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Editorial Comment

EDITORIAL COMMENT

The unaccomplished mission of reducing mortality in patients on kidney replacement therapy

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ABSTRACT

Six years ago, a comprehensive review by the EURECA-m working group of the ERA-EDTA thoroughly addressed the drivers of mortality in patients with end-stage kidney disease. Not unexpectedly, the key global driver of early death in these patients was the lack of access to kidney replacement therapy. However, and contrary to the expectations of non-nephrologists, mortality was still high when kidney replacement therapy was provided. This was due to excess cardiovascular and non-cardiovascular mortality, and the need to further characterize correctable risk factors and eventually test the impact of correcting them was emphasized. In this issue of *ckj*, seven reports address risk factors for death in non-dialysis chronic kidney disease (CKD), dialysis and kidney transplant patients. They characterize irreversible (e.g. sex; age; genetic variants of the *KL* gene encoding the anti-ageing protein Klotho) and reversible (obesity; mineral and bone disorder parameters; anti-depressant drugs, especially those that increase the QT; amputation; public health investments) factors associated with mortality of CKD patients on or off kidney replacement therapy.

Keywords: anti-depressant, chronic kidney disease, gender, kidney replacement therapy, Klotho, mortality, obesity, risk factors

Chronic kidney disease (CKD) is one of the fastest growing causes of death worldwide [1, 2]. While early stages of CKD are already associated with an increased risk of death, the largest gap in mortality with the general population is found in patients on kidney replacement therapy [3]. Indeed, in the context of the coronavirus disease 2019 (COVID-19) pandemic, CKD on kidney replacement therapy confers the highest risk of death of any risk factor apart from age [4–6]. The December issue of *ckj* presents several manuscripts that add further insights into correlates of mortality in CKD, most of them in the context of kidney replacement therapy [7–13].

Cambray *et al.* reported on the association of 11 single-nucleotide polymorphisms (SNPs) of the *KL* gene that encodes the anti-ageing factor Klotho with non-cardiovascular death in 1016 CKD patients from the National Observatory of Atherosclerosis in Nephrology (NEFRONA) study [7]. In this population, non-cardiovascular deaths were 75% more common than cardiovascular deaths (108 versus 62 after 48 months of follow-up). This emphasizes the need to understand and address the drivers of non-cardiovascular deaths, since most research efforts are aimed at decreasing cardiovascular deaths in CKD [4]. A three-allele combination at rs562020, rs2283368 and rs2320762 (rs562020 GG/AG + rs2283368 CC/CT + rs2320762 GG) present in 7.5% of the population was associated with higher risk of non-cardiovascular death, while the low-risk combination of all the opposite genotypes was present in 9% of the population and was associated with lower than average risk. This genetic approach assessing a limited number of SNPs of the *KL*

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gene could be used to enrich clinical trials for CKD patients at high risk for non-cardiovascular death. A further research task is to understand how any functional impact of these alleles may modulate pathways linked to non-cardiovascular death. In this regard, the kidneys are the key source of Klotho and kidney Klotho is downregulated early in the course of CKD, well before a reduced kidney mass explains the lower Klotho production [14]. Early drivers of CKD, such as albuminuria and local inflammation, may decrease Klotho synthesis when the bulk of tubular cell mass is still preserved [15, 16]. However, understanding Klotho regulation in humans is marred by Klotho assay issues [17, 18]. Despite this, upregulation of circulating and urinary Klotho by pentoxifylline and other nephroprotective drugs has been described, often with cell culture experiments demonstrating a direct effect of these drugs on Klotho expression [19]. The impact of *KL* gene SNPs on Klotho levels in response to CKD or drug therapy or a functional impact of these gene variants should be explored.

Another report focused on peritoneal dialysis and wider healthcare investment approaches. Loesch *et al.* studied 5707 incident peritoneal dialysis patients from a prospective cohort in 78 Brazilian cities [8]. Public investment in healthcare manager training and community awareness was associated with longer patient survival at very modest levels of investment (>0.30 US dollars per capita), but investment in primary healthcare (within the range of investments studied) was not. Investment in medium and high complexity healthcare was also associated with longer survival, but to have a significant impact, it required a higher investment (higher than up to 79.6 US dollars per capita). These health economics studies will be key for resource allocation to adjust to a new COVID-19 world characterized by higher healthcare demand and tighter budgetary constraints.

Three manuscripts studied mortality in haemodialysis patients, addressing therapy for depression, the impact of incident comorbidities such as amputations, and the validation of an outcomes prediction score based on three routine metabolic bone disorder (MBD) markers.

A frequent problem in dialysis patients is that the efficacy and safety of drugs in dialysis patients is not specifically addressed by randomized clinical trials. This may lead to therapeutic nihilism, a key risk factor for mortality in end-stage kidney disease (ESKD) and characterized by the non-prescription of drugs that improve outcomes in the general population [4]. On the other side of the coin, the scarcity of ESKD studies may lead to inadvertent misuse of drugs. Thus, frequently, the use of drugs in dialysis is guided by pharmacokinetic/pharmacodynamic studies that may predict or assess how drugs and metabolites may behave when kidney function falls or how these compounds are cleared by dialysis. However, there are additional factors that may compromise efficacy or safety, such as the changing concentrations of electrolytes or uraemic retention solutes during the interdialytic period or the haemodialysis session that change the response to or safety of the drug, as well as predisposition of dialysis patients to certain drug effects due to pathophysiological changes related to uraemia. As an example, the USA highlights of prescribing information for escitalopram warn that no information is available about the pharmacokinetics in patients with severely reduced kidney function (creatinine clearance <20 mL/min) and that escitalopram should be 'used with caution in patients with severe renal impairment' ... whatever that means [20]. Indeed, a PubMed search on the topic of '(citalopram OR escitalopram) AND (dialysis OR hemodialysis)' on 25 October 2020 disclosed a Cochrane review through 20 January 2016 on anti-depressants for treating depression in adults with ESKD treated with dialysis [21]. This review identified four studies in 170 participants comparing anti-depressant therapy (fluoxetine, sertraline, citalopram or escitalopram) versus placebo or psychological training for 8–12 weeks. Both the duration and the number of patients are clearly insufficient to establish the safety of these drugs in ESKD. No more recent randomized clinical trials were found. However, observational studies reported on poor drug selection, overprescription, under-dosing and inadequate follow-up suggesting sub-optimal adherence to NICE guidelines for anti-depressant use in haemodialysis patients [22]. A further study focused on the selective serotonin reuptake inhibitors (SSRIs) citalopram and escitalopram as drugs that prolong the QT interval to the greatest extent in electrophysiologic studies as compared with fluoxetine, fluvoxamine, paroxetine and sertraline [23]. This was a retrospective analysis enrolling 30 932 haemodialysis patients who initiated citalopram and escitalopram and 34 722 (52.9%) who initiated SSRIs with lower QT-prolonging potential. Initiation of citalopram and escitalopram was associated with higher risk of sudden cardiac death than initiation of other SSRIs: adjusted hazard ratio (HR) 1.18, 95% confidence interval (95% CI) 1.05–1.31. The association was more pronounced in some subpopulations, including the elderly and females. Despite these findings, in 3252 Chronic Renal Insufficiency Cohort participants with at least one study electrocardiogram between 2003 and 2011, fluoxetine (+4 ± 1 ms), citalopram (+4 ± 1 ms), escitalopram (+3 ± 2 ms) and venlafaxine (+3 ± 1 ms) were associated with statistically significant QT interval corrected for heart rate prolongation after adjustment for comorbidities, potassium and calcium [24]. Thus, in routine clinical assessments, the overall QT prolongation impact of citalopram and escitalopram could not be distinguished from other SSRIs such as fluoxetine. In this issue of *ckj*, Chilcot and Farrington performed an exploratory analysis of the association between patient-reported anti-depressant use within 3 months prior to the study assessment and survival in 707 haemodialysis patients [9]. Of 76 patients on anti-depressants, 36% died during the study compared with 19% of patients not on anti-depressants. In adjusted analysis that also controlled for depression severity, anti-depressant use was significantly associated with mortality (adjusted HR 2.0, 95% CI 1.28–3.26). This increased risk was higher than that conferred by depression itself in prior reports. They further estimated an estimated absolute risk increase of death for those on an anti-depressant was 18%, with a quite low number needed to harm of around 5. As the authors point out, more robust studies assessing medication type, dose and treatment vintage, among other variables, may provide more reliable estimates of the absolute mortality risk provided by anti-depressants. These estimates are needed for regulatory authorities' reassessment of the safety of anti-depressants in dialysis patients, and the authors renew their call for empirical studies on the selective withdrawal of anti-depressants in patients with advanced kidney disease [25].

Schroijen *et al.* addressed survival of dialysis patients with specific comorbidities [10]. They focused on survival of dialysis patients after amputations in the Netherlands prospective cohort study of incident patients with ESKD. Amputation incidence was 10-fold higher (12% versus 1.2%) in diabetics than in non-diabetics and was associated with a 4-fold increased mortality risk both in diabetes and non-diabetes patients. Thus, diabetes does not appear to confer an increased risk of death once amputation has occurred.

Fuller *et al.* validated in an international cohort of haemodialysis patients a simple composite score based on the number

of MBD markers (MBD 0 to MBD 3) outside the reference range [11]. This score had been associated with an increased risk of clinical outcomes in USA prevalent haemodialysis patients [26]. The *ckj* study analysed 19 313 patients surviving ≥12 months in the Dialysis Outcomes and Practice Patterns Study Phases 3–5 (2005–15) from Europe, Canada and the USA. When focusing on the number of MBD markers (MBD 0 to MBD 3) above the following values: 10.2 mg/dL for calcium, 5.5 mg/dL for phosphorus and 600 pg/mL for parathyroid hormone, MBD 2/3 was present in 10–14% of patients across regions. MBD 2/3 was associated with increased risk of death (adjusted for disease risk score HR 1.41, 95% CI 1.10–1.82 versus MBD 0) and of a composite of death or hospitalization (adjusted HR 1.23, 95% CI 1.10–1.38) in the USA compared with MBD 0. The mortality association was only observed for older (≥65 years) individuals (adjusted HR 1.82, 95% CI 1.28–2.58). HRs in Canada and Europe were generally consistent but weaker. Thus, there was a gradient for the adjusted HR for death, which was 1.33 in Canada and 1.18, suggesting the influence of unmeasured factors, either related to patient or to the standard of care, on the risk of death conferred by the MBD score. A definition of the score as outside target, that is above or below a target range, conferred lower risk, and for Europeans this score was not associated with an increased risk of the composite outcome. Thus, while the MBD score is a simple tool that helps identify a high-risk older population, it remains to be assessed what factors explain the differences between the USA and Europe and whether correction of the out of range scores may decrease the mortality risk.

Two manuscripts addressed mortality in kidney transplant recipients, focusing on two specific populations: the elderly (those aged ≥65 years) and the obese [body mass index (BMI) ≥30 kg/m^2]. These studies represented single-centre or regional data and should be confirmed at a multinational, ideally pan-European level.

Schachtner *et al.* analysed patient and allograft outcomes in 244 kidney transplant recipients at the Eurotransplant Senior Program, which enrols kidney transplant recipients aged ≥65 years (age range 65–79 years) receiving kidneys from donors aged ≥65 years [12]. Patient survival at 1, 5 and 10 years was 92, 66 and 38%, respectively. Key mortality risk factors were male gender and T-cell-mediated rejection. Indeed, median patient survival was 40% shorter for males than for females (80 months versus 131 months). The longer survival in females than in males is in accordance with data for the kidney replacement therapy population in Europe and also for the general population [27, 28]. However, the median expected remaining lifetime of 6.7 years for male kidney recipients and 10.9 years for females was lower than the latest data for the general German population at 65 years of 17.9 and 21.1 years, respectively [29]. The gender gap in life expectancy was larger, both in absolute (4.2 in elderly kidney transplant recipients versus 3.2 years in general population elderly) and relative terms (38% versus 15% shorter for males in elderly kidney transplant recipients versus general population elderly, respectively) for elderly kidney transplant recipients than for the elderly general population (Figure 1). From a different point of view, the gap between female elderly kidney transplant recipients and general population females was 10.2 years (48% shorter life expectancy in elderly female kidney transplant recipients), and between male elderly kidney transplant recipients and general population males, 11.2 years (62% shorter life expectancy in elderly male kidney transplant recipients). A caveat is that the transplantation study also included patients >65 years. As Schachtner *et al.* suggest, research

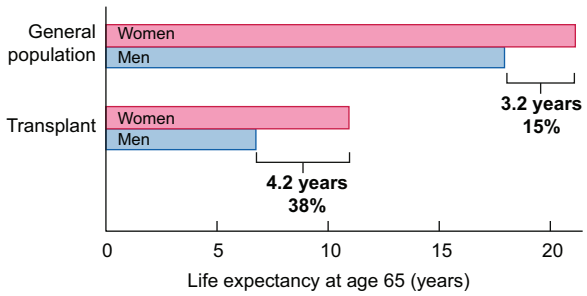

FIGURE 1: Life expectancy gap between males and females in the German general population at age 65 years [29] and males and females in the German single centre Eurotransplant Senior Program, which enrols kidney transplant recipients aged ≥65 years (median age 67 years) receiving kidneys from donors aged ≥65 years [12]. Notice the larger gap between transplanted males and females than between males and females in the general population, both in absolute and in relative terms.

on gender-specific care is warranted. Thus, in addition to exploring ways to increase overall survival in patients on kidney replacement therapy, additional items to address include the reasons and corrective measures for the larger gap in survival between elderly transplanted males and elderly general population males, as identified by Schachtner *et al.* [12]. Moreover, since the different data refer to different populations (elderly transplant patients versus all renal replacement therapy patients), the existence of both diverging trends should be confirmed in larger multinational studies, ideally within the context of the ERA-EDTA Registry.

Montero *et al.* analysed data from the Catalan Renal Registry on kidney transplantation recipients from 1990 to 2011 ($n = 5607$) to explore the impact of weight changes following kidney transplantation on outcomes [13]. Obesity (BMI >33.2 ± 3.3 kg/m^2) was observed in 609 patients (11%) at the time of transplantation and only small changes in weight were observed in this group, while a moderate increase in weight was observed in normal and pre-obese patients and a large increase in the underweight group, especially during the first 2 years. In obese patients, the incidence of delayed graft function was higher and short- and long-term graft survival and graft function were worse. However, BMI variations in obese patients were not associated with improved estimated glomerular filtration rate or graft or patient survival. Factors associated with lower patient survival in multivariate analysis included increasing age, male sex and pre-existent cardiovascular disease, but not obesity or weight change. Among modifiable variables, a dialysis vintage >1 year prior to transplantation was associated with lower patient survival. Thus, neither obesity nor decreasing body weight after kidney transplantation was associated with mortality. However, mean BMI in obese individuals in this study was 33.2 ± 3.3 kg/m^2 and results may not apply to more severe obesity typically observed in the USA.

In summary, the present issue of *ckj* contains several reports that shed light or identify novel avenues of research to further decrease the risk of premature death in CKD patients. An overall message is the diversity of risk factors that should be addressed as potential drivers of the increased mortality of advanced CKD patients. Likely, a holistic approach from funding of healthcare to correctable risk factors to unravelling the potential mechanisms linking non-correctable risk factors to mortality has the best chance of achieving the goal of approaching CKD mortality to that of the general population.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Foreman KJ, Marquez N, Dolgert A *et al.* Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018; 392: 2052–2090
2. Ortiz A, Sanchez-Niño MD, Crespo-Barrio M *et al.* The Spanish Society of Nephrology (SENEFRO) commentary to the Spain GBD 2016 report: keeping chronic kidney disease out of sight of health authorities will only magnify the problem. *Nefrologia* 2019; 39: 29–34
3. Perez-Gomez MV, Bartsch LA, Castillo-Rodriguez E *et al.* Clarifying the concept of chronic kidney disease for non-nephrologists. *Clin Kidney J* 2019; 12: 258–261
4. Ortiz A, Covic A, Fliser D *et al.* Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet* 2014; 383: 1831–1843
5. Williamson EJ, Walker AJ, Bhaskaran K *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430–436
6. Gansevoort RT, Hilbrands LB. CKD is a key risk factor for COVID-19 mortality. *Nat Rev Nephrol* 2020; 1–2; doi: 10.1038/s41581-020-00349-4 (Epub ahead of print)
7. Cambray S, Bermudez-Lopez M, Bozic M *et al.*; on behalf of the NEFRONA investigators. Association of a single nucleotide polymorphism combination pattern of the Klotho gene with non-cardiovascular death in patients with chronic kidney disease. *Clin Kidney J* 2020; 13: 1017–1024
8. Loesch G, Cruz JAW, Pecoits-Filho R *et al.*; on behalf of the BRAZPD Investigators. Public health investments and mortality risk in Brazilian peritoneal dialysis patients. *Clin Kidney J* 2020; 13: 1012–1016
9. Chilcot J, Farrington K. Self-reported antidepressant use in haemodialysis patients is associated with increased mortality independent of concurrent depression severity. *Clin Kidney J* 2020; 13: 1109–1110
10. Schroijen MA, van Diepen M, Hamming JP *et al.*; the NECOSAD Study Group. Mortality after amputation in dialysis patients is high but not modified by diabetes status. *Clin Kidney J* 2020; 13: 1077–1082
11. Fuller DS, Dluzniewski PJ, Cooper K *et al.* Combinations of mineral and bone disorder markers and risk of death and hospitalizations in the international Dialysis Outcomes and Practice Patterns Study. *Clin Kidney J* 2020; 13: 1056–1062
12. Schachtner T, Otto NM, Reinke P. Two decades of the Eurotransplant Senior Program: the gender gap in mortality impacts patient survival after kidney transplantation. *Clin Kidney J* 2020; 13: 1091–1100
13. Montero N, Quero M, Arcos E *et al.* Effects of body weight variation in obese kidney recipients: a retrospective cohort study. *Clin Kidney J* 2020; 13: 1068–1076
14. Fernández-Fernández B, Valiño-Rivas L, Sánchez-Niño MD *et al.* Albuminuria downregulation of the anti-aging factor klotho: the missing link potentially explaining the association of pathological albuminuria with premature death. *Adv Ther* 2020; 37: 62–72
15. Fernandez-Fernandez B, Izquierdo MC, Valiño-Rivas L *et al.* Albumin downregulates Klotho in tubular cells. *Nephrol Dial Transplant* 2018; 33: 1712–1722
16. Ruiz-Andres O, Sanchez-Niño MD, Moreno JA *et al.* Downregulation of kidney protective factors by inflammation: role of transcription factors and epigenetic mechanisms. *Am J Physiol Renal Physiol* 2016; 311: F1329–F1340
17. Sanchez-Niño MD, Fernandez-Fernandez B, Ortiz A. Klotho, the elusive kidney-derived anti-ageing factor. *Clin Kidney J* 2020; 13: 125–127
18. Neyra JA, Moe OW, Pastor J *et al.* Performance of soluble Klotho assays in clinical samples of kidney disease. *Clin Kidney J* 2020; 13: 235–244
19. Navarro-González JF, Sánchez-Niño MD, Donate-Correa J *et al.* Effects of pentoxifylline on soluble Klotho concentrations and renal tubular cell expression in diabetic kidney disease. *Diabetes Care* 2018; 41: 1817–1820
20. Prescribing information for Lexapro® (escitalopram oxalate). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021323s047lbl.pdf (26 October 2020, date last accessed)
21. Palmer SC, Natale P, Ruospo M *et al.* Antidepressants for treating depression in adults with end-stage kidney disease treated with dialysis. *Cochrane Database Syst Rev* 2016; CD004541
22. Guirguis A, Chilcot J, Almond M *et al.* Antidepressant usage in haemodialysis patients: evidence of sub-optimal practice patterns. *J Ren Care* 2020; 46: 124–132
23. Assimon MM, Brookhart MA, Flythe JE. Comparative cardiac safety of selective serotonin reuptake inhibitors among individuals receiving maintenance hemodialysis. *J Am Soc Nephrol* 2019; 30: 611–623
24. Snitker S, Doerfler RM, Soliman EZ *et al.* Association of QT-prolonging medication use in CKD with electrocardiographic manifestations. *Clin J Am Soc Nephrol* 2017; 12: 1409–1417
25. Chilcot J, Farrington K. The case for selective withdrawal of antidepressants in patients with advanced kidney disease. *J Am Soc Nephrol* 2019; 30: 1339–1340
26. Danese MD, Halperin M, Lowe KA *et al.* Refining the definition of clinically important mineral and bone disorder in hemodialysis patients. *Nephrol Dial Transplant* 2015; 30: 1336–1344
27. Fernandez-Prado R, Fernandez-Fernandez B, Ortiz A. Women and renal replacement therapy in Europe: lower incidence, equal access to transplantation, longer survival than men. *Clin Kidney J* 2018; 11: 1–6
28. Kramer A, Pippias M, Noordzij M *et al.* The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2016: a summary. *Clin Kidney J* 2019; 12: 702–720
29. Average life expectancy (period life table): Germany, period of years, sex, completed age. https://www-genesis.destatis.de/genesis/online? operation=previous&levelindex=1&step=1&titel=Result&levelid=1603712436829&acceptscookies=false#abreadcrumb (25 October 2020, date last accessed)