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ORIGINAL ARTICLE

# Impact of arteriovenous fistula formation on trajectory of kidney function decline: a target trial emulation

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## ABSTRACT

**Background.** Prior nonrandomized studies have suggested nephroprotective effects of arteriovenous fistula (AVF) formation, but these are plausibly susceptible to immortal time and selection biases.
**Methods.** We studied patients attending nephrology clinics in the West of Scotland during 2010–22 with an estimated glomerular filtration rate (eGFR) ≤15 mL/min/1.73 $m^2$ and no prior AVF. Using target trial emulation and a sequential trial design, we simulated a hypothetical trial that would randomize patients to either undergo AVF formation immediately or not to undergo AVF formation. The primary outcome was the difference in eGFR slope for the first 6 months of follow-up, estimated using a mixed-effects model. The secondary outcomes were 5-year absolute risks of dialysis and death, estimated using the Aalen–Johansen and Kaplan–Meier estimators respectively.
**Results.** A total of 1364 unique patients (mean age 51.1 years, 55.7% male) contributed 3125 person-trials, with 561 in the AVF and 2564 in the no AVF group. Mean eGFR was 12.6 mL/min/1.73 $m^2$ and the median number of eGFR measurements per person-trial was 7 (interquartile range 4–12). Slope of eGFR decline did not differ significantly between the AVF and no AVF groups (between-group difference –0.67 mL/min/1.73 $m^2$/year, 95% CI –1.43, 0.10). The 5-year absolute risk of dialysis was 87% (95% CI 84, 91) in the AVF group and 75% (95% CI 73, 77) in the no AVF group, and the 5-year survival probability was 77% (95% CI 70, 83) in the AVF group and 67% (95% CI 64, 69) in the no AVF group.
**Conclusions.** In this study of patients with advanced chronic kidney disease, there was no evidence of a nephroprotective effect of AVF formation.

**Keywords:** arteriovenous fistula, chronic kidney disease, target trial emulation

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## KEY LEARNING POINTS

**What was known:**

- Previously published retrospective studies were suggestive of a nephroprotective effect of arteriovenous fistula formation.
- These study designs are susceptible to selection and immortal time biases.

**This study adds:**

- In this study, these biases are addressed with target trial emulation and a sequential trial design.
- Using these statistical techniques, we identified no impact of arteriovenous fistula formation on estimated glomerular filtration rate slope for the first 6 months of the trial.

**Potential impact:**

- While important for reliable long-term haemodialysis access, arteriovenous fistula formation has no role as a treatment to delay chronic kidney disease progression.

## INTRODUCTION

Stabilizing renal function in chronic kidney disease (CKD) and thus delaying the initiation of dialysis is a prime goal of nephrology care. Pharmacological strategies offering proven benefit include blood pressure control [1, 2], renin–angiotensin–aldosterone system inhibition [3, 4] and, more recently, treatment with finerenone [5] and sodium-glucose cotransporter 2 inhibitors [6, 7]. Over recent years, arteriovenous fistula (AVF) formation has been noted in several observational studies to be associated with a reduced rate of decline in estimated glomerular filtration rate (eGFR) and delayed initiation of dialysis, hence being postulated to have a 'nephroprotective' effect [8–11].

The first report of this potential protective effect of AVF was published in 2015 and showed a slowing of eGFR decline in an observational uncontrolled study of 123 patients undergoing AVF formation [8]. A subsequent large nationwide study conducted in 6540 US veterans showed a significant reduction in the rate of eGFR decline in the AV access group compared with a group of patients starting dialysis via a central venous catheter (CVC) [9]. Two other cohort studies compared patients undergoing AVF formation to those worked up for peritoneal dialysis (PD), with one concluding that AVF formation was nephroprotective and the other one showing no significant difference between groups [10, 11]. All these studies are characterized by potential weaknesses in the selection of the control groups, as only individuals surviving to CVC or PD catheter insertion would be included, introducing immortal time bias.

Given these methodological challenges, it remains unclear whether AVF formation causally impacts the rate of eGFR loss in patients with advanced CKD. Our hypothesis was that the observed effect is unlikely to be solely attributed to AVF creation, and that confounding and immortal time or selection biases may have artificially produced eGFR time-trends suggesting a falsely protective effect of AVF. The primary aim of our study was to investigate the difference in eGFR slopes between patients undergoing AVF formation and a control group using target trial emulation methodology [12]. Our secondary aim was to investigate whether any changes in eGFR slope translate into differences in time to initiation of dialysis and death.

## MATERIALS AND METHODS

### Data sources

Strathclyde Electronic Renal Patient Record (SERPR, VitalPulse, Chelmsford, UK) is a regional renal database with information on outpatient renal care, dialysis and transplantation, covering a population of 1.7 million in the West of Scotland since 2010. It has full coverage of patients receiving nephrology care in this region. This database has been used extensively in health and biomedical research in Scotland [13–15]. SERPR has active interfaces with regional Scottish Care Information Stores across the region that ensure complete capture of laboratory results and outcomes such as date of death.

We used SERPR to identify patients with CKD stage 5 (eGFR $\leq$15 mL/min/1.73 m$^2$) and retrieved clinician and administrative-entered data such as clinical notes, diagnoses, registers of prescriptions, outpatient clinic appointments, laboratory tests, blood pressure and weight.

The study protocol and use of routine healthcare data was approved by the National Health Service (NHS) Greater Glasgow and Clyde data protection officer (Caldicott Guardian approval reference number NHSGGC/1061/04May23).

### Target trial protocol

We specified a protocol for a hypothetical target trial [16] which would randomize patients attending a pre-dialysis nephrology clinic with eGFR $\leq$15 mL/min/1.73 m$^2$ to immediately receive AVF surgery vs not to immediately receive AVF surgery. Next, we emulated each component of the target trial protocol using observational data. The mapping of the target trial domains onto elements of an emulated trial is illustrated in Supplementary data, Table S1

### Eligibility criteria

Adult patients (aged 18–65 years) who had a Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 [17] eGFR of $\leq$15 mL/min/1.73 m$^2$ and attended the pre-dialysis outpatient nephrology clinic in the West of Scotland, or were otherwise marked as pre-dialysis by a healthcare practitioner, between 1 January 2010 and 1 May 2022 were identified. Individuals older than 65 years of age were excluded to attempt to limit the effect on frailty on the sample, and to avoid unintentionally including patients who had no likelihood of being candidates for AV fistula formation. Patients with incomplete AV access records, pre-existing AVF or AV graft (AVG) creation and those with a history of dialysis were excluded. The eligibility criteria are listed in Supplementary data, Table S1.

### Treatment strategies and treatment assignment

The treatment strategies of interest were immediate AVF formation vs no AVF formation. A sequential trial approach was used to assign eligible participants to the treatment groups [18]. A similar approach has recently been employed to analyse the survival benefit of renal transplantation [19]. Every patient had a date when they were first eligible to enter the trial, i.e. when all eligibility criteria were met. Each eligible patient undergoing AVF formation was assigned to the AVF group on the date of their procedure. For every patient entering the trial in the AVF group, a sequential trial was generated. The interval between the date they were first eligible, and the start of the trial was applied to all other participants and if they had not undergone AVF formation and met the eligibility criteria, the participants were assigned to the no AVF group. As such, patients could be assigned to the no AVF group multiple times, and patients undergoing AVF formation could also be assigned to the no AVF group prior to their procedure, which mitigates immortal time bias [20]. Importantly, within each sequential trial a patient in the AVF group could not be compared to themselves prior to AVF formation. In each sequential trial, persons in the no AVF group were also matched to the AVF group for sex, age (within 5 years) and eGFR (within 0.5 mL/min/1.73 $m^2$) at time of trial. Supplementary data, Section S1 shows an example of how sequential trials were generated.

### Start and end of follow-up

Follow-up (time zero) started at treatment assignment. For the primary outcome, patients were followed up to 6 months from treatment assignment, or dialysis/death if these occurred before then. For the secondary outcomes, patients were followed up to dialysis, death, loss to follow-up or administrative censoring. Loss to follow-up was defined as no serum creatinine available in the last 6 months of the trial, where dialysis or death had not occurred. If a serum creatinine was not available in this time period, follow-up ended on the date of the last available serum creatinine. Patients who underwent pre-emptive kidney transplantation were censored at the time of transplantation. Observation ceased on 30 December 2022, allowing at least 6 months of follow-up.

### Outcomes

The primary outcome was the between-group difference in eGFR slope during the first 6 months of follow-up. A 6-month period was judged to be sufficient to detect a meaningful haemodynamic effect of AVF formation, while balancing the risk of events such as acute kidney injury affecting the eGFR slope with no relation to AVF formation.

Secondary outcomes were absolute risks of dialysis and death at 5 years and eGFR at the time of dialysis onset.

### Statistical analysis

Multivariable logistic regression was used to calculate propensity scores, with interactions used to improve balance of the model. Stabilized inverse probability of treatment weights (IPTW) [21] were then derived and used to adjust for baseline confounders. These variables included age, sex, number of renal unit admissions in the year prior to trial date, Scottish Index of Multiple Deprivation [22], comorbidities, medication use, serum and urine biochemical measurements, systolic and diastolic blood pressure, weight, and a marker for 'late presenters' to the nephrology clinic (eGFR <20 mL/min/1.73 $m^2$ at first attendance). Supplementary data, Table S2 lists all the baseline confounders measured. Baseline confounders were updated at the start of each sequential trial. The last available laboratory test was sampled within the 6-month window prior to trial date, with the exception of urinary protein:creatinine ratio, blood pressure and weight, where a 12-month window was used. Standardized mean differences were used to assess covariate balance before and after weighting. We considered values between –0.1 and 0.1 to be indicative of no major imbalance [23].

Where data were missing, these were imputed by multiple imputation by chained equations with 20 imputations using R package 'mice: multivariate imputation by chained equations' [24].

eGFR values were collected for the 6-month period following the start of follow-up and used to analyse the primary outcome. Slopes were estimated using a mixed-effects model with time in years and treatment with AVF formation as fixed effects, and patient identifier as a random effect allowing for individual-level variation weighted for IPTW. For the secondary outcomes, the Aalen–Johansen estimator was used to calculate the absolute risk for dialysis while accounting for competing risk of death, and the Kaplan–Meier estimator for all-cause death. eGFR at onset of dialysis was analysed using the Student's *t*-test.

Each analysis was carried out weighted for IPTW, for each imputed dataset. Standard errors [and thus 95% confidence intervals (CIs)] were estimated using a non-parametric bootstrap with 1000 samples for each imputed dataset. This was employed primarily to limit the inflating effect upon variance that the sequential trial design could induce by having patients exist multiple times in the no AVF group. Rubin's rules were then used to derive an estimate for each result and its corresponding 95% CI. This method has been described as 'MI Boot' in prior literature [25].

All analyses were performed using R Studio v 4.2.2 [26].

## RESULTS

### Baseline characteristics

Figure 1 details how exclusion criteria were applied. A total of 1364 patients met all eligibility criteria, of which 813 (59.6%) had undergone AVF formation. After re-applying the exclusion criteria on the date of surgery, the number of person-trials in the AVF group was 561 (200 excluded due to dialysis initiation before AVF formation, 3 due to AV graft formation, 32 due to AVF formation older than 65 years, and 17 due to AVF formation after administrative censoring). Sequential trials generated 2592 person-trials in the no AVF group, forming a dataset of 3153 person-trials. After excluding patients lost to follow-up at the start of the trial, the final dataset consisted of 3125 records.

The baseline characteristics of the pre-sequential trial population are presented in Supplementary data, Table S3 2.2% of the baseline variables were missing and therefore multiply imputed. Supplementary data, Table S4 details the missing data for each parameter.

The distribution of the stabilized IPTW calculated is shown in Supplementary data, Fig. S1, and Fig. S2 shows plots of the distributional overlap of propensity scores before and after IPTW. The characteristics of the study cohort at treatment allocation of sequential trials before and after IPTW adjustment are detailed in Table 1, with Supplementary data, Table S5 detailing laboratory tests and medications. The standardized mean difference of

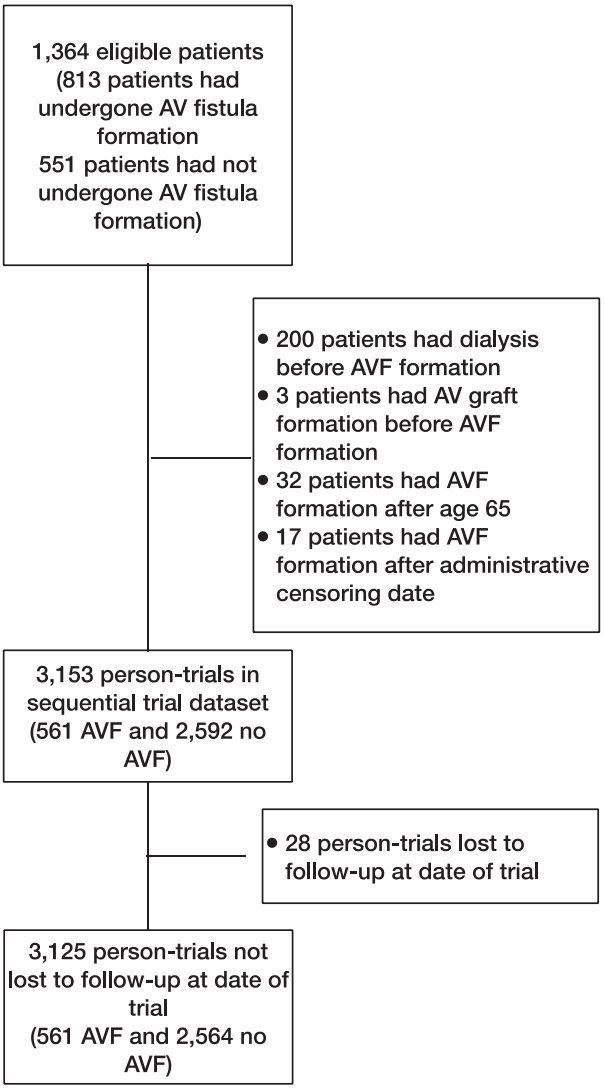


**Figure 1:** Flow diagram showing creation of trial dataset.

the baseline variables before and after IPTW adjustment are also shown in Table 1 and illustrated in Supplementary data, Figs S3 and S4 The post-adjustment standardized mean difference was between –0.1 and 0.1 for all baseline variables.

### Effect of AVF on eGFR slope analyses

The median number of eGFR measurements for the first 6 months of follow-up per person-trial was 7 (interquartile range 4–12).

In the first 6 months of the trial, adjusting with IPTW, annualized eGFR decline was not significantly different in the AVF group compared with the no AVF group (–0.67 mL/min/1.73 $m^2$/year, 95% CI –1.43, 0.10) (Table 2). Figure 2 shows a boxplot of eGFR slope calculated with univariate mixed effect models (with CIs derived from bootstrapped estimates) for the AVF and no AVF groups, for the 6 months before and after the start of the trial. The rate of eGFR decline decelerated in both groups [AVF group: from –11.92 mL/min/1.73 $m^2$/year (95% CI –13.43, –10.41) to –4.31 mL/min/1.73 $m^2$/year (95% CI –5.10, –3.53); no AVF group: –11.63 mL/min/1.73 $m^2$/year (95% CI –12.21, –11.05) to –3.41 mL/min/1.73 $m^2$/year (95% CI –3.80, –3.02)].

### Association between AVF creation and subsequent dialysis initiation and death

In the unadjusted population of 1364 patients, 1050 (77.0%) were dialysed [720 (88.6%) in the AVF group and 330 (59.9%) in the no AVF group], and 488 (35.8%) died [281 (34.6%) in the AVF group and 207 (37.6%) in the no AVF group] during follow-up. The IPTW-adjusted mean time to dialysis was 356 days for the AVF group and 437 days for the no AVF group.

In an IPTW-adjusted analysis, the absolute risk for dialysis was significantly higher in the AVF group [50% (95% CI 43, 57) and 87% (95% CI 84, 91) at 1 and 5 years, respectively] compared with the no AVF group [40% (95% CI 38, 42) and 75% (95% CI 73, 77) at 1 and 5 years, respectively]. The AVF group had a higher survival probability [96% (95% CI 95, 98) and 77% (95% CI 70, 83) at 1 and 5 years, respectively] compared with the no AVF group [93% (95% CI 92, 94) and 67% (95% CI 64, 69) at 1 and 5 years, respectively] (Tables 3 and 4). The cumulative incidence for dialysis calculated using the Aalen–Johansen estimator is shown in Fig. 3 and the survival probability derived from the Kaplan–Meier estimator is shown in Fig. 4.

The IPTW-adjusted mean eGFR at initiation of dialysis for the AVF group was 8.98 mL/min/1.73 $m^2$, compared with 8.64 mL/min/1.73 $m^2$ for the no AVF group ($t = 1.5$, $P = .243$).

## DISCUSSION

We applied target trial emulation methodology to study AVF formation as an intervention to delay the progression of CKD. We found that AVF formation was not associated with a significant change in the rate of decline of eGFR in the first 6 months following the intervention, which goes against a nephroprotective effect. Further to this, the finding that there was no difference in the eGFR at start of dialysis suggests comparable criteria for offering dialysis for both groups. We observed an association between AVF formation and higher risk of dialysis and lower risk of death, albeit with no significant difference in eGFR at the time of dialysis onset—these findings should be interpreted with caution as they most likely represent residual confounding.

Previous studies have largely supported a nephroprotective effect of AVF formation. Indeed, a recent meta-analysis of retrospective observational studies addressing this question supported a positive effect of AVF formation on eGFR trajectory though with a low level of certainty [27]. Golper *et al.* [8] was the first to suggest such an effect in a small exploratory study with no control group and no adjustment for potential confounders. In a propensity score–matched cohort study of 6540 US veterans, Sumida *et al.* [9] showed a significant deceleration of eGFR decline in patients with an AVF or AVG (from –5.6 to –4.1 mL/min/1.73 $m^2$/year) as opposed to an acceleration in eGFR decline in patients starting dialysis via a CVC. However, in this study the CVC group had a higher prevalence of comorbidities such as cardiovascular disease and congestive heart failure, and there is growing evidence suggesting that undergoing dialysis via a CVC is a surrogate of frailty [28, 29]. Furthermore, a deceleration in the rate of eGFR decline was shown in the AVF group regardless of fistula maturation, which indicates other factors may be implicated in the observed time-trend. A Canadian propensity score–matched study [10] of patients with AVF vs patients

**Table 1: Characteristics of the study cohort at treatment allocation of sequential trials.**

| | | Unadjusted | | | IPTW adjusted | | |
|---|---|---|---|---|---|---|---|
| Category | Parameter | AVF $n = 561$ | No AVF $n = 2564$ | Standardized mean difference | AVF $n = 561$ | No AVF $n = 2564$ | Standardized mean difference |
| Basic data | Male sex, *n* (%) | 315 (56.15) | 1615 (62.99) | –0.068 | 344 (61.32) | 1587 (61.90) | –0.002 |
| | Mean age at trial (SD) | 52.33 (10.25) | 55.00 (7.30) | –0.299 | 54.78 (8.54) | 54.45 (7.98) | 0.037 |
| | Late presenter—eGFR CKD-EPI ≤20 mL/min/1.73 $m^2$ at first OPC, *n* (%) | 181 (32.26) | 868 (33.85) | –0.016 | 204 (36.36) | 875 (34.13) | 0.025 |
| | Systolic BP (mmHg, SD) | 144.31 (21.73) | 142.94 (21.95) | 0.063 | 143.23 (21.27) | 143.20 (21.81) | 0.002 |
| | Diastolic BP (mmHg, SD) | 80.88 (12.16) | 80.32 (11.50) | 0.047 | 80.65 (11.17) | 80.43 (11.57) | 0.019 |
| | Weight (kg, SD) | 87.97 (25.20) | 85.57 (21.16) | 0.103 | 83.42 (20.61) | 85.39 (21.22) | –0.085 |
| Admissions in year before trial start date, *n* (%) | 0 | 206 (36.72) | 2278 (88.85) | –0.521 | 440 (78.43) | 2036 (79.41) | –0.005 |
| | 1 | 260 (46.35) | 196 (7.64) | 0.387 | 83 (14.80) | 378 (14.74) | 0.002 |
| | 2 | 67 (11.94) | 59 (2.30) | 0.096 | 22 (3.92) | 97 (3.78) | 0.001 |
| | 3 | 19 (3.39) | 25 (0.98) | 0.024 | 9 (1.60) | 36 (1.40) | 0.003 |
| | 4 | 9 (1.60) | 5 (0.20) | 0.014 | 3 (0.53) | 13 (0.51) | –0.000 |
| | 5 | 0 (0.00) | 1 (0.04) | 0.000 | 0 (0.00) | 1 (0.04) | –0.000 |
| Scottish Index of Multiple Deprivation (SIMD) quintiles, *n* (%) | 1—most deprived 20% | 266 (47.42) | 958 (37.36) | 0.101 | 246 (43.85) | 1013 (39.51) | 0.046 |
| | 2 | 108 (19.25) | 455 (17.75) | 0.015 | 89 (15.86) | 457 (17.82) | –0.019 |
| | 3 | 75 (13.37) | 407 (15.87) | –0.026 | 81 (14.44) | 391 (15.25) | –0.008 |
| | 4 | 58 (10.34) | 354 (13.81) | –0.036 | 80 (14.26) | 339 (13.22) | 0.011 |
| | 5–least deprived 20% | 55 (9.80) | 390 (15.21) | –0.055 | 62 (11.05) | 363 (14.16) | –0.030 |
| Comorbidities, *n* (%) | Diabetes mellitus | 259 (46.17) | 1079 (42.08) | 0.041 | 209 (37.25) | 1076 (41.97) | –0.045 |
| | Ischaemic heart disease | 74 (13.19) | 375 (14.63) | –0.014 | 72 (12.83) | 372 (14.51) | –0.017 |
| | Peripheral vascular disease | 9 (1.60) | 54 (2.11) | –0.005 | 12 (2.14) | 53 (2.07) | 0.001 |
| | Stroke | 33 (5.88) | 136 (5.30) | 0.006 | 24 (4.28) | 139 (5.42) | –0.011 |
| | Cancer | 37 (6.60) | 178 (6.94) | –0.003 | 52 (9.27) | 179 (6.98) | 0.024 |
| | COPD | 13 (2.32) | 30 (1.17) | 0.011 | 6 (1.07) | 35 (1.37) | –0.003 |
| | Heart failure | 20 (3.57) | 90 (3.51) | 0.001 | 10 (1.78) | 91 (3.55) | –0.017 |
| | Hypertension | 265 (47.24) | 1231 (48.01) | –0.008 | 271 (48.31) | 1226 (47.82) | 0.007 |

For the IPTW-adjusted proportions and means, weighted proportions and means were calculated using IPTW as weights, for each multiple imputation. A mean of the results across all 20 imputations is presented on this table. The standardized mean difference provided is the mean for all imputations.
SD, standard deviation; BP, blood pressure; COPD, chronic obstructive pulmonary disease; OPC, outpatient clinic.

**Table 2: Results of a mixed effects model analysis of eGFR 6 months after start of the trial, with AVF formation and time in years as fixed effects and patient identifiers as random effects to allow for individual level variation.**

| Variable | Estimate | 95% CI |
|---|---|---|
| Intercept (eGFR in mL/min/1.73 $m^2$) | 12.79 | 12.69, 12.89 |
| AVF formation (eGFR change in mL/min/1.73 $m^2$) | –1.29 | –1.48, –1.09 |
| Time in years (eGFR change in mL/min/1.73 $m^2$/year) | –3.38 | –3.76, –2.99 |
| AVF formation * time in years (eGFR change in mL/min/1.73 $m^2$/year) | –0.67 | –1.43, 0.10 |

95% CIs calculated by non-parametric bootstrap with 1000 samples.

undergoing PD catheter placement also showed a decelerating effect of AVF formation on the eGFR trajectory. In this study, the PD patients were younger with a lower body mass index, and a lower rate of cardiovascular disease. Most importantly, the PD group had a significantly higher 12-month dialysis initiation rate compared with the AVF group (78.7% vs 39.3%), suggesting the decision to site a PD catheter was timed differently from AVF formation. A Swedish study by Lundström *et al.* [11] compared patients undergoing AV access formation vs PD catheter insertion, and although the eGFR decline was decelerated after AV access placement, a similar trend in eGFR decline was also noted in the PD group. No prospective randomized controlled trials have addressed the impact of AVF formation on eGFR decline, but in a clinical trial of AVF ligation (vs not) in stable kidney transplant recipients, no change in eGFR trajectory was seen after AVF ligation compared with the control group [30].

In our secondary outcomes analyses, AVF formation was associated with an increased risk of dialysis, but no difference in eGFR at dialysis onset. Importantly, the latter suggests the same criteria were applied for both groups, indicating the difference in dialysis risk is not attributable to a difference in how and when dialysis is initiated. The AVF group also had a lower risk of death compared with the no AVF group. It is likely that these observations indicate a degree of residual confounding. Although we were able to adjust for traditional predictors of CKD progression (male sex, age, proteinuria, cardiovascular disease and the rate of eGFR decline) [31, 32], there are additional important unmeasured variables at play. Frailty, for example, was not available as a variable in our dataset and is associated both with dialysis and mortality [33]. Patients with higher frailty scores may be overrepresented in the no AVF group as they are usually not referred for AVF formation, and this could explain the observed differences in absolute risk of dialysis and death, with the increased risk of death competing with dialysis initiation. Further to this, it is possible that reverse causation bias at least in part explains the higher risk of dialysis in patients undergoing AVF formation. It is clinically plausible that the decision for dialysis initiation has been made by the time a patient is referred for AVF formation, and as such the outcome has in

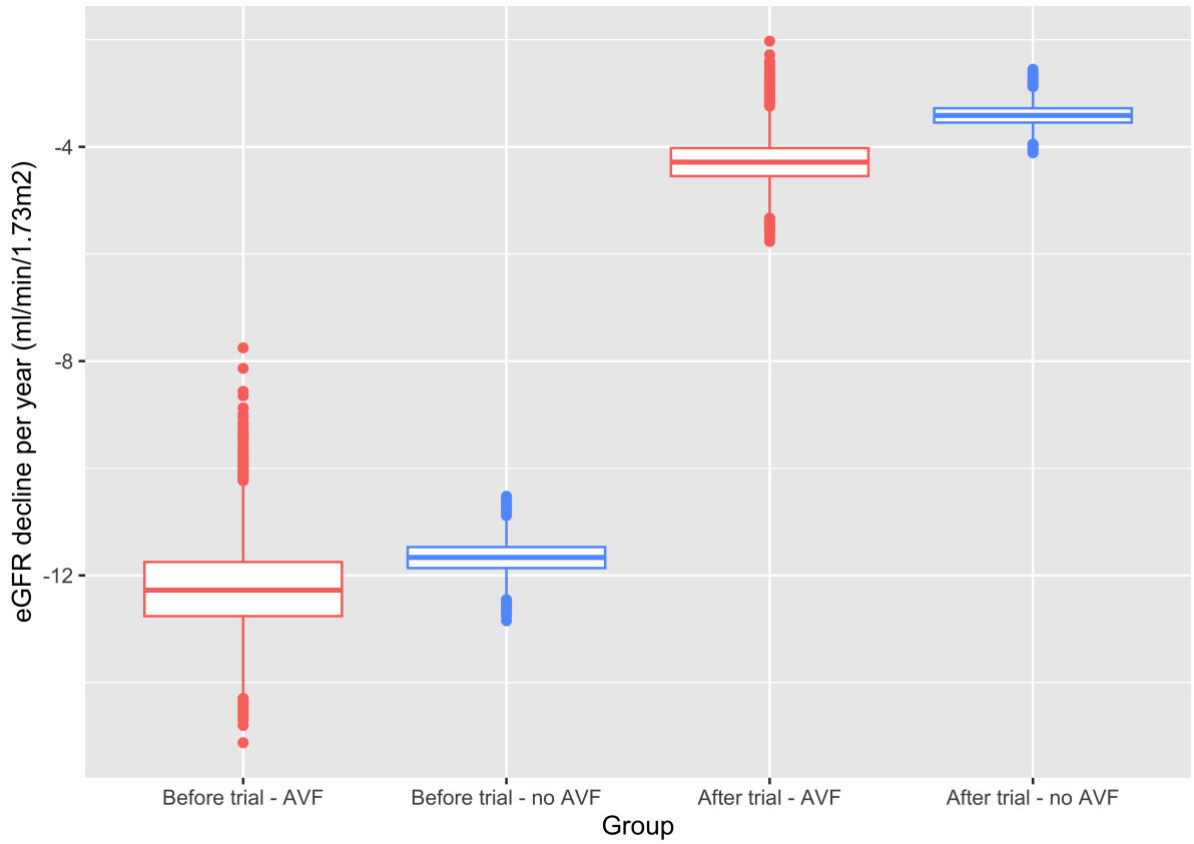


**Figure 2:** Boxplot showing eGFR slope estimates (mL/min/1.73 $m^2$/year) calculated by mixed-effects model with non-parametric bootstrapping (1000 samples) for the 6-month period before trial start date, and the first 6 months of trial, for AVF and no AVF groups.

**Table 3: Absolute risk (cumulative incidence) of dialysis estimated using Aalen–Johansen estimator.**

| | | Absolute risk (%) of dialysis at each time of follow-up (95% CI) | | | | |
|---|---|---|---|---|---|---|
| Outcome | Group | 1 year | 2 years | 3 years | 4 years | 5 years |
| Dialysis | AVF | 50 (43, 57) | 75 (69, 81) | 82 (77, 87) | 86 (82, 90) | 87 (84, 91) |
| | No AVF | 40 (38, 42) | 59 (57, 61) | 67 (65, 69) | 73 (71, 75) | 75 (73, 77) |

**Table 4: Survival probability estimated using Kaplan–Meier estimator.**

| | | Survival probability (%) at each time of follow-up (95% CI) | | | | |
|---|---|---|---|---|---|---|
| Outcome | Group | 1 year | 2 years | 3 years | 4 years | 5 years |
| Death | AVF | 96 (95, 98) | 94 (92, 96) | 89 (85, 92) | 81 (76, 86) | 77 (70, 83) |
| | No AVF | 93 (92, 94) | 87 (85, 88) | 80 (78, 82) | 73 (71, 75) | 67 (64, 69) |

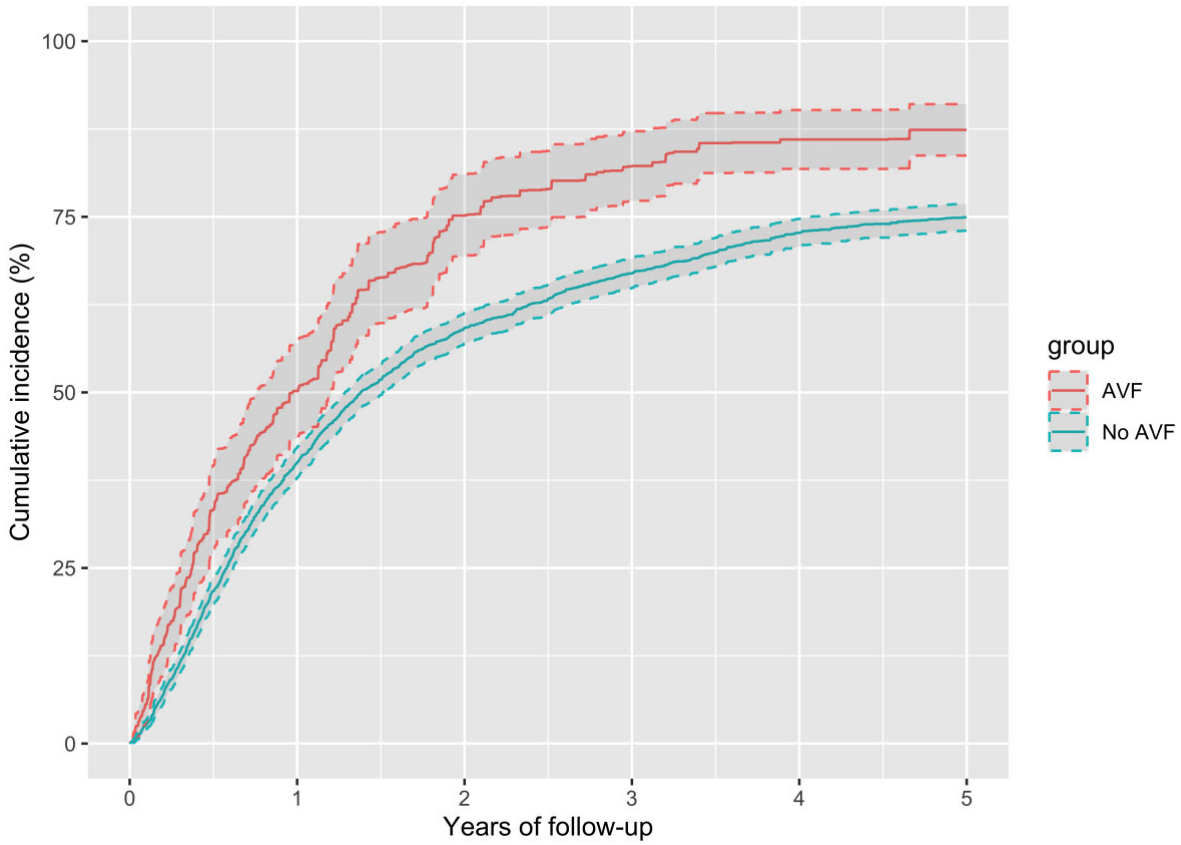


**Figure 3:** Five-year cumulative incidence plot for dialysis, calculated using Aalen–Johansen estimator. The 95% CIs are estimated using non-parametric bootstrap with 1000 samples.

effect been preselected by this exposure. Finally, the presence of a functioning dialysis access may lower the uremic threshold at which dialysis is initiated, as it would not require the logistics and procedural risk of CVC placement, which by its nature tends to be inserted within a less rigid timeframe than an AVF. The lack of a significant difference in eGFR at start of dialysis however, suggests this is unlikely to fully explain the observed associations.

It is important to consider why a reduction in the rate of eGFR decline was observed in both groups. Loss of muscle mass in patients with advancing CKD can artifactually change the eGFR trajectory dissociating it from the underlying true progression rate. Termed 'uraemic sarcopenia', this is a complex phenomenon attributed to inflammation, metabolic acidosis and growth hormone/insulin resistance [34]. As CKD progresses, loss of muscle mass is likely to contribute to reduced creatinine

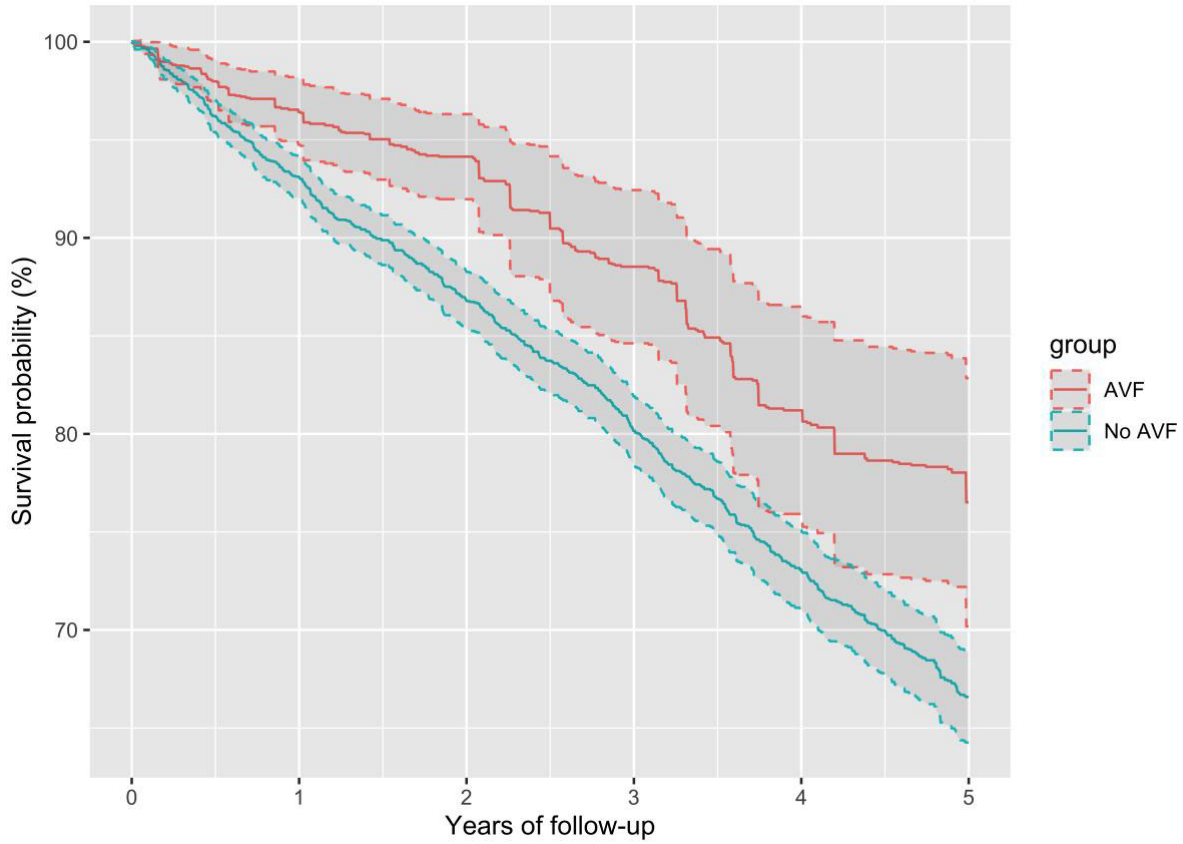


**Figure 4:** Five-year Kaplan–Meier plot. The 95% CIs are estimated using non-parametric bootstrap with 1000 samples.

generation, leading to an overestimation of eGFR [35]. This is a particularly valid confounder when considering the mean eGFR for AVF formation was between 12 and 13 mL/min/1.73 $m^2$, with dialysis initiation happening between 8 and 9 mL/min/1.73 $m^2$, and this phenomenon is most likely to occur at low eGFRs such as this. Alternate explanations for this deceleration in both groups include the diluting effect of volume expansion in more advanced CKD, or potentially better concordance with pharmacotherapy as patients progress in their CKD journey.

This study brings some strengths in addressing this research question. We have applied target trial emulation methodology with a sequential trial approach limiting selection and immortal time biases that were present in prior studies. We also adjusted our dataset for a wider variety of relevant variables than prior studies addressing this question. Nevertheless, target trial emulation by itself is not able to remove confounding by indication [16].

Our study also has several limitations that need to be acknowledged. In designing a study that included all CKD5 patients, it is possible that at least some participants will not have been realistically eligible to receive the treatment intervention. As already discussed, we could not adjust for physicians and patients' preferences nor for frailty, which are likely sources of residual confounding, especially for the outcome of all-cause mortality and dialysis. We did however adjust for multiple comorbidities and limited the age of study participants to younger than 65 years of age in an attempt to mitigate this shortcoming. We also could not include data on muscle mass, volume status or uraemic symptoms, which would allow for a more nuanced understanding of key confounders in creatinine time-trends and in decisions to start dialysis. The lack of robust data on AVF maturation also meant we could not carry out any further stratification of our analysis based on the presence or not of a functional AV access.

In summary, using advanced statistical techniques and high-quality observational data in a cohort of patients with stage 5 CKD, our study does not support the existence of a nephroprotective effect of AVF formation indicating the lack of a specific benefit from AVF creation on the progression rate. Ultimately, a prospective clinical trial remains the optimal way to address this question given muscle mass, uraemia, volume overload, frailty, nephrologists' perceptions and patients' preferences are key unmeasured confounders and rarely included in existing databases.

## SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* Online.

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## AUTHORS' CONTRIBUTIONS

L.L.H., P.C.T., J.P.T., P.B.M. and S.S. designed the study. E.L.F. provided advice on study design and statistical analysis. L.L.H. and

J.P.T. extracted the data from the electronic record database. L.L.H. analysed the data. All authors approved the manuscript prior to submission.

## DATA AVAILABILITY STATEMENT

The data underlying this article were provided by NHS Greater Glasgow and Clyde by permission. Data may be shared on request to the corresponding author with permission of NHS Greater Glasgow and Clyde.

## CONFLICT OF INTEREST STATEMENT

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