Interventions to Improve Survival in People with End-Stage Kidney Disease on Dialysis

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Reducing premature death in people with end-stage kidney disease (ESKD) requires a multifaceted intervention strategy. People with ESKD are at risk due to life-threatening infections, cardiovascular issues, and dialysis-related issues. Therefore, Fresenius Medical Care is instituting and advocating for a range of practical interventions to improve quality of life and survival rates among people with ESKD, who are at ongoing risk of life-threatening infections, cardiovascular disease, and dialysis-related complications.

People with ESKD on dialysis have a higher risk of death than the general population, and these risks are particularly high in the first 90 days after initiating dialysis.[1] Cardiovascular (CV) disease is reported as the leading cause of mortality among people on dialysis followed by infection (Figure 1).[2]

Prior to the onset of the COVID-19 pandemic, there was a slow but steady improvement in adjusted all-cause mortality among U.S. patients with ESKD from 179.8 deaths per 1000 patients in 2011 to 159.1 deaths per 1000 patients in 2019.[3] The crucial challenge continues to be reducing premature death in people with ESKD on dialysis. Evidence-based clinical interventions with the potential to lower CV and infection-related mortality in people with ESKD are of paramount importance in improving their quality and quantity of life.[4]

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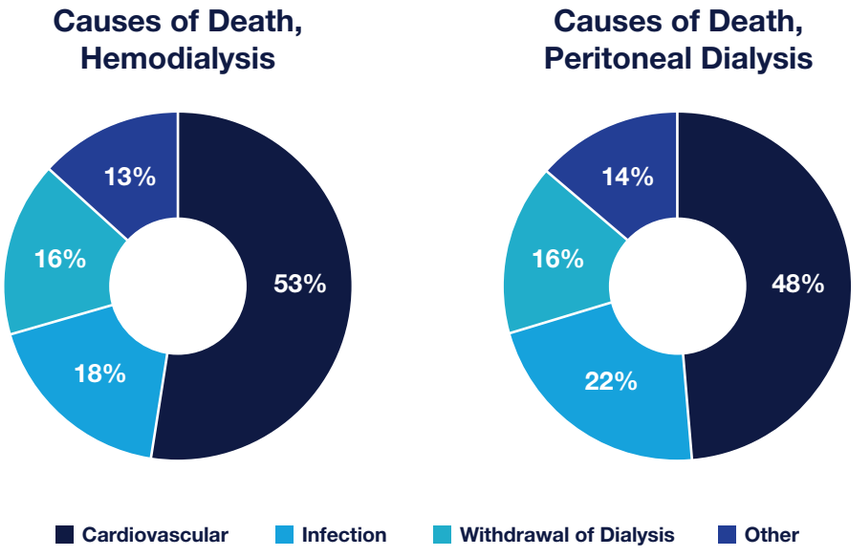
I. Interventions to Lower CV Mortality

Increasing the frequency and/or the duration of hemodialysis (HD) is often referred to as Extended HD (EHD). Several studies have examined the relationship between EHD and mortality.[5,6,7,8] While neither extended-nocturnal hemodialysis thrice-weekly nor 5-treatments/week daily dialysis have been shown to improve mortality, both types of EHD can reduce myocardial stress by lowering interdialytic weight gains and improve left ventricular hypertrophy by lowering blood pressure and optimizing volume status. The three-day weekend interdialytic time interval, which has been associated with increased all-cause, CV, and infection-related mortality,[9,10] can be avoided by prescribing more frequent HD.

FIGURE 1 | CAUSE OF DEATH AMONG PEOPLE WITH ESKD WITH A REPORTED CAUSE OF DEATH IN THE U.S., BY MODALITY

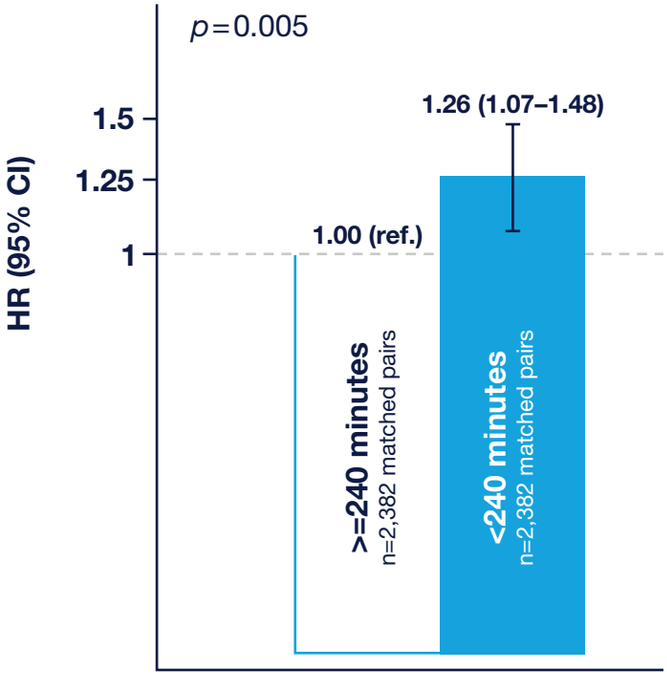


Many studies have shown that shorter-length dialysis sessions are associated with decreased survival. In a large national cohort of U.S. HD patients, session lengths shorter than 240 minutes showed significant association with increased all-cause mortality (Figure 2).[8] Prescribing at least 4 hours of HD may assist with better volume management and BP control, improve HD tolerance, and reduce mortality.

Missed and shortened HD treatments are associated with a higher risk of death,[9] with half of missed treatments due to treatment non-adherence.[10] Clearly, interventions that mitigate the effects of missed treatments due to nonadherence can potentially reduce the risk of hospitalization and mortality. Avoidance and rapid rescheduling of missed treatments are opportunities for reducing CV events and avoidable hospitalizations, with one study showing that missed and rescheduled treatments reduced rates of hospitalization in the subsequent 7 days by 20% compared to not rescheduling treatment (incidence rate ratio of 1.68 (1.29–2.21 95% Confidence Interval (CI)) for rescheduling versus 2.09 (1.76–2.49 95% CI) for not rescheduling).[10]

Interdialytic weight gain is a perennial challenge in the management of people with ESKD receiving in-center hemodialysis, and concomitant high ultrafiltration requirements are often associated with poor tolerance of the hemodialysis session and intradialytic hypotension. For patients with residual urine output, diuretics to maximize urine output is an underutilized intervention, with a recent study showing as many as 46% of incident HD patients prescribed diuretics 90 days after HD initiation, considerably higher than the 23% reported in a Dialysis Outcomes and Practice Patterns Study (DOPPS) publication from 2007.[11] High-dose diuretic use in ESKD has been associated with fewer hospitalizations, lower interdialytic weight gains, and reduced intradialytic hypotension episodes, though not with improved mortality.[12] The use of blood volume monitoring technology and bioimpedance can improve the accuracy of assessment of fluid overload.[13,14]

FIGURE 2 | ASSOCIATION BETWEEN DIALYSIS SESSION LENGTH AND RELATIVE RISK OF DEATH IN PEOPLE ON HEMODIALYSIS[8]



Targeted pharmacologic treatment of heart failure with reduced ejection fraction (HFrEF) has been shown to provide additional benefit.[15] Drug classes with established efficacy in HFrEF are often continued in the ESKD setting, but well-designed and sufficiently powered studies demonstrating mortality benefits are few and far between. There is increasing interest in whether the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) realized in patients with chronic kidney disease (CKD)[16,17,18] provide mortality benefits in ESKD, and several studies examining this question are ongoing.[19,20,21]

The multicenter CONVINCE trial recently demonstrated a mortality benefit for patients undergoing high-volume hemodiafiltration (HVHDF), reporting a reduction in all-cause mortality compared to conventional high-flux hemodialysis (Hazard Ratio (HR) 0.77, 0.65–0.93 95% CI).[22] Most of the benefits of HVHDF seem to be due to reduced CV mortality, and the benefits were particularly found in patients age > 65 (HR 0.68, 0.53–0.89 95% CI), patients without diabetes (HR 0.65, 0.48–0.87 95% CI), and patients with an arteriovenous (AV) fistula (HR 0.77, 0.64–0.94 95% CI). Additional real-world evidence will provide insight into other patient populations who may likewise benefit from HVHDF. It remains to be seen whether additional interventions to improve cardiovascular risk in patients with ESKD will be additive to the observed benefits of HVHDF.

II. Interventions to Lower Bacterial Infection-Related Mortality

The management of ESKD with HD increases the risk of bloodstream infections (BSIs) because it requires frequent access to the bloodstream via needles or central venous catheters (CVCs). Patients with ESKD are at additional risk for BSIs due to ESKD-related interventions in multiple arms of the immune system.[23] BSIs in people treated with hemodialysis have decreased steadily over the last decade with better infection control practices. The National Healthcare Safety Network (NHSN) reported a decrease in CVC-related BSIs from 2.16 infections per 100 patient months in 2014 to 1.21 infections per 100 patient months in 2019.[24] This finding was attributed to implementing a set of "core interventions" for BSI reduction, including patient and staff education, structured access observation, chlorhexidine use, and catheter hub disinfection, as well as antimicrobial ointment use at the catheter exit site.[25]

However, a recent meta-analysis has drawn attention to the high rates of bias and overall lack of well-designed clinical trials in this area.[26] Additional infection control measures used during the early part of the SARS-CoV-2 pandemic have been suggested as a cause for reduced BSI observed in 2020. Despite these observed improvements, there has been a growing trend toward CVC dialysis starts, a trend worsened by the COVID-19 pandemic.[27] System-level effort to improve the rate of timely permanent vascular access placement and maturation assessments is important, as is focusing on CVC avoidance at the time of dialysis initiation.

ClearGuard (Figure 3) is a chlorhexidine-impregnated cap-plus-dipstick designed to screw onto the arterial and venous hubs of a CVC. A couple of landmark studies have shown that ClearGuard use significantly reduced the risk of BSIs in dialysis patients (Figure 4).[28,29] Recently, the LOCK IT-100 Trial examined the efficacy of a CVC antibiotic lock solution containing taurolidine and heparin and demonstrated a 71% rate reduction and a 6% absolute risk reduction in BSIs compared to heparin alone.[30] While efforts to reduce the high prevalence of CVCs are important, the high rate of CVC use means that routinely deploying reliable and scalable approaches to reduce CVC infections must also be a patient safety priority.

Among people treated with peritoneal dialysis (PD), peritonitis has a negative impact on clinical outcomes. Several studies have shown that peritonitis is independently associated with higher risk of all-cause, infection-related, and CV mortality.[31] With increasing uptake of PD in the U.S., initiatives that lower peritonitis risk, such as the application of topical antibiotic cream to the PD catheter exit site, proper exit site care, and antimicrobial prophylaxis prior to invasive gastrointestinal or invasive gynecological procedures, are key to allowing patients to continue to use PD safely and effectively over the long term by quickly resolving or avoiding peritonitis.[32]

Approximately 20% of infections in people with ESKD on dialysis are due to pulmonary etiology and the mortality rate is more than 10-fold higher than the general population.[33] The COVID-19 pandemic brought into focus the important role of other respiratory illnesses, including influenza and *Streptococcus pneumoniae*. Vaccinations are a vital strategy for reducing morbidity and mortality in dialysis patients, who typically mount poor overall antibody response when compared to healthy individuals.

High-dose diuretic use in ESKD has been associated with fewer hospitalizations, lower interdialytic weight gains, and reduced intradialytic hypotension episodes, though not with improved mortality.[12]

FIGURE 3 | CLEARGUARD ANTIMICROBIAL BARRIER CAP

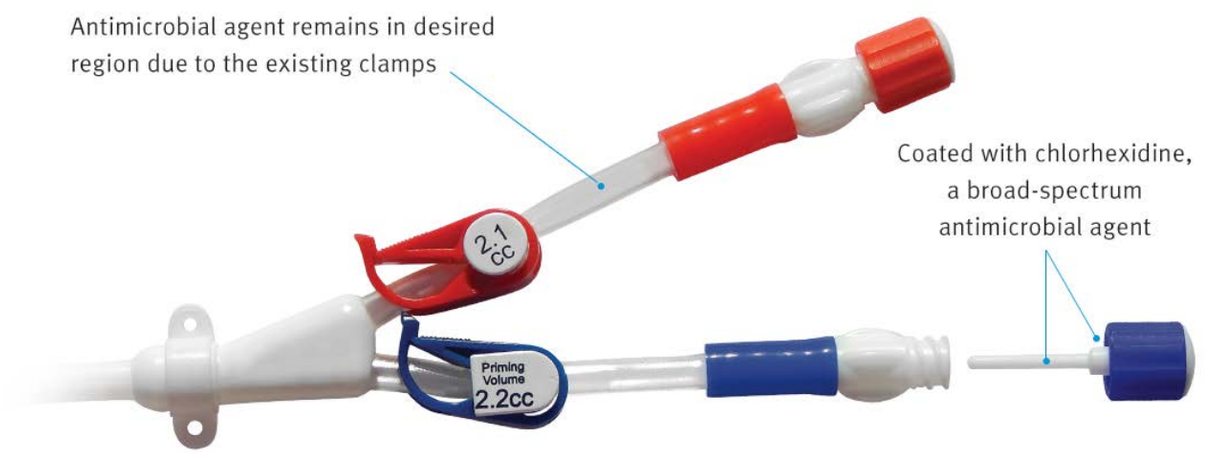
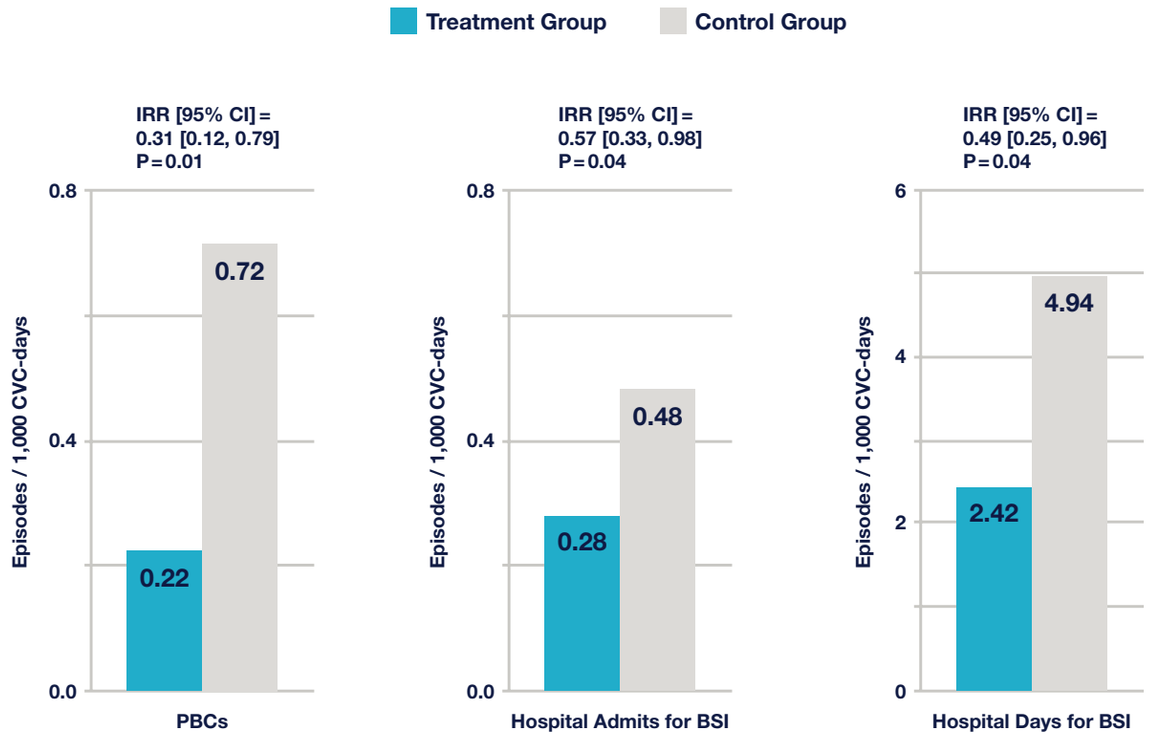


FIGURE 4 | REDUCTION IN CATHETER-RELATED BLOODSTREAM INFECTIONS WITH CLEARGUARD AND TAUROLIDINE/HEPARIN[28]



A primary series of COVID-19 vaccination reduced infection risks in patients with ESKD by 45% compared to unvaccinated patients.[34] In May 2022, approximately 70% of prevalent patients with ESKD had at least one COVID-19 vaccination, and about 50% received subsequent vaccinations.[35] Since September 2022, the fraction of patients with ESKD who remain up to date with COVID-19 vaccination has fallen well below 10%.[36] Even as the SARS-CoV-2 pandemic shifts to "endemic" status, redoubling efforts to ensure patients with ESKD receive updated COVID-19 vaccines remains one of the most effective preventive public health strategies.

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Influenza has been associated with pneumonia as well as multisystem complications leading to increased mortality in individuals with ESKD.[25] The Advisory Committee on Immunization Practices (ACIP) recommends yearly inactivated or recombinant quadrivalent influenza vaccine for people on dialysis.[37] ACIP also recommends that all people with ESKD should receive pneumococcal vaccination, which has been shown to reduce mortality, with frequency dependent on the vaccine type and vaccine history of the patient. Older data strongly suggests that both influenza and pneumococcal vaccination reduce all-cause mortality, with influenza vaccination alone yielding an adjusted odds ratio for mortality of 0.71 (0.65–0.77 95% CI), pneumococcal vaccination alone an adjusted odds ratio of 0.76 (0.70–0.82 95% CI), and both vaccines together an adjusted odds ratio of 0.61 (0.55–0.68 95% CI) for mortality, compared to receiving neither vaccine.[38]

Multifaceted interventions as outlined in Figure 5 can help reduce mortality in individuals with ESKD. Instituting these strategies remains a key priority for the Global Medical Office of Fresenius Medical Care.

FIGURE 5 | PRACTICAL INTERVENTIONS TO REDUCE MORTALITY IN PATIENTS WITH ESKD

- Reduce missed and shortened treatments
- Reduce interdialytic weight gains
  - **Routine reassessment of dry weight**
  - **Moderate sodium and fluid intake during interdialytic interval**
  - **Diuretic use if residual kidney function**
- Optimize dialysis session length for volume management
- Pharmacologic interventions in HFrEF
- Expansion of high-volume hemodiafiltration
- CVC avoidance and reduction strategies
- Routine utilization of catheter caps to reduce catheter infections
- Peritonitis risk reduction
- Widespread vaccination programs for SARS-CoV-2, influenza, and *Streptococcus pneumoniae*

Dinesh Chatoth, MD
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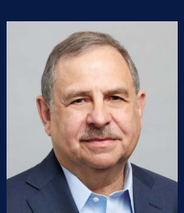
Dr. Chatoth is the Chief Clinical Officer of Fresenius Kidney Care and serves as Chair of the Pharmaceutical & Therapeutics Committee. He is the former president and Chief Executive Officer of Georgia Nephrology, a 16-member physician practice in Atlanta, Georgia. Dr. Chatoth has also served in different leadership roles at the Gwinnett Health System in Georgia, including serving as the Chair of the Department of Medicine. He is also the former Co-Chair of the East Division Medical Advisory Board for Fresenius Medical Care. He has worked with the K-DOQI workgroup for Peritoneal Dialysis and currently serves as a member of the PDOPPS US Advisory Workgroup. He has a keen interest in promoting home dialysis as a modality of choice for patients requiring renal replacement therapy and oversees home therapy initiatives for the Global Medical Office.

Benjamin Hippen, MD, FASN, FAST
Global Head of Clinical Affairs, Global Medical Office
Chief Medical Officer, Care Delivery

As the Global Head of Clinical Affairs and Chief Medical Officer of Care Delivery, Dr. Hippen oversees the global clinical care delivery programs for Fresenius Medical Care, ensuring we deliver exceptional care and support to all patients under our care. Dr. Hippen specializes in ethical, organizational, and public policy issues including nephrology and transplantation. His contributions have advanced patient care initiatives and influenced broader clinical leadership, integrating transplantation into the dialogue among practicing nephrologists and within our Care Delivery framework.

Dr. Hippen received an undergraduate degree from Rice University and completed his medical school and internal medicine residency training at the Baylor College of Medicine. Thereafter, he completed a general nephrology and transplant nephrology fellowship at the University of Alabama in Birmingham. After completing his nephrology and transplant training, Dr. Hippen joined Metrolina Nephrology Associates, P.A. in Charlotte, North Carolina, a 40-nephrologist private practice, where he served as the medical director of two in-center hemodialysis facilities and, for several years, served as the medical director of a home therapies facility. During his time in Charlotte, he became a Clinical Professor of Medicine at the UNC Chapel Hill School of Medicine. Prior to joining Fresenius Medical Care in September 2021, Dr. Hippen served terms on the Ethics Committee and Membership and Professional Standards Committees of the Organ Procurement and Transplantation Network, served on the Board of Directors and was the chair of the Medical Advisory Board of ESRD Network 6, and served on the founding physician practice board of InterWell Health. Consonant with his ongoing research interests in ethical, organizational, and public policy issues in nephrology and transplantation, Dr. Hippen is the author of more than 70 peer-reviewed articles, essays, reviews, and book chapters.



Jeffrey L. Hymes, MD
Senior Consultant to the Global Chief Medical Officer

Dr. Hymes joined FME as Associate Chief Medical Officer in 2007 after three decades in nephrology practice and governance. He became Senior Vice President and Associate CMO for FMCNA in 2012, and in 2020, became Chief Medical Officer, Care Delivery, and Executive Vice President, Global Head of Clinical Affairs, serving in this role until 2024.

He co-founded REN Corporation in 1986 and National Nephrology Associates (NNA) in 1998. He served as NNA's President and Chief Medical Officer from 1998 to 2004. He was President of Nephrology Associates, a 32-physician nephrology practice serving Middle Tennessee, from 1989 to 2012 and is a former member of the Renal Physician Association's Board of Directors.

He is a graduate of Yale College and the Albert Einstein College of Medicine. He served his medical internship and residency at Yale New Haven Medical Center and received subspecialty training in nephrology at Boston University. Dr. Hymes is board certified in internal medicine and nephrology and was previously certified in critical care.

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