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COMMENTARY

# The Broader Effects of Delayed Progression to End-Stage Kidney Disease: Delaying the Inevitable or a Meaningful Change?

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## ABSTRACT

A global rise in the prevalence of patients with chronic kidney disease (CKD) with end-stage kidney disease (ESKD) has led to a considerable and increasing burden to health systems, patients, and society. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are proven to reduce incidence of cardio-renal outcomes, including onset of ESKD. Recent post hoc analyses of SGLT2 inhibitor trials extrapolate substantial delays in the average time to ESKD over a patient's lifetime. In this article, we explore the possible real-world effects of such a delay by considering the available evidence reporting outcomes following onset of ESKD. From the patient perspective, a delay in reaching ESKD could substantially improve health-related quality of life and result in additional life years without the need for kidney replacement therapies, a target relevant to all CKD subpopulations. Furthermore, should a patient initiate dialysis at an older age as a result of CKD progression, the time spent in receipt of dialysis, and therefore associated healthcare costs, may also be reduced. A delay in progression may also lead to changes in the management of ESKD, such as increased election of conservative care in preference to dialysis, particularly in elderly populations. For younger patients with CKD, those who reach ESKD while employed face considerable work impairment and productivity loss, as may families and care partners of working age. Therefore, a delay to the onset of ESKD will reduce the proportion of their working lives affected by productivity losses or unemployment due to medical reasons. In conclusion, optimised treatment of CKD may lead to a shift in treatment options, but proper and timely implementation is essential for the realisation of improved outcomes.

**Keywords:** Chronic kidney disease; End-stage kidney disease; Kidney failure; Primary prevention; Health-related quality of life; Productivity loss; Mortality

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**Key Summary Points**

Recent post hoc analyses of trial data estimate considerable potential delays to end-stage kidney disease (ESKD) via improved management of chronic kidney disease (CKD) with sodium–glucose cotransporter 2 (SGLT2) inhibitors. The objective of this commentary is to explore the tangible effects of such a delay to ESKD.

As patients reach ESKD at an older age, a delayed requirement to initiate dialysis may lead to fewer years spent on dialysis than if they had reached ESKD at a younger age.

Delaying the need for initiation of dialysis may increase the use of conservative care, in effect manage patient symptoms with non-invasive interventions in preference to dialysis, especially in elderly populations.

For younger patients with CKD, delaying the time to initiation of dialysis may temper an escalating trend of productivity loss for patients and caregivers while they are of working age.

## INTRODUCTION

The global increase in patients with chronic kidney disease (CKD) with end-stage kidney disease (ESKD) is an escalating burden to health systems, to patients, and to society [1–4]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors slow progression of CKD in patients with or without type 2 diabetes (T2D) when used in addition to standard therapy, with attenuated decline of estimated glomerular filtration rates (eGFR) leading to fewer patients reaching ESKD versus placebo [5, 6]. Furthermore, other antidiabetic agents, specifically glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and non-steroidal mineralocorticoid receptor agonists (ns-MRAs), have demonstrated clinical efficacy in preventing adverse kidney-related outcomes in patients with both T2D and CKD [7, 8].

However, owing to the chronic, progressive nature of CKD, the broader effects of these newer therapies in delaying any eventual progression to ESKD cannot be fully explored within the restricted trial follow-up periods. Recent post hoc analyses of observed trial data (Table 1) estimate potential delays to CKD progression and ESKD in patients with CKD through treatment with SGLT2 inhibitors to be considerable [9–11]. Similar analyses of combination therapy (SGLT2 with ns-MRAs and GLP-1 RAs) further characterise the potential for delayed kidney outcomes via optimised management of patients with T2D and CKD [12, 13].

An open question thus remains as to what effects may materialise if such a delay in progression to ESKD were achieved from several perspectives, including the affected patients, healthcare payers, and society overall.

Therefore, the objective of this commentary is to explore the tangible effects of a delay to ESKD in specific subpopulations, with a particular focus on three questions:

- Might a delay in progression to ESKD reduce the burden of dialysis or simply shift it into the future?
- Could a delay in progression lead to changes in application of conservative care in ESKD?
- What might the implications of delayed progression be for societal productivity?

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## MIGHT A DELAY IN PROGRESSION TO ESKD REDUCE THE BURDEN OF DIALYSIS OR SIMPLY SHIFT IT INTO THE FUTURE?

Patients with CKD who reach ESKD and initiate kidney replacement therapy (KRT) exist in complex and costly scenarios, comprising a diverse array of situations for patients, and their families. ESKD substantially reduces life expectancy of patients and, while alive, they experience poor health-related quality of life (HRQoL)

**Table 1** Published estimates for potential delays to CKD progression through optimised management

| Study | Population(s) | Intervention(s) | Comparator(s) | Incremental delays to kidney-related outcomes (lifetime) | Data source(s) |
|---|---|---|---|---|---|
| Fernandez-Fernandez et al. [9] | Patients with CKD (EMPA-KIDNEY) | Empagliflozin plus standard care[a] | Placebo plus standard care[a] | ESKD: 1.9–26.6 years (according to baseline eGFR) | EMPA-KIDNEY [46] |
| Heerspink et al. [12] | 50-year-old patients with T2D and CKD | Combination treatment (SGLT2i, ns-MRA, standard care[a]) | Placebo plus standard care[a] | Composite outcome[b]: 6.7 years (95% CI 5.5, 7.9) | CREDENCE [47]; CRIC [48]; DAPA-CKD [5]; FIDELIO-DKD [7] |
| McEwan et al. [11] | Patients with CKD and elevated albuminuria[c] | Dapagliflozin plus standard care[a] | Placebo plus standard care[a] | ESKD: 6.6 years (95% CI 2.8, 10.8)<br>≥ 40% eGFR decline: 5.9 years (95% CI 3.4, 8.7) | DAPA-CKD [5]; DECLARE-TIMI 58 [49] |
| | Patients with CKD with/without albuminuria[d] | | | ESKD: 6.3 years (95% CI 2.1, 9.5)<br>≥ 40% eGFR decline: 6.8 years (95% CI 3.8, 9.2) | |
| Neuen et al. [13] | 50-year-old patients with T2D and albuminuria | Combination treatment (SGLT2i, GLP-1 RA, ns-MRA, and standard care[a]) | Placebo plus standard care[a] | Composite outcome[b]: 5.5 years (95% CI, 4.0–6.7) | SGLT2i trials: CANVAS [50]; CREDENCE [47]<br>ns-MRA trials: FIDELIO-DKD [7]; FIGARO-DKD [51]<br>NMA of GLP-1 RA trials [52]: ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, REWIND, PIONEER 6, and AMPLITUDE-O |

**Table 1** continued

| Study | Population(s) | Intervention(s) | Comparator(s) | Incremental delays to kidney-related outcomes (lifetime) | Data source(s) |
|---|---|---|---|---|---|
| Vart et al. [10] | 50-year-old patients with albuminuric CKD without T2D[e] | SGLT2i plus standard care[a] | No treatment | Composite outcome[b]: 7.4 years (95% CI 6.4, 8.7) | REIN [53, 54]; Guangzhou [55]; DAPA-CKD [5] |

*ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *GLP-1 RA* glucagon-like peptide-1 receptor agonists, *ns-MRA* non-steroidal mineralocorticoid receptor agonist, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *T2D*: type 2 diabetes, *UACR* urine albumin-creatinine ratio

[a]Standard care refers to renin-angiotensin blockade (ACEi or ARBs) if not otherwise contraindicated

[b]The composite outcome comprised of a doubling of serum creatinine from baseline, ESKD or death

[c]Population aligned to the DAPA-CKD trial (eGFR 25–75 ml/min per 1.73 $m^2$; UACR 200–5000 mg/g)

[d]Data from the DAPA-CKD trial were pooled with a subpopulation of the DECLARE-TIMI 58 trial to create a combined CKD population spanning a range of CKD stages

[e]Until the age of 75 years

[14], physical and economic dependence and, in some environments without health costs coverage, financially catastrophic scenarios [15, 16]. Families and those close to patients with ESKD also face major challenges, including provision of care and its implications to HRQoL, financial burden and independence [17, 18]. Finally, the increasing healthcare costs and resource use to the system is a major challenge [2, 19], with total costs for patients on dialysis significantly higher than for patients in receipt of transplant or otherwise not on dialysis [3, 20]. The direct cost per-patient for in-centre haemodialysis is substantial (£31,785 in the UK and $99,325 in the US, annually) [21, 22], with direct UK National Health Service (NHS) and US Medicare fee-for-service expenditure for patients, irrespective of dialysis modality, estimated to be £1.05 billion and $26.9 billion, respectively [21, 23].

An important point to consider is that most patients with ESKD are elderly, particularly given that the age of initiation has been increasing in recent years, coinciding with improved life expectancy in high-risk populations such as those with T2D, thereby elevating the risk of ESKD [24]. Patients initiate kidney replacement therapy at a median age of 63.7 years in the UK, and at a median age of 67.9 years in Europe [25, 26].

What might a delay in the progression to ESKD mean for older patients? As patients reach older age, the risks of comorbidities and mortality naturally increase and patients may have a higher risk of death for reasons unrelated to CKD [27]. Furthermore, a decline in kidney function in earlier stages of CKD is associated with higher rates of all-cause mortality, in part due to elevated mortality from cardiovascular causes [28]. As a result, with decreasing life-years remaining as patients age, a delayed initiation of dialysis may also mean fewer years on average per patient with KRT, than if they had reached ESKD at a younger age (Fig. 1). For example, in the UK and US, five-year survival in patients initiating KRT at 75 years of age or older was approximately 23% and 22% compared to 42% and 35% in 65–74 year olds, respectively [21, 26]. Maintaining patients in healthier states and delaying the requirement for KRT may thus reduce the total number of life-years spent on KRT, relieving (and not delaying) the healthcare burden in terms of costs for KRT (Fig. 1). Further

analyses may be required to consider the effect of increased cardiovascular or other causes of mortality in a population which experiences a substantial delay to KRT initiation, even with the demonstrated clinical benefit of SGLT2 inhibitors in the prevention of cardiovascular outcomes and death from any cause [5]. Furthermore, by reducing the demand for a transplant, a delay to kidney failure could potentially reduce the time for patients who are on transplant waiting lists, consequently leading to reduced time on dialysis (Fig. 1).

## COULD A DELAY IN PROGRESSION LEAD TO CHANGES IN APPLICATION OF CONSERVATIVE CARE IN ESKD?

An additional consideration for the ageing patient is the trade-off between the potential benefits of KRT and the treatment-related burden. Dialysis itself is associated with a substantial treatment burden, including poorer HRQoL [29] and increased risk of infections and cardiovascular disease [28, 30], among other factors. As a result, an estimated 10–20% of people with advanced kidney failure opt not to undergo dialysis [31, 32].

Delaying the need for KRT initiation by several years may increase the use of conservative care to manage patient symptoms with non-invasive interventions, especially in elderly populations [33]. Studies have indicated that there is no HRQoL advantage to initiating dialysis versus conservative management, due to the advanced stage CKD of patients at the time of initiating KRT [34, 35]. For patients with shorter life expectancy, the limited survival benefit afforded by KRT may not be worth the potential risk compared with conservative management [34], with further reduced survival benefit in patients with comorbidities [35].

The delay in progression to ESKD through optimised management of CKD may thus lead to increased consideration of conservative care, as KRT may be considered of more limited benefit and therefore less suitable to patients or healthcare systems as ESKD is reached at a later age (Fig. 1). The National Institute for Health and Care Excellence has acknowledged the issue and has advocated for future research into quantifying the clinical and cost-effectiveness of conservative management versus dialysis in frail, older individuals [36]. Accordingly, the Prepare for Kidney Care trial and the DIALysis or not: Outcomes in older patients with GerIatriC Assessment (DIALOGICA) observational study will collect comparative data in relation to HRQoL, and clinical and economic outcomes for patients treated with dialysis versus conservative care to aid decision-making between patients and clinicians [37, 38].

While all of the above are relevant in terms of treatment planning and decision-making for ESKD, the effect of delayed progression provides a clinical benefit to elderly patients, whereby the prognostic implications of KRT and the likelihood of significantly improved survival are more limited compared with younger patients [39]. The most important benefit of delayed progression through effective treatment is that a larger proportion of patients will remain on stages 3a, 3b, and 4, particularly in the elderly who are at elevated risk of progression [40].

The mean delay in the time to ESKD may be lower in older patient populations initiating treatment with SGLT2 inhibitors (given the overall greater risk of CKD progression or mortality [41]), the influence of such a delay is nevertheless important. Treatment with SGLT2 inhibitors can lead to a shift in outcomes for patients based on delay to ESKD, with KRT less likely to be the most suitable option as the average age of initiation in these populations increases.

## WHAT MIGHT THE IMPLICATIONS OF DELAYED PROGRESSION BE FOR SOCIETAL PRODUCTIVITY?

For younger patients with CKD, the above considerations may be less significant factors in decision-making, given they can typically expect greater improvement to life expectancy upon progression to ESKD through initiation of

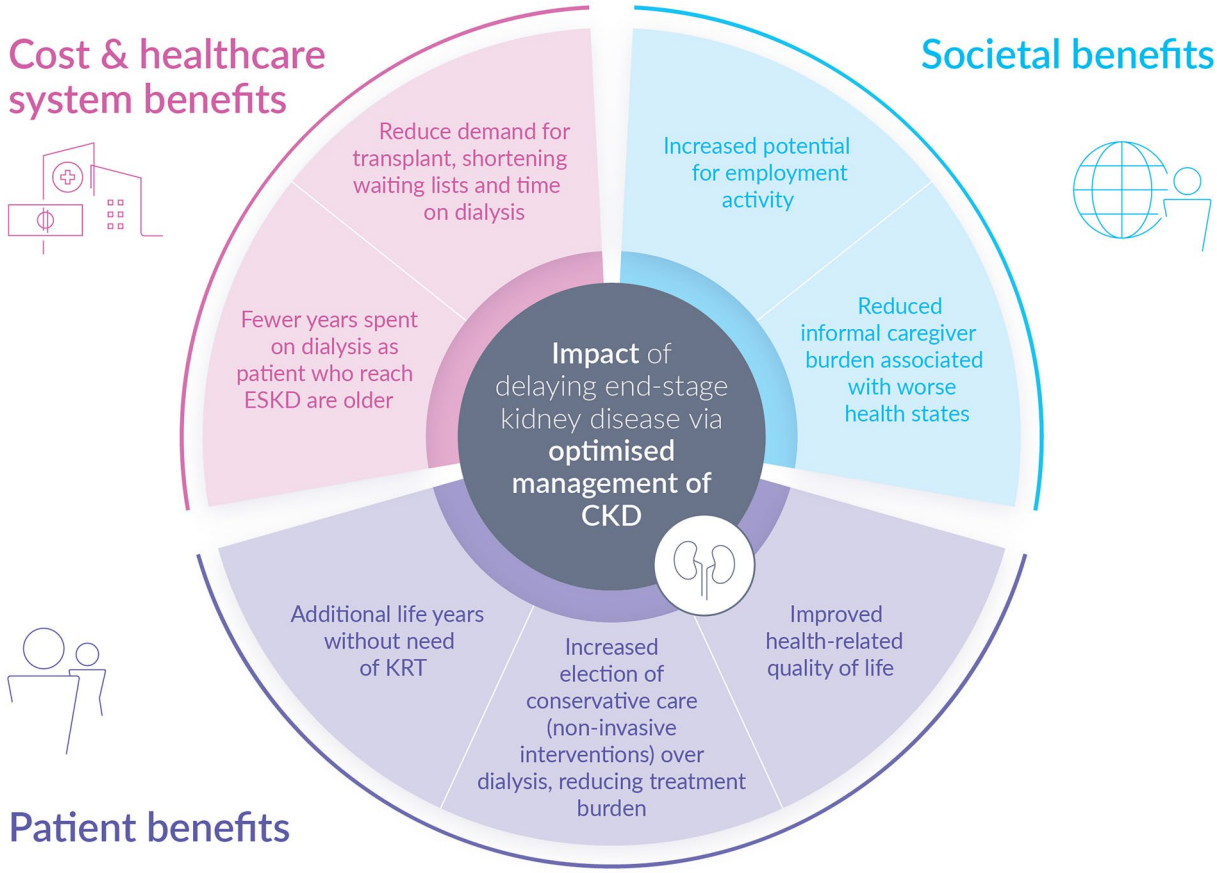


**Fig. 1** The broader positive effects of delayed progression to ESKD through optimised management of CKD. *CKD* chronic kidney disease, *ESKD* end-stage kidney disease, *KRT* kidney replacement therapy

KRT than older populations [21, 26]. Therefore, conservative care, though an option for younger patients, would be considered on the basis of personal choice rather than on the basis of limited incremental clinical benefit. For patients treated with SGLT2 inhibitors of any age who inevitably progress to ESKD even with treatment, a treatment-mediated delay in the progression of CKD would correspond to overall fewer life–years spent on dialysis, with more time spent in earlier CKD stages that represent significantly less burden to the healthcare system (Fig. 1).

Another important element from a societal perspective, and from the perspective of the patient, is that, by increasing the time prior to the need for KRT, the time for which patients are able to work will also increase. A major consequence of ESKD is the detrimental effect dialysis imposes on patients' ability to work; a systematic review of employment rates in patients receiving KRT found that patients on dialysis had a considerably lower employment rate of 26% versus those not on dialysis, of whom 59% were economically active [42]. Recent US surveys of financial burden in patients with CKD indicate that those patients who are dialysis-dependent typically report more losses to work productivity and greater work impairment than patients who were not dialysis-dependent [43, 44].

Extending beyond the burden associated with patients, delaying ESKD through optimised CKD management would also likely improve the productivity of relatives or people who would be their unpaid caregivers, particular for those who require dialysis (Fig. 1). Unpaid caregivers often may be younger than the person with CKD for whom they provide care; therefore, delaying

time to ESKD may also have a broader societal impact as a result of its effects on caregivers' ability to work. In the aforementioned surveys, caregivers also reported reduced work productivity when caring for dialysis-dependent patients versus caregivers for patients with CKD who were not dialysis-dependent [43, 44].

In the UK, missed work due to dialysis was estimated to cost the UK economy £372 million in productivity losses, which was estimated to rise to £2 billion by 2033, owing to improved life expectancy of patients on dialysis who are of working age [23]. Therefore, delaying the time to initiation of dialysis may limit this escalating trend by reducing the amount of time lost at work to patients or caregivers while they are of working age (Fig. 1).

## CONCLUSIONS

Optimisation of CKD management according to treatment guidelines [45] with SGLT2 inhibitors in addition to historical standard of care has the potential to slow the progression of the disease and thereby delay the onset of ESKD [9–11]. These delays may reduce the time spent on KRT and facilitate additional deployment of conservative care, thereby reducing healthcare costs and societal burden. If successful, it is expected that patient care at stages 3–4 should increase significantly and there will be need for more and better prepared primary and secondary care practitioners for all public health systems as a result. Delaying ESKD development may have a double effect: extending the life span of those affected with CKD and provide them with a better life experience based on more time in better health states, improving their HRQoL. Caregivers may also benefit from such delays if they are not exposed to situations that limit their own everyday experiences, financial status and HRQoL. Finally, society as a whole should benefit from enabling an increase in the employability of patients or caregivers of working age, and reduced health costs related to KRT, which represent the most expensive status for patients with CKD. The demonstrated clinical trial results observed for SGLT2 inhibitors in their reduction of CKD progression thus have the potential to translate into real-world effects of benefit to patients, healthcare systems and payers. They may lead to a shift in treatment options, yet all will depend on proper and timely implementation, as previous studies have demonstrated decades of delay for implementation of new treatment modalities.

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***Data Availability.*** Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

### *Declarations*

***Conflict of Interest.*** Ricardo Correa-Rotter has received honoraria as consultant from AstraZeneca, Boehringer Ingelheim, Bayer, Chinook, AbbVie, Novo Nordisk, and research support from AstraZeneca, Boehringer Ingelheim, Roche and Novo Nordisk. He has received speaking fees

from AstraZeneca, Boehringer Ingelheim, Novo Nordisk and Amgen. David C. Wheeler provides ongoing consultancy services to AstraZeneca in the last two years and has received honoraria and/or consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, Eledon, Galderma, Gilead, GlaxoSmithKline, George Clinical, Janssen, Merck Sharp and Dohme, ProKidney, Takeda, Vifor, and Zydus. He also reports speaking fees from Astellas, AstraZeneca and Vifor, and support for travel/meeting attendance from Astellas, AstraZeneca and Pro. He has served on DSMBs for Eledon, Galderma, Merck, and ProKidney. He is National Institute of Health Research Lead for Renal Disorders in the UK. Phil McEwan is an employee of Health Economics and Outcomes Research Ltd. Health Economics and Outcomes Research Ltd. received fees from AstraZeneca in relation to this study.

***Ethical Approval.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.



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