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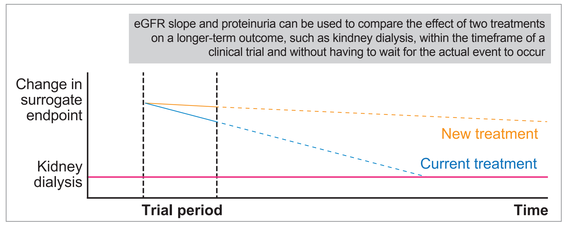
Novel endpoints in chronic kidney disease: Trends in the use of eGFR slope and proteinuria as efficacy endpoints in clinical trials

Ally Robert, James Beggs, Michaela Lysakova-Ivanova; Avalere Health, Knutsford, UK

Introduction

Patient access to new treatments for chronic kidney disease (CKD), such as empagliflozin, dapagliflozin—both SGLT2 inhibitors—and finerenone, a mineralocorticoid, has greatly reduced the rate of decline in kidney function, which is great news for patients. However, it has complicated clinical trials for subsequent treatments as it is difficult for emerging treatments to show comparative clinical benefit over the course of a typical 3-year trial.

Figure 1: Benefits of a surrogate endpoint in CKD



This issue could be mitigated by leveraging surrogate endpoints such as eGFR slope and proteinuria. A collaborative workshop between the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and National Kidney Foundation (NKF) in 2018[1] helped cement regulatory and payer interest in these two surrogate endpoints. Since then, eGFR slope and change in proteinuria have become increasingly popular as endpoints in new clinical trials.

Objectives

By analyzing trends in the use of both eGFR slope and proteinuria in clinical trials, we can characterize the likelihood of these endpoints becoming established, validated, and ultimately accepted by the global payer community.

Methods

A search of clinicaltrials.gov was carried out for industry-led trials listed between January 2020 and December 2023 that included eGFR slope or proteinuria as an endpoint.[2] Trial details were then extracted and analyzed to identify any key trends in surrogate use in renal indications, including CKD.

Results

eGFR

eGFR slope is calculated from creatinine levels in the blood, using one of a number of recognized and validated formulae. It is a measure of the rate of decline in GFR, which is indicative of the rate of deterioration in kidney health. eGFR slope has been shown in meta-analyses to correlate with and be predictive of traditional renal endpoints, including need for dialysis and renal death.

Leveraging eGFR slope as a primary endpoint can reduce the observation time and follow-up time of pivotal trials by up to 2 years, and allow for a smaller sample size in clinical trials. Reducing the size and length of clinical trials reduces the cost, making CKD a more attractive area for pharmaceutical manufacturers to invest in.

Between January 2020 and December 2023, 34 industry-sponsored trials were identified that included eGFR slope as either a primary or secondary endpoint.[2] No trials were identified with eGFR slope as a sole primary endpoint. Of these, 22 (65%) were Phase 3 studies and 7 (21%) were Phase 2 studies. Just over half of the trials involving eGFR slope have commenced in the past 2 years and are currently active. In general, the number of trials listing eGFR slope over the past 3 years have increased year on year. The majority of studies leveraging eGFR slope were investigating either Fabry Disease (19%) or CKD (14%), but other indications included IgA neuropathy, focal segmental glomerulosclerosis, heart failure, and diabetes.

Figure 2: eGFR slope in clinical trials, 2020-2023, clinicaltrials.gov[2]

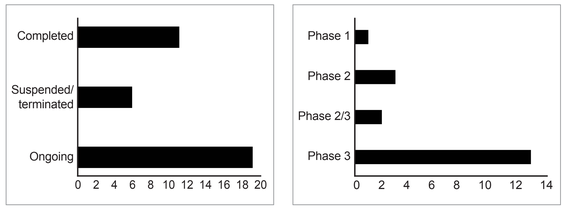
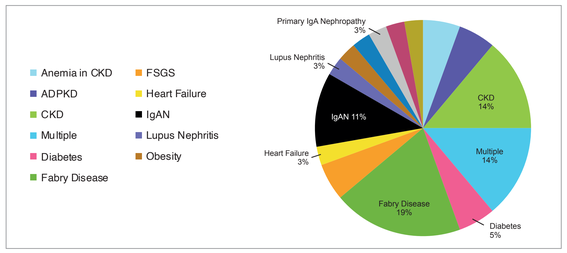


Figure 3: Percentage split in use of the eGFR slope endpoint in clinical trials, 2020-2023, by condition



ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A (IgA) nephropathy

Proteinuria

Proteinuria (also referred to as albuminuria) occurs when the kidneys have been damaged in a way that allows albumin, a type of protein, to leak into the urine. Repeated testing of the urine albumin-creatinine ratio (uACR) can help establish whether a patient might have chronic proteinuria. Chronic proteinuria is part of the differential diagnosis for CKD progression and is often monitored to guide and tailor clinical management and treatment. As such, it is correlated with long-term renal endpoints such as the need for dialysis or transplantation.

Between January 2020 and December 2023, 115 industry-sponsored trials were identified that included change in proteinuria as a primary or secondary endpoint—a far greater number than those leveraging eGFR slope.[2] Of these, 45 (40%) were Phase 3 studies and 56 (49%) were Phase 2. While there were a small number of trials that listed proteinuria as a sole primary endpoint, these were all Phase 1 or 2 studies. Of the trials listing proteinuria as an endpoint, 51% are active. Proteinuria was used as an endpoint in a greater range of indications than eGFR slope. While proteinuria was listed in trials for CKD (5%), this endpoint was listed in studies more for rare renal indications, including lupus nephritis (28%) and IgA neuropathy (18%).

Figure 4: Proteinuria in clinical trials, 2020-2023, clinicaltrials.gov[2]

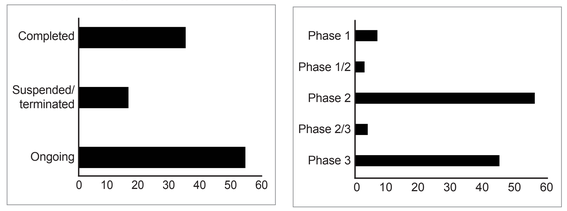
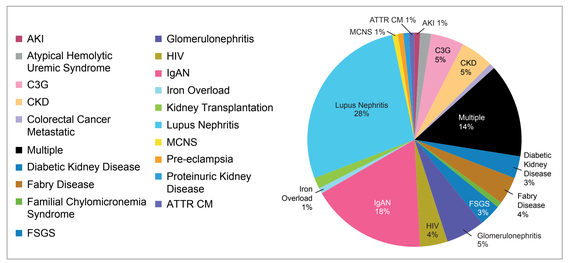


Figure 5: Percentage split in use of the proteinuria endpoint in clinical trials, 2020-2023, by condition



AKI, Acute kidney injury; ATTR CM, Transthyretin amyloid cardiomyopathy; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; IC-MPGN, immune-complex-mediated glomerulonephritis; IgAN, immunoglobulin A (IgA) nephropathy; MCNS, minimal change nephrotic syndrome

eGFR slope vs proteinuria

Like eGFR slope, a change in proteinuria is thought to be a predictor of treatment effect in CKD; however, because CKD is not the only cause of proteinuria, it is not suitable as a standalone primary endpoint in clinical trials in patients with CKD. The advantage of proteinuria compared with eGFR slope is that it can be measured over a shorter time period and be predictive of risk of progression, as well as treatment benefit, earlier on in the disease.

The results of this study show that eGFR slope is more commonly used in later stage (Phase 3) trials (65% eGFR slope v 40% proteinuria), whereas proteinuria is most commonly used in Phase 2 trials (49% proteinuria v 21% eGFR slope). eGFR slope is more commonly listed in CKD trials than proteinuria (14% eGFR slope v 5% proteinuria), but proteinuria is being used more in rarer diseases, such as lupus nephritis (28% proteinuria v 3% eGFR slope).

Conclusions

As eGFR slope and proteinuria become commonly used as endpoints in clinical trials, more health technology assessment (HTA) submissions are expected to include data based on these endpoints. However, until HTA agencies and payers are convinced by the surrogacy of eGFR slope and proteinuria for longer-term, hard clinical endpoints, they will expect these submissions to also include data for hard clinical endpoints, such as time to kidney failure. Activities that manufacturers could consider undertaking to support regulatory and payer acceptance of eGFR slope and/or proteinuria as surrogates in CKD include building an evidence base for surrogacy and designing robust payer communication strategies to convey the holistic value of surrogate endpoints beyond their correlation to long-term renal endpoints.

Activities that can help HTA and payer acceptance of surrogate endpoints in CKD:

1. Conduct feasibility studies to explore the potential for conducting network meta-analyses demonstrating the treatment benefit of existing drugs in terms of eGFR slope and proteinuria
2. Use real-world evidence to show a strong correlation between surrogate endpoints and a need for kidney dialysis.
3. Sponsor and publish white papers and opinion pieces on the value of the surrogate endpoint in:
   - Predicting mortality risk
   - Informing treatment choice and monitoring requirements
   - Identifying subgroups of patients who are at risk of incurring higher medical costs.

References

1. Holtkamp F, et al. Change in Albuminuria and Estimated GFR as End Points for Clinical Trials in Early Stages of CKD: A Perspective From European Regulators. Am J Kidney Dis.2020 Jan;75(1):6-8. doi: 10.1053/j.ajkd.2019.07.019. Epub 2019 Oct 28. PMID: 31672251.
2. Clinicaltrials.gov [accessed March 28, 2024].

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