



# Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study

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## ABSTRACT OBJECTIVE

To identify the optimal estimated glomerular filtration rate (eGFR) at which to initiate dialysis in people with advanced chronic kidney disease.

## DESIGN

Nationwide observational cohort study.

## SETTING

National Swedish Renal Registry of patients referred to nephrologists.

## PARTICIPANTS

Patients had a baseline eGFR between 10 and 20 mL/min/1.73 m<sup>2</sup> and were included between 1 January 2007 and 31 December 2016, with follow-up until 1 June 2017.

## MAIN OUTCOME MEASURES

The strict design criteria of a clinical trial were mimicked by using the cloning, censoring, and weighting method to eliminate immortal time bias, lead time bias, and survivor bias. A dynamic marginal structural model was used to estimate adjusted hazard ratios and absolute risks for five year all cause mortality and major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) for 15 dialysis initiation strategies with eGFR values between 4 and 19 mL/min/1.73 m<sup>2</sup> in increments of 1 mL/min/1.73 m<sup>2</sup>. An eGFR between 6 and 7 mL/min/1.73 m<sup>2</sup> (eGFR<sub>6-7</sub>) was taken as the reference.

## RESULTS

Among 10 290 incident patients with advanced chronic kidney disease (median age 73 years; 3739 (36%) women; median eGFR 16.8 mL/min/1.73 m<sup>2</sup>), 3822 started dialysis, 4160 died, and 2446 had a major adverse cardiovascular event. A parabolic relation was observed for mortality, with the lowest risk for eGFR<sub>15-16</sub>. Compared with dialysis initiation at eGFR<sub>6-7</sub>, initiation at eGFR<sub>15-16</sub> was associated with a 5.1% (95% confidence interval 2.5% to 6.9%) lower absolute five year mortality risk and 2.9% (0.2% to 5.5%) lower risk of a major adverse cardiovascular event, corresponding to hazard ratios of 0.89 (95% confidence interval 0.87 to 0.92) and 0.94 (0.91 to 0.98), respectively. This 5.1% absolute risk difference corresponded to a mean postponement of death of 1.6 months over five years of follow-up. However, dialysis would need to be started four years earlier. When emulating the intended strategies of the Initiating Dialysis Early and Late (IDEAL) trial (eGFR<sub>10-14</sub> v eGFR<sub>5-7</sub>) and the achieved eGFRs in IDEAL (eGFR<sub>7-10</sub> v eGFR<sub>5-7</sub>), hazard ratios for all cause mortality were 0.96 (0.94 to 0.99) and 0.97 (0.94 to 1.00), respectively, which are congruent with the findings of the randomised IDEAL trial.

## CONCLUSIONS

Very early initiation of dialysis was associated with a modest reduction in mortality and cardiovascular events. For most patients, such a reduction may not outweigh the burden of a substantially longer period spent on dialysis.

## Introduction

Worldwide, more than 3 million people with kidney failure need maintenance dialysis treatment for survival.<sup>1-4</sup> These numbers are expected to double by 2030.<sup>2</sup> The societal and individual burden of kidney failure treated by dialysis is high: for instance, the US Medicare fee-for-service spending for beneficiaries with kidney failure was \$36.6bn in 2018.<sup>3</sup> The mean annual healthcare costs per haemodialysis patient are \$93 191 in the US,<sup>3</sup> and similar numbers are reported for European countries.<sup>5-8</sup> Dialysis treatment also places a large burden on patients' daily lives.<sup>9 10</sup> Determining the optimal timing of dialysis is therefore of substantial importance.

Despite extensive previous literature, evidence on whether an optimal glomerular filtration rate to start dialysis exists, and if so where it lies, is lacking. Previous observational studies that attempted to investigate multiple estimated glomerular filtration

## WHAT IS ALREADY KNOWN ON THIS TOPIC

The IDEAL trial showed no differences between early and late dialysis initiation in patients with advanced kidney disease, but the achieved separation in glomerular filtration rate (GFR) was narrow

Previous observational studies compared a limited number of dialysis initiation strategies, used small sample sizes, or were significantly affected by immortal time, lead time, and survivor biases

The optimal timing of dialysis initiation to reduce mortality and cardiovascular events is therefore unclear

## WHAT THIS STUDY ADDS

Early dialysis initiation (estimated GFR 15-16 mL/min/1.73 m<sup>2</sup>) was associated with a 5.1% lower absolute risk of five year mortality compared with eGFR 6-7 mL/min/1.73 m<sup>2</sup>

The absolute risk of major adverse cardiovascular events was 3.3% lower for earlier initiation

To obtain this survival benefit, dialysis would need to be started on average four years earlier

rate (eGFR) strategies have been limited by insufficient power,<sup>11-13</sup> immortal time bias,<sup>14,15,16,17</sup> or lead time and selection biases.<sup>16-32</sup> In 2010 the Initiating Dialysis Early and Late (IDEAL) trial showed that a strategy to start dialysis at an eGFR of 10-14 mL/min/1.73 m<sup>2</sup> was not superior to one of waiting until symptoms develop or eGFR is 5-7 mL/min/1.73 m<sup>2</sup>.<sup>33</sup> This is reflected in subsequent guidelines, which recommend starting dialysis when symptoms and signs attributable to kidney failure arise rather than at a specific kidney function.<sup>34-40</sup> However, IDEAL compared only two strategies, from which an optimal eGFR cannot be derived. In addition, the achieved eGFR separation in IDEAL was 1.8 (9.0 v 7.2) mL/min/1.73 m<sup>2</sup> by the Modification of Diet in Renal Disease equation. That a kidney function outside this range exists at which starting dialysis is associated with better outcomes therefore remains possible, and uncertainty on this question among providers persists.<sup>41</sup>

In the absence of evidence on an optimal eGFR level, decision making may be influenced by other factors. Large between country variation exists in the mean eGFR at start of dialysis, from approximately 5 mL/min/1.73 m<sup>2</sup> in Taiwan to 8.5 mL/min/1.73 m<sup>2</sup> in the UK and 11 mL/min/1.73 m<sup>2</sup> in the US.<sup>36</sup> Some health systems in the US even start at a mean eGFR of 16-17 mL/min/1.73 m<sup>2</sup>,<sup>42</sup> which may be partly explained by potential financial incentives and differences in patient case mix (for example, diabetes, sodium intake, and overweight). This broad heterogeneity may lead to differences in outcomes and healthcare costs.

Ideally, this complex question would be studied in a multi-armed randomised trial. However, such a trial is unlikely to be conducted because the sample size needed is large and recruitment is problematic: IDEAL recruited 828 patients over eight years. In the absence of trial evidence, clinical decisions could be aided by well conducted observational studies that explicitly mimic the strict design criteria of a multi-armed trial. We therefore used novel analytical methods to investigate the effects of different dialysis initiation strategies based on eGFR levels, using data from a nationwide cohort of non-dialysis dependent patients with advanced chronic kidney disease under the care of a nephrologist. In other words, our study investigated what would happen if the decision to start dialysis was based on eGFR only.

## Methods

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>43</sup>

## Data sources

We used data from the Swedish Renal Registry, a nationwide registry of patients with chronic kidney disease categories G3-5 attending routine nephrologist care in Sweden,<sup>44 45</sup> during the period 2007-17. The Swedish Renal Registry includes information from outpatient nephrologist visits, including aetiology of chronic kidney disease, laboratory tests, blood

pressure, and other results obtained from routine clinical examination, as well as the date of kidney replacement therapy (either kidney transplantation or long term dialysis). Enrolment in the registry is mandatory in Sweden when patients reach an eGFR <30 mL/min/1.73 m<sup>2</sup>, but some clinics may start reporting them earlier. Subsequent outpatient visits to nephrology care (on average two to three a year per patient) are registered until death or emigration. Nearly all (96%) nephrology clinics in Sweden report to the Swedish Renal Registry, and the estimated national coverage is >75% for patients referred to nephrologists with chronic kidney disease G4-5.<sup>46</sup>

Using each citizen's unique personal identification number, we linked the Swedish Renal Registry data to other national registries. The Swedish Prescribed Drug Registry provided complete information on all prescribed drugs dispensed at Swedish pharmacies<sup>47</sup>; the Swedish Patient Registry added information on all outpatient specialist consultations and hospital admissions occurring in Swedish healthcare since 1997 and was used to obtain information on comorbidities and outcomes<sup>48</sup>; and the Swedish Death Registry added information on the date and causes of death.<sup>49</sup> All these registries are run by the Swedish National Board of Welfare, a government institution, and are considered to have no or minimal loss to follow-up. All patients are informed about their participation in the registry and have the possibility to opt out at any time.

## Study design and patient selection

This observational study emulated a pragmatic clinical trial comparing the effect of initiating dialysis at various eGFR levels on mortality and cardiovascular outcomes in people with advanced chronic kidney disease,<sup>50</sup> and it generally follows the approach proposed by Sjölander and colleagues.<sup>51</sup> Supplementary table A outlines the protocol of such a trial and the emulation procedure. Explicit emulation of a trial, and in particular aligning the start of follow-up with the assignment of treatment strategies, eliminates immortal time bias, selection/survivor bias, and lead time bias, which significantly affected previous observational studies.<sup>51-53</sup> A detailed explanation of how these biases arise can be found in the supplementary methods. Our analysis included patients who met the following eligibility criteria between 1 January 2007 and 31 December 2016: age 18 years or older; an eGFR measurement between 10 and 20 mL/min/1.73 m<sup>2</sup>, with a previous eGFR measurement between 10 and 30 mL/min/1.73 m<sup>2</sup> as confirmation; no history of kidney replacement therapy; and at least one available measurement of systolic blood pressure, diastolic blood pressure, total calcium, phosphate, albumin, and haemoglobin. We defined baseline as the first time when all of these eligibility criteria were met. We calculated eGFR with the Chronic Kidney Disease Epidemiology equation from routine plasma creatinine measurements performed by enzymatic or corrected Jaffe methods traceable to isotope dilution mass spectroscopy standards.<sup>54</sup> As information on ethnicity is not available in Sweden by

law, we assumed all patients to be of white European ethnicity.

### Treatment strategies

We compared 15 dialysis initiation strategies with eGFR values ranging between 4 and 19 mL/min/1.73 m<sup>2</sup> in increments of 1 mL/min/1.73 m<sup>2</sup>. We took an eGFR between 6 and 7 mL/min/1.73 m<sup>2</sup> (eGFR<sub>6-7</sub>) as the reference group, as this is the eGFR at which most patients start dialysis in Sweden. The treatment strategies under investigation are based solely on eGFR values and do not include other factors that may drive the decision to start dialysis in clinical practice, such as volume overload or symptoms.

### Study outcomes

The primary outcome was five year all cause mortality. The secondary outcome was major adverse cardiovascular events (defined as a composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). ICD-10 (international classification of diseases, 10th revision) codes for ascertainment of cardiovascular outcomes are listed in supplementary table B. We followed each patient until the first of occurrence of an event, five years after baseline, or administrative censoring (1 June 2017).

### Statistical analysis

We used the method of cloning, censoring, and weighting to emulate a target trial comparing the effects of different dialysis initiation strategies<sup>50 52 55-57</sup> (see supplementary methods and supplementary figure A for a detailed discussion on target trial emulation and the cloning, censoring, and weighting method). Briefly, we created a dataset with 15 copies of each eligible patient (cloning step) and assigned each of the replicates to one of the treatment strategies at the start of follow-up. Thereafter, we assessed at monthly intervals whether replicates adhered to their assigned treatment strategy; replicates were censored as soon as their actual treatment deviated from their assigned treatment strategy, thereby ensuring that replicates followed their assigned strategy (censoring step). To adjust for the potential selection bias induced by this artificial censoring, each patient received a time varying inverse probability weight<sup>58</sup> (weighting step). Informally, the denominator of the weights was the probability that a replicate remained uncensored during follow-up (that is, remained on the assigned treatment strategy). These weights created 15 pseudopopulations in which censoring was independent of measured prognostic factors. We estimated the time varying weights by fitting a pooled logistic model for the monthly probability of remaining uncensored, including variables for time and the baseline and time varying covariates listed in supplementary table B. Models were fitted separately for each treatment strategy to allow for treatment-covariate interaction.<sup>57 59</sup> The variables for each model and their regression coefficients for the eGFR<sub>6-7</sub> strategy are reported in supplementary table C. To avoid undue

influence of outliers, weights were truncated at the 99.95th centile.<sup>60</sup>

After cloning, censoring, and weighting, we estimated the effect of each dialysis initiation strategy on five year all cause mortality and major adverse cardiovascular events by using a weighted pooled logistic regression model, including an indicator for treatment strategy (modelled as restricted cubic spline with knots at 5, 8, 11, 14, and 17 mL/min/1.73 m<sup>2</sup>), month, month squared, their interactions to allow for non-proportional hazards, and all baseline covariates. This weighted model estimates the parameters of a dynamic marginal structural model when the covariates include all joint determinants of censoring and the outcome.<sup>55</sup> We used the predicted probabilities from this logistic model to estimate the adjusted five year probability of mortality and major adverse cardiovascular events under each treatment strategy and to produce weighted cumulative incidence curves, which were standardized to the baseline distribution of confounders.<sup>61 62</sup> From these probabilities, we also derived five year risk differences, risk ratios, and hazard ratios. We estimated cause specific cumulative incidences to account for the competing event of kidney transplantation.<sup>63 64</sup> In addition, we calculated the five year restricted mean survival times and the differences in these between the dialysis initiation strategies. The restricted mean survival time is interpreted as the average survival time over a fixed follow-up period. Graphically, it corresponds to the area under the survival curve.<sup>65</sup> The difference in five year restricted mean survival time compares the areas under the survival curves for the different dialysis initiation strategies. It is interpreted as the mean postponement of the outcome in one group compared with the reference. We calculated pointwise 95% confidence intervals by using non-parametric bootstrap based on 500 full samples. We compared the five year restricted mean survival time difference with the postponement of dialysis initiation to provide insight into this trade-off. We determined postponement of dialysis initiation by the average eGFR decline before dialysis initiation by using a linear mixed model (supplementary methods). We used R version 3.6.2 for all statistical analyses.

### Sensitivity analyses

We pre-specified several analyses to test the robustness of our main results. Firstly, we emulated the IDEAL trial comparing early initiation (eGFR<sub>10-14</sub>) versus late initiation (eGFR<sub>5-7</sub>) on mortality and major adverse cardiovascular events to validate our analytical methods. We added a third “intermediate initiation” arm (eGFR<sub>7-10</sub>), which includes the mean achieved eGFR in the early initiation arm in IDEAL. Secondly, we did stratified analyses by age ( $\geq 70$  v  $< 70$  years), sex, presence of diabetes, eGFR at baseline (10-15 v 15-20 mL/min/1.73 m<sup>2</sup>), presence of ischaemic heart disease, and presence of heart failure. Thirdly, we investigated the influence of adjustment for measured confounders on our point estimates by sequentially adjusting for baseline and time varying

confounders. Fourthly, we compared results when using non-truncated weights. Fifthly, we excluded patients with cancer at baseline. Sixthly, we used a different analytical method for the competing event of kidney transplantation. We modelled the direct effect of dialysis initiation strategies on mortality, not mediated through kidney transplantation, by adding additional inverse probability of censoring weights.<sup>63</sup> Intuitively, this models the effect of dialysis initiation strategies in a hypothetical world in which no kidney transplantations occur. Seventhly, we additionally adjusted for time dependent measures of urinary albumin to creatinine ratio and plasma potassium in our analyses. This analysis was restricted to the 4286 patients with these measurements available. Although these laboratory values are routinely measured in this population, reporting them to the Swedish Renal Registry was not mandatory until 2015. Because some physicians chose to report this information, whereas others did not, we assumed that these data were missing completely at random.<sup>44</sup> Eighthly, we censored patients who chose conservative treatment (that is, patients explicitly chose treatment of kidney failure without dialysis). We used additional inverse probability of censoring weights to account for informative censoring. Intuitively, this models the effect of dialysis initiation strategies in a hypothetical world in which no patients choose conservative management. Lastly, we analysed our data by using the “from initiation” and “from threshold” method analogous to previous observational studies,<sup>14-29</sup> to show that immortal time bias and selection/survivor bias give an artificial survival advantage to late dialysis initiation.<sup>51 52</sup> A detailed description of these methods and how bias arises is provided in the supplementary methods. Owing to computational efficiency and lower power with 15 strategies, we did subgroup and sensitivity analyses using three dialysis initiation strategies only.

#### Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. As the study was based on anonymised nationwide register data, we have no plans to disseminate the results of the research to study participants. A member of the public read the manuscript after submission to improve its quality and readability.

#### Results

Of 30 180 patients registered in the Swedish Renal Registry during the study period, 10 290 with an eGFR between 10 and 20 mL/min/1.73 m<sup>2</sup> were eligible for inclusion in our study. Supplementary figure B shows the patient selection flowchart, and table 1 describes their baseline characteristics. At baseline, patients had a median age of 73 (interquartile range 63-80) years, 35.7% were women, and 42.1% had diabetes.

The median eGFR was 16.8 (14.3-18.6) mL/min/1.73 m<sup>2</sup>, and 68.9% of the study population had an eGFR between 15 and 20 mL/min/1.73 m<sup>2</sup>.

During follow-up, 3822 patients started dialysis, most with an eGFR between 5 and 8 mL/min/1.73 m<sup>2</sup> (supplementary figure C). Haemodialysis was the initial dialysis modality in 2339 (61.2%) patients and peritoneal dialysis in 1483 (38.8%).

#### Dialysis initiation strategies and risk of mortality or major adverse cardiovascular event

During a median follow-up of 3.1 (1.7-5.0) years, 4160 (40.4%) patients died and 2446 (23.8%) had a major adverse cardiovascular event. Table 2 and figure 1 (top) show the five year absolute risks, risk differences, hazard ratios, and cumulative incidence curves for all cause mortality for all dialysis initiation strategies. For mortality, the absolute risk decreased from eGFR<sub>18-19</sub> to a nadir at eGFR<sub>15-16</sub> and progressively increased again between eGFR<sub>15-16</sub> and eGFR<sub>4-5</sub>. Compared with eGFR<sub>6-7</sub>, five year absolute risk differences varied between an increase of 0.8% (95% confidence interval 0.0% to 1.6%) for eGFR<sub>4-5</sub> and a decrease of 5.1% (2.5% to 6.9%) for eGFR<sub>15-16</sub> (fig 2, top), with corresponding hazard ratios of 1.01 (95% confidence interval 1.00 to 1.02) and 0.89 (0.87 to 0.92), respectively. When we took the mean eGFR at start of dialysis in the US as the reference group (that is, eGFR<sub>11-12</sub>), risk differences varied between an increase of 2.8% (0.5% to 5.3%) and a decrease of 3.1% (0.9% to 5.2%) (supplementary table D). Compared with eGFR<sub>6-7</sub>, the maximum difference in five year restricted mean survival time was 1.6 (95% confidence interval 1.0 to 2.0) months for eGFR<sub>15-16</sub>, and these patients would need to start dialysis on average 47.9 (46.2 to 49.6) months earlier than those with eGFR<sub>6-7</sub> (supplementary tables E and F; fig 3).

For major adverse cardiovascular events, the absolute risk was lowest between eGFR<sub>17-18</sub> and eGFR<sub>11-12</sub> and then progressively increased between eGFR<sub>11-12</sub> and eGFR<sub>4-5</sub> (supplementary table G; fig 2, bottom). Compared with eGFR<sub>6-7</sub>, risk differences varied between an increase of 1.5% and a decrease of 3.3% (fig 2, bottom), and hazard ratios between 1.04 and 0.91, respectively. For eGFR<sub>15-16</sub>, the absolute risk was 2.9% (0.2% to 5.5%) lower and the hazard ratio was 0.94 (0.91 to 0.98). When we took eGFR<sub>11-12</sub> as the reference group, risk differences varied between an increase of 4.7% for eGFR<sub>4-5</sub> and a decrease of 0.2% for eGFR<sub>12-13</sub> (supplementary table H). The five year differences in restricted mean survival time varied between -0.3 and 0.7 months (supplementary table E).

#### Supporting and sensitivity analyses

In our analysis mirroring the GFR thresholds from the IDEAL trial, early dialysis initiation (eGFR<sub>10-14</sub>) was associated with a 3.3% (1.3% to 5.3%) lower five year mortality risk and 3.6% (1.0% to 6.0%) lower risk of major adverse cardiovascular events compared with late initiation (eGFR<sub>5-7</sub>), with hazard ratios of 0.96 (0.94 to 0.99) and 0.96 (0.93 to 1.00), respectively



**Table 1 | Baseline characteristics of patients under nephrologist care with estimated glomerular filtration rate (eGFR) 10-20 mL/min/1.73 m<sup>2</sup> registered in Swedish Renal Registry during January 2007 to December 2016, overall and stratified by early, intermediate, and late dialysis initiation. Values are numbers (percentages) unless stated otherwise**

	Overall (n=10 290)	Dialysis initiation		
		Early (n=10 290)*	Intermediate (n=10 290)*	Late (n=10 290)*
<b>Demographics</b>				
Median (IQR) age, years	73.0 (63.0-80.0)	73.0 (63.0-80.0)	73.0 (63.0-80.0)	73.0 (63.0-80.0)
Age group, years:				
<50	1057 (10.3)	1057 (10.3)	1057 (10.3)	1057 (10.3)
50-59	1030 (10.0)	1030 (10.0)	1030 (10.0)	1030 (10.0)
60-69	2119 (20.6)	2119 (20.6)	2119 (20.6)	2119 (20.6)
70-79	3247 (31.6)	3247 (31.6)	3247 (31.6)	3247 (31.6)
≥80	2837 (27.6)	2837 (27.6)	2837 (27.6)	2837 (27.6)
Female sex	3739 (36.3)	3739 (36.3)	3739 (36.3)	3739 (36.3)
<b>Primary kidney disease</b>				
Diabetes	2427 (23.6)	2427 (23.6)	2427 (23.6)	2427 (23.6)
Hypertension/renovascular	2277 (22.1)	2277 (22.1)	2277 (22.1)	2277 (22.1)
Glomerulonephritis	1066 (10.4)	1066 (10.4)	1066 (10.4)	1066 (10.4)
Polycystic kidney disease	636 (6.2)	636 (6.2)	636 (6.2)	636 (6.2)
Pyelonephritis	313 (3.0)	313 (3.0)	313 (3.0)	313 (3.0)
Other	2083 (20.2)	2083 (20.2)	2083 (20.2)	2083 (20.2)
Unknown	1488 (14.5)	1488 (14.5)	1488 (14.5)	1488 (14.5)
<b>Clinical and laboratory values</b>				
Median (IQR) eGFR before baseline, mL/min/1.73 m <sup>2</sup> †	20.4 (16.4-22.7)	20.4 (16.4-22.7)	20.4 (16.4-22.7)	20.4 (16.4-22.7)
Median (IQR) baseline eGFR, mL/min/1.73 m <sup>2</sup> †	16.8 (14.3-18.6)	16.8 (14.3-18.6)	16.8 (14.3-18.6)	16.8 (14.3-18.6)
Baseline eGFR 15-20 mL/min/1.73 m <sup>2</sup> †	7087 (68.9)	7087 (68.9)	7087 (68.9)	7087 (68.9)
Mean (SD) systolic BP, mm Hg	139.6 (21.0)	139.6 (21.0)	139.6 (21.0)	139.6 (21.0)
Systolic BP category, mm Hg:				
<120	1270 (12.3)	1270 (12.3)	1270 (12.3)	1270 (12.3)
120-139	3774 (36.7)	3774 (36.7)	3774 (36.7)	3774 (36.7)
140-159	3315 (32.2)	3315 (32.2)	3315 (32.2)	3315 (32.2)
≥160	1931 (18.8)	1931 (18.8)	1931 (18.8)	1931 (18.8)
Mean (SD) diastolic BP, mm Hg	76.6 (11.8)	76.6 (11.8)	76.6 (11.8)	76.6 (11.8)
Diastolic BP category, mm Hg:				
<80	5346 (52.0)	5346 (52.0)	5346 (52.0)	5346 (52.0)
80-89	3354 (32.6)	3354 (32.6)	3354 (32.6)	3354 (32.6)
90-99	1201 (11.7)	1201 (11.7)	1201 (11.7)	1201 (11.7)
≥100	389 (3.8)	389 (3.8)	389 (3.8)	389 (3.8)
Mean (SD) body mass index‡	27.9 (5.7)	27.9 (5.7)	27.9 (5.7)	27.9 (5.7)
Mean (SD) total calcium, mmol/L	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)
Total calcium category, mmol/L:				
<2.0	351 (3.4)	351 (3.4)	351 (3.4)	351 (3.4)
2.0-2.19	2156 (21.0)	2156 (21.0)	2156 (21.0)	2156 (21.0)
2.20-2.44	6502 (63.2)	6502 (63.2)	6502 (63.2)	6502 (63.2)
≥2.45	1281 (12.4)	1281 (12.4)	1281 (12.4)	1281 (12.4)
Mean (SD) phosphorus, mmol/L	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)
Phosphorus category, mmol/L:				
<0.8	45 (0.4)	45 (0.4)	45 (0.4)	45 (0.4)
0.8-1.49	6628 (64.4)	6628 (64.4)	6628 (64.4)	6628 (64.4)
1.50-1.99	3215 (31.2)	3215 (31.2)	3215 (31.2)	3215 (31.2)
≥2.0	402 (3.9)	402 (3.9)	402 (3.9)	402 (3.9)
Mean (SD) albumin, g/L	36.5 (4.7)	36.5 (4.7)	36.5 (4.7)	36.5 (4.7)
Albumin category, g/L:				
<25	152 (1.5)	152 (1.5)	152 (1.5)	152 (1.5)
25-29	555 (5.4)	555 (5.4)	555 (5.4)	555 (5.4)
30-39	6889 (66.9)	6889 (66.9)	6889 (66.9)	6889 (66.9)
≥40	2694 (26.2)	2694 (26.2)	2694 (26.2)	2694 (26.2)
Mean (SD) haemoglobin, g/L	119.4 (14.1)	119.4 (14.1)	119.4 (14.1)	119.4 (14.1)
Haemoglobin category, g/L:				
<90	143 (1.4)	143 (1.4)	143 (1.4)	143 (1.4)
90-99	585 (5.7)	585 (5.7)	585 (5.7)	585 (5.7)
100-114	3071 (29.8)	3071 (29.8)	3071 (29.8)	3071 (29.8)
≥115	6491 (63.1)	6491 (63.1)	6491 (63.1)	6491 (63.1)
Median (IQR) UACR, mg/mmol‡	57.6 (11.6-180.0)	57.6 (11.6-180.0)	57.6 (11.6-180.0)	57.6 (11.6-180.0)
UACR category, mg/mmol:				
A1 (<3)	570 (9.9)	570 (9.9)	570 (9.9)	570 (9.9)
A2 (3-29)	1698 (29.4)	1698 (29.4)	1698 (29.4)	1698 (29.4)
A3.1 (30-70)	815 (14.1)	815 (14.1)	815 (14.1)	815 (14.1)
A3.2 (≥70)	2701 (46.7)	2701 (46.7)	2701 (46.7)	2701 (46.7)

(Continued)

Table 1 | Continued

	Overall (n=10 290)	Dialysis initiation		
		Early (n=10 290)*	Intermediate (n=10 290)*	Late (n=10 290)*
Mean (SD) potassium, mmol/L‡	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)
Median (IQR) C reactive protein, ng/mL‡	5.0 (2.1-10.0)	5.0 (2.1-10.0)	5.0 (2.1-10.0)	5.0 (2.1-10.0)
Median (IQR) ferritin, ng/mL‡	150.0 (77.0-274.0)	150.0 (77.0-274.0)	150.0 (77.0-274.0)	150.0 (77.0-274.0)
<b>Comorbidities</b>				
Hypertension	8796 (86.5)	8796 (86.5)	8796 (86.5)	8796 (86.5)
Acute coronary syndrome	1906 (18.5)	1906 (18.5)	1906 (18.5)	1906 (18.5)
Other ischaemic heart disease	3177 (30.9)	3177 (30.9)	3177 (30.9)	3177 (30.9)
Heart failure	2612 (25.4)	2612 (25.4)	2612 (25.4)	2612 (25.4)
Diabetes	4329 (42.1)	4329 (42.1)	4329 (42.1)	4329 (42.1)
Valve disorders	670 (6.5)	670 (6.5)	670 (6.5)	670 (6.5)
Stroke	1243 (12.1)	1243 (12.1)	1243 (12.1)	1243 (12.1)
Other cerebrovascular disease	1300 (12.6)	1300 (12.6)	1300 (12.6)	1300 (12.6)
Atrial fibrillation	1808 (17.6)	1808 (17.6)	1808 (17.6)	1808 (17.6)
Other arrhythmia	898 (8.7)	898 (8.7)	898 (8.7)	898 (8.7)
Peripheral vascular disease	1415 (13.8)	1415 (13.8)	1415 (13.8)	1415 (13.8)
Chronic obstructive pulmonary disease	792 (7.7)	792 (7.7)	792 (7.7)	792 (7.7)
Other lung disease	1605 (15.6)	1605 (15.6)	1605 (15.6)	1605 (15.6)
Venous thromboembolism	816 (7.9)	816 (7.9)	816 (7.9)	816 (7.9)
Cancer in previous year	1025 (10.0)	1025 (10.0)	1025 (10.0)	1025 (10.0)
Liver disease	368 (3.6)	368 (3.6)	368 (3.6)	368 (3.6)
Fracture in previous year	297 (2.9)	297 (2.9)	297 (2.9)	297 (2.9)
<b>Drug use</b>				
β blocker	6736 (65.5)	6736 (65.5)	6736 (65.5)	6736 (65.5)
Calcium channel blocker	6348 (61.7)	6348 (61.7)	6348 (61.7)	6348 (61.7)
Diuretic	7356 (71.5)	7356 (71.5)	7356 (71.5)	7356 (71.5)
ACE inhibitor/ARB	6971 (67.7)	6971 (67.7)	6971 (67.7)	6971 (67.7)
Lipid lowering drug	5610 (54.5)	5610 (54.5)	5610 (54.5)	5610 (54.5)
Potassium binder	1270 (12.3)	1270 (12.3)	1270 (12.3)	1270 (12.3)
Phosphate binder	1034 (10.0)	1034 (10.0)	1034 (10.0)	1034 (10.0)
Erythropoietin stimulating agent	3160 (30.7)	3160 (30.7)	3160 (30.7)	3160 (30.7)
Vitamin D	5977 (58.1)	5977 (58.1)	5977 (58.1)	5977 (58.1)
Digoxin	158 (1.5)	158 (1.5)	158 (1.5)	158 (1.5)
Nitrate	1474 (14.3)	1474 (14.3)	1474 (14.3)	1474 (14.3)
Antiplatelet agent	4345 (42.2)	4345 (42.2)	4345 (42.2)	4345 (42.2)
Anticoagulant	1214 (11.8)	1214 (11.8)	1214 (11.8)	1214 (11.8)
Sodium bicarbonate	4381 (42.6)	4381 (42.6)	4381 (42.6)	4381 (42.6)
<b>Calendar year</b>				
2007-10	3211 (31.2)	3211 (31.2)	3211 (31.2)	3211 (31.2)
2011-13	3473 (33.8)	3473 (33.8)	3473 (33.8)	3473 (33.8)
2014-16	3606 (35.0)	3606 (35.0)	3606 (35.0)	3606 (35.0)
<b>Hospital admissions</b>				
Median (IQR) hospital admissions in previous year	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)
Any hospital admission in previous year	4770 (46.4)	4770 (46.4)	4770 (46.4)	4770 (46.4)
Hospital admission due to cardiovascular causes in previous year	1614 (15.7)	1614 (15.7)	1614 (15.7)	1614 (15.7)

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; BP=blood pressure; IQR=interquartile range; SD=standard deviation; UACR=albumin to creatinine ratio.

\*Owing to cloning step in cloning, censoring, and weighting method, patients' characteristics are identical at baseline for early, intermediate, and late dialysis initiation groups. For detailed explanation of cloning, censoring, and weighting method, see methods section and supplementary methods.

†eGFR was calculated with 2009 Chronic Kidney Disease Epidemiology formula. Patients were required to have two eGFR measurements to be eligible for inclusion. Median time between baseline and previous eGFR measurement was 154 (IQR 93-234) days.

‡Body mass index was missing in 25.8% of patients, UACR in 43.8%, potassium in 29.1%, C reactive protein in 15.9%, and ferritin in 60.3%, because reporting these variables to Swedish Renal registry was not mandatory (supplementary table B). Owing to high degree of missingness, these variables were not used in further analyses and are presented for descriptive purposes only.

(supplementary table I; fig 4). We found similar results when comparing late versus intermediate (eGFR<sub>7-10</sub>) dialysis initiation, in keeping with the achieved eGFR at initiation in the earlier arm of IDEAL. Compared with late dialysis initiation, intermediate initiation was associated with a 2.7% (0.7% to 4.6%) lower five year mortality risk, corresponding to a hazard ratio of 0.97 (0.94 to 1.00).

We observed a lower mortality risk for early dialysis initiation among all subgroups of age, sex, diabetes, eGFR, and ischaemic heart disease (supplementary tables J and K; supplementary figures D-F). Patients with diabetes or heart failure had high absolute five

year mortality and major adverse cardiovascular event risks. For instance, for the early dialysis initiation strategy the five year absolute mortality risk was 59.1% (54.9% to 65.4%) in the subgroup of patients with diabetes and 80.5% (74.1% to 86.1%) in the subgroup with heart failure. Among patients with diabetes, early dialysis initiation (eGFR<sub>10-14</sub>) was associated with a 5.4% (2.1% to 8.1%) lower five year mortality risk and 4.3% (0.2% to 9.1%) lower risk of major adverse cardiovascular events compared with late initiation (eGFR<sub>5-7</sub>), with hazard ratios of 0.96 (0.92 to 1.00) and 0.98 (0.93 to 1.04), respectively. Among patients with heart failure, early dialysis

**Table 2 | Five year absolute risks, risk differences, risk ratios, and hazard ratios for all cause mortality associated with initiating dialysis at estimated glomerular filtration rate (eGFR) values between 4 and 19 mL/min/1.73 m<sup>2</sup> in increments of 1 mL/min/1.73 m<sup>2</sup>, with 6-7 mL/min/1.73 m<sup>2</sup> as reference**

Dialysis initiation strategy (mL/min/1.73 m <sup>2</sup> )	No of patients*	No of outcomes	Median (IQR) eGFR at dialysis initiation† (mL/min/1.73 m <sup>2</sup> )	Five year absolute risk, % (95% CI) <sup>‡c</sup>	Risk difference, % (95% CI) <sup>‡c</sup>	Risk ratio (95% CI) <sup>‡</sup>	Hazard ratio (95% CI) <sup>‡#</sup>
18-19	3483	484	18.5 (18.2-18.7)	50.9 (44.0 to 55.3)	-2.9 (-7.2 to -0.1)	0.95 (0.86 to 1.00)	0.97 (0.87 to 1.02)
17-18	4911	742	17.6 (17.3-17.8)	50.6 (44.1 to 54.4)	-3.2 (-6.9 to -0.8)	0.94 (0.87 to 0.99)	0.93 (0.87 to 0.97)
16-17	6079	1037	16.5 (16.3-16.8)	49.5 (43.9 to 53.9)	-4.3 (-6.8 to -2.1)	0.92 (0.87 to 0.96)	0.90 (0.87 to 0.94)
15-16	7087	1312	15.5 (15.3-15.7)	48.7 (43.9 to 53.4)	-5.1 (-6.9 to -2.5)	0.90 (0.87 to 0.95)	0.89 (0.87 to 0.92)
14-15	7932	1595	14.5 (14.3-14.7)	48.9 (44.1 to 54.0)	-4.9 (-6.6 to -2.5)	0.91 (0.88 to 0.95)	0.90 (0.88 to 0.94)
13-14	8657	1888	13.5 (13.2-13.8)	49.9 (45.2 to 54.8)	-4.0 (-5.5 to -1.9)	0.93 (0.90 to 0.96)	0.92 (0.90 to 0.95)
12-13	9281	2187	12.6 (12.3-12.8)	51.0 (46.3 to 55.8)	-2.8 (-4.4 to -1.1)	0.95 (0.92 to 0.98)	0.95 (0.93 to 0.97)
11-12	9808	2426	11.5 (11.3-11.7)	51.8 (47.1 to 56.4)	-2.0 (-3.7 to -0.4)	0.96 (0.93 to 0.99)	0.96 (0.94 to 0.99)
10-11	10 290	2704	10.5 (10.2-10.8)	52.4 (47.6 to 56.9)	-1.5 (-3.0 to -0.1)	0.97 (0.94 to 1.00)	0.98 (0.95 to 0.99)
9-10	10 290	2839	9.5 (9.2-9.8)	52.7 (48.2 to 57.1)	-1.1 (-2.3 to 0.0)	0.98 (0.96 to 1.00)	0.98 (0.97 to 1.00)
8-9	10 290	2991	8.5 (8.2-8.7)	53.1 (48.6 to 57.4)	-0.7 (-1.5 to 0.0)	0.99 (0.97 to 1.00)	0.99 (0.98 to 1.00)
7-8	10 290	3088	7.5 (7.3-7.8)	53.5 (48.9 to 57.6)	-0.4 (-0.8 to 0.0)	0.99 (0.99 to 1.00)	0.99 (0.99 to 1.00)
6-7	10 290	3168	6.5 (6.2-6.7)	53.8 (49.2 to 58.0)	Reference	Reference	Reference
5-6	10 290	3196	5.5 (5.3-5.8)	54.2 (49.6 to 58.5)	0.4 (0.0 to 0.8)	1.01 (1.00 to 1.01)	1.01 (1.00 to 1.01)
4-5	10 290	3188	4.6 (4.3-4.8)	54.6 (49.2 to 58.0)	0.8 (0.0 to 1.6)	1.01 (1.00 to 1.03)	1.01 (1.00 to 1.02)

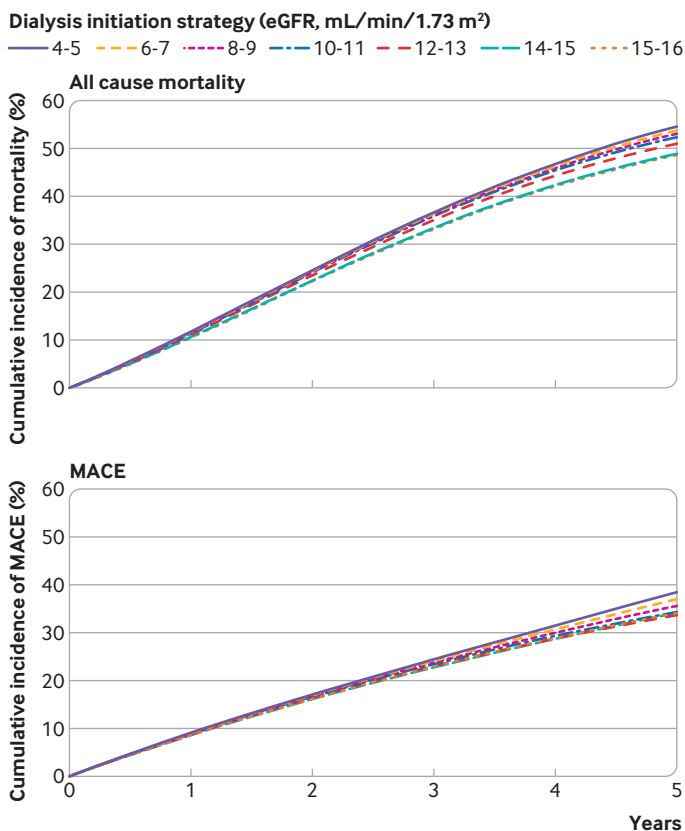
Five year risk differences and risk ratios comparing any two strategies can be readily calculated from five year absolute risks by subtraction or division of absolute risks. This is not possible for hazard ratios.

IQR=interquartile range.

\*Because inclusion criteria include second eGFR in range 10-20 mL/min/1.73 m<sup>2</sup>, patients enter study with eGFR throughout that range. They are immediately censored from all strategies that start dialysis at eGFR higher than patient's baseline eGFR. This accounts for progressively smaller number of patients available for higher eGFR strategies. All patients, however, are able to contribute to analyses of starting dialysis at eGFR of  $\leq 10$  mL/min/1.73 m<sup>2</sup>. Below that point, number of patients initially available for each strategy does not vary. For detailed step by step explanation of cloning, censoring, and weighting method, see supplementary methods.

†Among patients who initiate dialysis without being censored.

‡Analyses were adjusted for 83 variables: age, sex, baseline eGFR, time varying eGFR, time varying previous eGFR, primary kidney disease, calendar year, baseline and time varying laboratory measurements (systolic blood pressure, diastolic blood pressure, total calcium, phosphate, albumin, haemoglobin), baseline and time varying comorbidities (acute coronary syndrome, other ischaemic heart disease, heart failure, diabetes mellitus, valve disorders, stroke, other cerebrovascular disease, atrial fibrillation, other arrhythmias, peripheral vascular disease, chronic obstructive pulmonary disease, other lung disease, venous thromboembolism, cancer, liver disease, fracture in previous year), baseline and time varying drug use ( $\beta$  blockers, calcium channel blockers, diuretics, renin-angiotensin system inhibitors, lipid lowering drugs, potassium binder, phosphate binder, erythropoiesis stimulating agents, vitamin D, digoxin, nitrates, antiplatelet agents, anticoagulants, sodium bicarbonate), and baseline and time varying hospital admissions (total number of admissions in previous year, cardiovascular admission in previous year).



**Fig 1 | Weighted, standardised cumulative incidence curves for mortality (top) and major adverse cardiovascular events (MACE) (bottom), stratified by different dialysis initiation strategies. eGFR=estimated glomerular filtration rate**

initiation was associated with a 3.3% (-0.1% to 6.1%) lower five year mortality risk but no difference in risk of major adverse cardiovascular events (0.3%; -5.2% to 5.0%) compared with late initiation, with hazard ratios of 0.95 (0.92 to 0.99) and 1.03 (0.97 to 1.08), respectively. Adjustment for confounders moved the risk difference away from the null (supplementary table L). As an example, the unadjusted five year risk difference between eGFR<sub>5-7</sub> and eGFR<sub>10-14</sub> was -0.11% and became -3.33% after full adjustment. Using untruncated weights, excluding patients with cancer, applying an alternative analytical approach for the competing risk of kidney transplantation, additionally adjusting for urinary albumin to creatinine ratio and potassium, or censoring patients who chose conservative care did not alter our results (supplementary tables M-Q).

When we used traditional analytical approaches that introduced immortal time bias as in previous observational studies<sup>14-17</sup> (supplementary methods), early dialysis initiation was associated with worse outcomes, the opposite of the association we identified in our trial emulation analysis. The hazard ratio for eGFR<sub>15</sub> was 1.46 (1.19 to 1.78) compared with eGFR<sub>5</sub> (supplementary figure G). In addition, when we started follow-up at dialysis initiation, which introduced selection/survivor bias and lead time bias,<sup>16-31</sup> the hazard ratio for eGFR<sub>15</sub> was 1.58 (1.37 to 1.83) compared with eGFR<sub>5</sub> (supplementary figure H).

## Discussion

In this large nationwide study of patients with advanced chronic kidney disease, we aimed to investigate the

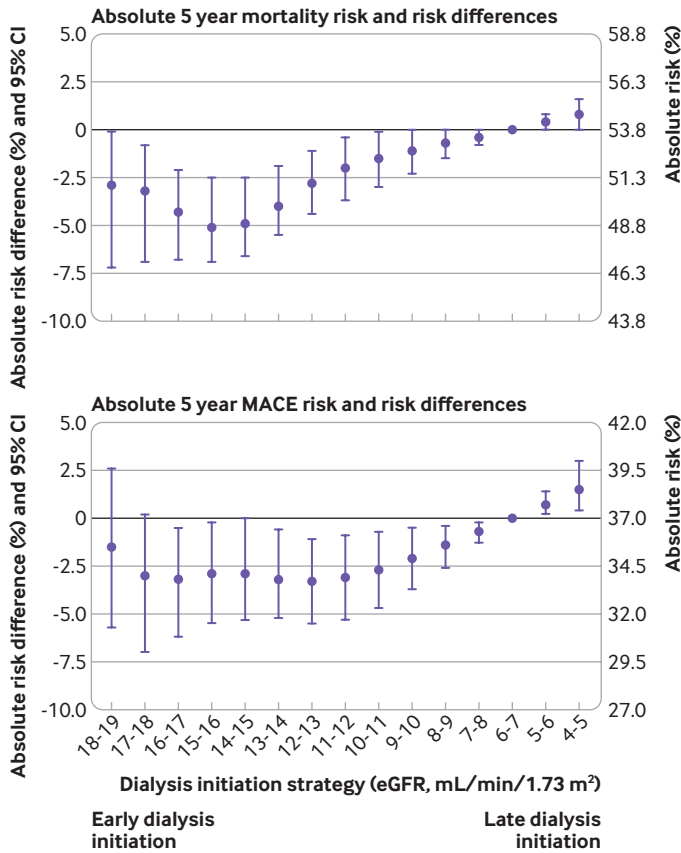


Fig 2 | Five year absolute risks and risk differences for mortality (top) and major adverse cardiovascular events (MACE) (bottom) associated with initiating dialysis with estimated glomerular filtration rate (eGFR) values between 4 and 19 mL/min/1.73 m<sup>2</sup> in increments of 1 mL/min/1.73 m<sup>2</sup>, with 6-7 mL/min/1.73m<sup>2</sup> as reference

effects of starting dialysis at different eGFR levels on mortality and major adverse cardiovascular events. Using novel trial emulation methods, we estimated

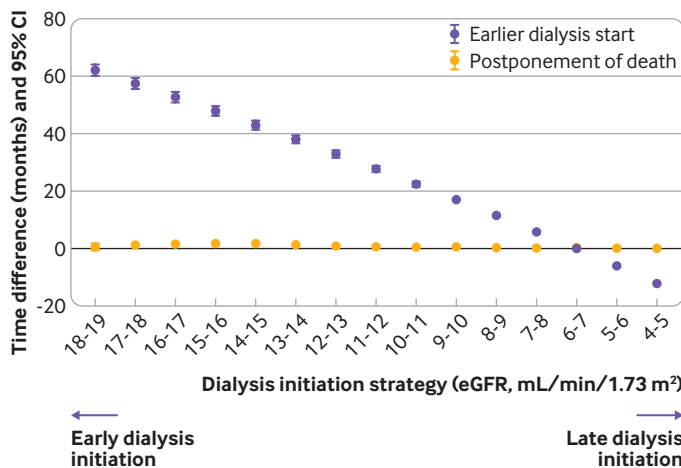


Fig 3 | Trade-off between additional survival time (five year restricted mean survival time difference) and time that dialysis has to be initiated earlier, for dialysis initiation strategies with estimated glomerular filtration rate (eGFR) values between 4 and 19 mL/min/1.73 m<sup>2</sup> in increments of 1 mL/min/1.73 m<sup>2</sup>, with 6-7 mL/min/1.73 m<sup>2</sup> as reference. Positive value indicates longer survival and earlier dialysis start compared with reference group. In study population, annual eGFR decline was 2-3 mL/min/1.73 m<sup>2</sup>, which was estimated with linear mixed model including linear and quadratic slope (see supplementary methods). In other words, about 5 months are needed for eGFR to decline 1 mL/min/1.73 m<sup>2</sup>

that the maximum absolute five year risk reductions were 5.1% for mortality (for eGFR<sub>15-16</sub> v eGFR<sub>6-7</sub>) and 3.3% for major adverse cardiovascular events (for eGFR<sub>13-14</sub> v eGFR<sub>6-7</sub>). These results were robust in various sensitivity analyses and subgroups, including older patients and those with comorbidities such as diabetes, ischaemic heart disease, or heart failure.

**Strengths and limitations of study**

Strengths of our study include its nationwide nature, large sample size, inclusion of a representative cohort of patients under routine care by nephrologists, long term follow-up, and adjustment for 83 time fixed and time varying confounders. Furthermore, we tested the robustness of our findings in several supplemental analyses and present information on absolute and relative risks and the trade-off between restricted mean survival time and earlier start of dialysis to provide a detailed picture.

Our study also has limitations. Firstly, despite adjustment for rich baseline and time varying covariates that are used in the decision making process (including time varying eGFR and previous eGFR measurements), residual confounding cannot be excluded, and the precise reasons for dialysis initiation were not available in our study. Patients initiating dialysis at higher eGFR levels may have started for different reasons (for example, volume overload), than patients who started at lower eGFR levels. Our study lacked information on important variables influencing this decision, including nutritional status or muscle mass stores, uraemic symptoms, volume status, quality of life, or physical activity. We believe, however, that we captured some of these variables indirectly through adjustment for biochemical variables, hospital admissions, drug use, and comorbidities. Additional adjustment for urinary albumin to creatinine ratio and potassium did not meaningfully alter our point estimates. Furthermore, in one of our sensitivity analyses, we sequentially adjusted for major confounder groups that are expected to induce strong confounding. However, additional adjustment resulted in at most a 1% increase in absolute risk. This, in combination with the strong probability that additional (unmeasured) confounders will be correlated with the variables for which we adjusted, reassures us that the effect of unmeasured confounders is unlikely to be large. In any case, the most compelling argument in favour of the validity of the findings is the congruence between our findings using trial emulation and those of the randomised IDEAL study.

Secondly, the Swedish Renal Registry did not record information on symptoms or quality of life during the study period. Future studies should include symptoms in their treatment strategies and study quality of life as an outcome. Thirdly, creatinine based estimates of eGFR may not be an accurate reflection of true kidney function, as they may be influenced by muscle wasting or cachexia; eGFR estimated by the Chronic Kidney Disease Epidemiology equation is accurate to within 30% of measured glomerular filtration



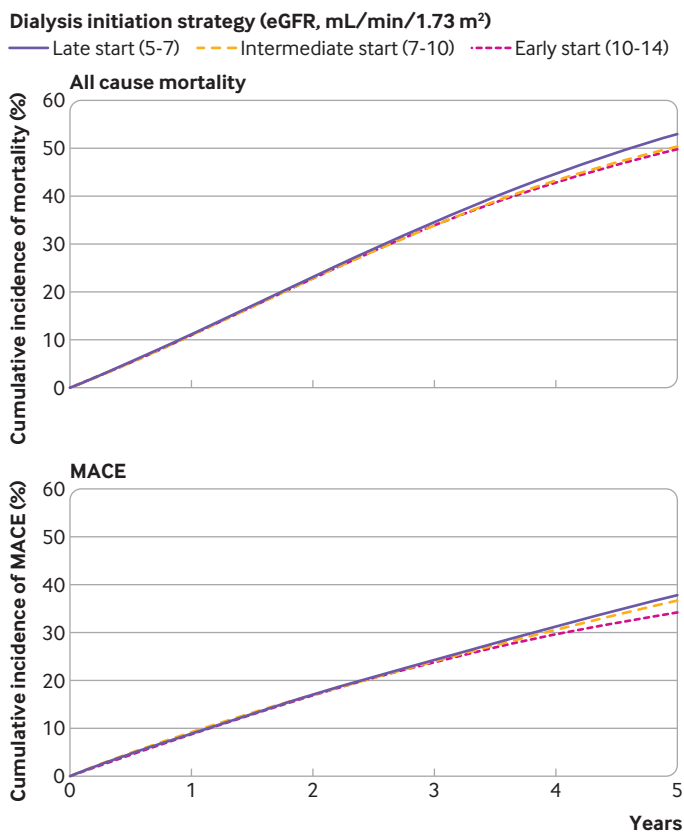


Fig 4 | Weighted, standardised cumulative incidence curves for mortality (top) and major adverse cardiovascular events (MACE) (bottom) for early, intermediate, and late dialysis initiation. eGFR=estimated glomerular filtration rate

rate 85% of the time.<sup>54</sup> However, eGFR is one of the factors that many physicians take into consideration at the time of decision making. Lastly, as Sweden has nationwide healthcare reimbursement, and patients in our analyses were all under care by nephrologists, generalising our results to other health systems should be done with caution. In the presence of between country differences in dialysis initiation practice (which include substantial differences in eGFR), the fact that as many as 39% of patients starting dialysis in Sweden received peritoneal dialysis, a higher proportion than in many other countries,<sup>3</sup> is noteworthy. We did not find effect modification for other relevant characteristics of patients, including age, diabetes, and heart failure, some of which may play a role in the decision to start peritoneal dialysis or haemodialysis. However, the optimal eGFR to start dialysis may still differ between haemodialysis and peritoneal dialysis.<sup>66</sup> If this is the case, our results would be less generalisable to other healthcare systems with different proportions of patients initiating peritoneal dialysis and haemodialysis. All in all, replication of our analyses in other healthcare systems is desirable.

#### Comparison with other studies

One randomised trial (IDEAL) and various observational studies have investigated the timing of dialysis. In a sensitivity analysis, we compared the same treatment arms as in the IDEAL trial to

benchmark our analytical methods.<sup>33</sup> In IDEAL, the achieved eGFR in the early and late arms were 7.2 and 9.0 mL/min/1.73 m<sup>2</sup>, respectively. In our study, mean eGFR for late (eGFR<sub>5-7</sub>) and intermediate (eGFR<sub>7-10</sub>) start were 6.0 and 8.3 mL/min/1.73 m<sup>2</sup>, respectively. In this comparison, we observed hazard ratios of 0.97 (0.94 to 0.99) for mortality and 1.00 (0.97 to 1.04) for major adverse cardiovascular events. These findings are congruent with those of IDEAL: 1.04 (0.83 to 1.30) and 1.23 (0.97 to 1.56), respectively.

Previous observational studies have investigated the timing of dialysis initiation,<sup>14-31</sup> but they have been criticised for the presence of immortal time, selection/survivor, and lead time biases.<sup>15 19 51</sup> For example, some reports found a strong protective effect of late dialysis initiation,<sup>18 20-24 26 27 29 30</sup> which conflicts with findings from IDEAL. In our sensitivity analyses, we showed that such findings may have been due to either immortal time bias or selection/survivor bias. Our study design based on cloning, censoring, and weighting prevents these biases by explicitly emulating a target trial, and aligning eligibility and treatment strategies at baseline. Although one previous observational study applied a similar design to ours, it did not adjust for time varying covariates and was limited in sample size.<sup>13</sup>

#### Policy implications

Our findings provide novel evidence on the optimal timing of dialysis initiation and show that even with maximum eGFR separations, the range of plausible effects is likely to be small. The modest increase in observed survival for initiation at higher eGFR comes at the expense of earlier dialysis initiation. Our results provide an insight into this trade-off: the maximum 5.1% absolute mortality reduction translated into a postponement of death of only 1.6 months over a five year follow-up period, whereas dialysis would need to be started on average four years earlier. For many patients, the modest survival benefit may not outweigh this increased time on dialysis. Our results further suggest that in the absence of symptoms or strong indications, initiation of dialysis may be postponed until lower eGFR values are reached (intent to defer),<sup>40 67</sup> without a large increase in mortality or cardiovascular events. From a societal perspective, the higher costs associated with earlier dialysis initiation make these strategies even less desirable. Current position papers highlight the importance of individualised decision making in deciding whether and when to start dialysis, taking into account outcomes, quality of life, and patients' preferences. Our findings should not be used to suggest a single eGFR cut-off to start dialysis in all patients. Rather, our finding of similar survival across the range of eGFR at which dialysis is usually considered (eGFR 5-14 mL/min/1.73 m<sup>2</sup>) should be a reassuring addition to the evidence base for clinicians: these data provide no support for any strategy other than starting dialysis on the basis of symptoms and patients' preferences, which is widespread clinical practice, recommended by guidelines, and a patient centred approach. Our

study compared different dialysis initiation strategies based on eGFR only: patients who did not adhere to their assigned strategy (that is, started too early or too late on the basis of their eGFR value) were censored in our analyses at the moment of nonadherence. Hence, our study did not investigate whether other parameters, such as volume overload or symptoms, should be taken into consideration when starting dialysis. This requires further study. Neither did our study investigate the effects of dialysis initiation versus comprehensive conservative management in patients with kidney failure. Conservative care has been proposed as a reasonable alternative to maintenance dialysis for selected older patients with comorbidities or poor functional status. Whether differences exist in survival and quality of life between dialysis and conservative management is unknown and is being investigated in the ongoing randomised PREPARE for Kidney Care Study.<sup>68</sup>

### Conclusions

In conclusion, although very early dialysis initiation was associated with a modest reduction in mortality and cardiovascular events, this may not outweigh the burden of a substantially longer period spent on dialysis.

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**Contributors:** ELF, FWD, and MvD initiated the study. ELF and MvD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ELF drafted the manuscript and did the statistical analysis. All authors contributed to the design of the study; the acquisition, analysis, and interpretation of data; and the critical revision of the manuscript for important intellectual content. ELF and MvD are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Ethical approval:** As data were de-identified, the study was judged not to need written informed consent. The study was approved by the regional ethical review board in Stockholm and the Swedish National Board of Welfare (#2011/618-31/4, #2017/793-31).

**Data sharing:** Data will be available on reasonable request by submitting a protocol to the Swedish Renal Registry. For inquiries about data access, please contact ME at [marie.evans@ki.se](mailto:marie.evans@ki.se).

The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:** The findings of this study will be disseminated to clinicians and advocacy groups via the Swedish Renal Registry network of participating centres, media departments, and websites of the authors' institutes, as well as (inter)national nephrology conferences. A plain language summary will be written to make the findings accessible to the public. The results will be shared on social media by the authors.

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### Web appendix: Supplementary materials