 Statistical methods

The primary objective was to evaluate the validity of the GFR slope as surrogate end points by assessing the association between treatment effects on GFR slope endpoint and the treatment effects on the clinical endpoint across studies. The secondary objective was to use these results to estimate the probability of clinical benefit associated with treatment effects on GFR slope for application to future studies.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), R 3.16.1 (R Project for Statistical Computing, www.r-project.org) (Viechtbauer 2010), and RSTAN 2.21.5 (Stan Development Team 2022).

7.2.1 Analyses of acute, chronic, and total GFR slope

Longitudinal measurements of GFR may exhibit complexities which lead to violations of standard linear mixed models which have been used for some previous analyses of GFR slope. These complexities include:

1. *Acute effects*: Some treatments have early effects which differ from the long-term trajectories (acute effects) as discussed in Section 3.3.
2. *Heterogeneity in GFR trajectories*:
    a. The variability of deviations of GFR measurements from the underlying trajectories is typically greater at higher GFR levels, leading to heteroskedasticity in the error variance.
    b. The variability of the chronic GFR slopes is often observed to be smaller in the active intervention group than the control group for trials in which a beneficial effect of the treatment is demonstrated. This has been hypothesized to be the result of non-uniform treatment effects in which the treatment has a larger effect on slope (when expressed in ml/min/1.73 m^2 per year) for faster progressors than slower progressors.
3. *Informative censoring*: Informative censoring may occur in which GFR follow-up is terminated by clinical events such as kidney failure or death which could be related to the underlying rate of CKD progression.

To accommodate a uniform method for analysis of GFR slope across many studies, a simplified mixed effects model was used based on a single slope starting at 3 months post randomization, with baseline GFR included in the model as a covariate. Any GFR measurements obtained after randomization and before 3 months were excluded from the analysis. In this approach, the acute effect is assumed to be complete by 3 months, but no assumptions are made concerning the GFR trajectory within the first 3 months after randomization. Random effect slope and intercept terms were included to accommodate variations in GFR trajectories between patients and a shared parameter model was used to address informative censoring by KRFT and death. In mathematical form, the simplified model for a particular trial is expressed as:

$$Y_{ij} = \left(\beta_{0c} + SBGFR_i\beta_{0,bgfr}\right) + \left(t_{ij}\beta_{1c} + SBGFR_i t_{ij}\beta_{1,bgfr}\right) + Z_i\beta_{0t} + Z_i t_{ij}\beta_{1t}$$

$$+b_{0i} + t_{ij}b_{1i} + \epsilon_{ij},$$

$T_i \sim$Piecewise Exponential with hazard function $\lambda(t) = \lambda_0(t)\exp\{\eta_0 Z_i + \eta_1 SBGFR_i + \eta_2 b_{0i} + \eta_3 b_{1i}\}$,

$\epsilon_{ij} \sim Normal\left(0, \sigma^2 \times \left(\mu_{ij}^2\right)^{\theta}\right)$.

Here,

t_{ij} = time of the i^{th} subjects j^{th} GFR measurement after month 3,

$Y_{ij} = i^{th}$subject's GFR measurement at time t_{ij},

$T_i =$ time of KFRT or Death for the i^{th} subject,

$Z_i =$ randomized treatment group for patient i,

$SBGFR_i =$ mean centered baseline GFR for patient i.

The terms β_{0c}, $\beta_{0,bgfr}$, β_{1c}, $\beta_{1,bgfr}$, β_{0t}, and β_{1t} are fixed effects coefficients which adjust for the baseline GFR level, and which express the mean acute effects and mean chronic slopes within the treatment and control groups. The adjustment for baseline GFR is analogous to the adjustment for the baseline level of the outcome in analysis of covariance and adjusts for random imbalances in the initial GFR level between the treatment groups to increase statistical power. The terms b_{0i} and b_{1i} are random effects to account for variation between the GFR trajectories for individual patients. The term $\lambda_0(t)$ is the baseline hazard for the time of the composite endpoint defined by KFRT or Death and is assumed to correspond to a piecewise exponential distribution. The terms η_0, and η_1 relate the risk of KFRT or death to baseline GFR and the randomized treatment assignment, and η_2 and η_3 relate the risk of ESKD or death to the random slope and intercept terms (these are the terms that govern the shared parameter component of the model). The ϵ_{ij} are normally distribution residuals for the observed GFR values around their underlying trajectory, σ^2 defines the squared SD of these residuals, and θ is the power of the mean parameter that accounts for the dependence of the residual variability on the GFR level.

Under this simplified 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 2 or 3 years follow-up factored by the follow-up duration from baseline represent the treatment effects on the acute, chronic, and total slopes, respectively. Thus, these are operational definitions for the purposes of analyses across the whole set of past trials. For the total slope computed at 2-year total slope is thus a weighted average of the acute and chronic slope corresponding to a 2-year time horizon, and the 3-year total slope, is the weighted average of the acute and chronic slope corresponding to a 3-year time horizon. The 2-year total slope provides greater weight to the acute slope relative to the chronic slope than the 3-year total slope, while the chronic slope provides 0 weight to the acute slope.

While the simplified model avoids assuming a particular form for the GFR trajectory between randomization and 3 months, the "acute slope" may nonetheless be defined as the ratio of the

mean difference in eGFR between time 0 and 3 months and the 3 month time interval. These analyses also allow a general unstructured covariance matrix for the random slopes and intercepts for the GFR trajectories and further allow the variance of the random slopes to differ between the active intervention and control groups to accommodate the possibility of non-uniform treatment effects which can occur when treatments slow progression by a greater extent among patients with faster GFR decline than for patients with slower GFR decline (Vonesh et al 2019). The rationale for allowing different between slope variances is that treatments that slow progression to a greater extent for fast progressing patients tend to shift the lower tail (corresponding to the fast progressors) of the slope distribution towards the center of the distribution, while having the upper tail corresponding to slower progressors relatively unchanged. The result is a contraction of the slope distribution, resulting in a smaller between-patient slope variance in the active treatment group compared to the control group.

The shared parameter component of the model was dropped for studies with fewer than 15 composite KRFT or death events, as model convergence becomes difficult to achieve when the number of events is too small, and the bias from removing the shared parameter component becomes negligible when the proportion of patients with events is small as well. See Vonesh et al 2006 and Rizopoulos 2012 for further discussion of shared parameter models for the longitudinal trajectories.

Across the 66 studies, the mixed models were further simplified in a small number of cases where convergence could not be obtained with the mixed effects model. As noted above, for studies without sufficient endpoints, the shared parameter model was not used. Other simplifications included using the same variance across both treatment arms and using the group mean in place of the power of the mean model. Table A-17 shows the models used across the set of studies.

The models were fit using the SAS (version 9.4) nonlinear mixed-effects regression procedure, NLMIXED. Documented computer code for a closely related 2-slope linear mixed model is provided in the supplemental materials of Vonesh et al 2019 (see Vonesh et al 2019 in Appendix C).

In applications of GFR slope analysis to individual studies, it will often be useful to tailor the mixed effects shared parameter model to account for the specific nature of the population, intervention, and study design. In particular, the simplified model may be extended to the 2-slope model described in Vonesh et al 2019 in Appendix C, and with the knot point demarking the transition from the acute to the chronic phase of follow-up defined as appropriate for the intervention investigated in that study. See the CKD-EPI Consortium Technical Report in Appendix C for an approach for determining the knot point empirically. Because the present joint analysis used a fixed time point of 3 months for the initiation of the chronic phase to achieve uniformity across the 66 trials, it may provide a conservative assessment of the performance that may be achieved when the knot point is tailored to a specific trial. In studies where the expected numbers of both the KFRT and death events are substantial, it may be useful to extend the model to allow distinct relationships between GFR trajectories and KFRT and death separately as described in the CKD Consortium Technical Report in Appendix C. The

Technical Report also describes extensions to accommodate a combination of informative and non-informative censoring by the KFRT and death events.

7.2.2 Trial-level analysis relating treatment effects on the clinical endpoint to treatment effects on GFR slope

Overview

A trial-level analysis was conducted to relate the treatment effects on the clinical endpoint (i.e., KFRT) to the treatment effects on the surrogate endpoint, GFR slope. The trial-level analysis requires two steps: intent-to-treat estimation of the treatment effects on the surrogate and clinical endpoints within each RCT followed by a meta-regression to relate the treatment effects on the surrogate and clinical endpoints across RCTs. The analytic approach for trial-level analyses was based on the causal association framework described in Joffe and Greene (Joffe and Greene 2009) in which the validity of surrogate endpoints is evaluated based on the relationship between the average causal effect of the treatment on the surrogate endpoint and the average causal effect of the treatment on the clinical endpoint across a population of randomized trials which are viewed as similar to a new randomized trial in which conclusions concerning clinical benefit are to be based on the surrogate endpoint. This approach takes advantage of the fact that the average causal effects on the surrogate and clinical endpoints can be estimated with little bias within each randomized trial by applying intent-to-treat analyses. The approach is closely related to frameworks for trial-level analyses which have been developed by other authors (Daniels and Hughes 1997, Burzykowski and Buyse 2006).

Value of Heterogeneity

In contrast to some settings, where heterogeneity complicates scientific inference, the empirical support for a surrogate endpoint is enhanced when the trial-level meta-regression is conducted over a heterogeneous rather than a homogenous collection of previously conducted randomized trials. This assertion stems from the observation that validation and subsequent application of a surrogate endpoint in a new randomized trial represents a type of inductive reasoning: The assertion of validity of the surrogate for application in the new trial is based on the observation that treatment effects on the surrogate accurately predicted treatment effects on the clinical endpoint across the series of previously conducted trials. Confidence in this induction is increased when the previously conducted trials provide evidence that the treatment effect on the clinical endpoint is consistently predicted from the treatment effect on the surrogate across a wide range of different interventions, disease subtypes and study designs with varying measurement schedules and durations of follow-up.

Analyses

In the first stage, for each randomized comparison of an active treatment versus control within each trial, separate analyses using shared parameter mixed effects models and Cox regression models were performed to estimate the effects of the treatment on the GFR slope and on the clinical endpoint, respectively. Treatment effects on GFR slope were expressed as mean difference between the GFR slope in treatment and control groups. For the clinical endpoint, treatment effects were expressed as log transformed HRs. GFR slope was expressed on the absolute scale (in ml/min/1.73 m^2/year) instead of as a percentage change per year based on an

analysis of log transformed GFR for several reasons. First, the majority of prior analyses of GFR slope in CKD RCTs have expressed slope on the absolute scale. Second, the exponents from our power of the mean model for residual GFR variance suggested that for most studies the optimum transformation stabilizing GFR residual variance was intermediate between the untransformed and log transformed scales, and closer to untransformed. Third, it was found that the trial level slope results were not substantially altered after excluding RCTs with a slow expected rate of progression. This suggests that using an absolute instead of a % difference in mean slopes is not skewing these results.

To express the statistical model precisely, let i = 1, 2, ..., denote the 66 randomized treatment comparisons included in the analysis. For simplicity, as most trials included a single treatment comparison, the notation is abused slightly by writing that the index *i* refers to the i^{th} trial. Let θ_i and γ_i denote the true treatment effects on the clinical endpoint and on change in GFR slope in the i^{th} trial, and use $\hat{\theta}_i$ and $\hat{\gamma}_i$ to indicate the estimated effects obtained as described above. The Stage 1 model relates the estimated and true treatment effects in the i^{th} trial by:

$$\begin{bmatrix}\hat{\theta}_i \\ \hat{\gamma}_i\end{bmatrix} \sim \text{MVN}\left(\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix}, \begin{bmatrix}\sigma_i^2 & r_i\sigma_i\delta_i \\ r_i\sigma_i\delta_i & \delta_i^2\end{bmatrix}\right).$$

Here, σ_i is the standard error of the estimated treatment effect on the clinical endpoint and δ_i is the standard error of the estimated treatment effect on GFR slope in the i^{th} trial, and r_i is the correlation between the estimated treatment effects. Robust sandwich estimates were used to estimate the correlations r_i within each trial. The notation MVN() indicates that the estimated treatment effects are assumed to follow a bivariate normal distribution given the true treatment effects within each trial; this assumption is satisfied to a high degree of accuracy due to the central limit theorem.

The second stage models the variation in the true treatment effects on GFR slope and on the clinical endpoint across the trials. The stage 2 model is expressed as

$$\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix} \sim N\left(\begin{bmatrix}\mu_\theta \\ \mu_\gamma\end{bmatrix}, \begin{bmatrix}\sigma_\theta^2 & \text{R}\sigma_\theta\sigma_\gamma \\ \text{R}\sigma_\theta\sigma_\gamma & \sigma_\gamma^2\end{bmatrix}\right)$$

where μ_θ and μ_γ are respectively the means of the true treatment effects on the clinical endpoint and on GFR slope in the population of trials represented by this meta-regression, σ_θ and σ_γ are the SD of the true treatment effects across the population of trials, and R is the correlation between the true treatment effects on the two endpoints.

Based on this 2-stage model, the slope and intercept of the meta-regression line predicting the true treatment effect on the clinical endpoint from the true treatment effect on the surrogate endpoint are given by $\beta = \text{R}\sigma_\theta/\sigma_\gamma$ and $\alpha = \mu_\theta - \beta\mu_\gamma$, respectively, and the root mean square error (RMSE) that defines the uncertainty in the treatment effect on the clinical endpoint given a particular treatment effect on the surrogate endpoint is RMSE = $\sigma_\theta \times (1 - R^2)^{\frac{1}{2}}$.

The second stage model was fit using Bayesian Monte-Carlo Markov Chain sampling, using diffuse prior distributions for the model parameters that were selected so that the final results would depend primarily on the data with little influence of the prior distributions. A Bayesian rather than a Frequentist approach for the trial level analyses was used to make available full posterior distributions when summarizing estimation of model parameters and to express inferences concerning clinical benefit as numeric probabilities.

The priors for the mean treatment effects on the clinical endpoint (expressed as a log HR) and on each GFR slope endpoint (expressed in ml/min/1.73 m^2/year) were taken to be normal distributions each with mean 0 and variance 10,000; the priors for the variances of the treatment effects on the clinical endpoint and on the GFR slope endpoints were each taken to be inverse gamma distributions with shape parameter 0.261. The scale parameter was 0.000408 for the clinical endpoint and 0.005 for the slope endpoints. The prior distribution for the clinical endpoint was selected by the investigators to assign 1/3 prior probabilities each to low treatment effect heterogeneity (defined as a treatment effect SD on the log scale ≤0.05), medium treatment effect heterogeneity (defined as a treatment effect SD on the log scale between 0.05 and 0.20), and high treatment effect heterogeneity (defined as a treatment effect SD on the log scale >0.20). For slope, the prior assigns a 1/3 prior probability to slope SDs ≤0.175 ml/min/1.73 m^2/year, 1/3 to a slope SD between 0.175 and 0.70 ml/min/1.73 m^2/year, and 1/3 to a slope SD >0.70 ml/min/1.73 m^2/year, respectively. It was checked that the prior distributions had only a small influence on the results by verifying that the results of each analysis were similar under alternative inverse gamma (0.001, 0.001) prior distributions for the variances for the treatment effects on the clinical endpoint and on GFR slope. It was also verified that there was approximate correspondence of the primary results under the Bayesian models to maximum likelihood estimates obtained under a frequentist formulation of the mixed effects meta-regression model.

Interpretation

The trial-level analysis will support GFR slope as a surrogate endpoint if the slope of the meta-regression relating the treatment effect on the clinical endpoint to the treatment effect on the designated GFR slope endpoint differs substantially and significantly from 0, the R^2 and RMSE or the meta-regression indicates that the estimated treatment effect on the GFR slope endpoint can reliably predict the treatment effect on the clinical endpoint, and the intercept of the meta-regression line is close to 0, indicating that the absence of a treatment effect on the GFR slope endpoint is not systematically associated with a non-zero treatment effect on the clinical endpoint.

7.2.3 Outlier assessment

It is important to note that the trial level meta-regression relates unobserved “true” treatment effects on the clinical endpoint to true treatment effects on GFR slope based on a statistical model that accounts for the sampling error in the estimated treatment effects on the two endpoints. Because the true treatment effects are latent variables, there is a risk of instability in the parameters that define the meta-regression with respect to inclusion or exclusion of individual studies, particularly the larger studies which are weighted most heavily in the analysis.

This is particularly the case for the residual RMSE of the meta-regression (denoted $RMSE$ above) and the trial-level $R^2 = 1 - \frac{RMSE^2}{\sigma_\theta^2}$, where σ_θ^2 is the variance of the true treatment effects on the clinical endpoint. This is because $RMSE = \sigma_\theta^2 - \beta^2\sigma_\gamma^2$ (where β is the meta-regression slope and σ_γ^2 is the variance in the treatment effects on the surrogate endpoint) is the difference between two unknown quantities which must be estimated from the data, and generally $RMSE$ is substantially smaller in magnitude than both of the terms σ_θ^2 and $\beta^2\sigma_\gamma^2$ which define this difference. As a result, small deviations in σ_θ^2 and $\beta^2\sigma_\gamma^2$ can lead to larger relative deviations in $RMSE$, and thus also in R^2. In order to address this risk, an extensive set of analyses was carried out to address the sensitivity of the main results to inclusion or exclusion of individual studies.

An outlier assessment was used to evaluate whether any of the individual trials used for the trial-level analyses appeared incompatible with the broader collection of trials. To evaluate trial incompatibility, a model-based posterior predictive distribution (PPD) for the predicted treatment effect on the clinical endpoint was compared to the point estimate for the observed estimated treatment effect on the clinical endpoint for each trial. Each trial's PPD represented a distribution of the treatment effect on the clinical endpoint one would expect to observe based on the modelled relationship between treatment effects on the clinical and surrogate endpoint and conditional on the specific estimated treatment effect on the surrogate observed for the trial. The PPD takes into account sampling error in the estimated treatment effects for each trial as well as uncertainty in the estimates of the meta-regression parameters. We specifically evaluated the percentile each trial's estimated treatment effect on the clinical endpoint fell within the corresponding PPD. If the estimated clinical effect fell within a tail of the PPD, this analysis provided evidence to suggest the pair of estimated effects on the clinical and surrogate endpoint for that trial did not align with the typical relationship between effects in the remaining trials. Because the PPD takes into account the sampling error in the effect estimates, the resulting outlier definition properly accounts for the effects of study size on the precision of the estimated treatment effects.

Consider here how a PPD for each trial i, for i = 1 ,..., N trials was generated. As a result of fitting a trial-level model described in the previous subsection, one would have, say, M total Markov Chain Monte-Carlo (MCMC) draws for the posterior distributions for each of μ_θ, μ_γ, σ_θ, σ_γ, and β. Let the mth of M posterior draws be super-scripted with (m). Based on the 2-level hierarchical model used for the trial-level analysis, for each trial i, we can write the conditional distribution of the estimated treatment effect on the clinical endpoint conditional on the estimated treatment effect on the surrogate endpoint and the mth of M MCMC draws for each meta-regression parameter as a normal distribution with mean $\mu_i^{(m)} = \mu_\theta^{(m)} + \frac{\left(r_i\sigma_i\delta_i + \beta^{(m)}\sigma_\gamma^{2(m)}\right)\left(\hat{\gamma}_i - \mu_\gamma^{(m)}\right)}{\sigma_\gamma^{2(m)} + \delta_i^2}$ and variance $\sigma_i^{2(m)} = \sigma_\theta^{2(m)} + \sigma_i^2 - \frac{\left(r_i\sigma_i\delta_i + \beta^{(m)}\sigma_\gamma^{2(m)}\right)^2}{\sigma_\gamma^{2(m)} + \delta_i^2}$. As such, to simulate draws for the ith trial's PPD, we would take M total draws of what we will denote $\hat{\theta}_i^p$ from the $N(\mu_i^{(m)}, \sigma_i^{2(m)})$ distribution.

To summarize incompatibility of the observed estimated treatment effects on the clinical endpoint and the corresponding distributions of predicted clinical effects, trials were identified for which the percentile of the observed effect was at or above the 95th percentile of the distribution, or below the 5th percentile of the corresponding predictive distribution. If a trial's observed effect on the clinical endpoint is below the 5th percentile of the predictive distribution, this indicates the observed effect is more beneficial than would be expected based on the observed effect on the surrogate and the model. Alternatively, if the observed effect is above the 95th percentile of the predictive distribution, this indicates the observed effect is less beneficial than would be expected. Descriptions are provided of the trials meeting this criterion to summarize whether specific trial categories more often appeared among the outlier trials.

For a second analysis evaluating the extent to which each trial could influence the meta-regression parameter posteriors, the trial-level model was repeatedly fit by leaving each trial out of the model fitting procedure. For each trial left-out of model fitting, posteriors were obtained (using the same MCMC algorithm described in the previous subsection) for the meta-regression intercept α, slope β, and for R^2. The posterior median and 95% credible interval were produced for each term for each model corresponding to a trial left-out, and it was assessed whether the posteriors differed meaningfully from those obtained from an analysis using the full collection of trials. The impact of removing studies that were outliers across all 3 slopes, potentially indicating study specific anomaly, was also examined.

7.2.4 Subgroup analyses

The trial-level analysis was performed for the primary analytic dataset overall and by subgroups defined by average study level of baseline GFR (< or ≥60 ml/min per 1.73 m^2), cause (diabetes and diabetic kidney disease, glomerular diseases, or other causes of CKD), and rate of progression on the control arm (fast or slow progression defined as chronic slope ≤ or >-2.6 ml/min per 1.73 m^2 per year, respectively). This threshold of rate of progression was used, as this was the median value for rate of progression in the control arm across all studies and rate >2 ml/min/1.72 m^2 per year is often considered fast.

In addition, a subgroup analysis by baseline ACR was conducted using patient-derived ACR cutpoint of 30 mg/g. This cutpoint was selected because this is the definition of CKD, it is consistent with prior results (Inker et al 2019a), which showed that change in albuminuria is a stronger surrogate when baseline ACR is greater than 30 mg/g, and because at higher levels of ACR, the subset would be substantially smaller, which would not allow a comparison.

For subgroup-specific trial-level analyses, the 2-level meta-regression model described in Section 7.2.2 was fit independently within subgroups of trials. The posterior median and 95% credible interval for the meta-regression intercept, slope, R^2, and RMSE obtained from fitting the meta-regression model within each subgroup was provided.

It is important to note that differences in the trial-level R^2 between subgroups may result both from differences between subgroups in the RMSE, which reflects the error of the meta-regression in predicting the treatment effect on the clinical endpoint, as well as from differences between the subgroups in the amount of heterogeneity of treatment effects on the surrogate

endpoint. Thus, the RMSE provides a more direct comparison of the precision of the trial-level meta-regression between subgroups than does the R^2. In practice, comparisons of both the RMSE and the trial-level R^2 between different subgroups are often challenging due to limited precision of the estimates of these quantities within subgroups in Section 7.2.3.

7.2.5 Sensitivity analysis

Several sensitivity analyses were performed. First, subsets of studies were excluded to ensure that results were not dominated by specific diseases. Glomerular diseases were excluded as these are all rare and small studies. The Applicant thought it best to include them in the overall set of studies due to the importance of heterogeneity for the robustness of the trial level analysis as described above and because some patients with glomerular disease would be included in the CKD studies. However, to ensure that the glomerular disease studies did not affect the results in any direction, the impact of excluding them was evaluated in a sensitivity analysis. It was also evaluated whether excluding CV studies, heart failure studies, and high CV risk studies as separate groups had an impact, as these all have slow progression and were not necessarily specifically recruited for CKD progression.

Second, as described above, a less diffuse prior was evaluated to ensure that the prior selected did not influence the results substantially. These less informed priors for the mean treatment effects on the clinical endpoint (expressed as a log HR) and on each GFR slope endpoint (expressed as difference between treatment arms in ml/min/1.73 m^2/year) were taken to be normal distributions each with mean 0 and variance 10,000.

7.2.6 Prediction intervals and positive predictive value

Bayesian prediction intervals and positive predictive values (PPVs) for clinical benefit (defined as a HR <1 for the clinical endpoint) were used to describe the uncertainty in predicting the treatment effect on the clinical endpoint from the treatment effect on the GFR slope in a newly conducted RCT based on the meta-regression model from previous RCTs. This was done only when the intercept of the meta-regression line is close to 0 (Section 7.2.2), as the PPV is influenced by factors other than the treatment effect on the surrogate when the intercept is substantially non-zero. The key assumption required for application of the meta-regression from previous RCTs to the new RCT is that of exchangeability between the new RCT and the previous RCTs. Heuristically, one can think of this assumption as requiring that in terms of the expected relationship between the treatment effects on slope and the clinical endpoint, the new RCT does not differ from the collection of prior RCTs by a greater amount then the prior RCTs differ from each other.

For a hypothetical scenario in which the treatment effect on GFR slope is assumed to be known without error, prediction intervals and PPVs were calculated by simulating the posterior distribution of $\alpha + \beta \times$ True. $\text{Eff}_{slope} + \Delta_0$, where True. Eff_{slope} is the designated true treatment effect on early change in GFR slope, $\alpha + \beta \times$ True. Eff_{slope} represents the corresponding predicted mean true treatment effect on the clinical endpoint based on the meta-regression from the 2-stage model, and Δ_0 is normally distributed with mean 0 and SD given by the RMSE from the meta-regression. Here Δ_0 represents the variation in the treatment effects on the clinical endpoint across different trials with the same treatment effect on GFR slope. The resulting

prediction intervals and PPV calculations account for uncertainty in the estimation of α, β, and RMSE that define the meta-regression. The RMSE defines the amount of variation in the true treatment effects on the clinical endpoint about the meta-regression line for different trials.

When the trial level meta-regression is applied to an actual newly conducted randomized trial, there is an additional source of uncertainty that results from imprecision in the estimation of the treatment effect on GFR slope in the new trial. This added uncertainty depends on the sample size and is smaller when the sample size for the new trial is large. For purposes of illustration, examples were considered based on a large-, modest-, or small-sized RCT. For all, we assumed a follow-up period of 3 years with measurements every 6 months. A large RCT corresponded to a total sample size (N) of about 1600 for RCTs whose average follow-up accorded with the RCTs in the analysis. A modest-sized RCT was defined as a sample size of 800. A small-sized RCT was defined as a sample size of 400.

The 95% prediction intervals were obtained for the treatment effect in a new trial that takes into account this uncertainty by again sampling from the posterior distribution of $\alpha + \beta \times$ True. $\text{Eff}_{slope} + \Delta_0$, but now assuming that True. Eff_{slope} has a random distribution to reflect the uncertainty in its estimation in the new trial instead of taking True. Eff_{slope} to be a fixed value. Specifically, we assumed that True. Eff_{slope} is normally distributed with mean equal to the estimated treatment effect on GFR slope and SD given by the standard error for the estimated treatment effect on GFR slope based on the sample size. The distribution for True. Eff_{slope} reflects a fully non-informative prior distribution for the treatment effect and is not influenced by the estimated distribution of treatment effects on GFR slope in the trials contributing to the meta-regression. A fully noninformative prior for True. Effslope_{slope} was chosen so that the estimation of the treatment effect in the new trial would depend only on the relationship between the treatment effects on the clinical endpoint and on GFR slope, and not on the average treatment effect on GFR slope in the previously conducted trials.

A similar sampling approach to that described above was used for the posterior distribution of $\alpha + \beta \times$ True. $\text{Eff}_{slope} + \Delta_0$ to compute prediction intervals and PPVs based on estimated treatment effects on GFR slope. PPVs were calculated based on the probability that the log HR for the clinical endpoint in the new trial would fall below 0 (corresponding to a treatment benefit) given the estimated treatment effects on GFR slope in the new trial. These latter quantities provide estimates of the PPV for demonstrating a benefit of the treatment on the clinical endpoint given designated values for the observed treatment effects on GFR slope. The threshold associated with the smallest observed treatment effect was computed on either the chronic or total slope that would assure a high probability of benefit of the treatment on the clinical end point, which was defined as the treatment effect on the GFR slope end point providing a PPV of 97.5%.

7.3 Characteristics on the included studies

There were 66 studies that included 187,323 participants, representing 17 interventions across 4 broad disease groups. Table 5 summarizes the aggregate characteristics of the populations in the studies included in the analyses, for the overall pooled data set and stratified by underlying disease. Patient characteristics by individual study, treatment comparisons, and causal disease are summarized in Table A-6.

The pooled dataset had a mean (SD) age of 63.5 (10.7) years, was 34.9% female, 8.2% Black, and 64.1% had diabetes. Average baseline mean (SD) eGFR was 67.3 (24.7) ml/min per 1.73 m^2 and geometric mean (SD) ACR was 69 (9.0) mg/g. Thus, the studies included in the trial-level analyses included a broad range of populations across causal diseases and multiple interventions, and across a broad range of baseline eGFR and ACR levels.

As shown in Table 5, there was variability in baseline characteristics across causal diseases and interventions. As expected, the population with established CKD had lower mean eGFR than the populations with diabetes, glomerular disease, or CVD, and higher geometric mean ACR than those with CVD.

Table 5 Clinical characteristics of the population stratified by disease cause and intervention

	N studies	N participants	Age	Female	Black	Diabetes	eGFR	ACR (geom. mean/SD)
All Studies	66	187323[a]	63.5 (10.4)	58894 (34.8)	12989 (7.9)	127450 (68.0)	67.8 (109.5)	69 (2417.0)
Disease								
CKD	28	20149	57.5 (13.7)	7621 (37.8)	3288 (16.3)	4856 (24.1)	39.1 (20.5)	235 (6.3)
Diabetes	21	102016	63.9 (8.7)	35659 (35.0)	4356 (4.7)	102016 (100.0)	69.0 (88.8)	72 (506.9)
Glomerular	10	1527	38.6 (14.3)	562 (36.8)	72 (4.7)	5 (0.3)	78.7 (40.5)	1471 (2.3)
Cardiovascular	7	63631	67.1 (9.5)	15052 (32.8)	5273 (11.8)	20573 (32.3)	74.9 (39.2)	16 (18.1)
Intervention								
RASB vs CONTROL	21	35692	62.1 (11.3)	12036 (35.0)	2255 (6.4)	25914 (72.6)	65.8 (44.0)	67 (41.6)
RASB vs CCB	4	2293	57.6 (9.1)	832 (36.3)	862 (37.6)	1520 (66.3)	52.1 (20.5)	498 (6.0)
RASB+CCB	1	11482	68.5 (6.8)	4531 (39.5)	1412 (12.3)	6932 (60.4)	75.0 (18.1)	18 (4.9)
Immunosuppression	9	1374	38.7 (14.7)	466 (33.9)	72 (5.2)	2 (0.1)	78.4 (41.5)	1537 (2.3)
Low vs Usual BP	7	12081	63.5 (12.8)	4374 (36.2)	4061 (33.6)	452 (3.7)	67.5 (23.6)	24 (5.5)
SGLT-2 Inhibitor	4	25407	63.0 (9.2)	8416 (33.3)	1096 (4.4)	24143 (95.0)	68.4 (44.7)	76 (91.5)
Antiplatelet	3	31586	63.5 (9.3)	3823 (27.7)	314 (2.3)	10373 (32.8)	76.4 (21.0)	1032 (2.3)
DPP-4 Inhibitor	3	18329	63.8 (9.7)	6706 (36.8)	949 (5.3)	18329 (100.0)	68.9 (24.3)	52 (8.3)
Allopurinol	2	471	64.6 (12.5)	172 (36.5)	1 (0.2)	250 (53.1)	33.0 (12.5)	319 (7.2)
GLP-1 Agonist	2	16446	64.2 (8.0)	5259 (32.0)	882 (7.3)	16446 (100.0)	78.9 (21.4)	33 (5.9)[a]
Low vs Usual Diet	2	839	51.8 (12.4)	332 (39.6)	66 (7.9)	43 (5.1)	34.5 (13.5)	200 (5.4)
MRA	2	9106	68.6 (9.6)	3453 (37.9)	565 (6.2)	6785 (74.5)	52.2 (18.2)	392 (6.4)
Nurse-coordinated Care	2	1098	62.4 (10.9)	449 (40.9)	74 (6.7)	300 (27.3)	41.2 (14.4)	114 (4.0)
Albuminuria Targ Protocol	1	339	50.9 (13.7)	126 (37.2)	0 (0.0)	0 (0.0)	29.0 (13.4)	1068 (1.7)
Endothelin rec. antagonist	1	3659	64.5 (8.8)	945 (25.8)	224 (6.1)	3659 (100.0)	42.5 (14.2)	479 (2.7)
Intensive Glucose	1	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	17 (4.0)
Statin+Ezetimibe	1	6245	62.9 (11.7)	2363 (37.8)	119 (1.9)	1426 (22.8)	26.2 (12.3)	174 (6.6)

[a] 18 of these participants were not included in the treatment effect on clinical endpoint.

Two of the diabetes studies (one studying DPP-4 Inhibitor and the other GLP-1 Agonist) and 3 CV studies (2 studying antiplatelets and the other studying RASB v control) did not have ACR measurements.

ACR, Albumin:creatinine ratio; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, Cardiovascular; ; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; MRA, Mineralocorticoid receptor antagonist; RASB, renin-angiotensin system blocker; SD, standard deviation; SGLT-2, sodium-glucose cotransporter 2; Targ, targeted.

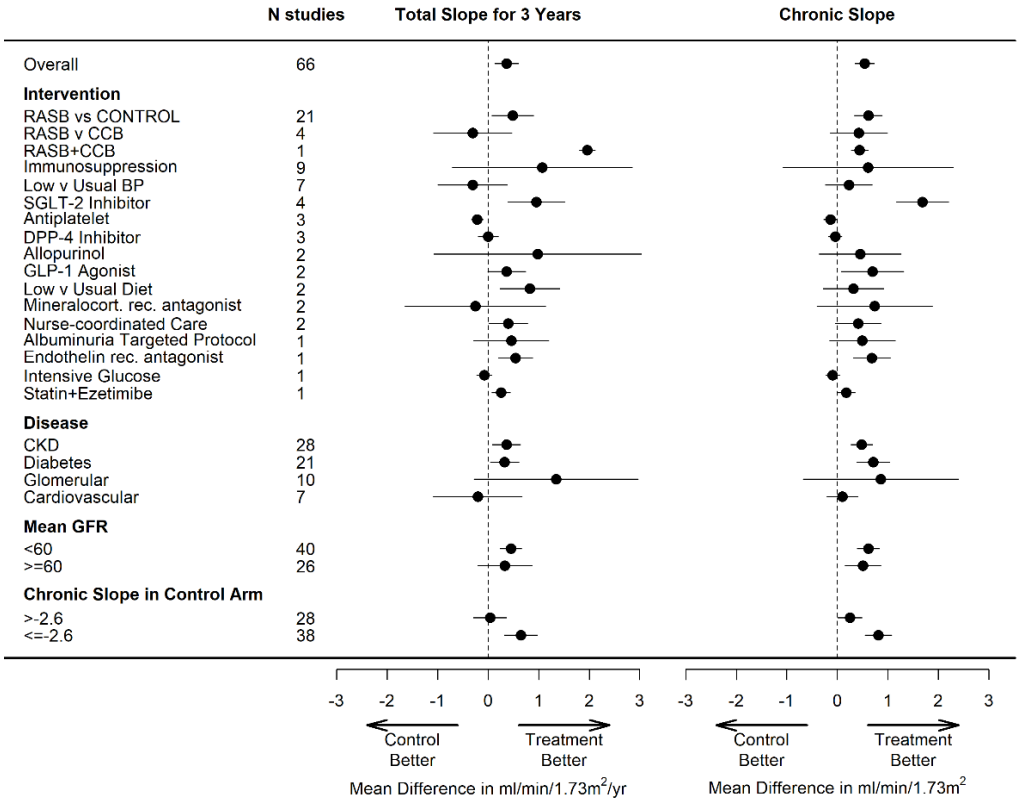
7.4 Treatment effects on GFR slope and the clinical endpoint

7.4.1 Mean slopes in the treatment and control arms and treatment effects on GFR slope

For the pooled dataset and across most individual studies, the mean total slope computed over 3 years and the chronic slope were slightly attenuated in the active treatment compared with the control arms, indicating benefit, with mean (95% CI) treatment effects of 0.36 (0.12, 0.60) and 0.54 (0.35, 0.73) ml/min per 1.73 m^2, respectively (Figure 7 and Table A-7). As shown, there is considerable variability in treatment effects across interventions and across groups based on rate of progression in the control arm, as compared to across causal diseases and GFR subgroups.

For a tabular summary of the same results, as well as slopes in each of the treatment and control arms, see Table A-7a, b, and c. The treatment effects by study are presented in Figure A-3 through Figure A-6.

Figure 7 **Treatment effect on total slope computed at 3 years and on chronic slope by disease, intervention, GFR categories and chronic slope categories**



Chronic slope ≤-2.6 ml/min per 1.73 m^2/yr identifies studies with faster progression.

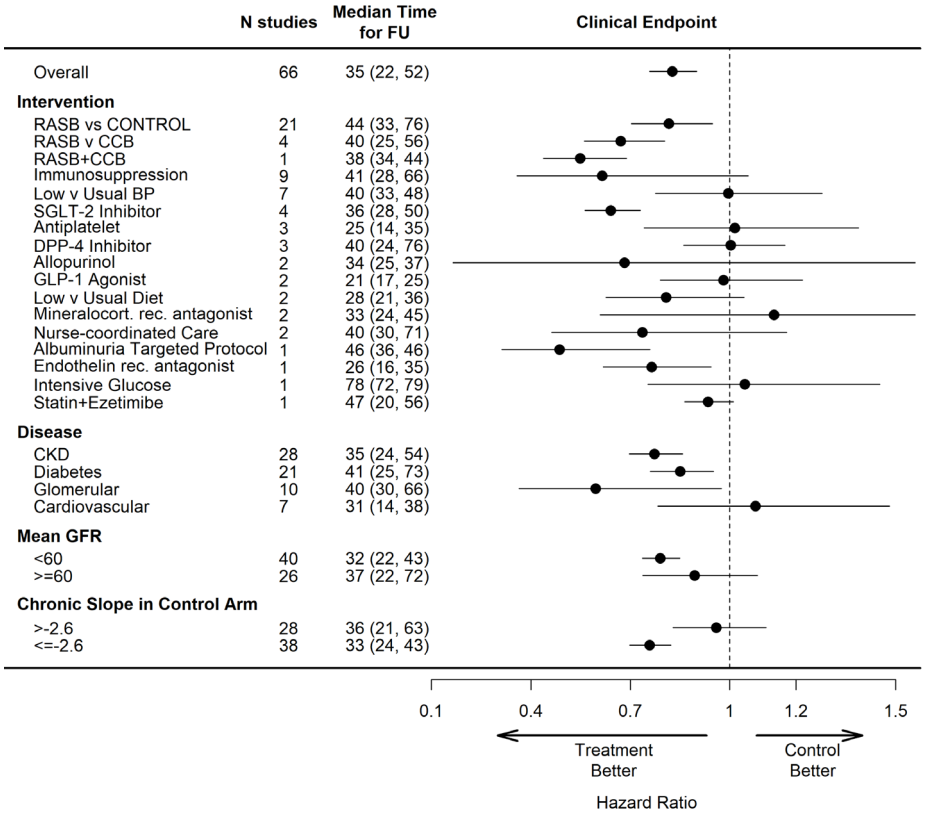
BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4. GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; Mineralocort. Rec, Minderalocorticoid receptor antagonist; RASB, renin-angiotensin system blocker; SGLT-2, sodium-glucose cotransporter 2.

7.4.2 Treatment effects on the clinical endpoint

In the pooled dataset, a total of 11558 patients reached the composite clinical endpoint over a median follow up of 35 (22, 52) months.

Figure 8 summarizes the treatment effect on composite clinical endpoint, by intervention, by causal disease, by baseline GFR, and chronic slope in the treatment arm. As can be seen, there is substantial variability in treatment effect across all of these categories. Table A-8 shows these results in tabular format and Figure A-3 shows the treatment effect on the clinical endpoint by study.

Figure 8 Treatment effect on clinical endpoint, by disease, intervention, GFR categories, and chronic slope categories



Units of GFR are ml/min per 1.73 m^2 and chronic slope in the control are ml/min per 1.73 m^2/yr.

BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; DPP-4, Dipeptidyl peptidase 4; FU, Follow-up; GFR, Glomerular filtration rate; GLP-1, Glucagon-like peptide 1; N, Number; RASB, Renin-angiotensin system blocker; SGLT-2, sodium-glucose cotransporter 2.

7.5 Results of trial-level analyses

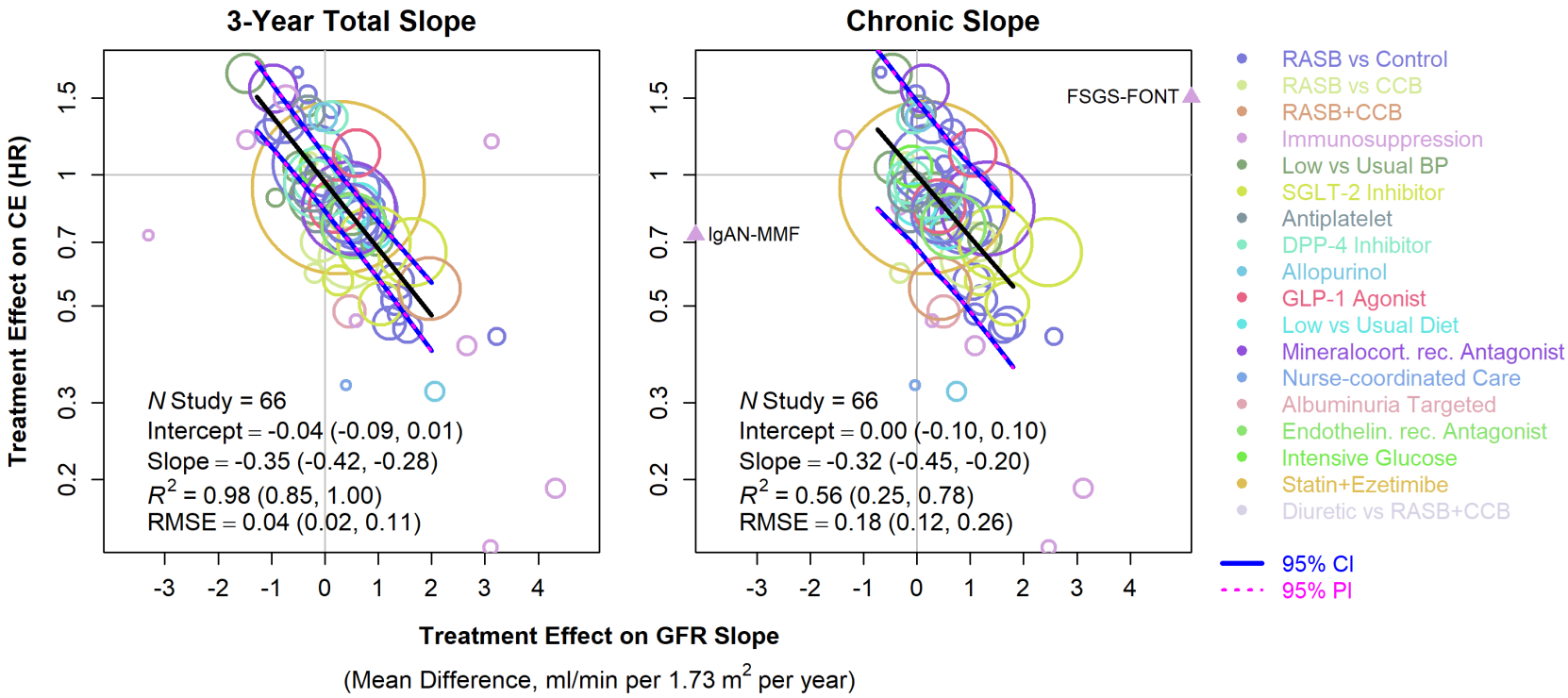
In the sections below, the results of the trial-level analyses are presented. Results are described first for total slope (Section 7.5.1), and then chronic slope (Section 7.5.2). Figure 9 shows the results for both, but subsequent tables present results specific to each slope within the respective sections.

7.5.1 Results for total slope

There was strong agreement between the treatment effects on the total slope estimated at 3 years and treatment effects on the clinical endpoint (Figure 9). The median estimate for R^2 was 0.98 (95% BCI, 0.85 to 1.00). The slope of the meta-regression line was significant at -0.35 (95% BCI -0.42, -0.28) per mL/min per 1.73 m^2/year). For example, this indicates that a 0.75 ml/min per 1.73 m^2/year greater beneficial treatment effect on the total slope was associated with an average 23% lower hazard for the clinical end point (95% BCI, 19% to 27%). The entire BCI for the intercept is close 0, with a posterior median -0.04 and 95% BCI from -0.09 to 0.01. This indicates that when the treatment had no effect on the total slope computed at 3 years, there was a low probability of having a meaningful treatment effect on the clinical endpoint.

These results are consistent with those previously reported for total slope computed at 3 years (Inker et al 2019a), but with tighter CIs reflecting the inclusion of an additional 19 randomized treatment comparisons in an additional 126,703 participants.

Figure 9 **Trial-level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint**



Shown is the relationship between estimated treatment effects on the clinical endpoint (KFRT, GFR <15 ml/min per 1.73 m^2, or doubling of serum creatinine) on the vertical axis and estimated treatment effects on the GFR slope (total over 3 years) on the horizontal axis. Treatment effects on GFR slope are expressed as mean difference in treatment minus control and are expressed in ml/min per 1.73 m^2/yr. Treatment effect on the clinical endpoint is expressed as HR. The colors indicate intervention type. Each circle represents a separate randomized treatment comparison, with the size of the circle proportional to the number of events for the clinical endpoint. The black line is the line of meta-regression line through the studies. The blue line is the 95% pointwise Bayesian confidence band. The pink dashed lines are the 95% pointwise Bayesian prediction bands computed from the model.
BP, blood pressure; CCB, calcium channel blocker; CE, Clinical endpoint; CI, confidence interval; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; GFR, glomerular filtration rate; GLP-1, Glucagon-like peptide 1; HR, hazard ratio; KFRT, Kidney failure with replacement therapy; MMF, Mycophenolate mofetil; N, Number; PI, Prediction interval; RASB, renin angiotensin system blockers; RMSE, Root mean square error; SGLT-2, Sodium glucose cotransporter 2.

7.5.1.1 Outlier assessments for total slope computed at 3 years

The outlier assessment for total slope computed at 3 years is shown in Table 6. A total of 11 outliers were identified as defined trials for which the percentile of the observed treatment effect on the clinical endpoint was at or above the 95th percentile of the corresponding model-based predictive distribution or at or below the 5th percentile of the distribution. Note that a liberal criterion was used for defining outliers to provide a comprehensive assessment of the potential influence of individual studies, as one would expect approximately 7 of the 66 trials to meet the outlier definition by random chance.

Of the outliers, for 8 trials the meta-regression model underestimated clinical benefit; that is, predicted a higher HR for the clinical endpoint than was observed. These 8 trials were AASK [CCB], CANVAS, Donadio 1999, EMPA-REG, IDNT (CCB), IgA-MMF, Maschio, and ROAD). For 3 trials, the meta-regression model overestimated clinical benefit (CAROLINA, CREDENCE, and Harmony). When each outlier trial was removed from the analysis (Table 6), there was no substantial impact on the overall meta-regression.

Trials with large acute effects were more prominent among the outlier trials, but acute effects do not appear to fully explain all outliers. There was no other apparent pattern with respect to GFR level, rate of progression in the control arm, intervention, or disease among the outliers. When studies that were outliers across all 3 slope analyses (computed at 3 or 2 years, and chronic slope) indicating possible study anomalies (Donadio 1999, ROAD, ACCOMPLISH), were removed, results of the meta-regression remained consistent (Table A-11).

Table 6 Analysis of outliers in trial level meta-regression – Total slope computed at 3 years

Trial Name	Observed log HR (SE)	Median Predicted log HR from PPD (95% CI)	Meta-regression results removing individual outlier study			Study characteristics				
			Intercept (95% BCI)	Slope (95% BCI)	R^2 (95% BCI)	AE	Disease	Intervention	Mean GFR	Progression rate
AASK (CCB)	-0.36 (0.18)	-0.02 (-0.32, 0.3)	-0.03 (-0.08, 0.01)	-0.35 (-0.42, -0.29)	0.98 (0.87, 1.00)	N	CKD	RASB v CCB	<60	Fast
CANVAS	-0.56 (0.23)	-0.12 (-0.58, 0.34)	-0.03 (-0.08, 0.02)	-0.35 (-0.42, -0.29)	0.98 (0.87, 1.00)	N	DM	SGLT-2I	>=60	Slow
CAROLINA	0.3 (0.22)	-0.07 (-0.50, 0.36)	-0.04 (-0.09, 0.01)	-0.35 (-0.42, -0.28)	0.98 (0.86, 1.00)	P	DM	DPP4I	>=60	Slow
CREDENCE	-0.41 (0.1)	-0.61 (-0.84, -0.39)	-0.03 (-0.08, 0.01)	-0.38 (-0.45, -0.31)	0.98 (0.89, 1.00)	N	DM	SGLT-2I	<60	Fast
Donadio 1999	-1.97 (0.65)	-0.6 (-1.87, 0.69)	-0.03 (-0.08, 0.01)	-0.35 (-0.42, -0.28)	0.98 (0.85, 1.00)	P	GN	IS	>=60	Fast
EMPA-REG	-0.68 (0.16)	-0.41 (-0.73, -0.08)	-0.03 (-0.08, 0.01)	-0.35 (-0.41, -0.28)	0.98 (0.87, 1.00)	N	DM	SGLT-2I	>=60	Slow
Harmony	0.12 (0.15)	-0.24 (-0.56, 0.07)	-0.04 (-0.09, 0.01)	-0.36 (-0.42, -0.29)	0.98 (0.87, 1.00)	N	DM	GLP-1A	>=60	Slow
IDNT (CCB)	-0.44 (0.12)	-0.19 (-0.43, 0.04)	-0.03 (-0.08, 0.01)	-0.35 (-0.42, -0.28)	0.98 (0.89, 1.00)	N	DM	RASB v CCB	<60	Fast
IgA-MMF	-0.32 (0.68)	0.7 (-0.5, 1.88)	-0.03 (-0.08, 0.01)	-0.36 (-0.42, -0.29)	0.98 (0.87, 1.00)	P	GN	IS	<60	Slow
Maschio	-0.79 (0.22)	-0.47 (-0.83, -0.12)	-0.03 (-0.08, 0.01)	-0.35 (-0.41, -0.28)	0.98 (0.86, 1.00)	N	CKD	RASB vs control	<60	Fast
ROAD	-0.72 (0.23)	-0.19 (-0.57, 0.18)	-0.03 (-0.07, 0.02)	-0.35 (-0.42, -0.29)	0.99 (0.89, 1.00)	P	CKD	Alb protocol	<60	Fast

Study characteristics for each study are described by category of acute effect based on median estimated treatment effect on the acute phase, disease and intervention category, mean level of GFR at baseline and rate of progression in the control arm. Mean GFR is expressed in ml/min per 1.73 m^2. A fast progression rate is defined as a chronic GFR slope less than or equal to -2.6 ml/min per 1.73 m^2 in the control arm and a slow progression rate is a chronic GFR slope greater than -2.6 ml/min per 1.73 m^2 in the control arm.

AE, Acute effects (N, negative; P, positive); Alb, Albumin; BCI, Bayesian credible interval; CI, Credible interval; CCB, Calcium channel blocker; CKD, Chronic kidney disease; DM, Diabetes mellitus; DPP4I, DPP4 inhibitor; EMPA-REEG, EMPA-REG Outcomes; FSGS, Focal segmental glomerulosclerosis; GN, Glomerulonephritis; Harmony, Harmony Outcomes; HR, hazard ratio; IgA, Immunoglobulin A; IS, Immunosuppression; MMF, Mycophenolate mofetil; PPD, Posterior predictive distribution; RASB, Renin angiotensin system blocker; SE, Standard error; SGLT-2I, Sodium-glucose cotransporter-2 inhibitor.

7.5.1.2 Subgroup analyses of trial-level analysis of treatment effects on total slope computed at 3 years

The association between treatment effects on total slope computed at 3 years and the clinical endpoint was similar across all subgroups by baseline GFR, causal disease, rate of progression on control arm (Table 7), or baseline ACR (Table 8). As expected, the BCIs were wider given fewer studies within each category, but overlapped, suggesting no definitive evidence that the overall effect varied by subgroups.

Table 7 Trial level analyses for the association between treatment effects on GFR total slope computed at 3 years and treatment effects on the clinical endpoint by subgroups

Group	Subgroup	N Studies (N Interv)	N Patients[a] (N Events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies		66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.85, 1.00)	0.04 (0.02, 0.11)
GFR	<60	40 (14)	53725 (8784)	-0.30 (-0.44, -0.15)	-0.06 (-0.15, 0.02)	0.88 (0.35, 0.99)	0.05 (0.01, 0.11)
	≥60	26 (11)	133580 (2771)	-0.37 (-0.46, -0.29)	-0.02 (-0.10, 0.07)	0.99 (0.85, 1.00)	0.05 (0.01, 0.19)
Progression rate in control arm	≤-2.6	38 (12)	48733 (6005)	-0.32 (-0.43, -0.20)	-0.07 (-0.16, 0.01)	0.95 (0.64, 1.00)	0.05 (0.02, 0.14)
	>-2.6	28 (14)	138572 (5550)	-0.35 (-0.45, -0.26)	-0.01 (-0.07, 0.06)	0.98 (0.77, 1.00)	0.04 (0.01, 0.14)
Disease	Diabetes	21 (10)	102013 (5065)	-0.32 (-0.47, -0.16)	-0.05 (-0.14, 0.03)	0.89 (0.35, 0.99)	0.06 (0.02, 0.17)
	Glomerular	10 (2)	1527 (237)	-0.31 (-0.50, -0.15)	-0.19 (-0.53, 0.17)	0.99 (0.48, 1.00)	0.05 (0.01, 0.49)
	Other CKD	28 (9)	20149 (5016)	-0.39 (-0.62, -0.14)	-0.04 (-0.19, 0.09)	0.93 (0.28, 1.00)	0.05 (0.02, 0.15)
	CVD	7 (5)	63616 (1237)	-0.34 (-0.45, -0.23)	0.02 (-0.11, 0.15)	0.99 (0.71, 1.00)	0.05 (0.01, 0.21)

[a] Number of patients based on Cox model sample size.
GFR and rate of progression in control arm units are ml/min per 1.73 m^2.
BCI, Bayesian credible interval; CKD, Chronic kidney disease; CVD, Cardiovascular disease; GFR, Glomerular filtration rate; Interv, Intervention; N, Number; RMSE, Root mean square error.

Table 8 Trial level analyses for the association between treatment effects on GFR slope over 3 years and treatment effects on the clinical endpoint by baseline ACR

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.85, 1.00)	0.04 (0.02, 0.11)
Restricted to studies with ACR available	55 (14)	90287 (7321)	-0.35 (-0.44, -0.26)	-0.06 (-0.13, 0.00)	0.97 (0.80, 1.00)	0.05 (0.01, 0.13)
Restricted to studies with ACR available and participants with ACR >30 mg/g	55 (14)	58059 (6946)	-0.34 (-0.44, -0.23)	-0.05 (-0.12, 0.02)	0.96 (0.74, 1.00)	0.05 (0.02, 0.12)

[a] Number of patients based on Cox model sample size.
ACR, Albumin:creatinine ratio; BCI, Bayesian credible interval; GFR, Glomerular filtration rate; Interv, Intervention; N, Number; RMSE, Root mean square error.

7.5.1.3 Sensitivity analyses for trial level analyses of treatment effect on slope over 3 years

As described in Section 7.2.5, sensitivity analyses were conducted to assess the robustness of the results of the trial-level analyses. These included evaluation of the effects of excluding subsets of studies based on causal disease or intervention and by evaluating a less diffuse prior compared with the prior selected for the analysis.

As shown in Table 9 and Table 10, neither approach had any impact on the results or conclusions.

Table 9 Trial level analyses for the association between treatment effects on GFR slope over 3 years and treatment effects on the clinical endpoint after excluding disease groups and interventions

Subgroup	N Studies (N Interv) included[a]	N patients[b] (N events) included[a]	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.85, 1.00)	0.04 (0.02, 0.11)
Exclude:						
GN	56 (16)	185778 (11318)	-0.34 (-0.42, -0.27)	-0.04 (-0.09, 0.01)	0.97 (0.81, 1.00)	0.04 (0.01, 0.11)
CVD	59 (16)	123689 (10318)	-0.36 (-0.46, -0.26)	-0.04 (-0.11, 0.01)	0.95 (0.72, 1.00)	0.05 (0.02, 0.13)
HF	63 (17)	174517 (11010)	-0.34 (-0.42, -0.27)	-0.04 (-0.10, 0.00)	0.97 (0.80, 1.00)	0.05 (0.02, 0.13)
High CV risk	62 (16)	136477 (10863)	-0.37 (-0.46, -0.29)	-0.04 (-0.09, 0.02)	0.97 (0.81, 1.00)	0.05 (0.01, 0.12)
RASB vs CCB	62 (16)	185012 (11064)	-0.35 (-0.41, -0.28)	-0.03 (-0.07, 0.02)	0.99 (0.92, 1.00)	0.03 (0.01, 0.09)
RASB vs CONTROL	45 (16)	151613 (8725)	-0.33 (-0.42, -0.25)	-0.06 (-0.12, 0.01)	0.93 (0.70, 1.00)	0.08 (0.02, 0.17)
Immuno-suppression	57 (16)	185931 (11341)	-0.34 (-0.41, -0.27)	-0.04 (-0.09, 0.01)	0.97 (0.79, 1.00)	0.04 (0.01, 0.11)
Low v Usual BP	59 (16)	175224 (10833)	-0.36 (-0.44, -0.28)	-0.04 (-0.10, 0.02)	0.95 (0.77, 1.00)	0.06 (0.02, 0.14)
Low v Usual Diet	64 (16)	186466 (11316)	-0.35 (-0.42, -0.29)	-0.04 (-0.09, 0.01)	0.98 (0.83, 1.00)	0.04 (0.01, 0.12)
Allopurinol	64 (16)	186834 (11461)	-0.35 (-0.41, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.86, 1.00)	0.04 (0.01, 0.11)
Antiplatelet	63 (16)	155734 (11253)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.97 (0.84, 1.00)	0.05 (0.02, 0.12)
Nurse-coordinated care	64 (16)	186207 (11376)	-0.35 (-0.42, -0.29)	-0.04 (-0.09, 0.01)	0.97 (0.85, 1.00)	0.05 (0.02, 0.12)
SGLT-2 Inhibitor	62 (16)	161898 (10486)	-0.37 (-0.45, -0.30)	-0.03 (-0.08, 0.02)	0.98 (0.88, 1.00)	0.04 (0.01, 0.10)
DPP-4 Inhibitor	63 (16)	168979 (10887)	-0.35 (-0.42, -0.29)	-0.04 (-0.09, 0.01)	0.97 (0.84, 1.00)	0.05 (0.01, 0.12)
MRA	64 (16)	178199 (10627)	-0.34 (-0.42, -0.27)	-0.05 (-0.10, 0.00)	0.96 (0.79, 1.00)	0.06 (0.02, 0.13)
GLP-1 Agonist	64 (16)	170859 (11132)	-0.35 (-0.42, -0.29)	-0.04 (-0.09, 0.01)	0.98 (0.88, 1.00)	0.04 (0.02, 0.11)

[a] N studies and N patients included in respective analysis after excluding the intervention shown in lefthand column.
[b] Number of patients based on Cox model sample size.
BCI, Bayesian credible interval; BP, Blood pressure; CCB, Calcium channel blocker; CV, Cardiovascular; CVD, Cardiovascular disease; DPP-4, Dipeptidyl peptidase 4. GFR, Glomerular filtration rate; GLP-1, Glucagon-like peptide 1; GN, Glomerulonephriitis; HF, Heart failure; Interv, Intervention; MRA, Mineralocorticoid receptor antagonist; N, Number; RASB, Renin-angiotensin system blocker; RMSE, Root mean square error; SGLT-2, Sodium-glucose cotransporter 2.

Table 10 Trial level analyses for the association between treatment effects on GFR slope over 3 years and treatment effects on the clinical endpoint by sensitivity for priors

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
More diffuse priors for variance parameters	66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.85, 1.00)	0.04 (0.02, 0.11)
Less diffuse priors for variance parameters	66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.96 (0.82, 0.99)	0.06 (0.02, 0.13)

[a] Number of patients based on Cox model sample size.
BCI, Bayesian credible interval; GFR, glomerular filtration rate; Interv, Intervention; N, Number; RMSE, root mean square error.

7.5.1.4 Results for total slope computed at 2 years

There was strong agreement between the treatment effects on total slope computed over 2 years and those on the clinical endpoint (Table A-10 and Figure A-5). The median estimate for R^2 was 0.89 [95% BCI 0.68, 0.98]) The meta-regression slope was substantially different from 0 at -0.27 [95% BCI -0.33, -0.21]). For example, this indicates that a 0.75 ml/min per 1.73 m^2/year greater beneficial treatment effect on the total slope was associated with an average 18% lower hazard for the clinical end point (95% BCI, 15% to 22%). Notably, the intercept was smaller than 0 (-0.11 [95% BCI -0.16, -0.06]), indicating that on average the total slope tends is provided conservative inference (less favorable to the treatment) compared to the clinical endpoint. The complete set of results for total slope computed at 2 years are available in Tables A-10 to A-16).

7.5.2 Results for chronic GFR slope

There was moderate agreement between the treatment effects on chronic GFR slope and those on the clinical endpoint (Figure 9). The median estimate for R^2 was 0.56 (95% BCI 0.25, 0.78). The slope of the meta-regression line was substantially different from 0 at -0.32 (95% BCI -0.45, -0.20) per mL/min per 1.73 m^2/year. For example, this indicates that a 0.75 ml/min per 1.73 m^2/year greater beneficial treatment effect on the total slope was associated with an average 21% lower hazard for the clinical end point (95% BCI, 14% to 29%). The intercept of the meta-regression line did not differ from 0, with a posterior median of 0 and 95% BCI of (-0.10, 0.10), suggesting no systematic trend towards false positive or negative with a non-significant result on GFR slope.

7.5.2.1 Outlier assessments

A total of 10 outlier trials were identified for the analysis of chronic slope (Table 11). For six trials the estimated treatment effect on chronic slope underestimated clinical benefit (ACCOMPLISH, Donadio 1999, Goicoeshea, IgA-MMF, IgA-steroid, and ROAD) and for 4 trials the estimated effect on chronic slope overestimated clinical benefit (CREDENCE, FSGS-FONT, Harmony, and TOPCAT). When each outlier was removed, there was no substantial impact on the overall meta-regression (Table 11).

Above, trials with large acute effects were more prominent among the outlier trials, but acute effects cannot fully explain the results. There was no other apparent pattern with respect to intervention or disease among the outliers.

When studies that were outliers across all slope analyses indicating possible study anomalies (Donadio 1999, ROAD ACCOMPLISH) were removed, results of the meta-regression remained consistent (Table A-11).

Table 11 Analysis of outliers in trial level meta-regression – Chronic slope

Trial Name	Observed log HR (SE)	Estimated log HR from PPD median (95% CI)	Meta-regression results removing individual outlier study			Study characteristics				
			Intercept	Slope	R^2	AE	Disease	Intervention	Mean GFR	Progression rate
ACCOMPLISH	-0.6 (0.12)	-0.15 (-0.58, 0.29)	0.01 (-0.08, 0.11)	-0.32 (-0.45, -0.21)	0.63 (0.33, 0.85)	N	CVD	RASB+CCB	>=60	Slow
CREDENCE	-0.41 (0.1)	-0.78 (-1.26, -0.32)	0.03 (-0.07, 0.13)	-0.41 (-0.56, -0.26)	0.64 (0.33, 0.84)	N	DM	SGLT-2I	<60	Fast
Donadio 1999	-1.97 (0.65)	-0.36 (-1.7, 0.96)	0 (-0.1, 0.1)	-0.32 (-0.45, -0.2)	0.55 (0.25, 0.78)	P	GN	IS	>=60	Fast
FSGS-FONT	0.41 (0.29)	-0.42 (-1.18, 0.31)	-0.01 (-0.11, 0.09)	-0.32 (-0.45, -0.2)	0.56 (0.26, 0.78)	N	GN	IS	>=60	Fast
Goicoechea	-1.14 (0.41)	-0.26 (-0.99, 0.49)	0.01 (-0.09, 0.11)	-0.33 (-0.45, -0.21)	0.59 (0.28, 0.8)	P	CKD	Allopurinol	<60	Slow
Harmony	0.12 (0.15)	-0.32 (-0.83, 0.18)	0 (-0.1, 0.09)	-0.33 (-0.46, -0.21)	0.59 (0.29, 0.8)	N	DM	GLP-1A	>=60	Slow
IgA-MMF	-0.32 (0.68)	0.79 (-0.51, 2.06)	0.01 (-0.09, 0.1)	-0.33 (-0.46, -0.21)	0.57 (0.27, 0.79)	P	GN	IS	<60	Slow
IgA-steroid	-1.65 (0.49)	-0.75 (-1.81, 0.28)	-0.01 (-0.1, 0.09)	-0.31 (-0.44, -0.18)	0.52 (0.22, 0.76)	P	GN	IS	>=60	Fast
ROAD	-0.72 (0.23)	-0.16 (-0.68, 0.35)	0.01 (-0.08, 0.11)	-0.33 (-0.45, -0.21)	0.61 (0.3, 0.82)	P	CKD	Alb protocol	<60	Fast
TOPCAT	0.45 (0.15)	-0.06 (-0.53, 0.43)	-0.02 (-0.11, 0.07)	-0.30 (-0.43, -0.18)	0.58 (0.27, 0.81)	N	CVD	MRA	>=60	Slow

Study characteristics, each study is described by category of acute effect based on median estimated treatment effect on the acute phase, disease and intervention category, mean level of GFR at baseline and rate of progression in the control arm. Mean GFR is expressed in ml/min per 1.73 m^2. A fast progression rate is defined as a chronic GFR slope less than or equal to -2.6 ml/min per 1.73 m^2 in the control arm and a slow progression rate is a chronic GFR slope greater than -2.6 ml/min per 1.73 m^2 in the control arm.
AE, Acute effects (N, negative; P, positive); Alb, Albumin; CCB, Calcium channel blocker; CI, Credible interval; CKD, Chronic kidney disease; CVD, Cardiovascular disease; DM, Diabetes mellitus; FSGS, Focal segmental glomerulosclerosis; GFR, Glomerular filtration rate; GLP1-A, Glucagon-like peptide 1 agonist; GN, Glomerulonephritis; Harmony, Harmony Outcomes; HR, hazard ratio; IgA, Immunoglobulin A; IS, Immunosuppression; MMF, Mycophenolate mofetil; MRA, Mineralocorticoid receptor antagonist; PPD, Posterior predictive distribution; RASB, Renin angiotensin system blocker; SE, Standard error; SGLT-2I, Sodium-glucose cotransporter-2 inhibitor.

7.5.2.2 Subgroup analyses of trial-level analysis of treatment effects on chronic slope

In trial-level analyses treatment effects on chronic slope by subgroups, there was substantial variation by baseline GFR (Table 12). In the subgroup with baseline GFR ≥60 ml/min per 1.73 m^2, the RMSE was higher, indicating less precision in this high GFR subgroup compared to lower GFR subgroup. Paradoxically, the R^2 was also higher in the baseline GFR ≥60 ml/min subgroup. As described in Section 7.2.4, the R^2 may reflect extent of heterogeneity of treatment effects on the surrogate endpoint as well as error in the meta-regression. The subgroup of GFR ≥60 ml/min per 1.73 m^2 has greater variation in the treatment effects than GFR <60 ml/min per 1.73 m^2, thus is it difficult to compare the results across the subgroups.

For subgroups based on rate of progression in the control arm and disease, there seemed to be greater variation than for total slope although the wide credible intervals for the meta-regression slope and RSME preclude definitive conclusions. Of note, compared with the overall analysis, the RMSE was higher for the small number of studies in the CVD subgroup and was lower for subgroups with CKD, diabetes, and glomerular disease.

There were no clear differences between the overall group of studies that had baseline ACR data available and the subgroup of participants with baseline ACR >30 mg/g (Table 12).

Table 12 Trial level analyses for the association between treatment effects on chronic GFR slope and treatment effects on the clinical endpoint by subgroups

Group	Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies		66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
GFR	<60	40 (14)	53725 (8784)	-0.15 (-0.26, -0.04)	-0.11 (-0.22, -0.02)	0.54 (0.04, 0.95)	0.08 (0.02, 0.17)
	≥60	26 (11)	133580 (2771)	-0.56 (-0.80, -0.33)	0.13 (-0.03, 0.29)	0.77 (0.37, 0.95)	0.22 (0.11, 0.38)
Progression rate in control arm	≤-2.6	38 (12)	48733 (6005)	-0.20 (-0.38, -0.06)	-0.10 (-0.24, 0.05)	0.56 (0.06, 0.94)	0.12 (0.03, 0.23)
	>-2.6	28 (14)	138572 (5550)	-0.44 (-0.71, -0.17)	0.06 (-0.08, 0.20)	0.55 (0.09, 0.89)	0.21 (0.10, 0.34)
Disease	Diabetes	21 (10)	102013 (5065)	-0.24 (-0.37, -0.12)	0.03 (-0.09, 0.15)	0.78 (0.24, 0.99)	0.09 (0.02, 0.21)
	Glomerular	10 (2)	1527 (237)	-0.39 (-0.71, -0.02)	-0.33 (-0.74, 0.08)	0.99 (0.14, 1.00)	0.08 (0.02, 0.69)
	Other CKD	28 (9)	20149 (5016)	-0.30 (-0.49, -0.11)	-0.07 (-0.20, 0.04)	0.83 (0.16, 0.99)	0.05 (0.01, 0.16)
	CVD	7 (5)	63616 (1237)	-1.02 (-1.95, 0.08)	0.11 (-0.16, 0.42)	0.69 (0.01, 1.00)	0.23 (0.03, 0.66)

[a] Number of patients based on Cox model sample size.
GFR and progression rate in control arm units are ml/min per 1.73 m^2.
BCI, Bayesian credible interval; CKD, Chronic kidney disease; CVD, Cardiovascular disease; GFR, Glomerular filtration rate; N, Number; RMSE, Root mean square error.

Table 13 Trial level analyses for the association between treatment effects on chronic GFR slope and treatment effects on the clinical endpoint by baseline ACR

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R_2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
Restricted to studies with ACR available	55 (14)	90287 (7321)	-0.30 (-0.43, -0.18)	-0.03 (-0.14, 0.08)	0.67 (0.32, 0.89)	0.15 (0.08, 0.24)
Restricted to participants with ACR >30	55 (14)	58059 (6946)	-0.22 (-0.34, -0.11)	-0.07 (-0.17, 0.03)	0.70 (0.24, 0.96)	0.11 (0.03, 0.20)

[a] Number of patients based on Cox model sample size.
ACR, Albumin:creatinine ratio; BCI, Bayesian credible interval; GFR, Glomerular filtration rate; N, Number; RMSE, Root mean square error.

7.5.2.3 Sensitivity analyses for trial level analyses of treatment effect on chronic slope

There was no impact of any of the sensitivity analyses on the results of trial-level analyses of the treatment effect on chronic slope (Table 14 and Table 15).

Table 14 Trial level analyses for the association between treatment effects on chronic GFR slope and treatment effects on the clinical endpoint after excluding disease groups and interventions

Subgroup	N Studies (N Interv) included[a]	N patients[b] (N events) included[a]	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
Exclude:						
GN	56 (16)	185778 (11318)	-0.30 (-0.43, -0.18)	0.00 (-0.10, 0.10)	0.50 (0.20, 0.74)	0.17 (0.11, 0.25)
CVD	59 (16)	123689 (10318)	-0.26 (-0.38, -0.15)	-0.04 (-0.14, 0.05)	0.66 (0.26, 0.98)	0.12 (0.02, 0.21)
HF	63 (17)	174517 (11010)	-0.31 (-0.43, -0.19)	-0.03 (-0.12, 0.08)	0.57 (0.25, 0.80)	0.17 (0.11, 0.25)

Table 14 Trial level analyses for the association between treatment effects on chronic GFR slope and treatment effects on the clinical endpoint after excluding disease groups and interventions

Subgroup	N Studies (N Interv) included[a]	N patients[b] (N events) included[a]	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
High CV risk	62 (16)	136477 (10863)	-0.29 (-0.43, -0.17)	-0.01 (-0.11, 0.09)	0.59 (0.25, 0.84)	0.15 (0.08, 0.24)
RASB vs CCB	62 (16)	185012 (11064)	-0.33 (-0.47, -0.20)	0.00 (-0.10, 0.11)	0.55 (0.24, 0.78)	0.19 (0.13, 0.28)
RASB vs CONTROL	45 (16)	151613 (8725)	-0.28 (-0.43, -0.14)	-0.04 (-0.15, 0.08)	0.48 (0.13, 0.77)	0.21 (0.12, 0.31)
Immuno-suppression	57 (16)	185931 (11341)	-0.31 (-0.44, -0.18)	0.00 (-0.10, 0.10)	0.51 (0.22, 0.76)	0.17 (0.11, 0.25)
Low v Usual BP	59 (16)	175224 (10833)	-0.31 (-0.45, -0.17)	-0.02 (-0.14, 0.09)	0.50 (0.17, 0.75)	0.20 (0.13, 0.28)
Low v Usual Diet	64 (16)	186466 (11316)	-0.33 (-0.47, -0.21)	0.01 (-0.10, 0.11)	0.57 (0.25, 0.79)	0.19 (0.12, 0.28)
Allopurinol	64 (16)	186834 (11461)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.58 (0.28, 0.80)	0.17 (0.11, 0.25)
Antiplatelet	63 (16)	155734 (11253)	-0.33 (-0.47, -0.20)	0.00 (-0.11, 0.11)	0.56 (0.25, 0.79)	0.18 (0.12, 0.27)
Nurse-coordinated care	64 (16)	186207 (11376)	-0.33 (-0.47, -0.20)	0.00 (-0.09, 0.11)	0.56 (0.25, 0.80)	0.19 (0.12, 0.26)
SGLT-2 Inhibitor	62 (16)	161898 (10486)	-0.43 (-0.65, -0.23)	0.03 (-0.08, 0.14)	0.55 (0.19, 0.80)	0.18 (0.11, 0.26)
DPP-4 Inhibitor	63 (16)	168979 (10887)	-0.32 (-0.46, -0.19)	-0.01 (-0.12, 0.10)	0.53 (0.22, 0.78)	0.19 (0.13, 0.27)
MRA	64 (16)	178199 (10627)	-0.32 (-0.46, -0.20)	-0.02 (-0.11, 0.07)	0.62 (0.31, 0.84)	0.16 (0.09, 0.24)
GLP-1 Agonist	64 (16)	170859 (11132)	-0.34 (-0.46, -0.22)	-0.01 (-0.10, 0.10)	0.60 (0.29, 0.81)	0.18 (0.12, 0.26)

[a] N studies and N patients included in respective analysis after excluding the intervention shown in lefthand column.
[b] Number of patients based on Cox model sample size.
BCI, Bayesian credible interval; BP, Blood pressure; CCB, Calcium channel blocker; CV, Cardiovascular; CVD, Cardiovascular disease; DPP-4, Dipeptidyl peptidase 4; GFR, Glomerular filtration rate; GLP-1, Glucagon-like peptide 1; GN, Glomerulonephritis; HF, Heart failure; Interv, Intervention; MRA, Mineralocorticoid receptor antagonist; N, Number; RASB, Renin-angiotensin system blocker; RMSE, Root mean square error; SGLT-2, Sodium-glucose cotransporter 2.

Table 15 Trial level analyses for the association between treatment effects on chronic GFR slope and treatment effects on the clinical endpoint by sensitivity for priors

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
More diffuse priors for variance parameters	66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
Less diffuse priors for variance parameters	66 (17)	187305 (11555)	-0.33 (-0.46, -0.20)	0.00 (-0.10, 0.10)	0.55 (0.25, 0.78)	0.19 (0.12, 0.26)

[a] Number of patients based on Cox model sample size.
More diffuse priors: Slope endpoint inverse gamma(shape=0.261,scale=0.005), clinical endpoint inverse gamma(shape=0.261,scale=0.000408).
Less diffuse priors: Slope endpoint inverse gamma(shape=0.001,scale=0.001), clinical endpoint inverse gamma(shape=0.001,scale=0.001).
BCI, Bayesian credible interval; GFR, Glomerular filtration rate; N, Number; RMSE, Root mean square error.

7.5.2.4 Exploration of differences in results between current and previously published findings

As described in the preceding sections, the updated analyses for chronic slope showed a weaker R^2 compared with the previously analyses (Inker et al 2019a)(Section 3.4.4, Table 2) To explore this difference, additional meta-regressions were performed whereby, one new of the new 19 studies was added at a time to the original set of studies.

Based on this analysis, the weaker associations appear to be explained in part by the addition of 2 large studies, FIDELIO-DKD, which evaluated the nonsteroidal MRA finerenone, and CREDENCE, which evaluated the effects of SGLT-2 inhibitor canagliflozin (Table A-10). The addition of these 2 studies dropped the R^2 substantially. These studies had stronger than expected treatment effects on the chronic slope than on the clinical endpoint in the model.

Based on this finding, a new meta-regression using chronic slope was done removing these 2 studies (Table 16). The analysis resulted in an increase in R^2 from 0.56 (95% BCI 0.25, 0.78) to 0.73 (95% BCI 0.40, 0.91). Mean estimates for the slope and intercept, without these 2 studies differed but with overlapping BCI.

Table 16 Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint by sensitivity for excluding FIDELIO-DKD and CREDENCE

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
Exclude FIDELIO-DKD and CREDENCE	64 (17)	177235 (10436)	-0.46 (-0.61, -0.30)	0.04 (-0.06, 0.14)	0.73 (0.40, 0.91)	0.15 (0.08, 0.23)

[a] Number of patients based on Cox model sample size.
BCI, Bayesian credible interval; DKD, Diabetic kidney disease; GFR, Glomerular filtration rate; N, Number; RMSE, root mean square error.

7.6 Prediction for a hypothetical future trial using GFR slope as a surrogate endpoint

To investigate the precision of the estimate of the treatment effect by effects GFR slope, the $PPV_{0.975}$ was computed for a hypothetical RCT of large, modest, or small size, assuming a follow-up period of 3 years. An infinite sample size is considered to provide the "true" effect. As stated in the methods for this analysis in Section 7.2.6, a large-sized trial was defined as a trial of corresponding to an N of 1600, a modest-sized trial was defined as a sample size of 800, and a small-sized trial as a sample size of 400.

Table 17 summarizes the predicted HRs and 95% prediction intervals for the treatment effects on the clinical endpoint and the corresponding PPVs across the total slope computed at 3 years and chronic slope endpoints. Table 18 shows the observed difference between the treatment and control groups in total slope computed over 3 years or chronic slope that would be needed to confer 97.5% probability of clinical benefit in a large, modest, or small RCT.

According, for a large-sized trial, a treatment effect of 0.75 ml/min per 1.73 m^2/year or greater on total slope computed at 3 years predicts a clinical benefit on CKD progress with 100% probability (Table 17). The threshold for a treatment effect to assure PPV ≥97.5% would be 0.43 ml/min per 1.73 m^2/year (Table 18). These results are consistent with those previously reported (Inker et al 2019a), in which a treatment effect of 0.75 ml/min per 1.73 m^2/year or greater on total slope computed at 3 years predicted a clinical benefit on CKD progress with 100% probability. For chronic slope, a treatment effect of 0.75 ml/min per 1.73 m^2/year or greater predicts a clinical benefit on CKD progress with 89% probability (Table 17). The threshold for a treatment effect to assure PPV ≥97.5% would be 1.24 ml/min per 1.73 m^2/year (Table 18).

Table 17 Application of GFR slope as surrogate endpoint in hypothetical new RCT: predicted treatment effect on clinical endpoint and PPV

GFR slope	Observed Treatment effect on change in GFR slope	Large RCT		Modest RCT		Small RCT	
		Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV
Total slope computed at 3 years	0.5	0.81 (0.66, 0.97)	0.99	0.81 (0.63, 1.03)	0.96	0.81 (0.58, 1.11)	0.91
	0.75	0.74 (0.61, 0.89)	1.00	0.74 (0.58, 0.94)	0.99	0.74 (0.54, 1.01)	0.97
	1	0.68 (0.55, 0.82)	1.00	0.68 (0.53, 0.86)	1.00	0.68 (0.49, 0.93)	0.99
Chronic slope	0.5	0.85 (0.56, 1.28)	0.80	0.85 (0.54, 1.32)	0.78	0.84 (0.52, 1.39)	0.76
	0.75	0.78 (0.52, 1.17)	0.89	0.78 (0.50, 1.22)	0.87	0.78 (0.47, 1.27)	0.84
	1	0.72 (0.47, 1.09)	0.94	0.72 (0.46, 1.11)	0.93	0.72 (0.43, 1.17)	0.91

PPV is for Prob(HR<1).
GFR, Glomerular filtration rate; HR, Hazard ratio; PPV, Positive predictive value; RCT, Randomized controlled trial.

Table 18 Threshold for treatment effect on GFR slope to assure PPV ≥97.5%

GFR slope	Large RCT	Modest RCT	Small RCT
Total slope computed at 3 years	0.43	0.57	0.78
Chronic slope	1.24	1.37	1.49

GFR, Glomerular filtration rate; PPV, Positive predictive value; RCT, Randomized controlled trial.

7.7 Summary of the trial-level analyses

The updated trial-level analyses presented in this application, which now includes data from 66 randomized treatment comparisons that tested 17 interventions in 187,323 participants across 4 broad disease groups (CKD [CNS], diabetes, glomerular disease, and CVD) included a considerable larger and broader set of studies than the prior analyses from the 2018 workshop (Inker et al 2019a).

In these updated analyses, with the computation of GFR slope using a robust method, treatment effects on the total slope computed at 3 years were found to have strong associations with the treatment effect on clinical endpoints. The correlation (posterior median R^2 0.98) was associated with very tight BCIs (0.85 to 1.00), i.e., the entire BCI falls within the designation

of a strong surrogate by Prasad et al, who defined a weak correlation as R^2 0 to 0.49, moderate as R^2 0.49 to 0.72, and strong as R^2 >0.72 (which correspond to ranges of 0 to 0.7, 0.7 to 0.85, and >0.85 for R) (Prasad et al 2015). The slope of the meta-regression line also differed substantially from 0, indicating that as the magnitude of the treatment effect on the slope increased, the magnitude of the clinical benefit would also increase. The range of the Bayesian CI for the intercept of the regression line was close to 0, indicating that when the treatment had no effect on the total slope years, there was a low probability of having a substantial treatment effect on the clinical endpoint.

Results for total slope computed over 2 years was not as strong as for the total slope computed over 3 years, but the posterior median and almost the entire range of the 95% BCI remained in the strong surrogate designation by Prasad (Prasad et al 2015).

Compared to the prior analyses, the updated analyses for total slope computed at 3 years have greater precision of estimated slope (95% BCI for the meta-regression slope coefficient was previously -0.55, -0.30 and is now -0.42, -0.28 per mL/min per 1.73 m^2/year), the intercept (95% BCI was previously -0.14, 0.02 and is now -0.09, 0.01) and R^2 (95% BCI was 0.78, 1.00 in the previous analysis and 0.85 to 1.00 now). This provides more confidence in the predictive ability of the 3-year slope endpoint (Figure 9). Subgroup consistent results by baseline GFR, rate in the control arm, and by causal disease, supporting the broad applicability of total slope computed at 3 years across different patient populations, in alignment with our stated context of use. Consistent results across sensitivity analyses demonstrated that the results were robust.

The posterior median R^2 for the chronic slope fell into the moderate association range with the clinical endpoint (median posterior R^2 0.56) which was lower than had been observed in our prior meta-analysis (Figure 9). Importantly, the slope of the meta-regression line was substantially different from 0 at -0.32 (95% BCI -0.45, -0.20). Further, the intercept of the meta-regression line did not differ from 0, with a posterior median of 0 and 95% BCI of -0.10, 0.10, suggesting no systematic trend towards false positive or negative with a non-significant result on GFR slope.

The results for chronic slope were more sensitive to specific studies as for example, the inclusion of 2 large studies with large acute and larger treatment effects on the clinical endpoint, FIDELIO-DKD, which evaluated the nonsteroidal MRA finerenone, and CREDENCE, which evaluated the effects of SGLT-2 inhibitor canagliflozin, although in these and other sensitivity analyses, did not substantially affect slope and intercept. Substantial variation was also observed for the meta-regression of the chronic slope depending on the level of baseline GFR.

For use in future trials, the total slope computed over 3 years provides more precise and stronger predicted HR than the chronic slope for clinical benefit (Table 17). The results of these analyses can also provide thresholds for minimum effects on change in GFR slope that provide high confidence for significant treatment effects on the clinical endpoint.

8. CONSIDERATIONS FOR CLINICAL TRIAL APPLICATIONS OF GFR SLOPE AS A SURROGATE ENDPOINT

8.1 Simulations to identify situations that improve the statistical power of GFR slope as a surrogate endpoint

The above analyses described in Section 6 and 7 are important to validate GFR slope as a surrogate endpoint for clinical trials of CKD progression. These analyses characterize the level of agreement between treatment effects on GFR slope as was defined for the purses of these analyses and treatment effects on the established clinical endpoint across broad collections of clinical trials. The decision for selection of the clinical endpoint, time to GFR decline, or GFR slope should be made in consideration of the study population, intervention and specific design parameters. In most circumstances, a sponsor or an investigator will only decide to use a surrogate if it provides improves power or efficiency compared to the clinical endpoint. The above analyses do not address these questions, as they can only speak about the experience in the past trials and not about future decisions regarding statistical power to allow smaller sample size or shorter duration without increasing the risk of false conclusions of benefit or harm.

Kidney failure, defined by uremic symptoms signifying a need for kidney replacement therapy, occurs when GFR reaches a level of about 5 to 15 mL/min/1.73 m^2, a narrow range relative to normal GFR. The relationship between GFR and kidney failure in conjunction with models for GFR trajectories could be applied based on previous CKD RCTs to perform a series of statistical simulations to define RCT situations where GFR slope shows improved statistical power as a surrogate endpoint compared with endpoints based on a 30% or 40% GFR decline, while preserving a low risk of bias and type 1 error (i.e., false positive conclusion when there is no treatment effect). This work has been previously published (see Greene et al 2019 in Appendix C).

8.2 Simulation methods

The objective of these simulations was to explore the performance of alternative slope and time-to-event endpoints when performed on the same dataset with the same underlying treatment effects. The input parameters addressed in the simulations are summarized in Table 19.

GFR trajectories were simulated based on inputs that reflected the results of longitudinal analyses from 47 randomized treatment comparisons of GFR slope available at the time the simulations were performed in 2019. The inclusion criteria and characteristics relevant to the simulation inputs used in that analysis are similar to those of the larger set of 69 randomized treatment comparisons of effects on GFR slope presented in Section 7.3 and 7.4. Full details on the dataset used for these simulations are presented in Greene et al 2019, Supplemental Appendix 2 (see Greene et al 2019 in Appendix C). The model used for GFR trajectories extended the random effects models used in a previous investigation of the validity and utility of a 30% or 40% GFR decline as a surrogate endpoint for progression to KFRT (Greene et al 2014).

GFR trajectories prior to active treatment intervention were simulated using a growth curve model in which each subject's GFR measurements varied randomly about subject-specific linear trajectories defined by random slopes and intercepts (Laird and Ware 1982). A range of different values for the mean slope and the slope SD was considered, reflecting the variation in the means and SDs of slopes provided by mixed effects models in previous trials. The assumption was made of a proportional relationship between the variance of residual GFRs and the GFR level and 2 proportionality constants reflecting lower and higher levels of residual GFR variability in previous trials were considered.

Three different models were used to characterize the long-term effects of the treatment: (1) a uniform effect, in which the same treatment effect is assumed for all patients, irrespective of their progression rates; (2) 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 >0 without the treatment; and (3) an intermediate model halfway between the uniform and proportional effect models. For conciseness, this report focusses on the intermediate effect model which appears to provide a better fit to results of previous studies than purely uniform or proportional effect models.

As described in Section 3.3.3, treatments in CKD trials may cause acute negative or positive effects that differ from long-term treatment effects on progression. Therefore, acute effects were addressed by allowing mean slopes during the first 3 months of treatment to differ from long-term mean slopes after 3 months of treatment. Simulations of both negative and positive acute effects were included. After 3 months, scenarios were considered in which acute effects were attenuated with no influence on time to KFRT or in which acute effects persisted without attenuation. Attenuation of the acute effect was simulated by using a model in which the acute effect is linearly related to the GFR level, with the size of the acute effect declining to zero when GFR reaches 15 ml/min per 1.73 m^2.

The mortality hazard rate in the simulations was assumed to be linearly related to the patients' underlying "predicted" GFR based on each patient's random slopes and intercepts, with higher death rates at lower GFR. KFRT was assumed to occur when the GFR trajectory first declined below a patient-specific uniformly distributed random threshold between 6 and 15 ml/min per 1.73 m^2.

Table 19 Input parameters in simulations

Category	Factor	Values considered in simulations
GFR decline	Mean long-term slope	-1.5, -3.25, or -5 ml/min per 1.73 m^2
	SD of long-term slope	3.0, 3.5, 4.0, or 4.5 ml/min per year/1.73 m^2
	Correlation of slope and intercept	-0.03
	Slope skewness	Slight negative skewness (generalized log shape parameter=3)
	Autocorrelation	0
	Size of residuals	Residual variance=0.67 x expected GFR (low variability) or 0.817 x expected GFR (moderate variability)

Table 19 Input parameters in simulations

Category	Factor	Values considered in simulations
Acute effect	Mean acute effect	-2.5, -1.25, 0, +1.25, or +2.5 ml/min per 1.73 m^2 at baseline GFR=42.5 ml/min per 1.73 m^2
	Attenuation of initial acute effect	Linear to 15 ml/min per 1.73 m^2 or no attenuation
	Variability of acute effect	Acute effect SD=1 ml/min per 1.73 m^2
Long-term treatment effect	Type of long-term treatment effect	Proportional, uniform or intermediate
	Size of long-term treatment effect	0% or 25%, reduction in the slope for a subject with an average long-term slope in the absence of treatment
Death and KFRT	Death rate per year	0.03375–0. 00025 x expected GFR (ranges from 0.030 at GFR=15 to 0.01125 at GFR=90 ml/min per 1.73 m^2)
	GFR level associated with onset of KFRT	Uniformly distributed between 6 and 15 ml/min per 1.73 m^2
Design and conduct	Accrual period and total follow-up	Short: 1 yr accrual and 1.5 yr further follow-up Medium: 1.5 yr accrual and 2.5 yr further follow-up Long: 2 yr accrual and 4 yr further follow-up
	Measurement frequency	Months 3, 6, and every 6 months thereafter
	Mean baseline GFR	27.5, 42.5, or 67.5 ml/min per 1.73 m^2
	No. of baseline GFRs	2
	Permanent loss to follow-up rate	2%/yr
	Intermittent missing GFRs	5%

GFR, Glomerular filtration rate; KFRT, Kidney failure with replacement therapy; SD, standard deviation.
See Greene et al 2019 Table 1 in Appendix C for additional details.
Adapted from: Greene et al 2019, Table 1.

Two surrogate endpoints were evaluated based on GFR slope:

1. Chronic GFR slope, defined as the mean rate of change in GFR after the acute phase; and
2. Total GFR slope, defined as the mean rate of change in GFR from baseline to a designated time late in follow-up, incorporating both the acute and chronic slopes. Total slope was defined over 2, 3, or 4 years for RCTs with follow-up periods of 2, 2.5 to 4, and 4 to 6 years, respectively.

Two alternative endpoints were also evaluated:

1. Time from randomization to a 30% GFR decline or kidney failure
2. Time from randomization to a 40% GFR decline or kidney failure

The clinical endpoint in the simulations was approximated as a 57% GFR decline, which closely approximates a doubling of serum creatinine, or kidney failure.

For each scenario, 800 simulated datasets were simulated, each with 500 patients (250 per treatment arm). For each simulated dataset, GFR slope was analyzed using the same mixed effects shared parameter model with a power of the mean model to account for heteroskedasticity in residual variance that was used for the trial level analyses of GFR slope. Time-to-event outcomes were analyzed using Cox proportional hazards regression.

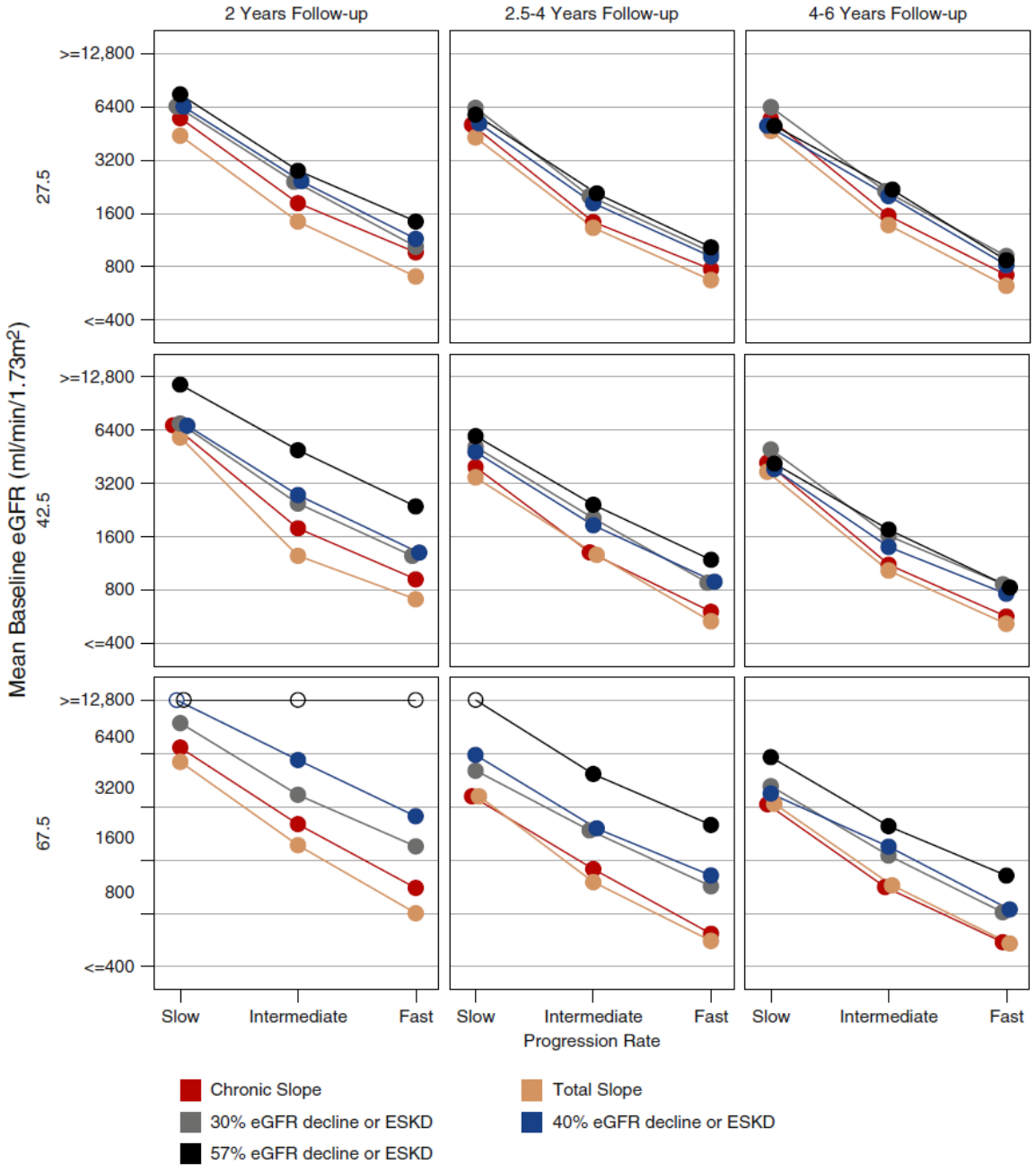
Averages and SD of the estimated treatment effects on each endpoint were obtained for each of the 800 simulated datasets. Standard errors (SE) were calculated for all sample sizes N that differed from 500 as SE(N)=SE(500) $\sqrt{500/N}$, where SE(500) is the SD of the estimated treatment effect across the 800 simulated datasets. The means and SE of the mean for treatment effects from the simulations were used to compare the statistical power provided by each outcome for simulated scenarios with a benefit of the treatment on the clinical endpoint time to KFRT, and to compare the risk of falsely concluding benefit or harm for scenarios with no treatment effect on the clinical endpoint.

Full details on the statistical methods are presented in Greene et al 2019 Supplemental Appendix 2 (see Greene et al 2019 in Appendix C).

8.3 Simulation results

Figure 10 shows the required sample sizes to obtain 90% power in trials with low, intermediate, and high baseline GFR and with slow, intermediate, or fast rates of progression. Using the total GFR slope allowed both sample size and trial duration to be reduced while maintaining the same power as any of the time-to-event endpoints across most scenarios. For example, when there is no acute effect and mean progression is intermediate or fast, substituting the total slope for the clinical endpoint allows investigators to reduce follow-up from 4 to 6 years to 2 years while simultaneously improving efficiency by 17% to 63% (corresponding to sample size savings of 14% to 39%) across the scenarios considered, including a 29% reduction for the intermediate case with baseline GFR 42.5 mL/min/1.73 m^2 and moderate GFR decline. The impact was highest in trials with higher baseline GFR (Figure 10, bottom panels).

Figure 10 **Required sample sizes to obtain 90% power across GFR slope and time-to-event endpoints with no acute effect, intermediate long-term effect, and slow, intermediate, and fast rates of progression**



The chronic and total slope often reduce the required sample size compared to the clinical endpoint when there is no acute effect and the long-term treatment effect is intermediate between proportional and uniform. Shown are the total sample sizes in both the treatment and control groups combined that are required for different endpoints to obtain 90% power with 2-sided a=0.05 when the treatment reduces the mean chronic slope by 25%. The panels correspond to trials in which the mean baseline GFR is low (27.5 ml/min per 1.73 m^2; top panels), intermediate (42.5 ml/min per 1.73 m^2; middle panels), or high (67.5 ml/min per 1.73 m^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. Within each panel, the required sample sizes are provided for slow (21.5 ml/min per 1.73 m^2 per year), intermediate (23.25 ml/min per 1.73 m^2 per year), or fast (25.0 ml/min per 1.73 m^2 per year) mean rates of GFR decline. Required sample sizes >12,800 are indicated by open circles. All required sample sizes assume there is no acute effect and that long-term treatment effects are intermediate between proportional and uniform.
eGFR, Estimated glomerular filtration rate; ESKD, End-stage kidney disease (or KFRT, Kidney failure with replacement therapy); GFR, Glomerular filtration rate.
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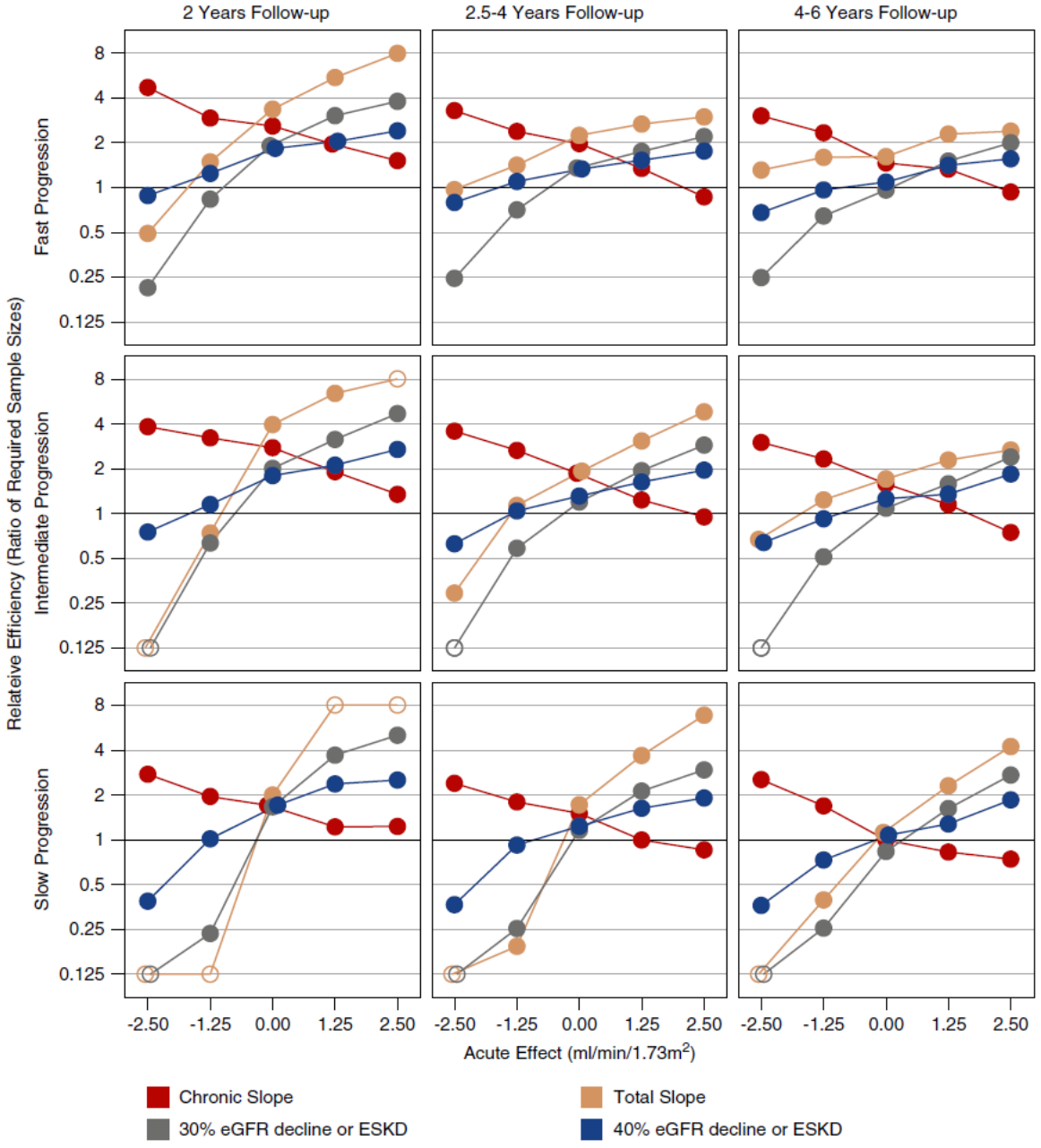
Negative or positive acute effects

Figure 11 displays the relative efficiency of GFR slope and time-to-event endpoints in scenarios with negative or positive acute effects ranging from -2.50 to +2.50 ml/min/1.73 m^2, assuming an intermediate mean baseline GFR of 42.5 ml/min/1.73 m^2 and an intermediate long-term treatment effect. Relative efficiencies are provided for trials in which mean control progression rates are fast, intermediate, or slow and across short, medium, or long trial durations. The size of the acute effect is assumed to be greater at higher levels of GFR and to fully attenuate to zero by the time GFR declines to 15 ml/min/1.73 m^2.

Across these simulations, when acute effects range from -1.25 to +1.25 ml/min/1.73 m^2, the relative efficiency of total slope is consistently higher than the time-to-event endpoints when the mean GFR decline is fast, but lower than the time-to-event endpoints when the acute effect is negative and the mean GFR decline is slow.

The relative efficiency of chronic slope is greater than the other endpoints when the acute effect is negative and is lower than the other endpoints when the acute effect is positive.

Figure 11 **Relative efficiency of GFR slope and time-to-event endpoints compared with clinical endpoint in relation to acute treatment effect, assuming intermediate long-term treatment effect**



Non-zero acute effects can strongly influence the relative efficiency of alternative endpoints. The figure displays the relationship of the relative efficiency of different endpoints compared to the clinical endpoint in relation to the acute effect of the treatment when the long-term treatment effect is intermediate between proportional and uniform. Relative efficiencies greater than one indicate higher power for the alternative end point than the clinical end point. Relative efficiencies are provided for trials in which the mean control group progression rate is fast (~5 ml/min per 1.73 m^2 per year; top panels), intermediate (~3.25 ml/min per 1.73 m^2 per year; middle panels), or slow (~1.5 ml/min per 1.73 m^2 per year; 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. All relative efficiencies

assume an intermediate mean baseline GFR of 42.5 ml/min per 1.73 m^2 and a long-term treatment effect which is intermediate between uniform and proportional. The size of the acute effect (either negative or positive) 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 per 1.73 m^2. Open circles indicate relative efficiencies which are >8 or <0.125.
eGFR, Estimated glomerular filtration rate; ESKD, End-stage kidney disease (or KFRT, Kidney failure with replacement therapy); GFR, Glomerular filtration rate.
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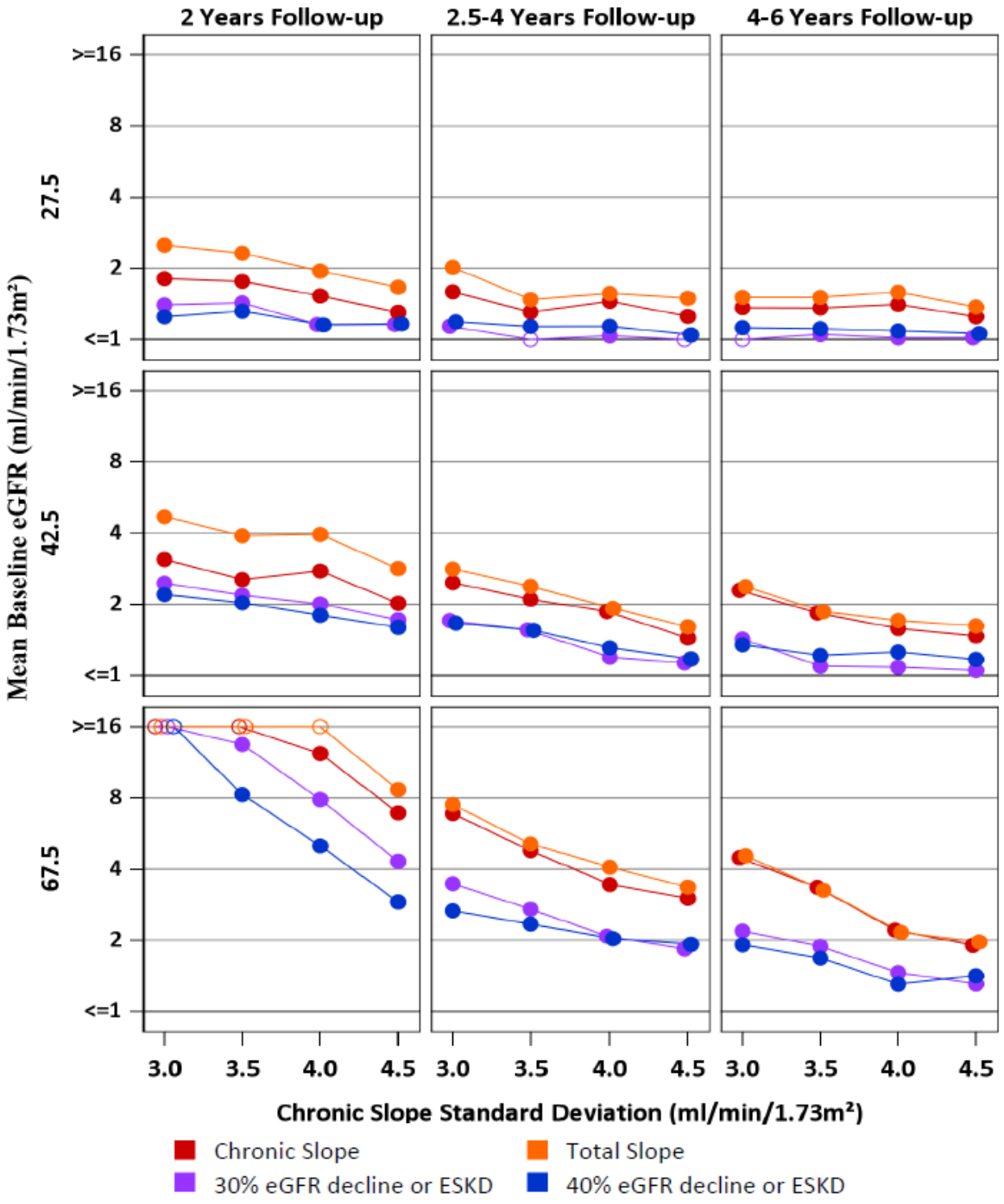
Effect of GFR slope variability

As shown in Figure 12, the relative efficiency of total or chronic GFR slope improves relative to time-to-event endpoints when GFR slope variability is smaller.

Figure 12 **Impact of GFR slope variability on the efficiency of slope versus time-to-event endpoints assuming no acute effects**



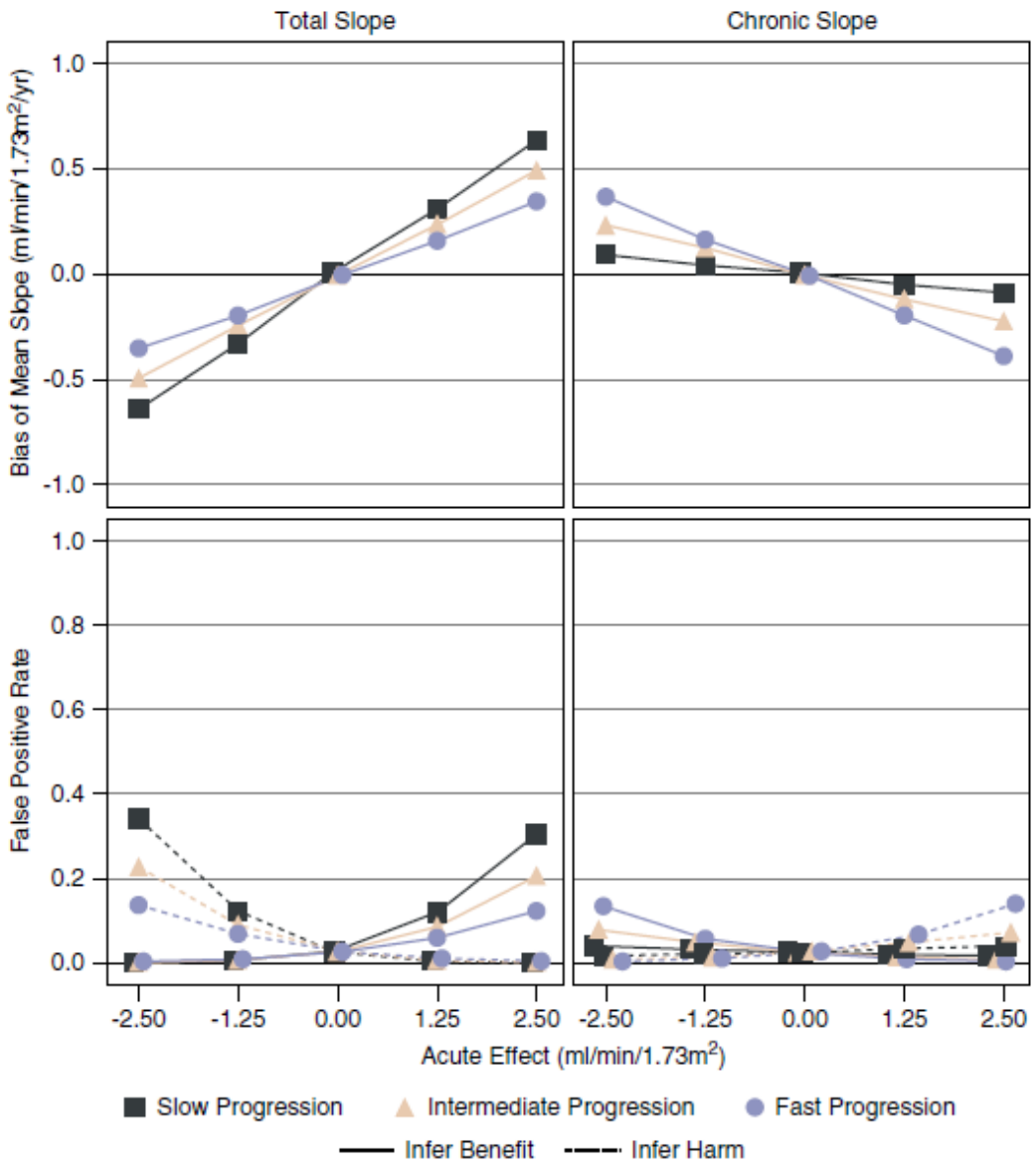
Shown are the relative efficiencies of the alternative endpoints compared to the clinical endpoint when the mean GFR slope in the control group is moderate (-3.25 mL/min/1.73 m^2/year) and the long-term treatment effect is intermediate between proportional and uniform. Relative efficiencies greater than 1 indicate higher power for the alternative endpoint than the clinical endpoint. Within each panel, the

SD 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/1.73 m^2; top panels), intermediate (42.5 mL/min/1.73 m^2; middle panels), or high (67.5 mL/min/1.73 m^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.
eGFR, Estimated glomerular filtration rate; ESKD, End-stage kidney disease (or KFRT, Kidney failure with replacement therapy); GFR, Glomerular filtration rate; SD, Standard deviation.
Reproduced with permission from Greene et al 2019.

Risk of bias and type 1 error

The top panels of Figure 13 show the estimated treatment effects on total 3-year and chronic slope when there is no long-term treatment effect and the acute effect fully attenuates before KFRT is reached for trials with moderate follow-up times (2.5 to 4 years). Since there is no treatment effect, non-zero estimated effects represent bias in these scenarios. The bottom panels of Figure 13 show the corresponding estimates of the risk of false inference of treatment benefit or harm, which can be interpreted as risk of type 1 errors when the slope end points are used to assess clinical benefit. In this scenario, negative acute effects can lead to substantial biases against the treatment for the total slope, and somewhat smaller biases in favor of the treatment for the chronic slope. The reverse is seen for positive acute effects. The opposite direction of the biases for the chronic and total slopes arises because the biases in the chronic slope result from attenuation of the initial acute effect.

Figure 13 Impact of acute effects on the risk of bias and type 1 error



Acute effects which attenuate can lead to bias and risk of false positive results. The figure displays the bias and risk of false positive and false negative conclusions when there is no long-term treatment effect with medium follow-up time. 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 is assumed to increase linearly from a value of zero when GFR=15 ml/min per 1.73 m^2 to the values indicated on the horizontal axis at a GFR of 42.5 ml/min per 1.73 m^2 and follow-up is medium (2.5–4 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 per 1.73 m^2. Aside from the attenuation of the acute effect, no long-term effect of the treatment is assumed. In this setting there is no effect of the treatment on the time to KFRT or death, so any nonzero effects represent a bias relative to the treatment effect on the clinical end point. The bottom panels indicate the implications of these biases for the risk of false conclusions of treatment benefit or of treatment harm for a RCT with 1000 total patients. Negative acute effects lead to bias of the total slope against the treatment, with a consequent inflation of the risk of a false conclusion of treatment harm, whereas positive

acute effects lead to bias of the total slope in favor of the treatment, with a consequent inflation of the risk of a false conclusion of treatment benefit. The biases and risks of false conclusions of benefit or harm are in the reverse direction for the chronic slope due to attenuation of the initial acute effect.
GFR, Glomerular filtration rate; KFRT, Kidney failure with replacement therapy.
Reproduced with permission from Greene et al 2019.

8.4 Limitations of simulations

There are two principal limitations to the statistical simulations. First, results of statistical simulations are dependent on the assumptions which are encapsulated in the inputs used to generate the simulated data. To the extent possible, the assumptions made have been based on the results of analyses of real data from previous clinical trials. However, in at least 2 cases, these analyses leave important levels of uncertainty in input parameters that are sufficiently large to impact the conclusions of the simulations. First, the results presented in this report are based on simulations which assume that acute effects that occur in the first several weeks or months after randomization are dependent on the level of GFR so that the acute effects fully attenuate to 0 by the time the patient reaches kidney failure or a GFR of 15 ml/min/1.73 m^2/yr. There is some empirical support for the assumption that acute effects tend to be smaller at lower GFR levels, but full attenuation of the acute effect to 0 cannot be determined with certainty from the available data. Second, the simulations of this report assume a particular model for the dependence of the size of the treatment effect on the chronic slope on the underlying chronic GFR slope that would have been observed without the treatment. Again, there is empirical evidence to support a relationship of this general form, but uncertainties remain regarding the precise form of this relationship and the possibility that this relationship may vary between different treatments.

The second important limitation of these simulation analyses, as in statistical simulations in other settings, is that the simulations that have been performed address only a small fraction of the very large set of scenarios which could potentially occur in practice. A total of 19 different input parameters are noted in Table 19. The space of all possible combinations of these 19 parameters is very large, and it is feasible to explore only a limited portion of the many combinations which could be seen in practice.

8.5 Conclusions on simulations

The use of GFR as a surrogate endpoint can in some cases increase statistical power compared with clinical endpoints. When there is no acute effect and the long-term treatment effect is intermediate between the proportional and uniform effect, as presented in this report, slope endpoints can usually achieve the same power as the clinical endpoint or confirmed 30% or 40% GFR declines while substantially reducing both sample size and follow-up. The efficiency gains of slope endpoints are greatest for trials with higher baseline GFR ml/min per 1.73 m^2. As shown in Greene et al 2019, the gain in performance of GFR slope relative to the time-to-event endpoints is increased compared to the performance displayed in this report if the size of the treatment effect is unform irrespective of the patients' underlying rates of GFR decline, and is reduced if the size of the treatment effect is directly proportional to the GFR slope that would have been observed without the treatment. The optimality of GFR slope is

also influenced by rate of GFR decline, GFR variability, the type of treatment effect, and the study design.

The performance of slope-based analyses is more complicated when the treatment has an acute effect. A negative acute effect can reduce and, in some cases, reverse the power advantages of the total slope compared to the clinical endpoint. In contrast, the chronic slope usually provides greater power than either the clinical endpoint or alternative time-to-event endpoints when acute effects are negative. The simulations show that this advantage in power comes with a risk of false conclusions (Figure 13) that arises because the chronic slope evaluates GFR change from a post-randomization time point after the treatment has already modified the GFR. Attenuation of a negative acute effect as GFR declines or as some patients withdraw from treatment can increase risk of a falsely concluding treatment benefit. When a negative acute effect is expected but the size of the acute effect is relatively small (e.g., $\leq$1.25 ml/min/1.73 m^2), our simulations establish that enrichment of the study cohort with fast progressors combined with sufficiently long follow-up often provides a reasonable statistical power for the total slope which exceeds that of the clinical endpoint. In this setting the analysis of the total slope represents a viable and conservative approach for evaluating treatment benefit.

In settings with a positive acute effect or in which the feasible follow-up time is insufficient to overcome a negative acute effect, the recently proposed approach of analyzing the treatment effect on total GFR change from baseline to post-study GFR measurements obtained after discontinuing the treatment should retain most of the power advantages of the chronic slope while minimizing the risk of falsely concluding benefit.

9. STRENGTHS AND LIMITATIONS OF ANALYSES OF GFR SLOPE AS A SURROGATE ENDPOINT

Strengths of this study include the following:

- Use of a systematic literature search to include all available studies resulting in a large and diverse collection of RCTs.

- A rigorous evaluation using individual patient data. Because patient-level data were analyzed, the agreement between the GFR slope and clinical endpoints could be characterized after adjusting for spurious correlations in sampling error that resulted from inclusion of the same GFR measurements in the GFR slope and clinical endpoints.

- Application of a robust method for analysis of GFR slope that accounted for informative censoring and multiple potential sources of variability in GFR measurements over time, which allowed the application of a uniform analysis of GFR slope across all RCTs.

- Use of a Bayesian meta-regression model with diffuse prior distributions allowed us rigorously account for multiple sources of uncertainty and to translate treatment effects on the surrogate endpoints to probabilities of benefit on the clinical endpoint.

There are several limitations to these analyses:

- First, because ascertainment of clinical endpoints was limited to the follow-up period of each trial, only the association between the treatment effects on the surrogate and clinical endpoints during the RCTs could be evaluated, and it could not be determined if treatment effects on the surrogate endpoints predicted the longer term effects of the treatment on future clinical endpoints. Section 6 shows the Applicant's previously reported work on epidemiologic associations of GFR slope versus the clinical endpoint over a longer period of follow up. Indeed, it is possible that the better performance of the total slope versus chronic slope may have resulted in part from the ability to evaluate the clinical endpoint only during the trial, over the same period for which the total slope was evaluated. It is possible that chronic slope would perform better if it were possible to evaluate longer-term treatment effects on the clinical endpoint.

- Second, as the same slope model was used for each RCT, somewhat different results might be obtained if the model for slope were tailored to each RCT, including trial-specific strategies for informative censoring and designating the timing of the acute effect.

- Third, because most included trials were on average 40 months, it is not possible to be certain about the impact of lesser follow-up time on the results, nor could the impact of increased measurement frequencies on such shorter trials be considered.

- Fourth, these results were dependent on the specific RCTs that were available. Although this is likely the largest collection of studies used to evaluate surrogates, nevertheless application of these results to future trials with different characteristics than those included here must be done with caution. the high frequency of negative acute effects in past RCTs affected the observed results. Indeed, these results have shown that 2 studies have the power to affect the correlation although the estimated slope and intercept remained robust. A high frequency of positive acute effects would have had important impact on the results.

- Fifth, the chronic slope was computed using a simple linear model with a knot at 3 months. For studies with acute effects that occur over a longer period of time, this could affect estimates of the chronic slope.

10. DISCUSSION AND CONCLUSIONS

10.1 Overview and review of main results

This report provides an update of trial-level meta-analysis to support a positive qualification opinion by EMA on the use of GFR slope, the mean rate of change in GFR, as a surrogate endpoint for CKD progression for a broad context of use in trials for full regulatory approval and label claim acceptance. The body of work presented in this package provides robust support for the use of GFR slope as a validated endpoint and shows that GFR slope meets the 3 criteria for acceptance as a valid surrogate endpoint (outlined in Section 3.2.2).

There is strong biologic plausibility of GFR slope as an endpoint for CKD trials. GFR is an established and widely used measure of kidney function, and GFR decline is on the path of progression to kidney failure for all kidney diseases (Section 3.1). The level of GFR is also very strongly related to development of kidney failure and its complications. There exists strong epidemiologic data demonstrating association of decline in GFR to subsequent development of kidney failure (Section 6 shows the results of large meta-analysis examining slope specifically).

GFR slope also has several advantages over clinical endpoints based on KFRT and accepted surrogates of larger GFR declines. This includes improved statistical power for many clinical trial designs, expediting development of new medicines and allowing shorter follow-up times or smaller sample sizes. Additionally, the use of GFR slope allows for the inclusion of all participants in assessment of GFR decline for all study participants, including those who may not progress to the clinical endpoint within the time period of the trial.

Presented here is an updated trial-level analysis of data from 66 RCTs that included 187,323 participants, representing 17 interventions across 4 broad disease groups. The results, presented in Section 7, confirmed a strong correlation between treatment effects on the GFR slope and treatment effect on the clinical endpoint as they had previously demonstrated.

Specifically, when treatment effect was computed over 3 years the median posterior trial level R^2 was 0.98 with very tight BCIs (0.85 to 1.00); the entire BCI falls within the designation of a strong surrogate by Prasad et al, [i.e., R^2 >0.72 (Prasad et al 2015)]. Results were similar across key subgroups, including patients with higher baseline GFR, faster and slower progression, and across diseases and intervention, and for people with at least moderate levels of albuminuria. Thus, these results show that the total GFR slope meets the 3rd critical criterion for a valid surrogate endpoint, the ability to predict the effect of the treatment on the clinical endpoint.

Treatment effect on total slope computed at 2 years remained strongly associated with treatment effect on the clinical endpoint (R^2=0.89 [95% BCI 0.68, 0.98]), but the intercept was less than 0. The negative intercept presumably reflects the overall negative direction and magnitude of the acute effects in the 66 RCTs, which on average causes the 2-year total slope to under-estimate the benefit of treatments on the clinical endpoint.

Treatment effects on the chronic slope were not as strongly associated with the treatment effects on the clinical endpoint as those of the total slope, with a posterior median trial-level R^2 of 0.56 with a 95% BCI of 0.25, 0.78, corresponding to a moderately strong surrogate endpoint in the terminology of Prasad et al (R^2 of 0.49 to 0.72) The trial level R^2 varied to some extent on inclusion of individual trials and also exhibited larger variations across different levels of baseline GFR. Although the trial level R^2 was not as strong for the chronic slope as for the total slope, the meta-regression slope relating the clinical endpoint to the chronic slope was substantially non-zero and precisely estimated, with a posterior median of -0.32 and 95% BCI of -0.45, -0.20. As a result, in spite of the lower trial level R^2 for the chronic slope, the meta-regression predicts a reasonably high probability of clinical benefit (as defined by a posterior probability of 0.89 that the HR for the effect of the treatment is less than 1) when the treatment effect on the chronic slope is at least 0.75 ml/min/1.73 m^2 in a well-powered clinical trial.

The understanding of relationship between GFR and kidney failure in conjunction with models for GFR trajectories based on previous CKD RCTs has allowed us to perform series of statistical simulations to define RCT situations where GFR slope shows improved statistical power as a surrogate endpoint compared with endpoints based on a 30% or 40% GFR decline, while preserving a low risk of bias and type 1 error (i.e., false positive conclusion when there is no treatment effect). These simulations show that in some important situations slope endpoints can achieve improved or similar power as the clinical endpoint or time to endpoints based on GFR declines (i.e., 30% or 40%), while reducing sample size and follow-up. The clearest gains are for trials with higher baseline GFR and when an acute effect is not expected. Additional factors that can influence optimal GFR slope performance are the rate of GFR decline, GFR variability, and the study design.

10.2 Magnitude of treatment effect on GFR slope required to translate to the clinical endpoint

Results from the trial-level meta-regressions allowed us to estimate the treatment effect on GFR slope that would be required to reliability predict a treatment benefit on the clinical endpoint for a future RCT. Thresholds have been provided for minimum effects on change in GFR slope that provide high confidence for significant treatment effects on the clinical endpoint, providing guidance as how to interpret treatment effects on GFR slope in future RCTs.

The results imply that although an effective treatment may reduce mean GFR decline by what might appear to be a small magnitude over the typical duration of RCTs, treatment effects for well powered trials in the range of 0.5 to 1.00 ml/min per 1.73 m^2/year for the total slope computed at 3 years can have high predictive values of greater than 98% for benefit on the clinical endpoint. Predictive values were less strong for chronic slope but were still reasonably strong at >0.8 for slopes of 0.5 to 1.00.

The analyses of epidemiologic data outlined Section 6.2 show that these changes are clinically meaningful, with a strong association between a change of 0.75 ml/min per 1.73 m^2 per year change and risk of KFRT.

10.3 Importance of acute effects as in selection of GFR slope as endpoint

Acute effects are frequent in interventions to slow CKD progression and therefore a critical consideration in endpoint selection. Specific considerations for endpoint selection in future studies are discussed below.

Duration of time over which GFR slope was assessed: As the updated trial-level analyses have demonstrated, use of total slope computed at 3 years rather than a shorter time interval limits the impact of the acute effect, and is highly robust with respect to intervention, disease, and variability in design across clinical trials performed to date. Total slope computed at 2 years was also strongly associated with a treatment-effect on the clinical endpoint, with similar strong associations across disease and intervention groups to those seen in the analyses of total slope computed at 3 years. However, the intercept was not always close to 0, presumably reflecting impact of acute effects in shorter trials, which on average causes the 2-year total slope to under-estimate the benefit of treatments on the clinical endpoint.

The variation in the intercept of the trial level associations between total slope computed at 3 versus 2 years, emphasizes the importance of the acute effect when determining the duration of time over which the GFR slope should be computed in a future trial.

Although the data cannot demonstrate this empirically, in our view in the absence of a large acute effect, total slope over a short time frame could be appropriate potential candidate endpoints.

Direction of acute effect: While negative acute effects have received the most attention and are most common in previous studies, our analyses suggest that positive acute effects are also present among CKD studies. If there is a suspicion that a positive acute effect may not indicate a true lasting impact on preservation of nephrons, use of time-to-event GFR decline or 30 or 40% (depending upon the magnitude of the effect) or of the total slope computed over a short time frame, may inflate risk of falsely concluding treatment benefit. In such circumstances, the chronic slope may represent the more conservative endpoint.

Use of chronic slope as a strategy to overcome acute effect: The difference between the total slope and chronic slope is that the acute effect is incorporated in the total slope but not the chronic slope. As such, the reason for the superior performance of the total stope compared the chronic slope suggest that acute effects do influence treatment effects on the clinical endpoint that are not captured by the treatment effects on the chronic slope. The acute effect will have diminished impact on the total slope when the total slope is computed over a sufficient time interval, with the length of term correlated with the magnitude of the acute effect.

Theoretically, if the acute effect is regarded as spurious and unrelated to progression to KFRT, the impact of the acute effect may also be reduced by using the chronic slope as the primary endpoint. However, there has been reluctance to use the chronic slope as a primary outcome since it is defined by change in GFR from a post-baseline time point at which the GFR has

already been modified by the treatment, incurring risk of bias due to attenuation of the acute effect or early discontinuation of the study medication.

When interpreting the data on chronic slope, it is important to realize that in the clinical trials used for the trial-level analyses, the clinical endpoint was ascertained within the 2 to 3 years follow-up period of the trials. Thus, the period of ascertainment for the clinical endpoint approximates the period over which the total slope is computed. It is possible that the relative performance of the chronic slope compared to the total slope would improve if clinical events subsequent to the administrative censoring dates for the trials could be included in the assessment of the clinical endpoint.

10.4 Variations across disease

The results of the trial-level analyses were consistent across diseases evaluated. It is not possible to make definitive conclusions about rare diseases or diseases not well represented among the included trials. However, removing glomerulonephritis did not change the results of the meta-regression for any of the slopes, suggesting that it is appropriate to include glomerulonephritis trials in the meta-regressions to inform predictions for more common diseases. Our results show no effect modification by underlying disease, supporting the potential utility of GFR slope as surrogate in trials which recruit rarer type of kidney disease.

10.5 Implications of the results of the trial-level analyses on study designs for future trials

The findings of the updated trial-level analyses reported here indicate that the use of GFR slope can be a valid, fit-for-purpose, and robust surrogate endpoint and can be considered in the design and implementation of a whole drug development pathway for all causes of CKD.

When applying these data to the design of a future trial, the most appropriate endpoint for the new trial should be decided upon in the context of the study population characteristics, treatment, and design. Some considerations are listed below, but these are not viewed as absolutes.

Clinical Trial Design: In the absence of an acute effect, or with a known minimal effect, duration of follow-up required to achieve adequate power may be substantially reduced by using GFR slope as the endpoint in conditions in which the event rate for the clinical endpoint is low, as typically occurs when baseline GFR is high.

In the presence of a large negative acute effect or a positive acute effect, the relative advantage or disadvantage of GFR slope over time to event endpoints is more complex and dependent upon other factors. For example, even in the presence of a large acute effect, advantage of GFR slope may be achieved with longer duration of follow-up (as is demonstrated in the total slope over 3-year data), higher GFR, or faster progression.

Of note, if the acute effect is negative, in principle, the risk of total slope ascertained over a shorter trial is insufficient statistical power and false negative conclusion of benefit. There is no increase in false positive conclusion on benefit.

The simulations help to define risk for false negative conclusion for benefit using total slope versus chronic slope according to existence of acute effects. In conditions with large negative acute effects, total slope has a risk for false negative conclusion for benefit and the chronic slope has a risk for false positive conclusion of benefit, although the magnitude of risk is smaller than with the total slope. The converse is true if the acute effect is positive. In conditions with large positive acute effects, total slope has risk of false conclusions for benefit.

The Applicant recognizes that use of GFR slope might be one component of a drug development pathway. For example, for drugs where there is clear understanding about the acute effect and the safety profile, it might be more appropriate to use shorter term study with chronic slope, or for drugs without known acute effects, and a well-established safety profile in a shorter study with total slope might be appropriate. This might occur as secondary evaluation or label extensions of a drug rather than the first pivotal study.

Subgroups: GFR slope might be helpful to characterize treatment effects on groups not well captured in traditional endpoint trials. Trials that utilize clinical endpoints will be most sensitive to fast progressors. GFR slope can also be used to demonstrate whether there is similar or different benefit among slow progressors. GFR slope also can be used to explore heterogeneous effects among subgroups for trials that are powered for the clinical endpoint. Similarly, GFR slope might be an appropriate endpoint for confirmatory studies in a subsequent study after initial RCT showed benefit on the clinical endpoint, but there is interest in demonstrating benefit of a drug in another population or with a study design where the clinical endpoint is not practical. This was the case in the finerenone development program, both in analyses of renal and CV outcomes in patients with diabetic kidney disease and in the ongoing study of finerenone in nondiabetic kidney disease (CKD-FIND), which has specified total GFR slope as the primary endpoint (clinicaltrials.gov NCT05047263).

10.6 Summary and conclusions

In aggregate, the results reported in this briefing package indicate that GFR slope can be viewed as a validated surrogate endpoint for CKD progression in clinical trials for standard marketing authorization and indication extension approvals. The duration of time over which the total GFR slope can be computed is dependent upon the presence and magnitude of an acute effect. The chronic slope may also be satisfactory in some situations. Decisions regarding the use of total versus chronic slope, as well as length of follow-up, are important and should be done carefully and with consideration of the study population, treatment, and study design in the context of specific drug development program.

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Request for CHMP Qualification Opinion - Appendices

Appendix A Supporting Tables and Figures for Trial-level Analyses

List of Tables

List of Figures

Table A-1 Search strategy in the OVID MEDLINE(R) platform for literature review

1	kidney disease$.mp.
2	chronic renal insufficiency.mp.
3	chronic kidney disease.mp.
4	renal disease.mp.
5	IgA nephropathy.mp.
6	lupus nephritis.mp.
7	diabetic nephropathy.mp.
8	glomerular disease.mp.
9	polycystic kidney disease.mp.
10	focal sclerosis.mp.
11	membranous nephropathy.mp.
12	CKD.mp.
13	Hypertension/ and (renal or kidney).mp.
14	albuminuria.mp.
15	proteinuria.mp.
16	or/1-15
17	randomized controlled trial.pt.
18	controlled clinical trial.pt.
19	randomized controlled trials/
20	Random Allocation/
21	Double-blind Method/
22	Single-Blind Method/
23	clinical trial.pt.
24	Clinical Trials.mp. or exp Clinical Trial/
25	(clinic$ adj25 trial$).tw.
26	((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
27	placebo$.tw.
28	Placebos/
29	random$.tw.
30	trial$.tw.
31	(latin adj square).tw.
32	or/17-31
33	16 and 32
34	limit 33 to (guideline or meta analysis or practice guideline or "review")
35	33 not 34
36	limit 35 to comment and (letter or editorial).pt.
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)
38	35 not (36 or 37)
39	limit 38 to animals/
40	38 not 39
41	limit 40 to humans
42	limit 40 to english language
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)")
44	limit 43 to yr="2007 -Current" [used different year ranges over the course of the research]
45	remove duplicates from 44

Table A-2 Study Inclusion Criteria

1. Randomized controlled trial
2. Articles published in English
3. Human subjects
4. Adults (18 years of age or older), except FSGS-FONT study where adults and children were included
5. Quantifiable albuminuria/proteinuria (i.e. not dipstick measurement)
6. GFR > 15 mL/min/1.73 m^2
7. First follow up albuminuria/proteinuria or serum creatinine latest at 12 months
8. Follow up more than 12 months after first follow up measurement of urine protein or GFR
9. Number of events (differ by disease)*

    a. Glomerular disease: 10 or more events

    b. Kidney disease (diabetes, hypertension, polycystic kidney disease, non-specified or other): follow-up 500 or more person-years and 30 or more events

    c. High risk population (diabetes, hypertension, cardiovascular disease, heart failure - not selected for having kidney disease): follow-up 1000 or more person-years and 30 or more events

    *Events - (end stage kidney disease, doubling or serum creatinine, GFR<15 ml/min per 1.73m^2

Table A-3 Studies pooled by intervention

Study	Pooled group
Pozzi 2004[33]	IgAN-Steroid
Katafuchi[35]	
Schena[34]	
Praga 2003[18]	IgAN-ACEI
HKVIN[17]	
Maes[30]	IgAN-MMF
Appel[28]	
Pozzi 2010[32]	IgAN-AZA
Pozzi 2012[26]	
Ponticelli 1989[38]	Mem-Nephropathy
Ponticelli 1992[39]	
Ponticelli 1998[37]	
Ponticelli 2006[40]	

ACEI, Angiotensin-converting enzyme; AZA, Azathioprine; IgAN, Immunoglobulin A nephropathy; Mem, Membranous; MMF, Mycophenolate mofetil.

Table A-4 Description of Included Studies

Intervention	Disease	Study Name	Year	Region	Creatinine calibration required[a]
RASB v Control	CKD (CNS)	Ihle/Kincaid[1]	1996	NA, Eur, Aus	Yes
	CKD (CNS)	Hou[2]	2006	Asia	Yes
	CKD (CNS)	Hannedouche[3]	1994	NA, Eur, Aus	Yes
	CKD (CNS)	Brenner[4]	1993	NA, Eur, Aus	Yes
	CKD (CNS)	Toto[4]	1993	NA, Eur, Aus	Yes
	CKD (CNS)	AIPRI[5]	1996	NA, Eur, Aus	Yes
	CKD (CNS)	REIN[6]	1999	NA, Eur, Aus	Yes
	CKD (CNS)	Van Essen[7]	1997	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[8]	2002	NA, Eur, Aus	Yes
	CKD (PKD)	HALT-PKD A[9]	2014	NA	No
	CKD (PKD)	HALT-PKD B[10]	2014	NA	No
	Diabetes	ADVANCE[11]	2008	International	Yes
	Diabetes	ALTITUDE[12]	2012	International	No
	Diabetes (CKD)	RENAAL[13]	2001	International	Yes
	Diabetes (CKD)	ORIENT[14]	2011	Asia	Yes
	Diabetes (CKD)	IDNT[15]	2001	International	Yes
	Diabetes (CKD)	Lewis 1993[16]	1993	NA	Yes
	Glom (IgAN)	HKVIN[17]	2006	Asia	Yes
	Glom (IgAN)	Praga 2003[18]	2003	Eur	Yes
	Heart failure	CHARM-Added[19]	2003	International	Yes
	Heart failure	PARADIGM-HF[20]	2014	International	No
RASB v CCB	CKD (CNS)	Zucchelli[21]	1992	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[8]	2002	NA, Eur, Aus	Yes
	Diabetes	ABCD[22]	2000	NA, Eur, Aus	Yes
	Diabetes (CKD)	IDNT[15]	2001	International	Yes
Intensive BP	CKD (CNS)	MDRD Study B[23]	1994	NA, Eur, Aus	Yes
	CKD (CNS)	REIN 2[24]	2005	NA, Eur, Aus	Yes
	CKD (CNS)	MDRD Study A[23]	1994	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[8]	2002	NA, Eur, Aus	Yes
	CKD (PKD)	HALT-PKD A[9]	2014	NA	No
	Diabetes	ABCD[22]	2000	NA, Eur, Aus	Yes
	High CV risk	SPRINT[25]	2015	NA, Eur, Aus	No
Low Protein Diet	CKD (CNS)	MDRD Study A[23]	1994	NA, Eur, Aus	Yes
	CKD (CNS)	MDRD Study B[23]	1994	NA, Eur, Aus	Yes
Immuno-suppression	Glom (IgAN)	Pozzi 2012[26]	2012	NA, Eur, Aus	No
	Glom (IgAN)	Donadio 2001[27]	2001	NA, Eur, Aus	Yes
	Glom (IgAN)	Appel[28]	2005	NA, Eur, Aus	Yes
	Glom (IgAN)	STOP-IgAN[29]	2015	Eur	No
	Glom (IgAN)	Maes[30]	2004	NA, Eur, Aus	Yes
	Glom (IgAN)	Donadio 1999[31]	1999	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2010[32]	2010	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2004[33]	2004	NA, Eur, Aus	Yes
	Glom (IgAN)	Schena[34]	2009	Eur	No
	Glom (IgAN)	Katafuchi[35]	2003	Asia	Yes
	Glom (Lupus)	Lewis 1992[36]	1992	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 1998[37]	1998	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 1989[38]	1989	NA, Eur, Aus	Yes

Table A-4 Description of Included Studies

Intervention	Disease	Study Name	Year	Region	Creatinine calibration required[a]
	Glom (Membran)	Ponticelli 1992[39]	1992	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 2006[40]	2006	NA, Eur, Aus	Yes
	FSGS	FSGS/FONT[41]	2011	NA, Eur, Aus	No
SGLT-2 Inhibitor	Diabetes	CANVAS[42]	2017	International	No
	Diabetes	EMPA-REG OUTCOME[43]	2010	International	Yes
	Diabetes - CKD	CREDENCE[44]	2019	International	No
	Diabetes - CKD	DAPA-CKD[45]	2020	International	No
DPP-4 Inhibitor	Diabetes	CAROLINA[46]	2019	International	No
	Diabetes	EXAMINE[47]	2013	International	No
	Diabetes	LEADER[48]	2016	International	No
	Diabetes - CKD	CARMELINA[49]	2019	International	No
GLP-1 Agonist	Diabetes	Harmony Outcomes[50]	2018	International	No
Diuretic v placebo	Diabetes - CKD	FIDELIO-DKD[51]	2020	International	No
	Heart failure	TOPCAT[52]	2014	International	No
Endothe. antagonist	Diabetes - CKD	SONAR[53]	2019	International	No
Antiplatelet	Diabetes - CKD	PEGASUS[54]	2015	International	No
Antiplatelet	Diabetes - CKD	SUN-MACRO[55]	2012	International	Yes
Antiplatelet	High CV risk	PLATO[56]	2009	International	Yes
Allopurinol	CKD (CNS)	Goicoechea[57]	2015	NA, Eur, Aus	Yes
	CKD (CNS)	CKD-FIX[58]	2020	NA, Eur, Aus	No
Albumin Protocol	CKD (CNS)	ROAD[59]	2007	Asia	Yes
Intensive glucose	Diabetes	ADVANCE[11]	2008	International	Yes
RASB+CCB	High CV risk	ACCOMPLISH[60]	2008	NA, Eur, Aus	No
Nurse Care	CKD (CNS)	MASTERPLAN[61]	2014	Eur	Yes
	CKD (CNS)	CanPREVENT[62]	2011	NA, Eur, Aus	No
Statin+Ezetimibe	CKD (CNS)	SHARP[63]	2011	NA, Eur, Aus	No

[a] 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.[64]
NA, Eur, Aus: study conducted in North America, Europe or Australia.
BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; CNS, Cause not specified; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; Glom, Glomerular; GLP-1, Glucagon-like peptide 1; HTN, Hypertension; IgAN, Immunoglobulin A nephropathy; Membran, Membranous; PKD, Polycystic kidney disease; RASB, Renin-angiotensin system blocker; SGLT-2, Sodium glucose cotransporter 2.

Table A-5 Categories of underlying causal diseases

Higher level disease category	Basic disease category
Diabetes	Diabetes
	Diabetes with CKD
CKD	CKD-Hypertension
	Polycystic kidney disease
	Other CKD (could not specify)
Glomerular	IgA nephropathy
	Lupus nephritis
	Membranous nephropathy
	Focal segmental glomerulosclerosis
Cardiovascular	High cardiovascular risk
	Heart failure

CKD, Chronic kidney disease; IgA, Immunoglobulin A.

Table A-6 Patient characteristics by study

Intervention	Disease	Study	N	Age Mean (SD)	Female n (%)	Black n (%)	Diabetes n (%)	eGFR Mean (SD)	ACR Geom. mean (Geom. SD)
RASB vs CONTROL	CKD	AASK	876	54.6 (10.7)	339 (38.7)	876 (100.0)	0 (0.0)	48.9 (15.8)	97 (4.8)
		Brenner	106	46.7 (13.2)	38 (35.8)	37 (34.9)	0 (0.0)	35.4 (17.2)	589 (4.2)
		HALT-PKD A	542	36.6 (8.3)	270 (49.8)	13 (2.4)	0 (0.0)	91.9 (17.7)	21 (2.6)
		HALT-PKD B	462	48.8 (8.2)	238 (51.5)	12 (2.6)	0 (0.0)	48.2 (11.8)	39 (3.3)
		Hannedouche	98	51.2 (14.1)	47 (48.0)	0 (0.0)	0 (0.0)	23.4 (7.8)	750 (3.4)
		Hou	224	44.7 (15.4)	113 (50.4)	0 (0.0)	0 (0.0)	16.8 (4.4)	893 (1.7)
		Ihle/Kincaid	67	45.5 (12.8)	34 (50.7)	0 (0.0)	0 (0.0)	16.5 (6.7)	832 (2.7)
		Kamper	55	49.8 (11.7)	28 (50.9)	0 (0.0)	0 (0.0)	14.8 (9.0)	637 (3.0)
		Maschio	562	50.9 (12.5)	157 (27.9)	0 (0.0)	0 (0.0)	38.6 (11.6)	426 (4.4)
		REIN	322	48.8 (13.6)	73 (22.7)	2 (0.6)	0 (0.0)	41.5 (18.8)	1581 (2.1)
		Toto	122	52.4 (11.6)	44 (36.1)	74 (60.7)	0 (0.0)	37.0 (17.5)	198 (3.3)
		Van Essen	103	50.6 (12.9)	35 (34.0)	1 (1.0)	0 (0.0)	48.1 (19.3)	330 (4.9)
	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	17 (4.0)
		ALTITUDE	8150	64.4 (9.7)	2572 (31.6)	267 (3.3)	8150 (100.0)	58.4 (21.2)	200 (7.3)
		Lewis 1993	407	34.5 (7.6)	191 (46.9)	32 (7.9)	407 (100.0)	73.2 (25.3)	1185 (2.5)
		IDNT	1135	58.8 (7.7)	363 (32.0)	139 (12.2)	1135 (100.0)	50.2 (19.5)	1870 (2.2)
		ORIENT	566	59.2 (8.1)	175 (30.9)	0 (0.0)	566 (100.0)	47.5 (12.1)	1202 (2.3)
		RENAAL	1513	60.2 (7.4)	557 (36.8)	230 (15.2)	1513 (100.0)	41.3 (13.2)	1255 (2.8)
	Cardiovascular	CHARM-Added	913	64.0[a]	209 (22.9)	108 (11.8)	338 (37.0)	73.3 (23.3)	NA
		PARADIGM-HF	8440	63.8 (11.7)	1846 (21.9)	427 (5.1)	2926 (34.7)	70.2 (20.1)	20 (4.4)
	Glomerular	HKVIN	109	40.5 (9.5)	79 (72.5)	0 (0.0)	3 (2.8)	75.1 (29.0)	1000 (2.0)
		IgAN-ACEI	153	37.9 (10.8)	96 (62.7)	0 (0.0)	3 (2.0)	81.7 (30.1)	987 (2.0)
		Praga 2003	44	31.6 (11.5)	17 (38.6)	0 (0.0)	0 (0.0)	98.1 (26.5)	955 (1.9)
RASB v CCB	CKD	AASK	652	54.4 (10.8)	255 (39.1)	652 (100.0)	0 (0.0)	48.7 (15.8)	92 (4.7)
		Zuchelli	121	55.4 (10.9)	47 (38.8)	0 (0.0)	0 (0.0)	24.9 (10.1)	562 (3.3)
	Diabetes	ABCD	392	59.0 (8.2)	130 (33.2)	63 (16.1)	392 (100.0)	72.1 (18.7)	195 (4.3)

Table A-6 Patient characteristics by study

Intervention	Disease	Study	N	Age Mean (SD)	Female n (%)	Black n (%)	Diabetes n (%)	eGFR Mean (SD)	ACR Geom. mean (Geom. SD)
		IDNT	1128	59.2 (7.5)	400 (35.5)	147 (13.0)	1128 (100.0)	50.1 (18.7)	1803 (2.1)
RASB+CCB	Cardiovascular	ACCOMPLISH	11482	68.5 (6.8)	4531 (39.5)	1412 (12.3)	6932 (60.4)	75.0 (18.1)	18 (4.9)
Immunosuppression	Glomerular	Appel	29	37.9 (12.3)	5 (17.2)	0 (0.0)	0 (0.0)	42.2 (26.6)	1392 (1.7)
		Lewis 1992	79	32.6 (12.0)	66 (83.5)	17 (21.5)	0 (0.0)	56.4 (36.3)	2319 (2.5)
		Donadio 1999	96	38.5 (13.4)	26 (27.1)	0 (0.0)	0 (0.0)	66.1 (22.5)	1274 (1.9)
		Donadio 2001	72	46.3 (13.1)	13 (18.1)	2 (2.8)	0 (0.0)	40.8 (14.4)	888 (2.9)
		FSGS-FONT	138	17.2 (10.1)	65 (47.1)	53 (38.4)	0 (0.0)	130.0 (78.2)	2480 (2.3)
		IgAN-AZA	243	39.8 (12.4)	64 (26.3)	0 (0.0)	0 (0.0)	65.8 (29.5)	1302 (1.7)
		IgAN-MMF	63	41.6 (12.2)	15 (23.8)	0 (0.0)	0 (0.0)	53.0 (24.7)	922 (2.4)
		IgAN-steroid	259	35.9 (11.5)	102 (39.4)	0 (0.0)	2 (0.8)	92.3 (22.7)	1001 (1.8)
		Katafuchi	81	35.6 (11.2)	48 (59.3)	0 (0.0)	0 (0.0)	98.8 (21.4)	841 (2.5)
		Pozzi 2004	83	38.6 (11.7)	25 (30.1)	0 (0.0)	0 (0.0)	87.2 (21.6)	1123 (1.4)
		Pozzi 2010	197	39.2 (12.6)	55 (27.9)	0 (0.0)	0 (0.0)	74.7 (25.5)	1239 (1.6)
		Pozzi 2012	46	42.0 (11.5)	9 (19.6)	0 (0.0)	0 (0.0)	27.8 (7.0)	1613 (1.9)
		Maes	34	44.8 (11.3)	10 (29.4)	0 (0.0)	0 (0.0)	62.2 (18.9)	649 (2.7)
		Mem-Ponticelli	273	47.4 (11.7)	81 (29.7)	0 (0.0)	0 (0.0)	86.9 (22.7)	3472 (1.6)
		Ponticelli 2006	31	49.3 (10.5)	12 (38.7)	0 (0.0)	0 (0.0)	92.6 (22.2)	3441 (1.5)
		Ponticelli 1989	75	44.4 (10.9)	15 (20.0)	0 (0.0)	0 (0.0)	87.7 (23.0)	3238 (1.5)
		Ponticelli 1992	76	46.7 (13.3)	26 (34.2)	0 (0.0)	0 (0.0)	89.0 (25.1)	3558 (1.6)
		Ponticelli 1998	91	49.9 (10.7)	28 (30.8)	0 (0.0)	0 (0.0)	82.5 (19.9)	3614 (1.7)
		Schena	95	33.7 (11.1)	29 (30.5)	0 (0.0)	2 (2.1)	91.3 (23.7)	1051 (1.5)
		STOP-IgAN	151	44.2 (12.4)	34 (22.5)	0 (0.0)	0 (0.0)	59.7 (27.6)	907 (1.6)
Low v Usual BP	CKD	AASK	1093	54.6 (10.7)	425 (38.9)	1093 (100.0)	0 (0.0)	48.7 (15.7)	95 (4.8)
		HALT-PKD A	542	36.6 (8.3)	270 (49.8)	13 (2.4)	0 (0.0)	91.9 (17.7)	21 (2.6)
		MDRD A	584	52.2 (12.2)	228 (39.0)	53 (9.1)	30 (5.1)	40.7 (11.0)	156 (5.5)
		MDRD B	255	50.8 (12.8)	104 (40.8)	13 (5.1)	13 (5.1)	20.3 (5.8)	354 (4.4)
		REIN 2	330	54.2 (14.9)	82 (24.8)	0 (0.0)	17 (5.2)	32.3 (18.1)	1401 (2.0)
	Diabetes	ABCD	392	59.0 (8.2)	130 (33.2)	63 (16.1)	392 (100.0)	72.1 (18.7)	195 (4.3)
	Cardiovascular	SPRINT	8885	67.9 (9.4)	3135 (35.3)	2826 (31.8)	0 (0.0)	72.5 (20.2)	13 (3.3)
	CKD	DAPA-CKD	4041	62.1 (12.1)	1352 (33.5)	189 (4.7)	2777 (68.7)	43.3 (12.4)	943 (2.4)

Table A-6 Patient characteristics by study

Intervention	Disease	Study	N	Age Mean (SD)	Female n (%)	Black n (%)	Diabetes n (%)	eGFR Mean (SD)	ACR Geom. mean (Geom. SD)
SGLT-2 Inhibitor	Diabetes	CANVAS	10031	63.3 (8.2)	3594 (35.8)	330 (3.3)	10031 (100.0)	78.7 (18.8)	20 (4.5)
		CREDENCE	4399	63.0 (9.2)	1493 (33.9)	223 (5.1)	4399 (100.0)	55.9 (16.8)	888 (2.8)
		EMPA-REG	6936	63.2 (8.6)	1977 (28.5)	354 (5.1)	6936 (100.0)	76.2 (19.9)	26 (5.8)
Antiplatelet	Diabetes	SUN-MACRO	1110	63.5 (9.3)	256 (23.1)	115 (10.4)	1110 (100.0)	33.7 (9.7)	1032 (2.3)
	Cardiovascular	PEGASUS	17788	65.3 (8.3)a	4251 (23.9)[a]	302 (1.7)[a]	5782 (32.5)	74.6 (17.8)	NA
		PLATO	12688	62[b]	3567 (28.1)	199 (1.6)	3481 (27.4)	82.6 (21.2)	NA
DPP-4 Inhibitor	Diabetes	CARMELINA	6964	65.8 (9.0)	2584 (37.1)	410 (5.9)	6964 (100.0)	55.6 (25.1)	160 (7.0)
		CAROLINA	5985	64.1 (9.5)	2393 (40.0)	323 (5.4)	5985 (100.0)	78.7 (18.0)	14 (4.3)
		EXAMINE	5380	60.9 (9.9)	1729 (32.1)	216 (4.0)	5380 (100.0)	75.2 (21.5)	NA
Allopurinol	CKD	CKD-FIX	358	62.4 (12.7)	132 (36.9)	1 (0.3)	208 (58.1)	30.7 (11.5)	519 (5.7)
		Goicoechea	113	71.8 (8.7)	40 (35.4)	0 (0.0)	42 (37.2)	40.5 (12.4)	69 (6.5)
GLP-1 Agonist	Diabetes	Harmony Outcomes	8913	64.0 (8.6)	2747 (30.8)	217 (2.4)	8913 (100.0)	79.0 (20.4)	NA
		LEADER	7533	64.3 (7.2)	2512 (33.3)	665 (8.8)	7533 (100.0)	78.8 (22.7)	33 (5.9)
Low v Usual Diet	CKD	MDRD A	584	52.2 (12.2)	228 (39.0)	53 (9.1)	30 (5.1)	40.7 (11.0)	156 (5.5)
		MDRD B	255	50.8 (12.8)	104 (40.8)	13 (5.1)	13 (5.1)	20.3 (5.8)	354 (4.4)
Mineralocort. rec. antagonist	Diabetes	FIDELIO-DKD	5671	65.6 (9.1)[a]	1689 (29.8)	264 (4.7)	5671 (100.0)	44.3 (12.6)	807 (2.7)
	Cardiovascular	TOPCAT	3435	68.6 (9.6)	1764 (51.4)	301 (8.8)	1114 (32.4)	65.1 (18.6)	26 (6.4)
Nurse-coordinated Care	CKD	CanPREVENT	458	65.1 (7.5)	250 (54.6)	25 (5.5)	144 (31.4)	47.6 (9.9)	78 (2.7)
		MASTERPLAN	640	60.5 (12.5)	199 (31.1)	49 (7.7)	156 (24.4)	36.7 (15.4)	149 (4.8)

Table A-6 Patient characteristics by study

Intervention	Disease	Study	N	Age Mean (SD)	Female n (%)	Black n (%)	Diabetes n (%)	eGFR Mean (SD)	ACR Geom. mean (Geom. SD)
Albuminuria Targeted Protocol	CKD	ROAD	339	50.9 (13.7)	126 (37.2)	0 (0.0)	0 (0.0)	29.0 (13.4)	1068 (1.7)
Intensive Glucose	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	17 (4.0)
Endothelin rec. antagonist	Diabetes	SONAR	3659	64.5 (8.8)	945 (25.8)	224 (6.1)	3659 (100.0)	42.5 (14.2)	479 (2.7)
Statin+Ezetimibe	CKD	SHARP	6245	62.9 (11.7)	2363 (37.8)	119 (1.9)	1426 (22.8)	26.2 (12.3)	174 (6.6)

Note: Included only participants who had a baseline GFR measurement or had age, sex, race information to estimate baseline GFR.

[a] Variable not provided to the study team hence this value is based on the published results.

[b] Median age; variable not provided hence this value is based on the published results

ACR, Albumin:creatinine ratio; BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; DPP4, Dipeptidyl peptidase 4; eGFR, Estimated glomerular filtration rate; Geom, Geometric; GLP-1, Glucagon-like peptide 1; n, Number of patients in subset; N, Number of patients overall; NA, not available per study protocol; RASB, Renin-angiotensin system blocker; SD, Standard deviation; SGLT-2, Sodium glucose cotransporter 2.

Table A-7 **Slopes in treatment and control and treatment effect by intervention, causal disease, and subgroups –total slope computed at 3 years, total slope computed at 2 years, chronic slope, and acute slope**

	N Studies	Treatment arm	Control Arm	Treatment Effect
		Mean slope	Mean slope	Mean Difference (95% CI)
A-7a) TOTAL SLOPE COMPUTED AT 3 YEARS				
Main analysis – all studies	66	-2.75 (-3.15, -2.34)	-3.17 (-3.63, -2.71)	0.36 (0.12, 0.60)
RASB vs CONTROL	21	-3.53 (-4.26, -2.80)	-4.08 (-4.95, -3.21)	0.48 (0.07, 0.90)
RASB v CCB	4	-3.07 (-4.94, -1.19)	-2.78 (-5.19, -0.37)	-0.31 (-1.08, 0.46)
RASB+CCB	1	-1.39 (-1.55, -1.23)	-3.35 (-3.46, -3.24)	1.96 (1.80, 2.12)
Immunosuppression	9	-1.65 (-2.79, -0.51)	-2.97 (-4.47, -1.47)	1.07 (-0.71, 2.85)
Low v Usual BP	7	-3.29 (-4.68, -1.90)	-3.14 (-4.85, -1.42)	-0.31 (-1.00, 0.38)
SGLT-2 Inhibitor	4	-2.17 (-3.29, -1.05)	-3.14 (-4.68, -1.61)	0.95 (0.39, 1.51)
Antiplatelet	3	-2.55 (-4.49, -0.61)	-2.34 (-4.32, -0.37)	-0.22 (-0.34, -0.10)
DPP-4 Inhibitor	3	-1.16 (-2.30, -0.02)	-1.10 (-2.32, 0.11)	0.00 (-0.20, 0.20)
Allopurinol	2	-1.68 (-3.21, -0.16)	-2.57 (-3.16, -1.99)	0.98 (-1.08, 3.03)
GLP-1 Agonist	2	-1.88 (-3.35, -0.41)	-2.27 (-3.36, -1.18)	0.37 (-0.01, 0.74)
Low v Usual Diet	2	-3.21 (-4.03, -2.40)	-4.02 (-4.54, -3.50)	0.82 (0.23, 1.42)
Mineralocort. rec. antagonist	2	-2.77 (-4.72, -0.82)	-2.51 (-5.85, 0.84)	-0.26 (-1.65, 1.14)
Nurse-coordinated Care	2	-1.73 (-2.28, -1.18)	-2.16 (-2.73, -1.59)	0.40 (0.02, 0.78)
Albuminuria Targeted Protocol	1	-2.93 (-3.67, -2.18)	-3.38 (-3.98, -2.78)	0.46 (-0.29, 1.20)
Endothelin rec. antagonist	1	-2.98 (-3.32, -2.65)	-3.52 (-3.76, -3.28)	0.54 (0.20, 0.88)
Intensive Glucose	1	-1.71 (-1.86, -1.57)	-1.63 (-1.74, -1.53)	-0.08 (-0.23, 0.07)
Statin+Ezetimibe	1	-1.79 (-1.97, -1.61)	-2.04 (-2.17, -1.91)	0.25 (0.07, 0.43)
CKD	28	-2.82 (-3.25, -2.40)	-3.25 (-3.76, -2.74)	0.36 (0.08, 0.64)
Diabetes	21	-3.05 (-3.90, -2.21)	-3.43 (-4.39, -2.47)	0.32 (0.04, 0.60)
Glomerular	10	-2.05 (-3.30, -0.80)	-3.53 (-5.25, -1.81)	1.34 (-0.28, 2.97)
Cardiovascular	7	-1.91 (-2.55, -1.27)	-1.74 (-2.64, -0.85)	-0.21 (-1.08, 0.67)
GFR<60	40	-3.23 (-3.78, -2.68)	-3.66 (-4.22, -3.11)	0.45 (0.24, 0.66)
GFR>=60	26	-1.95 (-2.35, -1.54)	-2.39 (-3.06, -1.72)	0.33 (-0.21, 0.87)
Rate of progression in control arm >-2.6	28	-1.70 (-1.98, -1.42)	-1.73 (-2.06, -1.41)	0.03 (-0.29, 0.36)
Rate of progression in control arm <=-2.6	38	-3.53 (-4.09, -2.97)	-4.27 (-4.83, -3.72)	0.64 (0.32, 0.97)

Table A-7 **Slopes in treatment and control and treatment effect by intervention, causal disease, and subgroups –total slope computed at 3 years, total slope computed at 2 years, chronic slope, and acute slope**

	N Studies	Treatment arm	Control Arm	Treatment Effect
		Mean slope	Mean slope	Mean Difference (95% CI)
A-7b) TOTAL SLOPE COMPUTED AT 2 YEARS				
Main analysis – all studies	66	-2.83 (-3.28, -2.37)	-3.17 (-3.66, -2.68)	0.28 (-0.01, 0.57)
RASB vs CONTROL	21	-3.70 (-4.50, -2.90)	-4.16 (-5.07, -3.26)	0.40 (-0.08, 0.89)
RASB v CCB	4	-3.12 (-5.33, -0.91)	-2.57 (-5.44, 0.31)	-0.61 (-1.64, 0.43)
RASB+CCB	1	-1.69 (-1.89, -1.49)	-4.41 (-4.55, -4.27)	2.72 (2.53, 2.92)
Immunosuppression	9	-1.66 (-4.11, 0.79)	-2.84 (-4.71, -0.97)	1.26 (-0.68, 3.20)
Low v Usual BP	7	-3.30 (-4.52, -2.07)	-2.89 (-4.53, -1.25)	-0.55 (-1.39, 0.28)
SGLT-2 Inhibitor	4	-2.56 (-3.65, -1.48)	-3.16 (-4.67, -1.66)	0.58 (-0.02, 1.18)
Antiplatelet	3	-2.80 (-4.90, -0.70)	-2.52 (-4.60, -0.43)	-0.26 (-0.39, -0.13)
DPP-4 Inhibitor	3	-1.16 (-2.29, -0.03)	-1.07 (-2.21, 0.07)	-0.06 (-0.39, 0.26)
Allopurinol	2	-1.57 (-3.66, 0.51)	-2.63 (-3.24, -2.02)	1.24 (-1.50, 3.98)
GLP-1 Agonist	2	-1.92 (-3.53, -0.32)	-2.15 (-3.49, -0.80)	0.20 (-0.06, 0.45)
Low v Usual Diet	2	-3.14 (-3.76, -2.52)	-4.22 (-4.66, -3.77)	1.07 (0.45, 1.69)
Mineralocort. rec. antagonist	2	-3.24 (-4.96, -1.53)	-2.48 (-5.71, 0.75)	-0.75 (-2.27, 0.77)
Nurse-coordinated Care	2	-1.64 (-2.06, -1.21)	-2.10 (-2.58, -1.62)	0.41 (-0.01, 0.84)
Albuminuria Targeted Protocol	1	-3.07 (-3.88, -2.26)	-3.51 (-4.15, -2.86)	0.44 (-0.37, 1.24)
Endothelin rec. antagonist	1	-2.96 (-3.30, -2.61)	-3.42 (-3.67, -3.18)	0.47 (0.12, 0.82)
Intensive Glucose	1	-1.91 (-2.10, -1.71)	-1.84 (-1.98, -1.70)	-0.07 (-0.27, 0.12)
Statin+Ezetimibe	1	-1.66 (-1.86, -1.46)	-1.95 (-2.10, -1.81)	0.29 (0.09, 0.49)
CKD	28	-2.82 (-3.29, -2.36)	-3.20 (-3.76, -2.64)	0.32 (-0.02, 0.67)
Diabetes	21	-3.26 (-4.15, -2.37)	-3.45 (-4.44, -2.46)	0.13 (-0.16, 0.41)
Glomerular	10	-1.91 (-3.98, 0.16)	-3.45 (-5.56, -1.34)	1.55 (-0.21, 3.31)
Cardiovascular	7	-2.38 (-3.37, -1.39)	-2.01 (-3.23, -0.79)	-0.40 (-1.64, 0.84)
GFR<60	40	-3.22 (-3.83, -2.60)	-3.63 (-4.22, -3.03)	0.37 (0.13, 0.62)
GFR>=60	26	-2.16 (-2.69, -1.63)	-2.45 (-3.18, -1.72)	0.21 (-0.45, 0.88)
Rate of progression in control arm >-2.6	28	-1.88 (-2.27, -1.50)	-1.83 (-2.24, -1.42)	-0.06 (-0.49, 0.36)
Rate of progression in control arm <=-2.6	38	-3.54 (-4.23, -2.85)	-4.21 (-4.84, -3.58)	0.56 (0.18, 0.93)

Table A-7 **Slopes in treatment and control and treatment effect by intervention, causal disease, and subgroups –total slope computed at 3 years, total slope computed at 2 years, chronic slope, and acute slope**

	N Studies	Treatment arm	Control Arm	Treatment Effect
		Mean slope	Mean slope	Mean Difference (95% CI)
A-7c) Chronic Slope				
Main analysis – all studies	66	-2.61 (-2.99, -2.22)	-3.16 (-3.60, -2.72)	0.54 (0.35, 0.73)
RASB vs CONTROL	21	-3.21 (-3.90, -2.53)	-3.92 (-4.75, -3.09)	0.61 (0.34, 0.89)
RASB v CCB	4	-2.95 (-4.31, -1.60)	-3.22 (-5.06, -1.38)	0.43 (-0.14, 0.99)
RASB+CCB	1	-0.79 (-0.96, -0.63)	-1.23 (-1.35, -1.12)	0.44 (0.27, 0.61)
Immunosuppression	9	-2.44 (-3.38, -1.50)	-3.21 (-4.48, -1.94)	0.61 (-1.07, 2.30)
Low v Usual BP	7	-3.32 (-5.21, -1.43)	-3.63 (-5.60, -1.67)	0.23 (-0.24, 0.69)
SGLT-2 Inhibitor	4	-1.39 (-2.60, -0.17)	-3.09 (-4.69, -1.50)	1.68 (1.17, 2.20)
Antiplatelet	3	-2.06 (-4.21, 0.08)	-2.00 (-4.11, 0.11)	-0.14 (-0.27, -0.01)
DPP-4 Inhibitor	3	-1.16 (-2.33, 0.00)	-1.17 (-2.55, 0.21)	-0.04 (-0.18, 0.09)
Allopurinol	2	-1.93 (-2.74, -1.12)	-2.36 (-2.96, -1.76)	0.45 (-0.36, 1.26)
GLP-1 Agonist	2	-1.80 (-3.00, -0.60)	-2.54 (-3.12, -1.96)	0.70 (0.08, 1.31)
Low v Usual Diet	2	-3.38 (-4.88, -1.89)	-3.65 (-4.60, -2.71)	0.32 (-0.29, 0.92)
Mineralocort. rec. antagonist	2	-1.83 (-4.26, 0.61)	-2.56 (-6.14, 1.01)	0.74 (-0.40, 1.88)
Nurse-coordinated Care	2	-2.01 (-3.30, -0.73)	-2.26 (-2.99, -1.53)	0.41 (-0.04, 0.86)
Albuminuria Targeted Protocol	1	-2.64 (-3.29, -1.99)	-3.13 (-3.67, -2.60)	0.50 (-0.15, 1.14)
Endothelin rec. antagonist	1	-3.04 (-3.41, -2.68)	-3.72 (-3.98, -3.46)	0.68 (0.32, 1.05)
Intensive Glucose	1	-1.32 (-1.45, -1.19)	-1.23 (-1.33, -1.13)	-0.09 (-0.22, 0.04)
Statin+Ezetimibe	1	-2.04 (-2.21, -1.87)	-2.22 (-2.34, -2.09)	0.17 (0.00, 0.35)
CKD	28	-2.82 (-3.21, -2.44)	-3.35 (-3.83, -2.86)	0.48 (0.27, 0.70)
Diabetes	21	-2.64 (-3.43, -1.84)	-3.38 (-4.31, -2.45)	0.71 (0.38, 1.04)
Glomerular	10	-2.60 (-3.48, -1.72)	-3.61 (-4.95, -2.28)	0.86 (-0.68, 2.39)
Cardiovascular	7	-1.06 (-1.37, -0.75)	-1.19 (-1.61, -0.77)	0.10 (-0.21, 0.40)
GFR<60	40	-3.25 (-3.73, -2.76)	-3.72 (-4.24, -3.20)	0.61 (0.39, 0.83)
GFR>=60	26	-1.60 (-1.99, -1.20)	-2.27 (-2.90, -1.64)	0.51 (0.15, 0.86)
Rate of progression in control arm >-2.6	28	-1.35 (-1.60, -1.10)	-1.55 (-1.80, -1.29)	0.25 (0.01, 0.49)
Rate of progression in control arm <=-2.6	38	-3.52 (-3.96, -3.07)	-4.37 (-4.84, -3.91)	0.81 (0.54, 1.07)

Table A-7 **Slopes in treatment and control and treatment effect by intervention, causal disease, and subgroups –total slope computed at 3 years, total slope computed at 2 years, chronic slope, and acute slope**

	N Studies	Treatment arm	Control Arm	Treatment Effect
		Mean slope	Mean slope	Mean Difference (95% CI)
A-7d) ACUTE SLOPE				
Main analysis – all studies	66	-4.35 (-6.97, -1.72)	-3.11 (-5.11, -1.12)	-1.38 (-3.10, 0.35)
RASB vs CONTROL	21	-6.78 (-10.26, -3.31)	-5.60 (-8.23, -2.97)	-1.31 (-3.62, 0.99)
RASB v CCB	4	-4.29 (-14.94, 6.36)	1.88 (-13.83,17.59)	-6.52 (-15.18, 2.14)
RASB+CCB	1	-7.96 (-9.58, -6.34)	-26.65 (-27.79, -25.51)	18.69 (17.07, 20.30)
Immunosuppression	9	0.58 (-33.97, 35.13)	1.50 (-11.19, 14.20)	1.83 (-16.57, 20.23)
Low v Usual BP	7	-2.58 (-9.12, 3.97)	2.79 (-3.07, 8.65)	-5.45 (-10.26, -0.63)
SGLT-2 Inhibitor	4	-10.84 (-13.02, -8.67)	-3.69 (-5.05, -2.33)	-7.18 (-9.36, -5.00)
Antiplatelet	3	-7.94 (-21.31, 5.42)	-6.11 (-17.34, 5.13)	-1.78 (-3.90, 0.33)
DPP-4 Inhibitor	3	-1.06 (-3.05, 0.93)	-0.46 (-2.04, 1.13)	-0.73 (-4.21, 2.75)
Allopurinol	2	0.88 (-12.93, 14.69)	-4.70 (-7.91, -1.49)	6.95 (-10.15, 24.05)
GLP-1 Agonist	2	-2.97 (-7.37, 1.44)	0.43 (-6.23, 7.09)	-3.16 (-5.39, -0.94)
Low v Usual Diet	2	-1.76 (-8.42, 4.89)	-8.32 (-12.41, -4.22)	6.55 (3.99, 9.11)
Mineralocort. rec. antagonist	2	-12.83 (-16.10, -9.55)	-2.16 (-3.10, -1.22)	-10.98 (-15.09, -6.88)
Nurse-coordinated Care	2	0.72 (-6.59, 8.03)	-1.30 (-3.22, 0.62)	1.61 (-4.43, 7.66)
Albuminuria Targeted Protocol	1	-6.10 (-8.98, -3.22)	-6.12 (-8.21, -4.02)	0.02 (-2.86, 2.90)
Endothelin rec. antagonist	1	-2.37 (-4.05, -0.70)	-1.34 (-2.53, -0.15)	-1.03 (-2.71, 0.64)
Intensive Glucose	1	-6.00 (-7.63, -4.37)	-6.07 (-7.23, -4.92)	0.07 (-1.56, 1.70)
Statin+Ezetimibe	1	1.03 (-0.10, 2.15)	-0.10 (-0.90, 0.70)	1.12 (0.00, 2.25)
CKD	28	-2.04 (-4.34, 0.26)	-1.76 (-4.64, 1.13)	-0.29 (-2.50, 1.91)
Diabetes	21	-7.66 (-10.37, -4.94)	-3.87 (-6.03, -1.71)	-3.96 (-5.72, -2.20)
Glomerular	10	-0.19 (-30.51, 30.12)	-0.72 (-12.80, 11.37)	4.00 (-9.46, 17.46)
Cardiovascular	7	-11.32 (-19.21, -3.44)	-7.48 (-16.21, 1.25)	-4.07 (-13.27, 5.12)
GFR<60	40	-3.14 (-5.67, -0.62)	-2.84 (-5.36, -0.31)	-0.71 (-2.37, 0.94)
GFR>=60	26	-8.06 (-15.75, -0.37)	-3.58 (-6.91, -0.25)	-2.78 (-6.65, 1.09)
Rate of progression in control arm >-2.6	28	-5.20 (-8.23, -2.17)	-3.63 (-6.49, -0.78)	-1.64 (-4.56, 1.27)
Rate of progression in control arm <=-2.6	38	-3.86 (-9.59, 1.87)	-2.68 (-5.53, 0.17)	-1.24 (-3.27, 0.79)

[a] N-values are based on slope model sample size.

GFR and rate of progression in control arm units are ml/min per 1.73 m^2.

BP, Blood pressure; CCB, Calcium channel blocker; CI, Confidence interval; CKD, Chronic kidney disease; DPP4, Dipeptidyl peptidase 4; GFR, Glomerular filtration rate; GLP-1, Glucagon-like peptide 1; N, Number; RASB, Renin-angiotensin system blocker; SGLT-2, Sodium glucose cotransporter 2.

Table A-8 Treatment effects on the clinical endpoint

Group Level	N studies	N patients	HR (95% CI)	FU clinical endpoint Median (25th, 75th %ile)
Main analysis – all studies	66	187323	0.83 (0.76, 0.90)	35 (22, 52)
RASB vs CONTROL	21	35692	0.82 (0.70, 0.95)	44 (33, 76)
RASB v CCB	4	2293	0.67 (0.56, 0.80)	40 (25, 56)
RASB+CCB	1	11482	0.55 (0.44, 0.69)	38 (34, 44)
Immunosuppression	9	1374	0.61 (0.36, 1.06)	41 (28, 66)
Low v Usual BP	7	12081	1.00 (0.78, 1.28)	40 (33, 48)
SGLT-2 Inhibitor	4	25407	0.64 (0.56, 0.73)	36 (28, 50)
Antiplatelet	3	31586	1.01 (0.74, 1.39)	25 (14, 35)
DPP-4 Inhibitor	3	18329	1.00 (0.86, 1.17)	40 (24, 76)
Allopurinol	2	471	0.68 (0.17, 2.82)	34 (25, 37)
GLP-1 Agonist	2	16446	0.98 (0.79, 1.22)	21 (17, 25)
Low v Usual Diet	2	839	0.81 (0.63, 1.04)	28 (21, 36)
Mineralocort. rec. antagonist	2	9106	1.13 (0.61, 2.11)	33 (24, 45)
Nurse-coordinated Care	2	1098	0.74 (0.46, 1.17)	40 (30, 71)
Albuminuria Targeted Protocol	1	339	0.49 (0.31, 0.76)	46 (36, 46)
Endothelin rec. antagonist	1	3659	0.76 (0.62, 0.94)	26 (16, 35)
Intensive Glucose	1	10876	1.05 (0.75, 1.45)	78 (72, 79)
Statin+Ezetimibe	1	6245	0.93 (0.86, 1.01)	47 (20, 56)
CKD	28	20149	0.77 (0.70, 0.86)	35 (24, 54)
Diabetes	21	102016	0.85 (0.76, 0.95)	41 (25, 73)
Glomerular	10	1527	0.60 (0.36, 0.97)	40 (30, 66)
Cardiovascular	7	63631	1.08 (0.78, 1.48)	31 (14, 38)
GFR<60	40	53725	0.79 (0.74, 0.85)	37 (22, 72)
GFR>=60	26	133598	0.89 (0.74, 1.08)	32 (22, 43)
Rate of progression in control arm >-2.6	28	138590	0.96 (0.83, 1.11)	36 (21, 63)
Rate of progression in control arm <=-2.6	38	48733	0.76 (0.70, 0.82)	33 (24, 43)

GFR and rate of progression in control arm units are ml/min per 1.73 m^2.

CCB, Calcium channel blocker; CI, Confidence interval; CKD, Chronic kidney disease; DPP-4, Dipeptidyl peptidase 4; FU, Follow-up; GFR, Glomerular filtration rate; GLP-1, Glucagon-like peptide 1; HR, Hazard ratio; RASB, Renin-angiotensin system blocker; SGLT2, Sodium glucose cotransporter 2.

Table A-9 Endpoints used, by study

Intervention	Disease	Study_alt	N	KFRT n (%)	Doubling of Scr n (%)	GFR < 15 n (%)	Composite clinical endpoint n (%)	FU clinical endpoint Median (25th, 75th %ile)
RASB vs CONTROL	CKD	AASK	876	130 (14.8)	96 (11.0)	73 (8.3)	171 (19.5)	54 (42, 65)
		Brenner	106	15 (14.2)	13 (12.3)	8 (7.5)	24 (22.6)	30 (10, 37)
		HALT-PKD A	542	1 (0.2)	27 (5.0)	2 (0.4)	27 (5.0)	73 (61, 85)
		HALT-PKD B	462	72 (15.6)	62 (13.4)	41 (8.9)	129 (27.9)	66 (48, 78)
		Hannedouche	98	26 (26.5)	25 (25.5)	14 (14.3)	37 (37.8)	27 (12, 38)
		Hou	224	83 (37.1)	47 (21.0)	5 (2.2)	111 (49.6)	31 (15, 37)
		Ihle/Kincaid	67	15 (22.4)	11 (16.4)	2 (3.0)	23 (34.3)	21 (8, 25)
		Kamper	55	21 (38.2)	9 (16.4)	0 (0.0)	23 (41.8)	29 (18, 37)
		Maschio	562	2 (0.4)	77 (13.7)	51 (9.1)	88 (15.7)	36 (24, 37)
		REIN	322	58 (18.0)	40 (12.4)	34 (10.6)	76 (23.6)	27 (10, 36)
		Toto	122	10 (8.2)	14 (11.5)	8 (6.6)	23 (18.9)	35 (15, 37)
		Van Essen	103	7 (6.8)	10 (9.7)	4 (3.9)	10 (9.7)	45 (31, 50)
	Diabetes	ADVANCE	10876	25 (0.2)	125 (1.1)	43 (0.4)	142 (1.3)	78 (72, 79)
		ALTITUDE	8150	218 (2.7)	427 (5.2)	280 (3.4)	528 (6.5)	39 (27, 45)
		Lewis 1993	407	35 (8.6)	65 (16.0)	33 (8.1)	69 (17.0)	39 (33, 49)
		IDNT	1135	131 (11.5)	231 (20.4)	72 (6.3)	284 (25.0)	31 (23, 42)
		ORIENT	566	101 (17.8)	168 (29.7)	105 (18.6)	201 (35.5)	30 (16, 37)
		RENAAL	1513	338 (22.3)	360 (23.8)	105 (6.9)	488 (32.3)	35 (24, 43)
	Cardiovascular	CHARM-Added	913	0 (0.0)	56 (100.0)	3 (0.3)	56 (6.1)	41 (26, 42)
		PARADIGM-HF	8440	24 (0.3)	271 (3.2)	15 (0.2)	297 (3.5)	28 (20, 37)
	Glomerular	HKVIN	109	3 (2.8)	6 (5.5)	6 (5.5)	8 (7.3)	35 (35, 35)
		IgAN-ACEI	153	18 (11.8)	12 (7.8)	7 (4.6)	23 (15.0)	35 (35, 49)
		Praga 2003	44	15 (34.1)	6 (13.6)	1 (2.3)	15 (34.1)	76 (61, 130)

Table A-9 Endpoints used, by study

Intervention	Disease	Study_alt	N	KFRT n (%)	Doubling of Scr n (%)	GFR < 15 n (%)	Composite clinical endpoint n (%)	FU clinical endpoint Median (25th, 75th %ile)
RASB v CCB	CKD	AASK	652	104 (16.0)	67 (10.3)	49 (7.5)	127 (19.5)	54 (42, 65)
		Zuchelli	121	21 (17.4)	22 (18.2)	10 (8.3)	32 (26.4)	37 (16, 37)
	Diabetes	ABCD	392	0 (0.0)	22 (5.6)	5 (1.3)	22 (5.6)	61 (49, 63)
		IDNT	1128	132 (11.7)	240 (21.3)	79 (7.0)	310 (27.5)	31 (23, 42)
RASB+CCB	Cardiovascular	ACCOMPLISH	11482	81 (0.7)	297 (2.6)	24 (0.2)	326 (2.8)	38 (34, 44)
Immunosuppression	Glomerular	Appel	29	7 (24.1)	0 (0.0)	2 (6.9)	7 (24.1)	15 (9, 27)
		Lewis 1992	79	15 (19.0)	9 (11.4)	8 (10.1)	17 (21.5)	22 (10, 41)
		Donadio 1999	96	16 (16.7)	3 (3.1)	3 (3.1)	17 (17.7)	36 (26, 44)
		Donadio 2001	72	18 (25.0)	8 (11.1)	5 (6.9)	19 (26.4)	27 (19, 38)
		FSGS-FONT	138	26 (18.8)	36 (26.1)	5 (3.6)	49 (35.5)	29 (12, 42)
		IgAN-AZA	243	24 (9.9)	21 (8.6)	13 (5.3)	29 (11.9)	67 (47, 88)
		IgAN-MMF	63	9 (14.3)	2 (3.2)	4 (6.3)	9 (14.3)	30 (15, 45)
		IgAN-steroid	259	20 (7.7)	30 (11.6)	18 (6.9)	30 (11.6)	78 (54, 90)
		Katafuchi	81	5 (6.2)	7 (8.6)	5 (6.2)	7 (8.6)	78 (60, 90)
		Pozzi 2004	83	7 (8.4)	13 (15.7)	8 (9.6)	13 (15.7)	102 (66, 126)
		Pozzi 2010	197	9 (4.6)	14 (7.1)	6 (3.0)	14 (7.1)	73 (53, 91)
		Pozzi 2012	46	15 (32.6)	7 (15.2)	7 (15.2)	15 (32.6)	50 (34, 63)
		Maes	34	2 (5.9)	2 (5.9)	2 (5.9)	2 (5.9)	45 (33, 45)
		Mem-Ponticelli	273	14 (5.1)	31 (11.4)	18 (6.6)	31 (11.4)	37 (25, 61)
		Ponticelli 2006	31	0 (0.0)	1 (3.2)	1 (3.2)	1 (3.2)	25 (16, 28)
		Ponticelli 1989	75	10 (13.3)	19 (25.3)	12 (16.0)	19 (25.3)	138 (60, 138)
		Ponticelli 1992	76	2 (2.6)	8 (10.5)	2 (2.6)	8 (10.5)	25 (19, 43)
		Ponticelli 1998	91	2 (2.2)	3 (3.3)	3 (3.3)	3 (3.3)	43 (25, 55)
		Schena	95	8 (8.4)	10 (10.5)	5 (5.3)	10 (10.5)	66 (42, 78)

Table A-9 Endpoints used, by study

Intervention	Disease	Study_alt	N	KFRT n (%)	Doubling of Scr n (%)	GFR < 15 n (%)	Composite clinical endpoint n (%)	FU clinical endpoint Median (25th, 75th %ile)
		STOP-IgAN	151	7 (4.6)	6 (4.0)	5 (3.3)	13 (8.6)	38 (37, 38)
Low v Usual BP	CKD	AASK	1093	174 (15.9)	120 (11.0)	90 (8.2)	222 (20.3)	53 (41, 65)
		HALT-PKD A	542	1 (0.2)	27 (5.0)	2 (0.4)	27 (5.0)	73 (61, 85)
		MDRD A	584	43 (7.4)	74 (12.7)	45 (7.7)	93 (15.9)	28 (22, 35)
		MDRD B	255	134 (52.5)	63 (24.7)	16 (6.3)	146 (57.3)	27 (18, 39)
		REIN 2	330	71 (21.5)	30 (9.1)	26 (7.9)	84 (25.5)	17 (11, 30)
	Diabetes	ABCD	392	0 (0.0)	22 (5.6)	5 (1.3)	22 (5.6)	61 (49, 63)
	Cardiovascular	SPRINT	8885	20 (0.2)	112 (1.3)	17 (0.2)	128 (1.4)	39 (34, 46)
SGLT-2 Inhibitor	CKD	DAPA-CKD	4041	239 (5.9)	260 (6.4)	213 (5.3)	452 (11.2)	29 (24, 32)
	Diabetes	CANVAS	10031	18 (0.2)	60 (0.6)	14 (0.1)	75 (0.7)	30 (24, 73)
		CREDENCE	4399	281 (6.4)	305 (6.9)	106 (2.4)	383 (8.7)	31 (26, 38)
		EMPA-REG	6936	26 (0.4)	138 (2.0)	25 (0.4)	159 (2.3)	44 (37, 53)
Antiplatelet	Diabetes	SUN-MACRO	1110	21 (1.9)	26 (2.3)	38 (3.4)	64 (5.8)	21 (15, 27)
	Cardiovascular	PEGASUS	17788	0 (0.0)	142 (0.8)	7 (0.0)	142 (0.8)	34 (28, 37)
		PLATO	12688	0 (0.0)	92 (0.7)	15 (0.1)	96 (0.8)	13 (10, 14)
DPP-4 Inhibitor	Diabetes	CARMELINA	6964	284 (4.1)	246 (3.5)	104 (1.5)	421 (6.0)	27 (19, 35)
		CAROLINA	5985	24 (0.4)	56 (0.9)	33 (0.6)	85 (1.4)	76 (72, 80)
		EXAMINE	5380	46 (0.9)	136 (2.5)	15 (0.3)	165 (3.1)	21 (13, 28)
Allopurinol	CKD	CKD-FIX	358	44 (12.3)	31 (8.7)	13 (3.6)	64 (17.9)	25 (22, 25)
		Goicoechea	113	17 (15.0)	29 (25.7)	22 (19.5)	30 (26.5)	66 (36, 90)
GLP-1 Agonist	Diabetes	Harmony Outcomes	8913	22 (0.2)	161 (1.8)	14 (0.2)	183 (2.1)	21 (17, 25)
		LEADER	7533	115 (1.5)	172 (2.3)	99 (1.3)	238 (3.2)	47 (44, 50)
Low v Usual Diet	CKD	MDRD A	584	43 (7.4)	74 (12.7)	45 (7.7)	93 (15.9)	28 (22, 35)
		MDRD B	255	134 (52.5)	63 (24.7)	16 (6.3)	146 (57.3)	27 (18, 39)

Table A-9 Endpoints used, by study

Intervention	Disease	Study_alt	N	KFRT n (%)	Doubling of Scr n (%)	GFR < 15 n (%)	Composite clinical endpoint n (%)	FU clinical endpoint Median (25th, 75th %ile)
Mineralocort. rec. antagonist	Diabetes	FIDELIO-DKD	5671	256 (4.5)	578 (10.2)	366 (6.5)	736 (13.0)	32 (24, 40)
	Cardiovascular	TOPCAT	3435	45 (1.3)	157 (4.6)	13 (0.4)	194 (5.6)	38 (24, 59)
Nurse-coordinated Care	CKD	CanPREVENT	458	3 (0.7)	6 (1.3)	4 (0.9)	8 (1.7)	34 (26, 34)
		MASTERPLAN	640	121 (18.9)	133 (20.8)	50 (7.8)	171 (26.7)	69 (44, 76)
Albuminuria Targeted Protocol	CKD	ROAD	339	58 (17.1)	65 (19.2)	17 (5.0)	85 (25.1)	46 (36, 46)
Intensive Glucose	Diabetes	ADVANCE	10876	25 (0.2)	125 (1.1)	43 (0.4)	142 (1.3)	78 (72, 79)
Endothelin rec. antagonist	Diabetes	SONAR	3659	287 (7.8)	251 (6.9)	145 (4.0)	349 (9.5)	26 (16, 35)
Statin+Ezetimibe	CKD	SHARP	6245	2126 (34.0)	787 (12.6)	491 (7.9)	2494 (39.9)	47 (20, 56)

BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; DPP-4, Dipeptidyl peptidase 4; FU, Follow-up; GFR, Glomerular filtration rate; GLP-1, Glucagon-like peptide 1; KFRT, Kidney failure with replacement therapy; N, Number of patients; n, Number of patients in subset; NA, Not available per study protocol; RASB, Renin-angiotensin system blocker; Scr, Serum creatinine; SGLT2, Sodium glucose cotransporter 2.

Table A-10 Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint overall, adding one new study at a time, and adding both FIDELIO and CREDENCE

Subgroup	N Studies (N interv)	N Patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% CI)	RMSE (95% BCI)
Total slope computed at 3 years						
Overall – new analyses	66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.85, 1.00)	0.04 (0.02, 0.11)
Old and CANVAS	48 (12)	70651 (7194)	-0.43 (-0.55, -0.31)	-0.05 (-0.13, 0.02)	0.97 (0.77, 1.00)	0.06 (0.01, 0.14)
Old and CREDENCE	48 (12)	65019 (7502)	-0.36 (-0.46, -0.25)	-0.07 (-0.15, 0.01)	0.93 (0.66, 1.00)	0.08 (0.02, 0.16)
Old and EXAMINE	48 (13)	65997 (7281)	-0.43 (-0.55, -0.32)	-0.05 (-0.12, 0.02)	0.97 (0.82, 1.00)	0.05 (0.02, 0.12)
Old and FIDELIO	48 (13)	66291 (7855)	-0.44 (-0.56, -0.31)	-0.03 (-0.11, 0.03)	0.98 (0.82, 1.00)	0.05 (0.02, 0.12)
Old and CARMELINA	48 (13)	67584 (7540)	-0.43 (-0.55, -0.31)	-0.05 (-0.12, 0.02)	0.97 (0.81, 1.00)	0.05 (0.01, 0.13)
Old and CAROLINA	48 (13)	66605 (7204)	-0.44 (-0.57, -0.32)	-0.03 (-0.11, 0.04)	0.98 (0.79, 1.00)	0.05 (0.01, 0.14)
Old and DAPA	48 (12)	64661 (7571)	-0.42 (-0.53, -0.31)	-0.04 (-0.13, 0.02)	0.97 (0.80, 1.00)	0.05 (0.02, 0.13)
Old and SPRINT	48 (12)	69505 (7247)	-0.42 (-0.52, -0.32)	-0.05 (-0.12, 0.01)	0.97 (0.84, 1.00)	0.06 (0.01, 0.14)
Old and TOPCAT	48 (13)	64055 (7311)	-0.44 (-0.56, -0.34)	-0.04 (-0.11, 0.03)	0.98 (0.85, 1.00)	0.05 (0.02, 0.13)
Old and Harmony	48 (13)	69533 (7304)	-0.43 (-0.55, -0.30)	-0.04 (-0.12, 0.04)	0.96 (0.74, 1.00)	0.06 (0.02, 0.15)
Old and LEADER	48 (13)	68153 (7357)	-0.43 (-0.56, -0.31)	-0.05 (-0.13, 0.03)	0.97 (0.78, 1.00)	0.06 (0.01, 0.13)
Old and ACCOMPLISH	48 (13)	72102 (7445)	-0.37 (-0.46, -0.28)	-0.06 (-0.14, 0.01)	0.96 (0.78, 1.00)	0.06 (0.02, 0.14)
Old and PARADIGM	48 (12)	69060 (7416)	-0.44 (-0.56, -0.32)	-0.04 (-0.12, 0.03)	0.98 (0.83, 1.00)	0.05 (0.01, 0.12)
Old and FONT	48 (12)	60758 (7168)	-0.44 (-0.56, -0.33)	-0.04 (-0.11, 0.03)	0.98 (0.83, 1.00)	0.05 (0.02, 0.12)
Old and PEGASUS	48 (12)	78402 (7261)	-0.43 (-0.55, -0.31)	-0.05 (-0.13, 0.02)	0.98 (0.81, 1.00)	0.05 (0.02, 0.13)
Old and CHARMAdd	48 (12)	61533 (7175)	-0.42 (-0.55, -0.31)	-0.05 (-0.13, 0.02)	0.97 (0.82, 1.00)	0.05 (0.02, 0.13)
Old and PLATO	48 (12)	73299 (7215)	-0.45 (-0.58, -0.33)	-0.03 (-0.11, 0.04)	0.98 (0.82, 1.00)	0.05 (0.01, 0.13)
Old and CKDFIX	48 (12)	60978 (7183)	-0.44 (-0.56, -0.31)	-0.04 (-0.12, 0.03)	0.97 (0.78, 1.00)	0.06 (0.02, 0.14)
Old and SONAR	48 (13)	64279 (7468)	-0.44 (-0.56, -0.32)	-0.04 (-0.12, 0.03)	0.98 (0.83, 1.00)	0.05 (0.01, 0.12)
Old and FIDELIO and CREDENCE	49 (13)	70690 (8238)	-0.36 (-0.46, -0.25)	-0.06 (-0.14, 0.01)	0.94 (0.71, 1.00)	0.07 (0.02, 0.14)
Total slope computed at 2 years						
Overall – new analyses	66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.89 (0.68, 0.98)	0.09 (0.04, 0.17)
Old and CANVAS	48 (12)	70651 (7194)	-0.30 (-0.42, -0.17)	-0.15 (-0.23, -0.07)	0.81 (0.43, 0.96)	0.13 (0.06, 0.21)
Old and CREDENCE	48 (12)	65019 (7502)	-0.30 (-0.41, -0.19)	-0.13 (-0.21, -0.05)	0.85 (0.51, 0.98)	0.11 (0.04, 0.20)
Old and EXAMINE	48 (13)	65997 (7281)	-0.31 (-0.43, -0.20)	-0.13 (-0.21, -0.05)	0.85 (0.52, 0.97)	0.11 (0.05, 0.20)
Old and FIDELIO	48 (13)	66291 (7855)	-0.31 (-0.43, -0.19)	-0.13 (-0.21, -0.06)	0.85 (0.52, 0.98)	0.11 (0.04, 0.19)
Old and CARMELINA	48 (13)	67584 (7540)	-0.31 (-0.42, -0.20)	-0.13 (-0.21, -0.05)	0.85 (0.54, 0.97)	0.11 (0.05, 0.19)
Old and CAROLINA	48 (13)	66605 (7204)	-0.31 (-0.43, -0.20)	-0.12 (-0.20, -0.04)	0.84 (0.49, 0.98)	0.12 (0.04, 0.21)
Old and DAPA	48 (12)	64661 (7571)	-0.31 (-0.43, -0.20)	-0.13 (-0.21, -0.05)	0.85 (0.53, 0.98)	0.11 (0.05, 0.19)

Table A-10 Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint overall, adding one new study at a time, and adding both FIDELIO and CREDENCE

Subgroup	N Studies (N interv)	N Patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% CI)	RMSE (95% BCI)
Old and SPRINT	48 (12)	69505 (7247)	-0.31 (-0.41, -0.22)	-0.13 (-0.21, -0.05)	0.89 (0.64, 0.98)	0.11 (0.05, 0.20)
Old and TOPCAT	48 (13)	64055 (7311)	-0.32 (-0.42, -0.23)	-0.12 (-0.20, -0.05)	0.89 (0.64, 0.99)	0.11 (0.04, 0.19)
Old and Harmony	48 (13)	69533 (7304)	-0.31 (-0.44, -0.19)	-0.12 (-0.21, -0.04)	0.83 (0.46, 0.98)	0.12 (0.04, 0.21)
Old and LEADER	48 (13)	68153 (7357)	-0.31 (-0.43, -0.19)	-0.13 (-0.21, -0.05)	0.86 (0.53, 0.98)	0.11 (0.05, 0.19)
Old and ACCOMPLISH	48 (13)	72102 (7445)	-0.25 (-0.34, -0.16)	-0.14 (-0.23, -0.07)	0.80 (0.47, 0.97)	0.13 (0.04, 0.21)
Old and PARADIGM	48 (12)	69060 (7416)	-0.31 (-0.43, -0.19)	-0.13 (-0.21, -0.05)	0.85 (0.51, 0.98)	0.11 (0.05, 0.20)
Old and FONT	48 (12)	60758 (7168)	-0.31 (-0.43, -0.20)	-0.12 (-0.21, -0.04)	0.85 (0.54, 0.97)	0.12 (0.05, 0.20)
Old and PEGASUS	48 (12)	78402 (7261)	-0.31 (-0.42, -0.19)	-0.13 (-0.21, -0.06)	0.85 (0.53, 0.98)	0.11 (0.05, 0.19)
Old and CHARMAdd	48 (12)	61533 (7175)	-0.29 (-0.40, -0.19)	-0.14 (-0.22, -0.07)	0.85 (0.52, 0.97)	0.12 (0.05, 0.20)
Old and PLATO	48 (12)	73299 (7215)	-0.33 (-0.45, -0.21)	-0.12 (-0.20, -0.04)	0.85 (0.57, 0.97)	0.12 (0.05, 0.20)
Old and CKDFIX	48 (12)	60978 (7183)	-0.32 (-0.44, -0.20)	-0.12 (-0.21, -0.04)	0.85 (0.52, 0.97)	0.12 (0.05, 0.20)
Old and SONAR	48 (13)	64279 (7468)	-0.31 (-0.43, -0.20)	-0.13 (-0.21, -0.05)	0.86 (0.53, 0.98)	0.11 (0.04, 0.19)
Old and FIDELIO and CREDENCE	49 (13)	70690 (8238)	-0.29 (-0.40, -0.19)	-0.13 (-0.21, -0.06)	0.84 (0.55, 0.97)	0.11 (0.05, 0.19)
Chronic slope						
Overall – new analyses	66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
Old and CANVAS	48 (12)	70651 (7194)	-0.46 (-0.62, -0.30)	0.02 (-0.10, 0.12)	0.95 (0.58, 1.00)	0.06 (0.01, 0.17)
Old and CREDENCE	48 (12)	65019 (7502)	-0.27 (-0.41, -0.14)	-0.08 (-0.19, 0.03)	0.66 (0.24, 0.95)	0.13 (0.04, 0.22)
Old and EXAMINE	48 (13)	65997 (7281)	-0.44 (-0.62, -0.28)	0.00 (-0.10, 0.10)	0.94 (0.60, 1.00)	0.06 (0.01, 0.15)
Old and FIDELIO	48 (13)	66291 (7855)	-0.34 (-0.52, -0.17)	-0.04 (-0.17, 0.08)	0.67 (0.25, 0.91)	0.13 (0.07, 0.23)
Old and CARMELINA	48 (13)	67584 (7540)	-0.47 (-0.63, -0.31)	0.02 (-0.07, 0.11)	0.96 (0.67, 1.00)	0.05 (0.01, 0.14)
Old and CAROLINA	48 (13)	66605 (7204)	-0.47 (-0.64, -0.32)	0.03 (-0.07, 0.12)	0.95 (0.65, 1.00)	0.05 (0.02, 0.15)
Old and DAPA	48 (12)	64661 (7571)	-0.37 (-0.52, -0.23)	-0.02 (-0.13, 0.09)	0.86 (0.45, 0.99)	0.09 (0.02, 0.18)
Old and SPRINT	48 (12)	69505 (7247)	-0.49 (-0.66, -0.34)	0.04 (-0.06, 0.13)	0.97 (0.69, 1.00)	0.05 (0.01, 0.16)
Old and TOPCAT	48 (13)	64055 (7311)	-0.50 (-0.67, -0.32)	0.04 (-0.08, 0.15)	0.90 (0.51, 0.99)	0.09 (0.02, 0.20)
Old and Harmony	48 (13)	69533 (7304)	-0.44 (-0.62, -0.26)	0.02 (-0.11, 0.13)	0.89 (0.44, 0.99)	0.08 (0.02, 0.19)
Old and LEADER	48 (13)	68153 (7357)	-0.46 (-0.63, -0.31)	0.02 (-0.08, 0.12)	0.96 (0.67, 1.00)	0.05 (0.01, 0.13)
Old and ACCOMPLISH	48 (13)	72102 (7445)	-0.44 (-0.63, -0.24)	-0.03 (-0.16, 0.09)	0.78 (0.32, 0.98)	0.12 (0.04, 0.21)
Old and PARADIGM	48 (12)	69060 (7416)	-0.46 (-0.63, -0.29)	0.01 (-0.10, 0.11)	0.94 (0.61, 1.00)	0.06 (0.02, 0.15)
Old and FONT	48 (12)	60758 (7168)	-0.48 (-0.64, -0.31)	0.03 (-0.08, 0.13)	0.96 (0.64, 1.00)	0.05 (0.02, 0.15)
Old and PEGASUS	48 (12)	78402 (7261)	-0.43 (-0.60, -0.27)	0.00 (-0.11, 0.09)	0.93 (0.55, 1.00)	0.07 (0.02, 0.17)
Old and CHARMAdd	48 (12)	61533 (7175)	-0.46 (-0.63, -0.30)	0.02 (-0.08, 0.11)	0.96 (0.67, 1.00)	0.05 (0.01, 0.14)

Table A-10 Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint overall, adding one new study at a time, and adding both FIDELIO and CREDENCE

Subgroup	N Studies (N interv)	N Patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% CI)	RMSE (95% BCI)
Old and PLATO	48 (12)	73299 (7215)	-0.49 (-0.65, -0.33)	0.04 (-0.06, 0.13)	0.97 (0.70, 1.00)	0.04 (0.01, 0.15)
Old and CKDFIX	48 (12)	60978 (7183)	-0.47 (-0.63, -0.30)	0.03 (-0.08, 0.12)	0.96 (0.62, 1.00)	0.05 (0.01, 0.16)
Old and SONAR	48 (13)	64279 (7468)	-0.46 (-0.63, -0.31)	0.02 (-0.08, 0.12)	0.97 (0.65, 1.00)	0.05 (0.02, 0.15)
Old and FIDELIO and CREDENCE	49 (13)	70690 (8238)	-0.24 (-0.38, -0.12)	-0.09 (-0.20, 0.02)	0.57 (0.18, 0.85)	0.14 (0.07, 0.23)

[a] Number of patients based on Cox model sample size.

BCI, Bayesian credible interval; CI, Confidence interval; GFR, Glomerular filtration rate; N, Number; RMSE, Root mean square deviation.

Table A-11 Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint by sensitivity for excluding the 3 outliers

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Total slope computed at 3 years						
Main analysis – all studies	66 (17)	187305 (11555)	-0.35 (-0.42, -0.28)	-0.04 (-0.09, 0.01)	0.98 (0.85, 1.00)	0.04 (0.02, 0.11)
Exclude outliers	63 (16)	177235 (10436)	-0.35 (-0.41, -0.29)	-0.03 (-0.08, 0.01)	0.98 (0.90, 1.00)	0.04 (0.01, 0.09)
Total slope computed at 2 years						
Main analysis – all studies	66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.89 (0.68, 0.98)	0.09 (0.04, 0.17)
Exclude outliers	63 (16)	177235 (10436)	-0.26 (-0.32, -0.20)	-0.10 (-0.16, -0.06)	0.92 (0.74, 0.99)	0.08 (0.03, 0.14)
Chronic slope						
Main analysis – all studies	66 (17)	187305 (11555)	-0.32 (-0.45, -0.20)	0.00 (-0.10, 0.10)	0.56 (0.25, 0.78)	0.18 (0.12, 0.26)
Exclude outliers	63 (16)	177235 (10436)	-0.33 (-0.45, -0.21)	0.00 (-0.08, 0.10)	0.63 (0.32, 0.83)	0.16 (0.10, 0.24)

[a] Number of patients based on Cox model sample size.

BCI, Bayesian credible interval; GFR, Glomerular filtration rate; N, Number; RMSE, Root mean square deviation.

Table A-12 Analysis of outliers in trial level meta-regression – Total slope computed at 2 years

Trial Name	Estimation of outlier		Meta-regression results removing individual outlier study			Study characteristics				
	Observed log HR (SE)	Estimated log HR from PPD median (95% CI)	Intercept	Slope	R^2	AE	Disease	Intervention	Mean GFR	Progression rate
AASK (CCB)	-0.36 (0.18)	0.07 (-0.28, 0.43)	-0.1 (-0.15, -0.05)	-0.27 (-0.33, -0.21)	0.92 (0.73, 0.99)	N	CKD	RASB v CCB	<60	Fast
CANVAS	-0.56 (0.23)	-0.05 (-0.53, 0.44)	-0.1 (-0.15, -0.05)	-0.27 (-0.34, -0.21)	0.9 (0.71, 0.98)	N	DM	SGLT2I	>=60	Slow
CAROLINA	0.3 (0.22)	-0.16 (-0.63, 0.3)	-0.11 (-0.16, -0.06)	-0.27 (-0.33, -0.21)	0.89 (0.69, 0.98)	P	DM	DPP4I	>=60	Slow
Donadio 1999	-1.97 (0.65)	-0.64 (-1.91, 0.63)	-0.11 (-0.16, -0.06)	-0.27 (-0.33, -0.2)	0.89 (0.67, 0.98)	P	GN	IS	>=60	Fast
EMPA-REG	-0.68 (0.16)	-0.3 (-0.67, 0.05)	-0.1 (-0.15, -0.05)	-0.26 (-0.32, -0.2)	0.91 (0.71, 0.99)	N	DM	SGLT2I	>=60	Slow
Harmony	0.12 (0.15)	-0.2 (-0.56, 0.14)	-0.11 (-0.16, -0.06)	-0.27 (-0.33, -0.21)	0.9 (0.71, 0.99)	N	DM	GLP-1A	>=60	Slow
IDNT (CCB)	-0.44 (0.12)	-0.15 (-0.44, 0.13)	-0.1 (-0.15, -0.05)	-0.27 (-0.33, -0.21)	0.92 (0.73, 0.99)	N	DM	RASB v CCB	<60	Fast
Maschio	-0.79 (0.22)	-0.37 (-0.78, 0.02)	-0.1 (-0.15, -0.05)	-0.26 (-0.32, -0.2)	0.91 (0.71, 0.99)	N	CKD	RASB vs CONTROL	<60	Fast
ROAD	-0.72 (0.23)	-0.23 (-0.64, 0.19)	-0.1 (-0.15, -0.05)	-0.27 (-0.33, -0.21)	0.92 (0.73, 0.99)	P	CKD	Alb protocol	<60	Fast

Study characteristics, each study is described by category of acute effect based on median estimated treatment effect on the acute phase, disease and intervention category, mean level of GFR at baseline and rate of progression in the control arm. Mean GFR is expressed in ml/min per 1.73 m^2. A fast progression rate is defined as a chronic GFR slope less than or equal to -2.6 ml/min per 1.73m^2 in the control arm and a slow progression rate is a chronic GFR slope greater than -2.6 ml/min per 1.73m^2 in the control arm.

AE, Acute effects (N, negative; P, positive); Alb, Albumin; BCI, Bayesian credible interval; CI, Credible interval; CCB, Calcium channel blocker; CKD, Chronic kidney disease; DM, Diabetes mellitus; DPP4I, DPP4 inhibitor; EMPA-REG, EMPA-REG Outcomes; FSGS, Focal segmental glomerulosclerosis; GFR, Glomerular filtration rate; GN, Glomerulonephritis; Harmony, Harmony Outcomes; HR, hazard ratio; IgA, Immunoglobulin A; IS, Immunosuppression; MMF, Mycophenolate mofetil; PPD, Posterior predictive distribution; RASB, Renin angiotensin system blocker; SE, Standard error; SGLT2I, Sodium-glucose cotransporter-2 inhibitor.

Table A-13 Trial level analyses for the association between treatment effects on GFR slope over 2 years and treatment effects on the clinical endpoint by subgroups

Group	Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies		66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.89 (0.68, 0.98)	0.09 (0.04, 0.17)
GFR	< 60	40 (14)	53725 (8784)	-0.25 (-0.41, -0.07)	-0.12 (-0.21, -0.04)	0.64 (0.07, 0.95)	0.08 (0.03, 0.16)
	≥ 60	26 (11)	133580 (2771)	-0.27 (-0.35, -0.20)	-0.07 (-0.18, 0.02)	0.94 (0.66, 1.00)	0.11 (0.02, 0.27)
Progression rate in control arm	<=-2.6	38 (12)	48733 (6005)	-0.27 (-0.38, -0.14)	-0.14 (-0.22, -0.07)	0.92 (0.52, 1.00)	0.06 (0.02, 0.15)
	>-2.6	28 (14)	138572 (5550)	-0.24 (-0.32, -0.17)	-0.04 (-0.12, 0.03)	0.93 (0.55, 1.00)	0.07 (0.01, 0.21)
Disease	Diabetes	21 (10)	102013 (5065)	-0.30 (-0.45, -0.14)	-0.12 (-0.20, -0.05)	0.82 (0.20, 0.99)	0.07 (0.02, 0.20)
	Glomerular	10 (2)	1527 (237)	-0.27 (-0.48, -0.12)	-0.17 (-0.52, 0.24)	0.99 (0.51, 1.00)	0.06 (0.01, 0.45)
	Other CKD	28 (9)	20149 (5016)	-0.23 (-0.49, 0.03)	-0.13 (-0.29, 0.01)	0.60 (0.01, 0.97)	0.10 (0.03, 0.22)
	CVD	7 (5)	63616 (1237)	-0.24 (-0.31, -0.15)	0.00 (-0.13, 0.12)	0.99 (0.70, 1.00)	0.05 (0.01, 0.21)

[a] Number of patients based on Cox model sample size.

GFR and progression rate in control arm units are ml/min per $1.73m^2$.

BCI, Bayesian credible interval; CKD, Chronic kidney disease; CVD, Cardiovascular disease; GFR, Glomerular filtration rate; N, Number; RMSE, Root mean square error.

Table A-14 Trial level analyses for the association between treatment effects on GFR slope over 2 years and treatment effects on the clinical endpoint by baseline ACR

Subgroup	N Studies (N Interv)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.89 (0.68, 0.98)	0.09 (0.04, 0.17)
Restricted to studies with ACR available	55 (14)	90287 (7321)	-0.30 (-0.39, -0.21)	-0.13 (-0.20, -0.08)	0.92 (0.62, 0.99)	0.08 (0.02, 0.17)
Restricted to participants with ACR >30 mg/g	55 (14)	58059 (6946)	-0.30 (-0.42, -0.18)	-0.12 (-0.19, -0.05)	0.91 (0.55, 0.99)	0.07 (0.02, 0.15)

[a] Number of patients based on Cox model sample size.
ACR, albumin:creatinine ratio; BCI, Bayesian credible interval; GFR, glomerular filtration rate; N, Number; RMSE, root mean square error.

Table A-15 Trial level analyses for the association between treatment effects on GFR slope computed at 2 years and treatment effects on the clinical endpoint by sensitivity excluding disease groups and interventions

Subgroup	N Studies (N Interv)[a]	N patients[b] (N events)[a]	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
Main analysis – all studies	66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.89 (0.68, 0.98)	0.098 (0.04, 0.17)
Exclude:						
GN	56 (16)	185778 (11318)	-0.26 (-0.33, -0.19)	-0.11 (-0.16, -0.06)	0.84 (0.55, 0.97)	0.10 (0.04, 0.17)
CVD	59 (16)	123689 (10318)	-0.30 (-0.40, -0.19)	-0.12 (-0.18, -0.05)	0.82 (0.47, 0.97)	0.10 (0.05, 0.18)
HF	63 (17)	174517 (11010)	-0.26 (-0.34, -0.19)	-0.11 (-0.17, -0.06)	0.86 (0.60, 0.97)	0.10 (0.04, 0.18)
High CV risk	62 (16)	136477 (10863)	-0.30 (-0.39, -0.21)	-0.11 (-0.17, -0.06)	0.88 (0.62, 0.98)	0.09 (0.04, 0.16)
RASB vs CCB	62 (16)	185012 (11064)	-0.27 (-0.33, -0.21)	-0.09 (-0.14, -0.05)	0.94 (0.77, 0.99)	0.07 (0.02, 0.14)
RASB vs CONTROL	45 (16)	151613 (8725)	-0.25 (-0.34, -0.17)	-0.12 (-0.19, -0.05)	0.79 (0.46, 0.95)	0.13 (0.06, 0.23)
Immunosuppression	57 (16)	185931 (11341)	-0.26 (-0.33, -0.19)	-0.11 (-0.16, -0.06)	0.84 (0.59, 0.97)	0.10 (0.04, 0.17)
Low v Usual BP	59 (16)	175224 (10833)	-0.27 (-0.35, -0.20)	-0.11 (-0.18, -0.05)	0.82 (0.55, 0.96)	0.12 (0.06, 0.20)
Low v Usual Diet	64 (16)	186466 (11316)	-0.27 (-0.34, -0.21)	-0.11 (-0.17, -0.07)	0.89 (0.68, 0.98)	0.10 (0.04, 0.17)
Allopurinol	64 (16)	186834 (11461)	-0.26 (-0.33, -0.20)	-0.11 (-0.17, -0.06)	0.87 (0.64, 0.98)	0.10 (0.04, 0.17)
Antiplatelet	63 (16)	155734 (11253)	-0.27 (-0.33, -0.20)	-0.11 (-0.17, -0.06)	0.88 (0.67, 0.98)	0.10 (0.04, 0.17)
Nurse-coordinated care	64 (16)	186207 (11376)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.88 (0.66, 0.97)	0.10 (0.05, 0.17)
SGLT-2 Inhibitor	62 (16)	161898 (10486)	-0.27 (-0.33, -0.20)	-0.09 (-0.15, -0.04)	0.91 (0.71, 0.99)	0.09 (0.02, 0.16)
DPP-4 Inhibitor	63 (16)	168979 (10887)	-0.27 (-0.34, -0.20)	-0.12 (-0.17, -0.06)	0.87 (0.65, 0.97)	0.11 (0.04, 0.18)
Mineralocort. rec. antagonist	64 (16)	178199 (10627)	-0.26 (-0.33, -0.19)	-0.11 (-0.17, -0.06)	0.86 (0.62, 0.97)	0.10 (0.04, 0.18)
GLP-1 Agonist	64 (16)	170859 (11132)	-0.27 (-0.33, -0.21)	-0.11 (-0.17, -0.06)	0.90 (0.70, 0.99)	0.09 (0.03, 0.16)

[a] N studies and N patients included in respective analysis after excluding the intervention shown in lefthand column.

[b] Number of patients based on Cox model sample size.

BCI, Bayesian credible interval; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; GN, glomerulonephritis; HF, heart failure; RASB, renin-angiotensin system blocker; RMSE, root mean square error; SGLT-2, sodium-glucose cotransporter 2.

Table A-16 Trial level analyses for the association between treatment effects on GFR slope over 2 years and treatment effects on the clinical endpoint by sensitivity for priors

Subgroup	N Studies (N Interventions)	N patients[a] (N events)	Meta-regression slope (95% BCI)	Intercept (95% BCI)	R^2 (95% BCI)	RMSE (95% BCI)
More sensitive prior	66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.89 (0.68, 0.98)	0.09 (0.04, 0.17)
Less sensitive prior	66 (17)	187305 (11555)	-0.27 (-0.33, -0.21)	-0.11 (-0.16, -0.06)	0.87 (0.65, 0.97)	0.10 (0.05, 0.18)

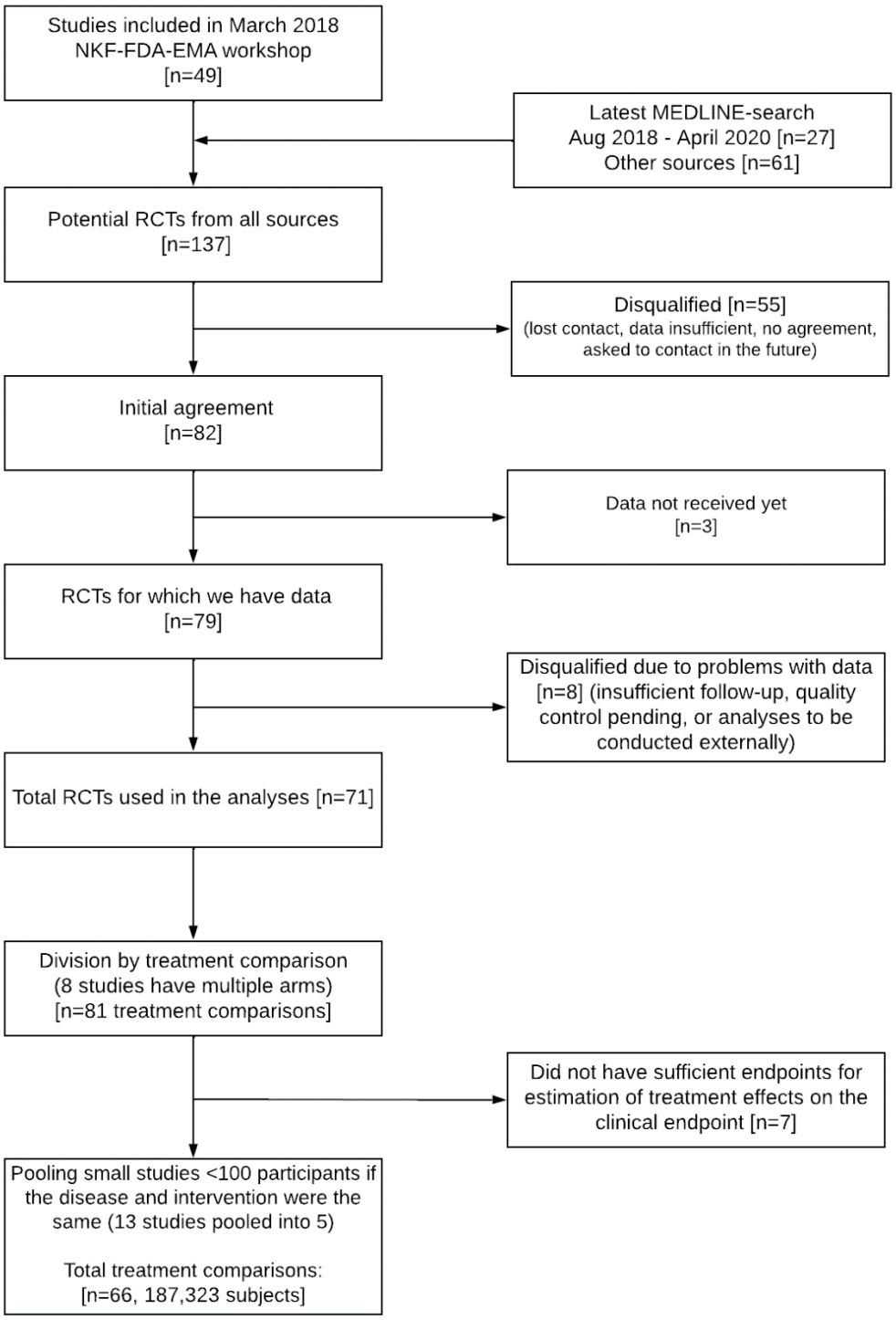
[a] Number of patients based on Cox model sample size.
BCI, Bayesian credible interval; GFR, glomerular filtration rate; RMSE, root mean square error.

Table A-17 Models used across the set of studies

Shared parameter (accounting for informative censoring	Kappa (accounting for heterogeneity in the treatment arms)	Power of the means (accounting for heterogeneity high vs low GFR)	Number of trials
Yes	Yes	Subject specific	41
Yes	No	Subject specific	4
Yes	Yes	No	1
Yes	Yes	Group mean GFR	5
No	No	No	5
No	Yes	Group mean GFR	1
No	Yes	Subject specific	9

GFR, Glomerular filtration rate.

Figure A-1 Flow diagram of studies included in trial-level analyses



EMA, European Medicines Agency; FDA, Food and Drug Administration; n, Number; NKF, National Kidney Foundation; RCTs, Randomized clinical trials.

Figure A-2 Evaluation of bias in studies

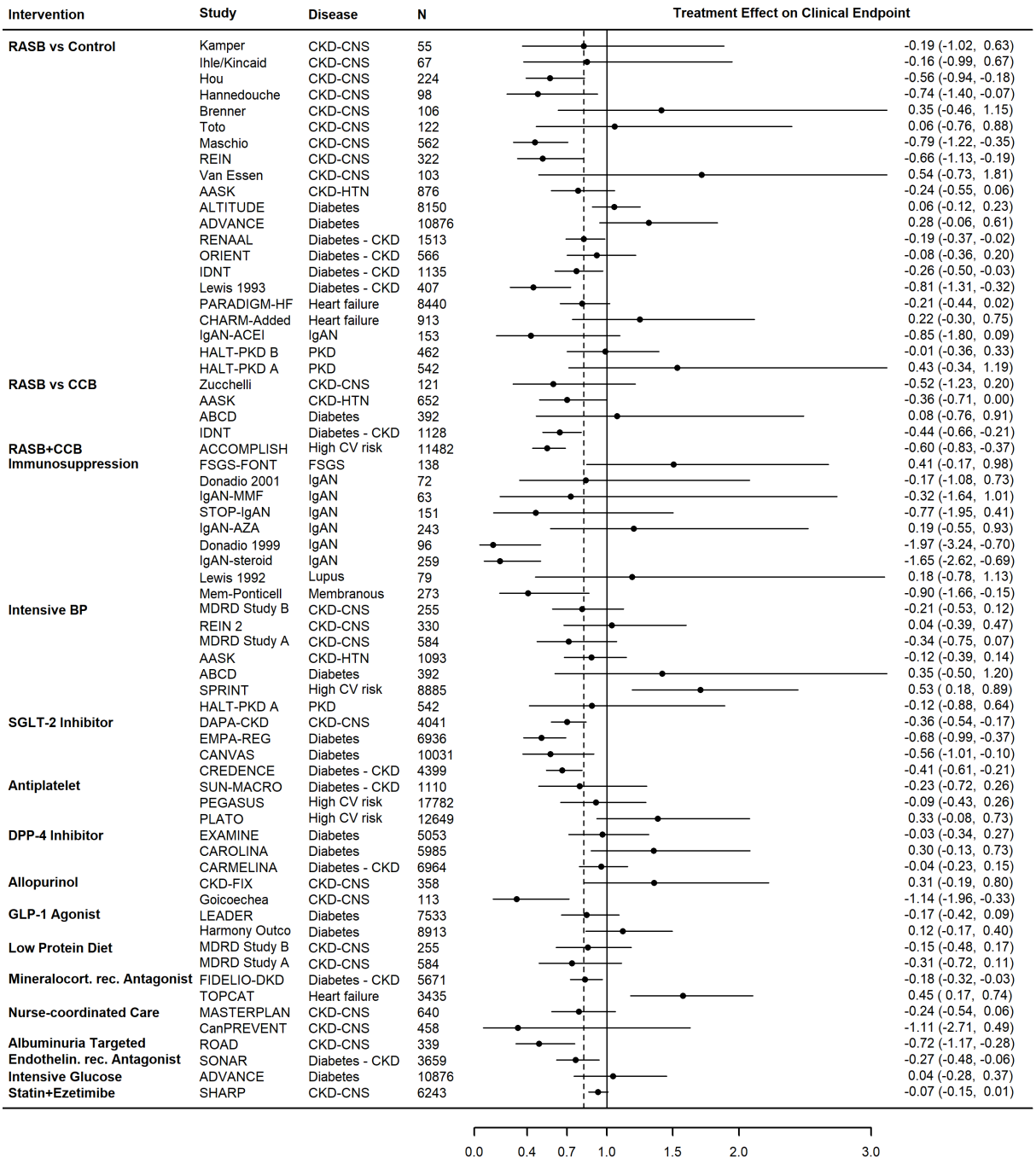
	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AASK	?	?	+	+	+	+
ABCD	?	?	+	+	+	+
ACCOMPLISH	+	+	+	+	+	+
ADVANCE	+	+	+	+	+	+
ALTITUDE	+	+	+	+	+	+
Appel	+	+	+	+	+	+
Brenner	+	?	+	+	-	+
CanPREVENT	-	+	-	+	?	+
CANVAS	+	+	+	+	+	+
CARMELINA	+	+	+	+	+	+
CAROLINA	+	+	+	+	+	?
Chan	+	?	-	+	+	+
CHARM-Added	+	?	+	+	+	?
CKD-FIX	+	+	+	+	+	+
CREDENCE	+	+	+	+	+	+
DAPA-CKD	+	+	+	+	+	+
Donadio 1999	?	?	-	+	?	+
Donadio 2001	-	-	-	+	+	+
EMPA-REG	+	?	+	+	+	+
EXAMINE	?	?	+	+	+	+
FIDELIO-DKD	?	+	+	+	+	+
FSGS/FONT	+	-	+	+	+	+
Goicoechea	+	?	-	+	+	+
HALT A	+	+	+	+	+	+
HALT B	+	?	+	+	+	+
Hannedouche	+	?	-	+	?	+
Harmony	+	+	+	+	+	?
HKVIN	+	+	+	+	+	+
Hou	+	+	+	+	+	+
IDNT	+	?	+	+	+	+
Ihle/Kincaid	?	?	+	+	+	+
Kamper	+	+	-	+	?	+
Katafuchi	-	?	-	-	+	+
LEADER	+	+	+	+	+	+
Lewis 1992	+	+	?	?	+	+
Lewis 1993	+	?	+	+	+	+
Maes	?	?	-	+	+	+
Maschio	?	?	+	+	+	+
MASTERPLAN	+	?	-	-	?	+

MDRD	+	+	-	+	?	+
ORIENT	?	?	+	+	?	+
PARADIGM-HF	+	+	+	+	+	?
PEGASUS	+	+	+	+	+	?
PLATO	?	?	+	?	+	+
Ponticelli 1989	+	+	-	+	+	+
Ponticelli 1992	?	?	?	+	+	+
Ponticelli 1998	+	?	-	+	+	+
Ponticelli 2006	+	+	?	?	+	+
Pozzi 2004	+	?	-	+	+	+
Pozzi 2010	+	?	-	+	?	+
Pozzi 2012	?	?	-	+	+	+
Praga 2003	+	+	-	+	+	+
Praga 2007	+	+	-	+	+	+
REIN	?	?	+	+	+	+
REIN 2	+	+	-	-	+	+
RENAAL	+	+	+	+	+	+
ROAD	+	+	-	+	+	+
Schena	+	+	-	+	+	+
SHARP	+	+	+	+	+	+
SONAR	+	+	+	+	+	+
SPRINT	?	-	-	+	+	+
STOP-IgAN	+	?	-	+	+	+
SUN-MACRO	+	?	+	+	+	+
TOPCAT	+	+	+	+	+	+
Toto	?	?	?	?	+	+
Van Essen	?	?	+	+	+	+
Zuchelli	?	?	?	+	+	+

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

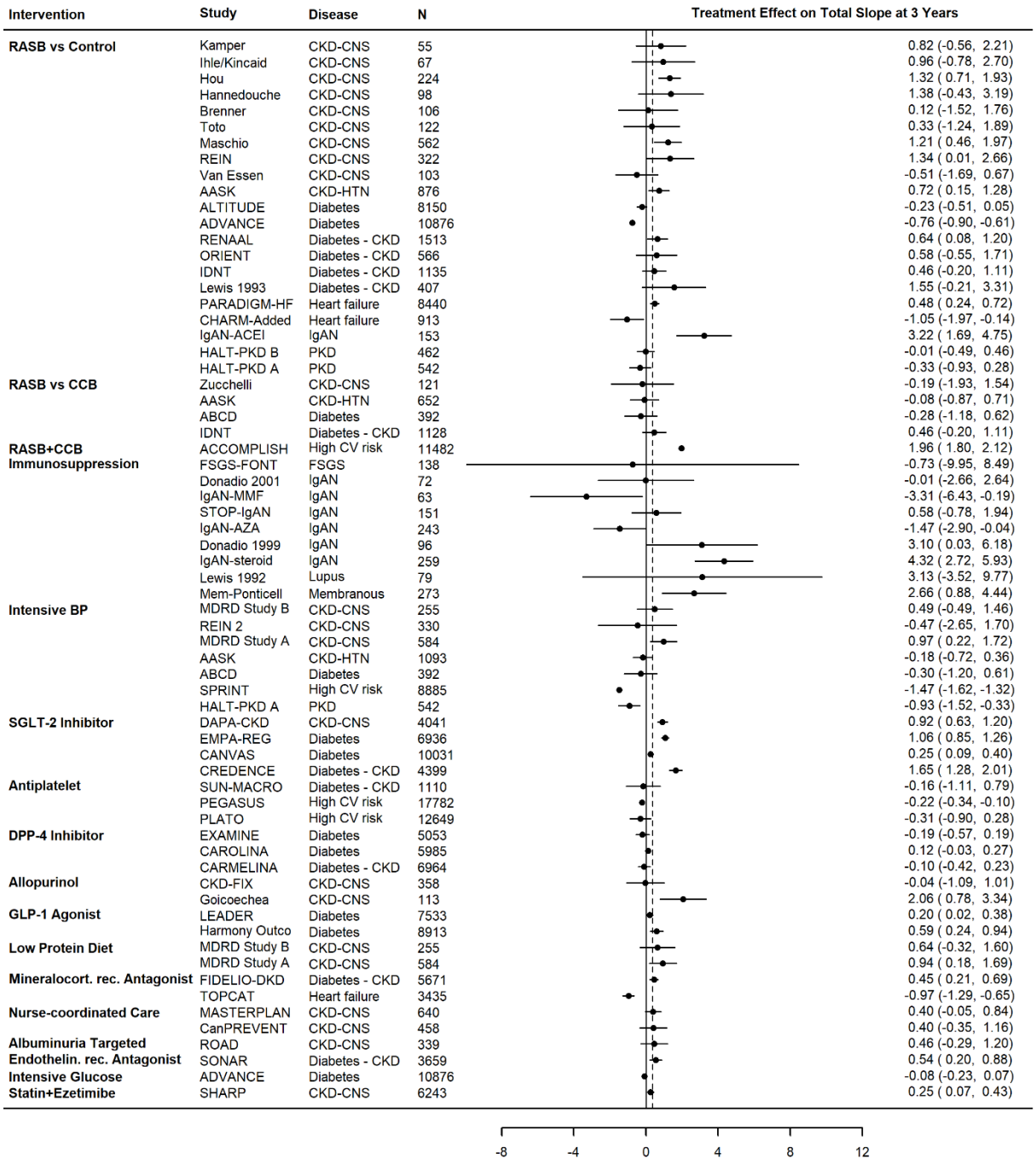
Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration. The tool includes these components: sequence generation (i.e. computer-generated random number, use of random number table or other truly random process); allocation concealment (i.e. web-based or telephone 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 Handbook.

Figure A-3 Treatment effect on the clinical endpoint



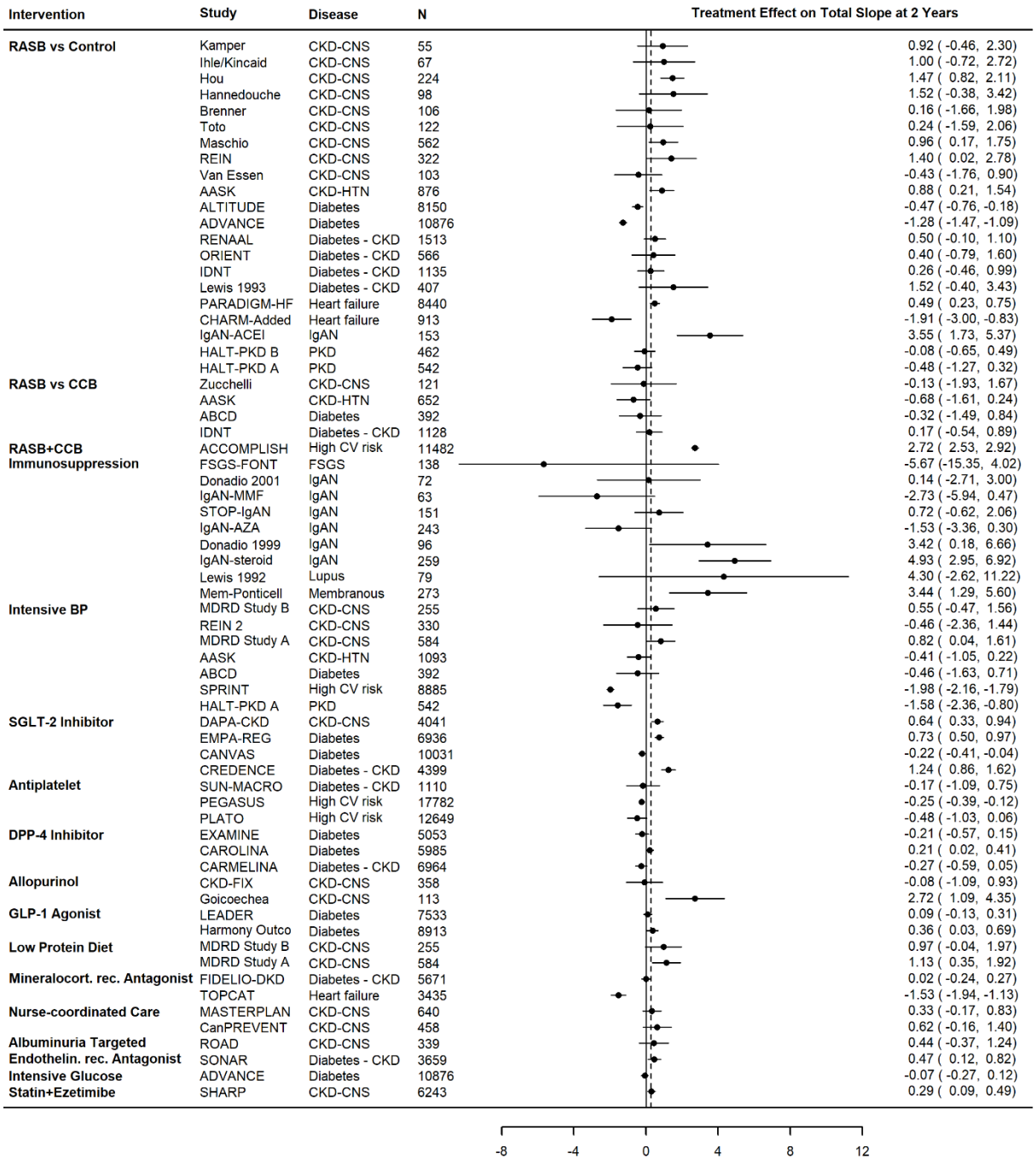
BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; CNS, Cause not specified; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; GLP-1, Glucagon-like peptide 1; HTN, Hypertension; IgAN, Immunoglobulin A nephropathy; N, Number of patients; PKD, Polycystic kidney disease; RASB, Renin-angiotensin system blocker; rec, Receptor; SGLT-2, Sodium glucose cotransporter 2.

Figure A-4 Treatment effect on total slope computed at 3 years



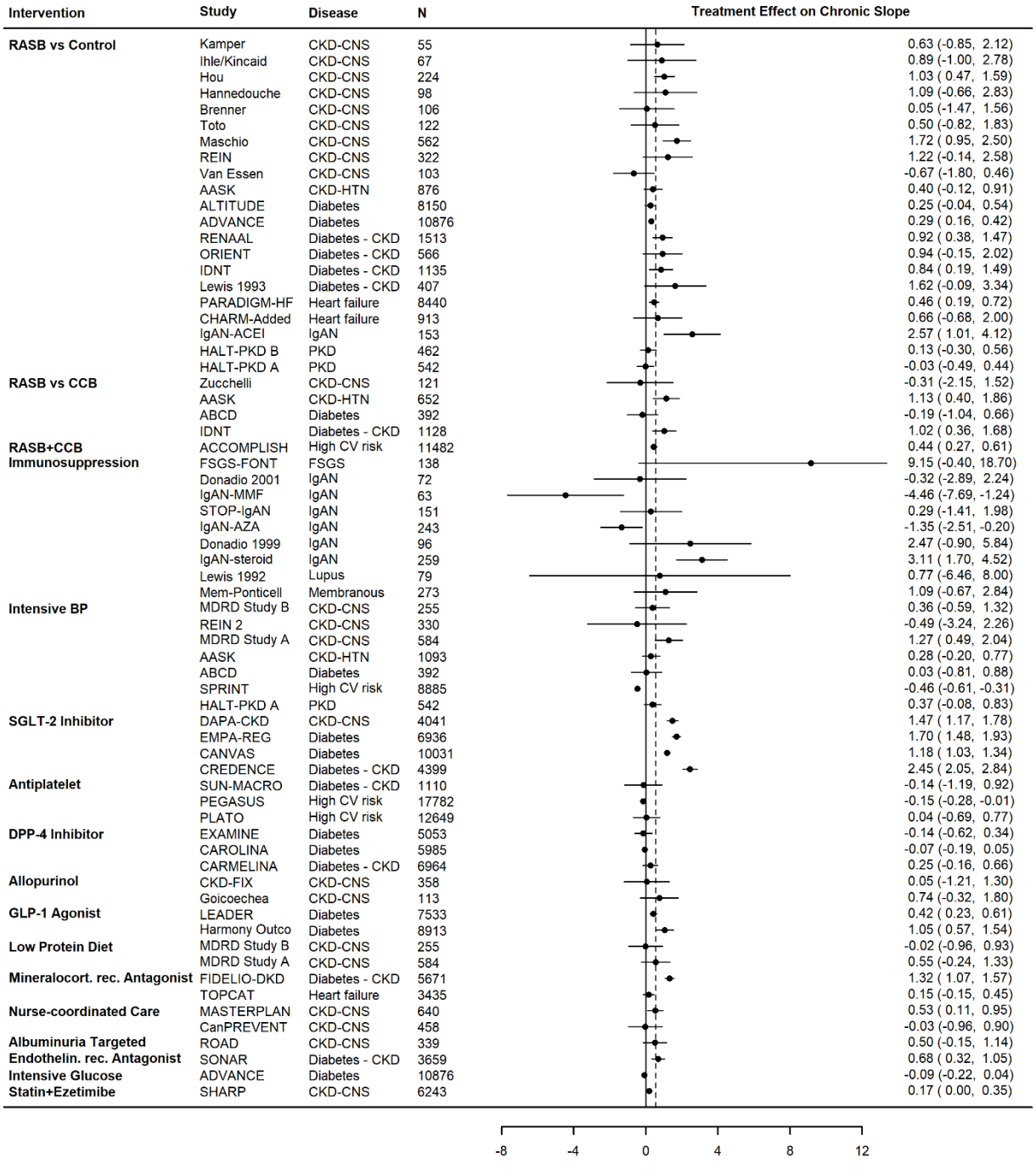
BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; CNS, Cause not specified; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; GLP-1, Glucagon-like peptide 1; HTN, Hypertension; IgAN, Immunoglobulin A nephropathy; N, Number of patients; PKD, Polycystic kidney disease; rec, Receptor; RASB, Renin-angiotensin system blocker; SGLT-2, Sodium glucose cotransporter 2.

Figure A-5 Treatment effect on total slope computed at 2 years



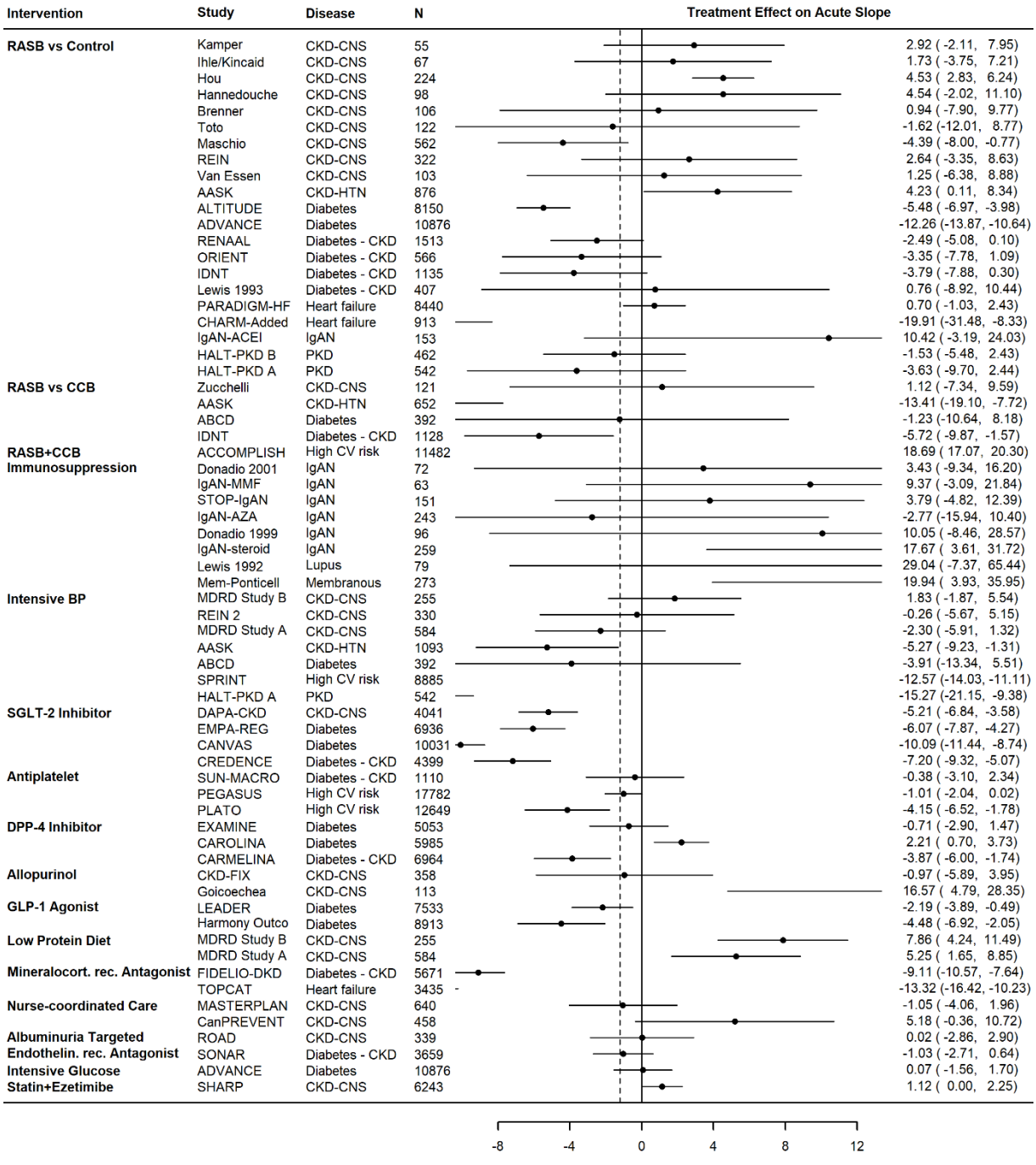
BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; CNS, Cause not specified; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; GLP-1, Glucagon-like peptide 1; HTN, Hypertension; IgAN, Immunoglobulin A nephropathy; N, Number of patients; PKD, Polycystic kidney disease; RASB, Renin-angiotensin system blocker; rec, Receptor; SGLT-2, Sodium glucose cotransporter 2.

Figure A-6 Treatment effect on chronic slope



BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; CNS, Cause not specified; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; GLP-1, Glucagon-like peptide 1; HTN, Hypertension; IgAN, Immunoglobulin A nephropathy; N, Number of patients; PKD, Polycystic kidney disease; RASB, Renin-angiotensin system blocker; SGLT-2, Sodium glucose cotransporter 2.

Figure A-7 Treatment effect on acute slope



BP, Blood pressure; CCB, Calcium channel blocker; CKD, Chronic kidney disease; CNS, Cause not specified; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide 1; HTN, Hypertension; IgAN, Immunoglobulin A nephropathy; N, Number of patients; PKD, Polycystic kidney disease; RASB, Renin-angiotensin system blocker; rec, Receptor; SGLT-2, Sodium glucose cotransporter 2.

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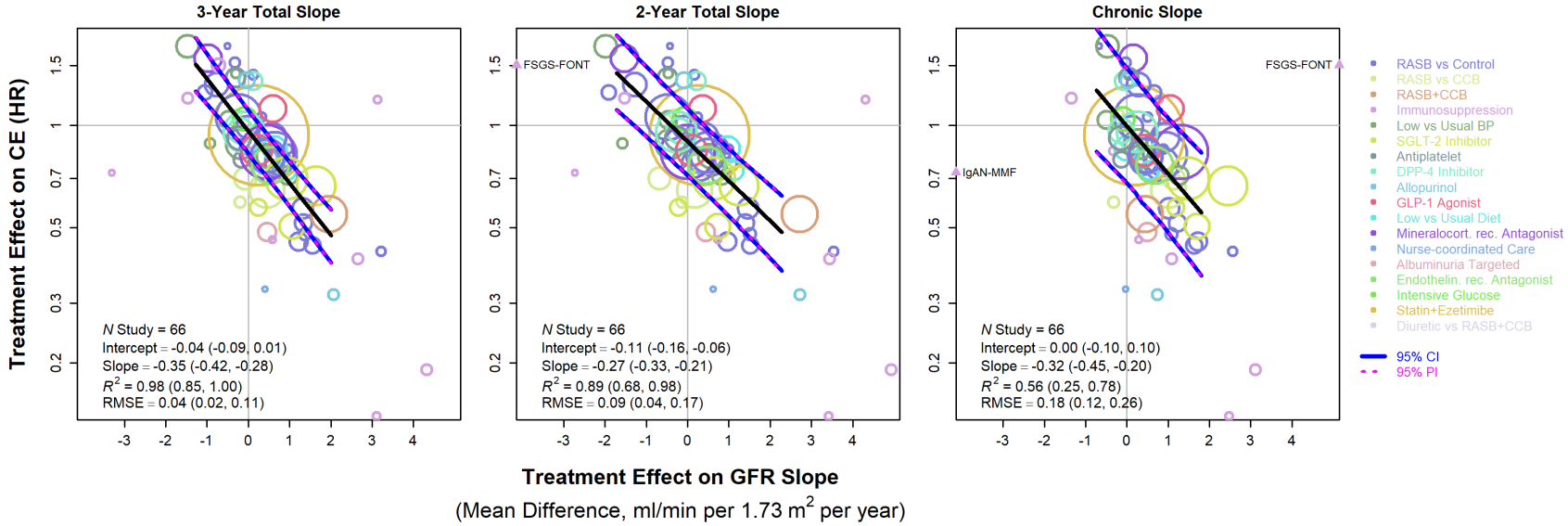
Figure A-8 Trial-level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint



Shown is the relationship between estimated treatment effects on the clinical endpoint (KFRT, GFR <15 ml/min per 1.73 m^2, or doubling of serum creatinine) on the vertical axis and estimated treatment effects on the GFR slope (total computed at 3 years, total slope computed at 2 years, or chronic slope) on the horizontal axis. Treatment effects on GFR slope are expressed as mean difference in treatment minus control and are expressed in ml/min per 1.73 m^2/yr. Treatment effect on the clinical endpoint is expressed as HR. The colors indicate intervention type. Each circle represents a separate randomized treatment comparison, with the size of the circle proportional to the number of events for the clinical endpoint. The black line is the line of meta-regression line through the studies. The blue line is the 95% pointwise Bayesian confidence band. The pink dashed lines are the 95% pointwise Bayesian prediction bands computed from the model.

Alb, albuminuria; BP, blood pressure; CCB, calcium channel blocker; CE, Clinical endpoint; CI, confidence interval; DPP-4, Dipeptidyl peptidase 4; FSGS, Focal segmental glomerulosclerosis; GFR, glomerular filtration rate; GLP-1, Glucagon-like peptide 1; HR, hazard ratio; IgAN, Immunoglobulin A nephropathy; KFRT, Kidney failure with replacement therapy; MMF, Mycophenolate mofetil; N, Number; RASB, renin angiotensin system blockers; RMSE, Root mean square error; SGLT2, Sodium glucose cotransporter.

APPENDIX A REFERENCES

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Appendix B CKD-EPI Structure, Collaborators, and Funding Sources

Chronic Kidney Disease Epidemiology Collaboration Clinical Trials Consortium (CKD-EPI CT)

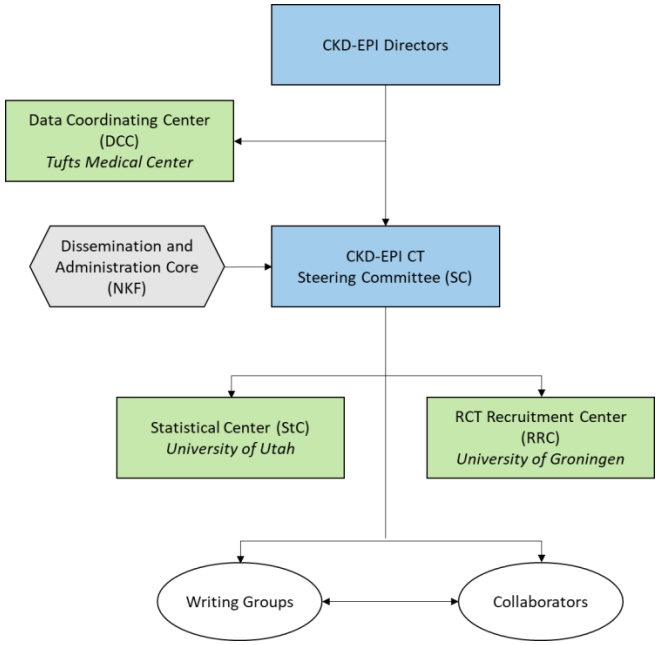
The CKD Epidemiology Collaboration (CKD-EPI) and the National Kidney Foundation (NKF) are co-applicants for this request for qualification.

The CKD Epidemiology Collaboration (CKD-EPI) is a research group with major interests in measurement and estimation of GFR (CKD-EPI GFR) and evaluation of surrogate endpoints for clinical trials (CKD-EPI CT) (https://www.tuftsmedicalcenter.org/research-clinical-trials/institutes-centers-labs/chronic-kidney-disease-epidemiology-collaboration/overview). Figure B-1 shows the organizational chart.

CKD-EPI CT includes analyses of randomized controlled trials (RCTs) and other studies initially collected for the purposes of evaluation of surrogate endpoints. Future analyses may go beyond the evaluation of surrogate endpoints but datasets will be restricted to RCTs (herein referred to as studies).

CKD-EPI directors are Andrew S Levey MD and Lesley A Inker MD MS. The steering committee (SC) for CKD-EPI CT guides the overall direction and policies specifically for the work on surrogate endpoints, and is chaired by Dr. Inker. The Data Coordinating Center (DCC) for CKD-EPI is at Tufts Medical Center, under the direction of Dr Inker. Dissemination and Administrative Core is directed by the National Kidney Foundation (NFK). The statistical center (StC) is at University of Utah under the direction of Tom Greene PhD. RCT Recruitment Center (RRC) is at the University of Groningen under the direction of Hiddo L. Heerspink PhD.

Figure B-1 Flow diagram of studies included in trial-level analyses



CKD-EPI CT Collaborators

Clinical Trial	Collaborators
AASK	Tom Greene
ABCD	Raymond O. Estacio, Rebecca Hanratty
ACCOMPLISH	Data received from Novartis via the Clinical Study Data Request platform
ADVANCE	Mark Woodward, John Chalmers
ALTITUDE	Hiddo JL Heerspink, Hans-Henry Parving
Appel	Gerald B. Appel, Pietro Canetta
Brenner	Barry M Brenner
canPREVENT	Brendan Barrett
CANVAS	Brendon Neuen, Vlado Perkovic, Bruce Neal
CARMELINA	Data received from Boehringer Ingelheim
CAROLINA	Data received from Boehringer Ingelheim
CHARM-Added	Data received from AstraZeneca
CKD-FIX	Sunil Badve, David Johnson
CREDENCE	Brendon Neuen, Vlado Perkovic, Bruce Neal
Lewis 1992, 1993	Julia B. Lewis
DAPA-CKD	Data received from AstraZeneca
Donadio 1999, 2001	Fernando Fervenza
EMPA-REG Outcome	Christoph Wanner, Maximilian von Eynatten
EXAMINE	Data received from GlaxoSmithKline via the Vivli platform
FIDELIO-DKD	Data received from Bayer
FSGS/FONT	Data received from NIDDK
Goicoechea	Marian Goicoechea, Eduardo Verde, Ursula Verdalles, David Arroyo

Clinical Trial	Collaborators
HALT-PKD A	Ronald D. Perrone, Arlene Chapman , Vicente Torres , Alan Yu , Godela Brosnahan
HALT-PKD B	Ronald D. Perrone, Arlene Chapman , Vicente Torres , Alan Yu , Godela Brosnahan
Hannedouche	Thierry Hannedouche
Harmony Outcomes	Data received from Takeda via the Vivli platform
HKVIN	Philip Kam-Tao Li, Kai-Ming Chow, Cheuk-Chun Szeto, Chi-Bon Leung
Hou	Di Xie, Fan Fan Hou
IDNT	Julia B. Lewis, Jamie Dwyer, Marc Pohl, Itamar Raz, Lawrence Hunsicker
Ihle/Kincaid	Gavin J. Becker, Benno U. Ihle, Priscilla S. Kincaid-Smith
Kamper	Annalise Kamper
Katafuchi	Ritsuko Katafuchi
LEADER	Data received from NovoNordisk
Maes	Bart D. Maes, An Vanacker, Thomas Malfait
Maschio	Tazeen H Jafar, Giuseppe Maschio, Francesco Locatelli
MASTERPLAN	Jan van den Brand, Jack FM Wetzels, Peter Blankestijn, Arjan van Zuilen
MDRD Study A	Tom Greene
MDRD Study B	Tom Greene
ORIENT	Enyu Imai, Fumiaki Kobayashi, Hirofumi Makino, Juliana C.N. Chan
PARADIGM-HF	Data received from Novartis via the Clinical Study Data Request platform
PEGASUS	Data received from AstraZeneca
PLATO	Data received from AstraZeneca
Ponticelli 1989, 1992, 1998, 2006	Patrizia Passerini
Pozzi 2004, 2010, 2012	Lucia Del Vecchio, Francesco Locatelli, Simeone Andrulli, Claudio Pozzi, Donatella Casartelli
Praga 2003	Manuel Praga, Hernando Trujillo, Teresa Cavero, Angel Sevillano
REIN-1 and 2	Piero Ruggenenti, Annalisa Perna, Fabiola Carrara, Giulia Gherardi
RENAAL	Hiddo JL Heerspink, William F Keane
ROAD	Di Xie, Fan Fan Hou
Schena	Francesco P. Schena, Carlo Manno
SHARP	Richard Haynes, William G. Herrington, Colin Baigent, Martin Landray
SONAR	Hiddo JL Heerspink
SPRINT	Data received from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center
STOP-IgAN	Jürgen Floege, Thomas Rauen, Claudia Seikrit, Stefanie Wied
SUN-MACRO	Julia B. Lewis
TOPCAT	Data received from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center
Toto	Robert D. Toto
van Essen	Dick de Zeeuw, Paul E. de Jong
Zucchelli	Tazeen H Jafar, Mauro Saddelli, Pietro Zucchelli

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)
ACCOMPLISH	Funded by Novartis
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
CANVAS	Funded by Janssen Research and Development
CARMELINA	Sponsored by Boehringer Ingelheim and Eli Lilly and Company
CAROLINA	Sponsored by Boehringer Ingelheim and Eli Lilly
CHARM-Added	This study was supported by AstraZeneca R&D, Mölndal, Sweden.
CKD-FIX	Funded by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand
CREDENCE	Funded by Janssen Research and Development
DAPA-CKD	Funded by AstraZeneca
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
Harmony Outcomes	Funded by GlaxoSmithKline.

Study Name	Funding
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
LEADER	Funded by NovoNordisk and the National Institutes of Health
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
PARADIGM-HF	Funded by Novartis
PEGASUS	Funded by AstraZeneca
PLATO	Funded by AstraZeneca
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, 2010, 2012	The authors did not receive any financial support
Praga 2007	This study was partially supported by Astellas
REIN	Supported by a grant from Hoechst Mario Roussel Clinical Research Institute, Frankfurt am Main, Germany.
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.
SONAR	Funded by AbbVie
SPRINT	Funded by the National Institutes of Health
STOP-IgAN	Supported by a grant (GFVT01044604) from the German Federal Ministry of Education and Research.
SUN-MACRO	Sponsored by Keryx Biopharmaceuticals, Inc.
TOPCAT	Funded by the National Heart, Lung, and Blood Institute
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

Study Name	Funding
	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

Appendix C Key Publications

CKD Consortium Technical Report 2022
Vonesh EF, Tighiouart H, Heerspink HL, Jafar TH, Wanner C, Greene T, Inker LA. CKD-EPI Consortium Technical Report: Timing and magnitude of acute treatment effects in clinical trials of chronic kidney disease. May 6, 2022.

Grams et al 2019
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. 2019;30(9):1746-55.

Greene et al 2019
Greene T, Ying J, Vonesh EF, Tighiouart H, Levey AS, Coresh J, et al. Performance of GFR slope as a surrogate endpoint for kidney disease progression in clinical trials: a statistical simulation. J Am Soc Nephrol. 2019;30(9):1756-69.

Inker et al 2019a
Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, Simon AL, 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 2019;30:1735-45.

Neuen et al 2022
Neuen BL, Tighiouart H, Heerspink HJL, Vonesh EF, Chaudhari J, Miao S, et al. Acute treatment effects on GFR in randomized clinical trials of kidney disease progression. J Am Soc Nephrol. 2022 Feb 1;33(2):291-303.

Vonesh et al 2019
Vonesh E, Tighiouart H, Ying J, Heerspink HL, Lewis J, Staplin N, et al. Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. Stat Med. 2019;38:4218–39.