Predictors of quality of life in incident hemodialysis patients based on baseline data from the PIVOTAL study.

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ABSTRACT

BACKGROUND:

Impaired quality of life (QoL) is common in patients with end-stage kidney disease. There are sparse data on factors influencing QoL in patients who have recently started hemodialysis, or its prognostic relevance in these patients. The PIVOTAL trial investigated the effects of proactive high-dose versus reactive low-dose intravenous (IV) iron in patients starting hemodialysis. We report the detailed baseline data related to QoL measures in trial participants enrolled into the study. We examine the potential relationship of QoL scores to the primary outcome (all-cause mortality, myocardial infarction, stroke, and hospitalization for heart failure), as well as associations of QoL scores with other key baseline characteristics including clinical and laboratory factors, presence of anemia, or iron deficiency.

METHODS AND RESULTS:

This was a post hoc analysis of 2141 patients enrolled in the PIVOTAL trial and followed up for a median of 2.1 years. QoL was measured using EQ5D index and Visual Analogue Scale (VAS), as well as the KD-QoL (Physical Component Score (CS) and Mental Component Score (MCS)). Mean baseline scores were 0.68 (0.85) and 60.7 (20.8) for EQ5D index and VAS and 33.7 (10.2), and 46.0 (11.3) for KD-QoL PCS and MCS, respectively. Female sex, higher BMI and a greater number of co-morbidities including diabetes mellitus, and history of myocardial infarction, stroke or heart failure were associated with significantly worse EQ5D index and VAS. Key laboratory measurements associated with QoL were CRP and transferrin saturation (TSAT), whilst hemoglobin was not an independent predictor of QoL. TSAT was an independent predictor of KD-QoL PCS. CRP was associated with most aspects of QoL; variables including age, sex, BMI, and a history of stroke impacted baseline QoL scores. Impaired functional status at baseline was associated with mortality.

CONCLUSION:

Quality of life was severely impaired in incident patients on hemodialysis with scores up to 30% below those in the general population, and was associated with mortality. CRP was the most consistent significant independent predictor of the majority of QoL scores. Hemoglobin at baseline (<100g/L vs >100g/L) or iron deficiency (TSAT ≤20% or serum ferritin ≤200 µg/L) do not impact patients' impressions of QoL but a baseline TSAT ≤20% independently affects physical component scores of QoL.

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Key Words: Quality of Life; mental health; physical function; hemodialysis; iron; PIVOTAL

INTRODUCTION

The global prevalence of chronic kidney disease (CKD) is estimated to be 10–13% and increasing; consequently, demand for dialysis services is also likely to increase worldwide [1]. There are limited data characterizing health related quality of life (QoL) in patients on hemodialysis (HD) using validated metrics. However, from the available data, hemodialysis is associated with impaired (QoL) and high morbidity and mortality [2].

QoL is defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value relative to both where they live and their aspirations, expectations, ideas, and concerns" [3]. The subjective awareness of each individual of their physical, mental, spiritual, emotional, social and functional wellbeing is critical to understanding the impact of treatments on QoL [4]. Both physical inactivity and impaired physical function as seen during the COVID-19 pandemic are also strongly associated with high morbidity, mortality and reduced QoL in patients on HD [5]. In prevalent hemodialysis patients a low physical component summary (PCS) has been associated with an increased adjusted risk of death [hazard ratio (HR), 1.55, 95% confidence interval (CI) 1.19–2.03] and hospitalization (HR, 1.29, 95% CI 1.09–1.54) and a low mental component summary (MCS) with increased risk of hospitalization (HR, 1.39, 95% CI 1.17–1.65) but no association between the symptoms of kidney disease, effects of kidney disease, and burden of kidney disease subscales [6]. There are no data in incident dialysis patients.

The PIVOTAL (Proactive IV irOn Therapy in hemodiALysis) trial investigated the effects of proactive high-dose versus reactive low-dose intravenous (IV) iron in patients starting hemodialysis. A pre-specified secondary outcome of PIVOTAL was change in QoL measures using the validated European Quality of life 5-dimension score (EQ5D) and kidney disease quality of life (KD-QoL) questionnaires [7. 8]. This is a blunt health status instrument of the perception of health rather than quality of life *per se*. These scores were measured at baseline

and 3-monthly for the first year, then 6 monthly until the end of the trial. There were no significant between-treatment (proactive high-dose versus reactive low-dose intravenous iron) differences in QoL from the data. We now report the detailed baseline data related to QoL measures in trial participants enrolled into the study (both the higher-dose approach (proactive regimen) and lower-dose approach (reactive regimen)),. We examine the potential relationship of QoL scores to the primary outcome (all-cause mortality, myocardial infarction, stroke, and hospitalization for heart failure), as well as associations of QoL scores with other key baseline characteristics including clinical and laboratory factors, presence of anemia, or iron deficiency Specifically we have examined baseline predictors of QoL, as well as the association of hemoglobin and other variables at baseline on QoL scores. We have also investigated whether the presence of iron deficiency, irrespective of hemoglobin, influences QoL, and the impact of baseline QoL measures on the primary outcome measure of the trial.

METHODS

The design, details of baseline characteristics, and the main outcomes of this prospective randomized, controlled study (open-label with blinded end-point evaluation) have been published previously [7, 8]. In brief, a total of 2,141 patients with ESKD on maintenance hemodialysis initiated ≤12 months before randomization were included. At baseline, inclusion criteria included a TSAT <30% and a ferritin level <400 ng/mL. Patients were randomized to a proactive regimen of intravenous (IV) iron (400 mg iron sucrose monthly, with cut-offs to interrupt IV iron therapy if the ferritin became greater than 700 ng/mL and/or the TSAT became greater than 40%) or to a reactive iron regimen (0 to 400 mg iron sucrose monthly to maintain a ferritin level of at least 200 ng/mL and a TSAT ≥20%. The median cumulative iron dose at one year was 3.8 g in the proactive arm and 1.8 g in the reactive arm. Patients received erythropoiesis-stimulating agents (ESAs) at a dose sufficient to keep hemoglobin levels between 100 and 120 g/L.

Participants were then requested to complete validated, structured health surveys (EQ5D and KD-QoL). The EQ5D includes overall index and a visual analogue scale (VAS) with a range from 0-100, with a higher score indicating better health and 5 separate questions covering mobility, self care, usual activities, pain or discomfort and anxiety/depression. EQ5D has been used in many patient populations including CKD [9, 10]. The KD-QoL is a valid measure of generic but disease-specific health-related quality of life (HRQoL) scoring system which is separated into 5 sub scales consisting of 2 general component summary measures (physical health composite scores (PCS) (PF+RF+BT+GH) and mental health composite scores (MCS)) (VT+SF+RE+MH). These include eight concept scales: physical functioning (PF) – the level of limitation of physical activity caused by health limitations, role-physical (RP)- measure the limitations of patient-specific physical activity caused by health problems), bodily pain (BP), general health (GH), vitality (VT)- measurement of energy and fatigue, social functioning (SF)- defines the level of social life limitations caused by physical and emotional discomfort, role emotional (RE) and mental health (MH) – defines the level of psychological stress and well-being. The other 3 subscales consist of kidney disease-targeted specific scores on burden of kidney disease, symptoms of kidney disease and and effects of kidney disease. This score is calculated with norm-based scoring so that 50 is the average score, with higher scores indicating a better QoL [11, 12].

STATISTICAL ANALYSIS

The detailed analysis of QoL data included stratifications based on the following parameters:

1. baseline hemoglobin >100g/L vs ≤100g/L

2. serum ferritin >200 vs ≤ 200ng/ml

3. TSAT > 20% vs ≤ 20%

4. erythropoiesis-stimulating agent (ESA) dose (units/week)

5. serum albumin (g/L)

6. sex – males versus females

7. impact of social demographic data including age

8. impact of etiology of CKD

9. Diabetes vs no diabetes

10. Ethnicity

11. Vascular access

12. Number of comorbidities

STATISTICAL METHODS

Baseline descriptive characteristics and analysis were summarized as means ± standard deviations (SD) for normally distributed data, and medians and inter-quartile ranges for not normally distributed data. Percentages and frequencies were used where appropriate. P-values for between-variable differences based on two sample t-tests, analysis of variance or chi-squared tests/Fishers exact tests, as appropriate, are provided. Analyses were performed using SAS software, version 9.4 (SAS Institute)**,** Minitab version 20.3 and R version 3.6.0.

A linear regression model adjusting for significant univariate predictors was used to identify independent predictors of HRQoL, using baseline characteristics and the randomized treatment allocation (proactive high-dose vs reactive low-dose intravenous iron). Time to first event outcomes were analysed using Cox proportional hazards models with estimation of hazard ratios, 95% confidence intervals and p-values from the Wald statistic.

RESULTS

Demographic data and disease related characteristics

The participant demographics have been described previously, but in brief a total of 2141 hemodialysis patients (1398 male; 743 female) were randomized, of which 79% were white,

and the mean age was 62.8 years. At baseline, 40.96% of patients were dialyzed using a central venous catheter while 59.04% had an arteriovenous graft or fistula. Diabetes was reported to be the cause of ESKD in 587 patients (27.4%). Additional causes of renal disease and co-morbidities are detailed in **Table 1**, in addition to laboratory measurements and erythropoiesis-stimulating agent (ESA) dose.

Predictors of the primary endpoint and all-cause mortality

After adjustment for randomized treatment (model 1), then adjusting for other baseline predictive variables (model 2), EQ5D Index (HR: 0.93; 95% CI: 0.9-0.97; p<0.001) and VAS (0.94: 0.89-0.98; p=0.006), and the KD-QoL PCS (0.84: 0.76-0.94) and MCS (0.90: 0.83-0.93) were independently associated with all-cause mortality (**Table 2**). Similar associations were found for the primary outcome (all-cause death, myocardial infarction, stroke or hospitalisation for heart failure): EQ5D Index (HR 0.93; 95% CI: 0.9-0.96; p<0.001) and VAS (0.93: 0.87-0.97; p<0.001), as well as the KD-QoL PCS (0.84: 0.77-0.93; p<0.001) and MCS (0.88: 0.82-0.95; p=0.0017). There was also an association with symptoms of kidney disease (0.95: 0.90-0.99; P=0.019) and effects of kidney disease (096: 0.92-1.99; p=0.046) (**Table 3**).

Key laboratory measurements associated with QoL were CRP and transferrin saturation (TSAT) whilst hemoglobin and ferritin were not independent predictors of QoL. TSAT was an independent predictor of KD-QoL PCS (**suppl Table 3**). CRP was associated with most aspects of QoL; variables included age, sex, a history of stroke and BMI impacted baseline QoL scores.

Baseline Predictors of Quality of Life
Variables associated with EQ5D index and EQ5D VAS

At baseline, the mean (SD) EQ5D index overall was 0.68 (0.85) and the mean (SD) overall VAS 60.7 (20.8). In the univariate analysis, being female (p=0.006 and 0.015), having a higher BMI (p<0.001: BMI > 27.5) and the presence of more co-morbidities, including diabetes mellitus, a history of MI, stroke or heart failure were associated with significantly worse EQ5D index and VAS scores (**Table 1 and Suppl Table 1**). The lowest scores and hence worse measures were observed in patients with a history of heart failure or stroke. CRP was a consistent association with EQ5D index and VAS scores.

A Hb >100g/L and TSAT>20% without raised inflammatory markers (CRP) was associated with better EQ5D index and VAS scores in univariable analysis (**Table 1**). However, after multivariable analysis, hemoglobin was not an independent predictor of any aspect of quality-of-life score at baseline (**Suppl Table 2**). The variables independently associated with EQ5D index were age, CRP, BMI, sex, heart failure and stroke and those independently predictive of VAS score were age, CRP, sex and stroke.

Factors associated with KD-QoL PCS and MCS score
At baseline, the mean (SD) PCS overall was 33.7 (10.2) and the mean (SD) overall MCS was 46.0 (11.3). The differences observed across the subgroups examined were qualitatively consistent with those observed for the EQ5D index and VAS, although atrial fibrillation was associated with a lower PCS than no atrial fibrillation **(Table 4).** PCS was substantially lower than MCS in all subgroups examined.

Interestingly, older age was associated with a better MCS score, while comorbidities were not associated with lower MCS scores. After adjustment, a history of stroke (p=0.048) and myocardial infarction (p=0.01) remained independent predictors of MCS while transferrin saturation (of > 20%) was a strong independent predictor of the PCS score (p=0.005) (**Suppl Table 3**). Serum ferritin had no independent effect of QoL scores in any domain analysed.

Factors associated with KD-QoL eight constitute domains analysis of PCS and MCS.
Overall scores for role physical (RP) and role emotional (RE) were much lower than other domains, while physical function (PF) was lower than the others. Further comparative statistical analysis of the 8 constitute domains of the KD-QoL scores demonstrated higher scores in PF, BP, GH, and VT in males compared to females (P<0.01; <0.01; <0.012 and <0.003 respectively: (**Table 5**).CRP impacted all 8 sub domains while factors including age, sex, BMI, comorbidities of diabetes, stroke and heart failure impacted the majority of the sub domains. In univariate analysis a low hemoglobin and TSAT were associated with the domains bodily pain (BP), general health (GH), and social functioning (SF), (**Table 5**).

Factors associated with kidney specific scales: KD-Qol Burden, Symptoms and Effects of kidney disease sub scales

The comparative statistical analysis of the scores of KD-QoL burden, symptoms and effects of kidney disease according to the categorical socio-demographic variables and categorical clinical and laboratory parameters are shown in **Table 6**. The findings related to burden, symptoms and effects again indicated that males (p=0.004, 0.046, 0.005 respectively for burden, symptoms and effects) were independently less affected; the presence of diabetes led to significantly worse scores in all 3 domains (p<0.001) and the presence of co-morbidities was less important. CRP was again an important significant independent predictive factor of burden (p=0.001), symptoms (p=0.004) and effects (p=0.04) (**Table 6**). A low hemoglobin impacted burden but not symptoms or effects of renal disease ,

DISCUSSION

Overall Findings

In this post hoc analysis of a large cohort of incident hemodialysis patients in the UK, overall QoL scores were 30% lower than the general population and similar to those found in prevalent dialysis patients, approximately 10% lower than patients on peritoneal dialysis and approximately 12% lower in comparison to kidney transplant patients in the physical component scale (PCS) [6, 13, 14]. Specific reductions were seen in our cohort in the sub domains of physical function, role physical and role emotional but not renal specific sub domains. A worse QoL at baseline was influenced by several parameters, the most consistent independent variable being a high CRP. Our study showed that at baseline these factors were consistent across several QoL scores and baseline QoL was predictive of all-cause mortality and the primary outcome measure. This has not been previously studied in incident hemodialysis patients.

In patients with chronic kidney disease not on dialysis, scores tend to be higher and associations exist with hospitalisations. There were strikingly low scores for HF and stroke which is not surprising given their impact on health. In the TREAT trial in patients with CKD and type 2 diabetes, treatment with darbepoetin led to a small improvement in fatigue and overall QoL over placebo although there was no benefit on other domains [15]. Despite finding in this study that a low transferrin saturation or hemoglobin was predictive of poor QoL, the subsequent follow-up data on proactive versus reactive iron did not show any significant benefit which might relate in part to the quantity of missing data, hence this was not studied in this current study.

Interestingly use of the disease-specific elements of the KD-QoL did not add any further information to the generic scores. These again were approximately 15% lower than those in transplant patients but higher than those in prelavent dialysis patients [13, 14].

All-cause mortality and the primary outcome

Our data confirmed that QoL is lower in the elderly and associated with death and hospitalization independent of demographic data [16]. QoL was an independent prognostic predictor and associated with mortality consistent with other studies [15] and increased hospitalizations [17, 18]. Indeed, impaired functional status is associated with early death after commencement of hemodialysis. [19, 20]

Sex and age

Male patients had better QoL scores, especially for KD-QoL burden, symptoms and effects but age had less impact. This has been seen in a previous systematic review and metanalyses [21]. A recent analysis of the DoPPS data from dialysis patients in Japan found that in 892 maintenance HD patients, those >70-79 years or >80 years had lower PCS scores compared to those aged >60y (43.1 vs 35.2) [22]. Again in a population of 980 dialysis patients in Singapore, age and male sex had higher scores [13]. Interestingly, in our population, the scores were much lower (34.4 vs 33.6) and were not significantly different. In addition, whereas there was a significant difference in MCS scores in our study which was better in the older age group, Ishiawtari A et al [22] did not find a significant difference in their population of Japanese patients. The reasons for this are unclear but may relate to the age differences examined or cultural differences between the two populations.

Hemoglobin and iron deficiency

Our patient population was identified on the basis of laboratory biomarkers of anemia and iron deficiency. Both Hb and TSAT led to a statistically significant difference in QoL, with a higher Hb and TSAT reflecting better baseline QoL scores for EQ5D index and VAS, and amongst the KD-QoL scores, bodily pain (BP), general health (GH), and social functioning (SF) but not vitality (VT) or physical functioning (PF) as seen in other studies of patients with CKD or on dialysis therapy [23-28]. However, after analysis for independent variables, only TSAT was an independent predictor of QoL for PCS. It may be that TSAT is a better predictor of functional iron deficiency which impacts on functional capacity and possible fatigue scores [29-32]. The TREAT study led to an improvement in FACT-fatigue score in these studies with ESA therapy [15, 33] while CHOIR demonstrated an improvement in the linear analogue scale assessment (LASA) in both groups (higher and lower Hb groups) and a trend for increased energy scores in the lower Hb group [34, 35]. However, there was no difference in the KD-QoL scores of energy or physical functioning domains in these studies [15, 33-35]. TREAT demonstrated that a 5 point or greater increase in score was clinically meaningful, leading to better outcomes (54% in the ESA group vs 49% in the placebo group; p=0.027). Our study showed that QoL scores, independent of Hb or iron status at baseline, were predictive of mortality and the primary outcome measure. This finding is perhaps important in considering those patients commencing dialysis therapy, at least in the UK. It would suggest that lower QoL scores are perhaps simply a marker of bad outcomes. Whether trying

to improve these prior to commencing dialysis with maximization of preventative therapies to minimize cardiovascular risk; consideration of dialysis therapy itself and strategies such as incremental dialysis remains unknown [36, 37]

Limitations

Our study has several strengths and limitations. This was a large study encompassing a diverse real world UK dialysis population with good baseline data collection. However, a prospective analysis of QoL over time was futile due to the volume of missing data. Another possible limitation is the lack of collection of socio- economic level data which has been previously shown to be impactful on outcomes [38].

A final consideration is that health-related QoL is a term that is commonly and misleadingly used to refer to health status tools such as the KD-QoLand EQ-5D, which may assess health and functioning but do not assess the impact of health and functioning on QoL [39, 40]. Health status includes aspects of a person's life such as their physical ability, daily functioning, and experience of symptoms. Indeed, it is controversial whether these health-status measures should be considered measures of quality of life at all [39]. Therefore, assumptions about the overall quality of life of individual patients should not be based on measures of their health status alone.

Summary

Overall, we have shown that in incident patients commencing hemodialysis, baseline QoL is predictive of mortality and the primary outcome measure of the PIVOTAL trial. Several factors influence a poorer quality of life score including female gender, the presence of diabetes and other co-morbidities. Markers of iron deficiency (TSAT) and inflammation (CRP) were also associated with poorer outcomes in many domains of QoL. Possible earlier optimization of patients prior to commencement of dialysis to tackle those modifiable factors associated with poor QoL scores needs attention to potentially reduce future mortality.

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Table 1. Overall statistical analysis of the total scores of EQ5D Index (mean: 0.681: SD 0.258; n=1777) and EQ5D VAS (mean: 60.75: SD 20.87; n=1787) summaries of patients with end stage kidney disease on hemodialysis, according to the categorical socio-demographic variables and categorical clinical and laboratory parameters. ESKD; end stage kidney disease. Data are expressed as means and Standard Deviations (SD)

Variable	Category	EQ5D Index			EQ5D VAS		
		N	Mean (SD)	P	N	Mean (SD)	P
Sex	Male	1152	0.69 (0.25)	0.014	1160	61.7 (20.8)	0.009
	Female	625	0.66 (0.26)		627	59.0 (20.9)	
Age	Age<=65	872	0.67 (0.27)	0.13	876	59.0 (21.2)	0.001
	Age>65	905	0.69 (0.24)		911	62.4 (20.4)	
Body Mass Index (BMI)	BMI<=27.5	859	0.72 (0.25)	<0.001	860	62.3 (20.8)	0.002
	BMI>27.5	895	0.65 (0.26)		903	59.2 (21.0)	
Smoking	Current	206	0.64 (0.27)	0.10	206	58.0 (21.6)	0.048
	Former	467	0.69 (0.25)		473	60.0 (20.5)	
	Never	1104	0.69 (0.26)		1108	61.6 (20.9)	
Diabetes	Yes	587	0.62 (0.27	<0.001	592	57.9 (21.8)	<0.001
	No	1190	0.71 (0.25)		1195	62.2 (20.3)	
Myocardial Infarction (MI)	Yes	166	0.63 (0.26)	0.012	165	57.4 (21.0)	0.035
	No	1611	0.69 (0.26)		1622	61.1 (20.8)	
Stroke	Yes	154	0.56 (0.27)	<0.001	155	54.7 (21.4)	<0.001
	No	1623	0.69 (0.25)		1632	61.3 (20.7)	
Heart Failure	Yes	71	0.55 (0.27)	<0.001	71	54.2 (24.6)	0.025
	No	1706	0.69 (0.26)		1716	61.0 (20.7)	
Peripheal arterial Disease	Yes	158	0.63 (0.27)	0.013	160	59.1 (19.6)	0.26
	No	1619	0.69 (0.26)		1627	60.9 (21.0)	
Atrial Fibrillation	Yes	142	0.68 (0.25)	0.84	142	60.1 (22.6)	0.70
	No	1635	0.68 (0.26)		1645	60.8 (20.7)	
Hypertension	Yes	1297	0.68 (0.26)	0.93	1301	60.6 (21.1)	0.58

	No	480	0.68 (0.25)		486	61.2 (20.2)	
Cause of ESKD	Hypertension	199	0.73 (0.21)	<0.001	203	65.2 (18.8)	<0.001
	Diabetes	587	0.62 (0.27)		592	57.9 (21.8)	
	Glomerular	317	0.72 (0.25)		318	61.9 (21.2)	
	Tubulo-interstitial	170	0.66 (0.27)		167	59.7 (20.0)	
	Renovascular	127	0.65 (0.26)		129	58.5 (21.4)	
	Other	104	0.70 (0.23)		101	61.8 (18.1)	
	Polycystic	98	0.76 (0.22)		99	63.8 (20.7)	
	Unknown	175	0.73 (0.25)		178	63.5 (20.1)	
Vascular access	Catheter	728	0.67 (0.27)	0.11	728	60.0 (21.0)	0.48
	Fistula	1012	0.69 (0.25)		1021	61.2 (20.8)	
	Graft	37	0.63 (0.30)		38	61.4 (19.6)	
Hemoglobin (Hb)	Hb<=100	637	0.66 (0.27)	0.018	637	59.1 (21.5)	0.015
	Hb>100	1140	0.69 (0.25)		1150	61.7 (20.5)	
Ferritin	Ferr<=200	792	0.69 (0.26)	0.15	800	60.9 (21.4)	0.83
	Ferr>200	985	0.67 (0.26)		987	60.7 (20.4)	
Transferrin Saturation (TSAT)	TSAT<=20	951	0.67 (0.26)	0.011	959	59.7 (21.0)	0.028
	TSAT>20	826	0.70 (0.25)		828	61.9 (20.6)	
C-Reactive Protein (CRP)	CRP<=6.0	832	0.72 (0.24)	<0.001	831	63.2 (20.8)	<0.001
	CRP>6.0	945	0.65 (0.27)		956	58.6 (20.7)	
Mean Cell Volume (MCV)	MCV<=93	942	0.67 (0.26)	0.19	950	60.0 (21.4)	0.12
	MCV>93	816	0.69 (0.26)		817	61.6 (20.2)	
ESA (units/week)	ESA<=8000	1129	0.69 (0.25)	0.034	1139	61.0 (20.7)	0.43
	ESA>8000	648	0.66 (0.27)		648	60.2 (21.1)	

Table 2: All-cause mortality. Model 1 adjusts for randomized treatment group. Model 2 additionally adjusts for log (CRP), albumin, ESA dose, vascular access status, smoking (current former, never), cause of end stage kidney disease (ESKD), age, duration of dialysis and histories (all yes/no) of myocardial infarction (MI), heart failure, atrial fibrillation, peripheral arterial disease and diabetes. Physical component score; PCS; mental component score; MCS. Results are Hazard ratio (HR) and 95% confidence interval (CI).

Variable	Model 1		Model 2	
	HR (95% CI)	P	HR (95% CI)	P
EQ5D Index (per 0.1)	0.91 (0.88, 0.94)	<0.001	0.93 (0.90, 0.97)	<0.001
EQ5D VAS (per 10)	0.92 (0.88, 0.96)	<0.001	0.94 (0.89, 0.98)	0.0056
PCS (per 10)	0.74 (0.67, 0.82)	<0.001	0.84 (0.76, 0.94)	0.0020
MCS (per 10)	0.91 (0.83, 0.99)	0.025	0.90 (0.83, 0.99)	0.029
Burden of kidney disease (per 10)	0.98 (0.95, 1.02)	0.35	1.01 (0.97, 1.04)	0.78
Symptoms of kidney disease (per 10)	0.96 (0.91, 1.01)	0.085	0.96 (0.91, 1.02)	0.17
Effects of kidney disease (per 10)	1.00 (0.96, 1.05)	0.81	0.98 (0.93, 1.02)	0.28

Table 3: Primary endpoint (fatal and non fatal myocardial infarction, stroke, hospitalisations for heart failure and all-cause mortality). Model 1 adjusts for randomized treatment group. Model 2 additionally adjusts for log (CRP), albumin, ESA dose, vascular access status, smoking (current former, never), cause of renal disease, age, duration of dialysis and histories (all yes/no) of MI, heart failure, atrial fibrillation, peripheral vascular disease and diabetes. Results are Hazard ratio (HR) and 95% confidence interval (CI).

Variable	Model 1		Model 2	
	HR (95% CI)	P	HR (95% CI)	P
EQ5D Index (per 0.1)	0.90 (0.87, 0.93)	<0.001	0.93 (0.90, 0.96)	<0.001
EQ5D VAS (per 10)	0.90 (0.87, 0.94)	<0.001	0.93 (0.89, 0.97)	<0.001
PCS (per 10)	0.75 (0.68, 0.82)	<0.001	0.84 (0.77, 0.93)	<0.001
MCS (per 10)	0.86 (0.80, 0.93)	<0.001	0.88 (0.82, 0.95)	0.0017
Burden of kidney disease (per 10)	0.97 (0.94, 1.00)	0.030	0.99 (0.96, 1.02)	0.50
Symptoms of kidney disease (per 10)	0.94 (0.90, 0.98)	0.0029	0.95 (0.90, 0.99)	0.019
Effects of kidney disease (per 10)	0.98 (0.94, 1.01)	0.24	0.96, 0.92, 1.00)	0.046

Table 4: Comparative statistical analysis of the mean scores of physical (PCS) and mental composite (MCS) summaries of patients with end stage kidney disease on HD, according to the categorical socio-demographic variables and categorical clinical and laboratory parameters. Results are represented as means and Standard Deviation (SD).

Variable	Category	KD-QoL PCS			KD-QoL MCS		
		n	Mean (SD)	P	n	Mean (SD)	P
Sex	Male	1124	34.7 (10.2)	<0.001	1124	46.5 (11.3)	0.029
	Female	592	32.7 (10.5)		592	45.2 (11.4)	
Age	Age<=65	859	34.4 (10.4)	0.10	859	44.2 (11.6)	<0.001
	Age>65	857	33.6 (10.3)		857	47.8 (10.9)	
BMI	BMI<=27.5	822	35.4 (10.2)	<0.001	822	46.7 (11.2)	0.024
	BMI>27.5	871	32.6 (10.3)		871	45.5 (11.5)	
Smoking	Current	201	32.7 (10.2)	0.003	201	44.5 (11.1)	0.045
	Former	448	33.0 (10.0)		448	46.9 (11.3)	
	Never	1067	34.7 (10.5)		1067	46.0 (11.5)	
Diabetes	Yes	567	32.5 (9.9)	<0.001	567	44.4 (11.7)	<0.001
	No	1149	34.7 (10.5)		1149	46.9 (11.1)	
MI	Yes	155	30.7 (9.1)	<0.001	155	45.3 (11.1)	0.39
	No	1561	34.3 (10.4)		1561	46.1 (11.4)	
Stroke	Yes	146	31.7 (7.9)	<0.001	146	42.8 (11.2)	<0.001
	No	1570	34.2 (10.5)		1570	46.3 (11.4)	
Heart Failure	Yes	64	30.0 (9.7)	0.001	64	43.6 (10.5)	0.065
	No	1652	34.2 (10.3)		1652	46.1 (11.4)	
PAD	Yes	153	31.6 (9.0)	0.001	153	46.4 (11.5)	0.73
	No	1563	34.2 (10.4)		1563	46.0 (11.4)	
Atrial Fibrillation	Yes	132	32.1 (9.2)	0.013	132	46.5 (12.9)	0.64
	No	1584	34.2 (10.4)		1584	46.0 (11.3)	
Hypertension	Yes	1244	34.1 (10.6)	0.65	1244	46.3 (11.3)	0.12
	No	472	33.8 (9.7)		472	45.3 (11.5)	
Cause of disease	Hypertension	194	36.2 (10.3)	<0.001	194	47.0 (11.0)	0.002
	Diabetes	567	32.5 (9.9)		567	44.4 (11.7)	

	Glomerular	308	35.0 (10.5)		308	46.3 (11.2)	
	Tubulo-interstitial	163	34.0 (10.2)		163	46.0 (11.2)	
	Renovascular	119	32.0 (10.1)		119	46.8 (11.4)	
	Other	99	34.4 (10.1)		99	47.1 (11.0)	
	Polycystic	96	35.8 (10.8)		96	47.7 (10.4)	
	Unknown	170	34.8 (10.9)		170	48.1 (11.5)	
Vascular access	Catheter	693	34.2 (10.3)	0.84	693	45.6 (11.4)	0.41
	Fistula	984	33.9 (10.4)		984	46.3 (11.4)	
	Graft	39	33.4 (10.2)		39	47.0 (11.9)	
Hb	Hb<=100	605	33.3 (10.2)	0.041	605	45.1 (11.5)	0.015
	Hb>100	1111	34.4 (10.4)		1111	46.5 (11.3)	
Ferritin	Ferr<=200	764	34.3 (10.4)	0.22	764	45.9 (11.7)	0.54
	Ferr>200	952	33.7 (10.3)		952	46.2 (11.1)	
TSAT	TSAT<=20	918	33.6 (10.3)	0.058	918	45.2 (11.1)	0.002
	TSAT>20	798	34.5 (10.3)		798	47.0 (11.6)	
CRP	CRP<=6.0	801	36.1 (10.4)	<0.001	801	46.6 (11.2)	0.066
	CRP>6.0	915	32.2 (10.0)		915	45.6 (11.5)	
MCV	MCV<=93	901	33.9 (10.2)	0.74	901	45.7 (11.6)	0.14
	MCV>93	795	34.1 (10.5)		795	46.5 (11.1)	
ESA (units/week)	ESA<=8000	1088	34.2 (10.3)	0.36	1088	46.2 (11.5)	0.36
	ESA>8000	628	33.7 (10.4)		628	45.7 (11.2)	

Table 5: Comparative statistical analysis of the 8 constitute domains of the KD-QoL scores. Physical Function (PF); Role physical (RP); bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH)

Variable		Physical Function (PF)	Role Physical (RP)	Bodily Pain (BP)	General Health (GH)	Vitality (VT)	Social Function (SF)	Role Emotional (RE)	Mental Health (MH)
Sex	Male	34.6 (11.3)	22.8 (3.8)	41.9 (13.0)	36.5 (12.1)	41.6 (11.7)	38.8 (12.9)	17.3 (5.1)	45.0 (10.5)
	Female	32.1 (10.9)	22.7 (3.7)	39.4 (13.6)	35.0 (11.9)	39.6 (11.3)	37.8 (12.8)	17.2 (5.2)	44.0 (10.5)
	P	<0.001	0.59	<0.001	0.012	0.003	0.13	0.77	0.12
Age	Age<=65	34.5 (11.4)	22.8 (3.8)	40.2 (13.2)	35.1 (12.2)	40.9 (11.8)	37.5 (12.5)	17.0 (5.1)	43.7 (10.9)
	Age>65	32.9 (11.0)	22.6 (3.7)	41.9 (13.3)	36.9 (11.9)	40.9 (11.4)	39.4 (13.2)	17.5 (5.1)	45.7 (10.0)
	P	0.001	0.21	0.007	0.002	1.00	0.001	0.031	0.001
BMI	BMI<=27.5	35.2 (11.6)	23.0 (3.9)	43.1 (13.1)	37.0 (12.0)	41.7 (11.6)	39.0 (12.9)	17.7 (5.1)	44.9 (10.4)
	BMI>27.5	32.3 (10.7)	22.5 (3.6)	39.1 (13.2)	35.0 (12.1)	40.1 (11.6)	37.9 (12.8)	16.9 (5.1)	44.4 (10.6)
	p	<0.001	0.011	<0.001	<0.001	0.010	0.090	0.002	0.47
Smoking	Current	32.9 (11.2)	22.4 (3.6)	39.3 (13.9)	33.5 (11.7)	39.4 (11.8)	36.5 (13.0)	16.9 (5.0)	43.4 (10.3)
	Former	33.2 (10.6)	22.3 (3.5)	41.1 (13.3)	35.2 (11.9)	40.2 (11.5)	38.9 (12.9)	17.5 (5.1)	44.8 (10.8)
	Never	34.0 (11.5)	23.0 (3.8)	41.4 (13.2)	36.8 (12.1)	41.5 (11.6)	38.6 (12.9)	17.3 (5.1)	44.8 (10.5)

	p	0.21	0.003	0.13	<0.001	0.038	0.070	0.35	0.35
Diabetes	Yes	32.0 (10.7)	22.5 (3.5)	39.3 (13.4)	34.0 (12.3)	40.1 (11.7)	36.6 (13.0)	16.7 (5.1)	43.6 (10.8)
	No	34.5 (11.4)	22.9 (3.8)	41.9 (13.1)	37.0 (11.8)	41.3 (11.6)	39.4 (12.7)	17.6 (5.1)	45.2 (10.3)
	p	<0.001	0.042	<0.001	<0.001	0.081	<0.001	0.001	0.020
MI	Yes	30.4 (10.6)	22.2 (3.3)	38.3 (13.8)	33.4 (11.4)	37.2 (10.7)	36.5 (13.1)	17.0 (5.0)	44.3 (11.0)
	No	34.0 (11.2)	22.8 (3.8)	41.3 (13.2)	36.3 (12.1)	41.3 (11.6)	38.6 (12.9)	17.3 (5.1)	44.7 (10.5)
	p	<0.001	0.041	0.005	0.003	<0.001	0.042	0.44	0.75
Stroke	Yes	31.2 (10.6)	21.7 (3.0)	39.0 (12.9)	33.4 (10.9)	38.6 (11.4)	35.0 (12.2)	15.9 (4.9)	42.2 (9.1)
	No	33.9 (11.3)	22.8 (3.8)	41.2 (13.3)	36.3 (12.2)	41.1 (11.6)	38.8 (12.9)	17.4 (5.1)	44.9 (10.6)
	p	0.004	<0.001	0.041	0.005	0.026	<0.001	0.001	0.015
Heart Failure	Yes	28.0 (9.3)	22.2 (3.5)	37.5 (13.5)	33.2 (12.0)	37.1 (10.0)	33.3 (13.6)	16.9 (5.1)	42.4 (10.9)
	No	33.9 (11.2)	22.8 (3.8)	41.2 (13.3)	36.1 (12.1)	41.1 (11.6)	38.7 (12.8)	17.3 (5.1)	44.7 (10.5)
	p	<0.001	0.22	0.023	0.044	0.017	0.001	0.49	0.16
PVD	Yes	31.0 (9.9)	22.3 (3.4)	39.4 (13.0)	34.9 (11.9)	41.8 (12.0)	36.9 (12.7)	17.0 (5.1)	43.6 (11.0)
	No	34.0 (11.3)	22.8 (3.8)	41.2 (13.3)	36.1 (12.1)	40.9 (11.6)	38.6 (12.9)	17.3 (5.1)	44.7 (10.5)
	p	0.001	0.11	0.091	0.23	0.39	0.11	0.56	0.29

Atrial Fibrillation	Yes	31.2 (11.0)	22.3 (3.5)	42.0 (13.4)	34.6 (12.1)	39.0 (10.7)	38.1 (13.5)	17.5 (5.1)	44.3 (10.9)
	No	33.9 (11.2)	22.8 (3.8)	41.0 (13.3)	36.1 (12.1)	41.1 (11.7)	38.5 (12.9)	17.3 (5.1)	44.7 (10.5)
	p	0.006	0.14	0.37	0.16	0.079	0.78	0.65	0.79
Hypertension	Yes	33.8 (11.4)	22.8 (3.8)	40.8 (13.3)	36.0 (12.2)	41.4 (11.9)	38.5 (13.0)	17.4 (5.1)	44.7 (10.4)
	No	33.3 (10.8)	22.4 (3.7)	41.7 (13.3)	35.9 (11.8)	39.6 (10.8)	38.3 (12.6)	17.1 (5.1)	44.5 (10.9)
	p	0.33	0.031	0.23	0.79	0.008	0.76	0.30	0.81
Cause of disease	Hypertension	35.3 (11.4)	23.2 (4.0)	44.5 (11.8)	37.8 (11.7)	42.2 (12.1)	39.8 (12.3)	17.6 (5.1)	45.7 (10.1)
	Diabetes	32.0 (10.7)	22.5 (3.5)	39.3 (13.4)	34.0 (12.3)	40.1 (11.7)	36.6 (13.0)	16.7 (5.1)	43.6 (10.9)
	Glomerular	35.1 (11.4)	22.8 (3.8)	41.6 (13.3)	37.0 (12.3)	41.2 (11.8)	39.0 (12.5)	17.7 (5.0)	45.0 (11.5)
	Tubulointerstitial	33.4 (11.2)	22.5 (3.8)	40.9 (12.6)	35.8 (11.3)	41.2 (11.4)	40.0 (12.5)	17.1 (5.1)	42.7 (9.3)
	Renovascular	31.9 (10.8)	22.5 (3.6)	39.3 (14.0)	35.7 (12.4)	40.8 (12.6)	37.6 (12.6)	17.3 (5.2)	45.3 (10.7)
	Other	33.6 (10.9)	22.9 (3.7)	41.4 (13.0)	38.0 (11.2)	40.9 (10.2)	38.9 (12.6)	17.8 (5.1)	45.2 (8.5)
	Polycystic	35.6 (11.1)	23.5 (4.2)	42.4 (13.4)	37.0 (11.5)	41.1 (11.4)	41.2 (12.7)	17.7 (5.1)	45.3 (10.7)

	Unknown	35.4 (12.0)	22.7 (3.9)	42.4 (13.8)	37.5 (11.8)	41.2 (11.0)	39.3 (13.9)	17.9 (4.9)	46.9 (9.3)
	p	<0.001	0.12	<0.001	<0.001	0.72	0.001	0.038	0.043
Vascular access	Catheter	33.6 (11.2)	22.7 (3.7)	41.6 (13.3)	35.3 (12.1)	41.4 (12.0)	38.0 (13.0)	17.2 (5.1)	44.4 (10.8)
	Fistula	33.7 (11.2)	22.7 (3.8)	40.7 (13.2)	36.5 (12.1)	40.6 (11.3)	38.7 (12.9)	17.3 (5.1)	44.8 (10.3)
	Graft	33.8 (11.1)	22.9 (3.9)	39.4 (13.9)	35.8 (11.1)	42.7 (11.8)	39.0 (12.6)	18.1 (5.2)	44.1 (12.1)
	p	0.98	0.90	0.32	0.15	0.33	0.49	0.50	0.84
Hb	Hb<=100	33.1 (11.1)	22.6 (3.7)	39.9 (13.6)	35.0 (12.3)	40.8 (11.9)	37.2 (13.0)	17.0 (5.2)	44.7 (10.6)
	Hb>100	34.0 (11.3)	22.8 (3.8)	41.7 (13.1)	36.6 (12.0)	41.0 (11.5)	39.1 (12.8)	17.4 (5.1)	44.6 (10.5)
	p	0.094	0.43	0.006	0.008	0.71	0.003	0.072	0.80
Ferritin	Ferr<=200	33.8 (11.2)	22.7 (3.7)	41.5 (13.4)	36.3 (12.3)	41.1 (11.8)	38.5 (13.0)	17.2 (5.1)	44.3 (11.0)
	Ferr>200	33.6 (11.2)	22.7 (3.8)	40.7 (13.2)	35.7 (11.9)	40.8 (11.5)	38.4 (12.8)	17.3 (5.1)	44.9 (10.2)
	p	0.77	1.00	0.21	0.30	0.62	0.95	0.59	0.27
TSAT	TSAT<=20	33.4 (11.1)	22.6 (3.7)	40.3 (13.4)	35.4 (11.9)	40.2 (11.6)	37.6 (12.7)	17.1 (5.1)	44.6 (10.4)
	TSAT>20	34.0 (11.4)	22.9 (3.8)	41.9 (13.1)	36.6 (12.3)	41.8 (11.6)	39.5 (13.1)	17.5 (5.1)	44.7 (10.6)
	p	0.30	0.12	0.010	0.035	0.007	0.002	0.053	0.88
CRP	CRP<=6.0	35.8 (11.5)	23.2 (3.9)	42.8 (12.8)	37.6 (12.4)	42.1 (11.6)	39.7 (12.5)	17.7 (5.1)	45.3 (10.3)

	CRP> 6.0	31.8 (10.6)	22.3 (3.5)	39.5 (13.5)	34.6 (11.6)	39.8 (11.5)	37.3 (13.2)	16.9 (5.1)	44.1 (10.8)
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.050
MCV	MCV <=93	33.6 (11.1)	22.7 (3.7)	41.2 (13.3)	35.7 (12.3)	41.0 (11.8)	37.9 (13.1)	17.2 (5.1)	44.6 (10.8)
	MCV >93	33.7 (11.4)	22.8 (3.9)	41.0 (13.3)	36.4 (11.8)	41.0 (11.4)	39.1 (12.7)	17.4 (5.1)	44.7 (10.3)
	p	0.83	0.38	0.78	0.21	0.90	0.042	0.41	0.94
ESA (units/week)	ESA< =8000	33.6 (11.1)	22.8 (3.8)	41.4 (13.2)	36.4 (12.2)	41.2 (11.6)	38.6 (13.0)	17.3 (5.1)	44.7 (10.5)
	ESA> 8000	33.8 (11.4)	22.6 (3.6)	40.5 (13.5)	35.4 (11.9)	40.6 (11.6)	38.2 (12.8)	17.2 (5.2)	44.5 (10.6)
	p	0.78	0.16	0.18	0.095	0.36	0.50	0.55	0.68

Table 6: The comparative statistical analysis of the scores of KD-Qol Burden (mean: 40.30; SD 27.84; n=1792), Symptoms (mean: 71.18; SD 18.39; n=1800) and effects (mean 66.48; SD 23.01; n=1798) according to the categorical socio-demographic variables and categorical clinical and laboratory parameters.

Variable	Category	KD-QoL Burden			KD-QoL Symptoms			KD-QoL Effects		
		n	Mean (SD)	P	N	Mean (SD)	P	n	Mean (SD)	P
Gender	Male	1165	41.2 (27.7)	0.056	1169	72.2 (18.2)	0.002	1167	67.7 (22.8)	0.003
	Female	627	38.6 (28.0)		631	69.4 (18.5)		631	64.3 (23.2)	
Age	Age<=65	882	37.2 (27.5)	<0.001	887	68.3 (19.6)	<0.001	883	60.7 (23.8)	<0.001
	Age>65	910	43.3 (27.8)		913	74.0 (16.6)		915	72.1 (20.7)	
BMI	BMI<=27.5	867	41.2 (28.0)	0.16	872	73.0 (17.6)	<0.001	867	68.7 (22.6)	<0.001
	BMI>27.5	901	39.4 (27.7)		904	69.5 (18.9)		907	64.4 (23.2)	
Smoking	Current	204	38.9 (27.3)	0.49	208	67.2 (20.2)	0.004	207	66.1 (23.2)	0.014
	Former	477	39.5 (27.4)		476	71.6 (17.5)		476	69.1 (21.9)	
	Never	1111	40.9 (28.1)		1116	71.8 (18.3)		1115	65.4 (23.4)	
Diabetes	Yes	588	36.6 (26.1)	<0.001	592	68.6 (19.0)	<0.001	594	63.2 (23.1)	<0.001
	No	1204	42.1 (28.5)		1208	72.5 (17.9)		1204	68.1 (22.8)	
MI	Yes	164	40.5 (27.3)	0.91	167	69.3 (17.9)	0.16	166	67.1 (23.2)	0.71
	No	1628	40.3 (27.9)		1633	71.4 (18.4)		1632	66.4 (23.0)	
Stroke	Yes	156	34.4 (25.0)	0.003	157	68.6 (19.7)	0.084	156	63.4 (22.7)	0.082
	No	1636	40.9 (28.0)		1643	71.4 (18.2)		1642	66.8 (23.0)	
Heart Failure	Yes	71	37.3 (26.9)	0.35	72	67.9 (18.3)	0.12	72	62.6 (25.3)	0.19
	No	1721	40.4 (27.9)		1728	71.3 (18.4)		1726	66.6 (22.9)	
PVD	Yes	157	37.3 (27.3)	0.15	157	70.1 (18.6)	0.44	159	64.8 (23.6)	0.36
	No	1635	40.6 (27.9)		1643	71.3 (18.4)		1639	66.6 (23.0)	
Atrial Fibrillation	Yes	140	40.4 (29.3)	0.97	141	72.6 (17.6)	0.34	144	70.0 (23.0)	0.061
	No	1652	40.3 (27.7)		1659	71.1 (18.4)		1654	66.2 (23.0)	
Hypertension	Yes	1298	40.4 (27.7)	0.81	1305	71.2 (18.7)	0.90	1303	66.7 (22.9)	0.57
	No	494	40.0 (28.2)		495	71.3 (17.6)		495	66.0 (23.4)	
	No	1331	40.7 (28.1)		1336	71.6 (18.2)		1332	66.8 (23.0)	

Cause of disease	Hypertension	200	43.0 (27.6)	0.002	200	74.5 (16.6)	0.001	201	70.4 (20.5)	<0.001
	Diabetes	588	36.6 (26.1)		592	68.6 (19.0)		594	63.2 (23.1)	
	Glomerular	322	39.6 (28.7)		321	70.9 (18.8)		322	63.4 (23.4)	
	Tubulointerstitial	171	43.9 (29.5)		174	71.3 (18.8)		171	68.7 (23.1)	
	Renovascular	129	39.5 (28.0)		129	72.1 (18.0)		130	70.8 (21.5)	
	Other	104	41.5 (27.3)		104	73.7 (15.2)		104	67.2 (21.2)	
	Polycystic	97	45.2 (28.4)		99	72.8 (17.3)		96	69.7 (23.9)	
	Unknown	181	44.5 (29.1)		181	73.6 (18.7)		180	71.4 (24.2)	
Vascular access	Catheter	729	39.9 (27.3)	0.82	733	70.9 (18.5)	0.21	728	65.7 (22.6)	0.39
	Fistula	1024	40.6 (28.2)		1028	71.6 (18.2)		1031	67.0 (23.4)	
	Graft	39	38.9 (29.3)		39	66.5 (20.1)		39	69.2 (20.0)	
Hb	Hb<=100	636	38.2 (27.3)	0.016	640	70.4 (18.4)	0.18	638	65.3 (23.2)	0.11
	Hb>100	1156	41.5 (28.1)		1160	71.6 (18.3)		1160	67.1 (22.9)	
Ferritin	Ferr<=200	794	40.3 (27.8)	0.96	793	70.9 (18.8)	0.59	791	66.2 (23.9)	0.62
	Ferr>200	998	40.3 (27.9)		1007	71.4 (18.0)		1007	66.7 (22.3)	
TSAT	TSAT<=20	953	39.4 (27.3)	0.16	956	70.5 (18.6)	0.079	957	65.8 (23.5)	0.17
	TSAT>20	839	41.3 (28.5)		844	72.0 (18.1)		841	67.3 (22.5)	
CRP	CRP<=6.0	841	42.1 (28.0)	0.010	844	72.8 (17.8)	<0.001	840	67.4 (23.1)	0.11
	CRP>6.0	951	38.7 (27.6)		956	69.7 (18.7)		958	65.7 (22.9)	
MCV	MCV<=93	943	39.1 (27.8)	0.041	949	70.2 (18.7)	0.014	951	64.8 (23.5)	0.001
	MCV>93	829	41.8 (27.8)		831	72.3 (18.1)		827	68.5 (22.3)	
ESA (units/week)	ESA<=8000	1140	41.2 (28.1)	0.078	1145	71.3 (18.4)	0.73	1145	66.8 (23.4)	0.42
	ESA>8000	652	38.8 (27.4)		655	71.0 (18.4)		653	65.9 (22.3)	

Supplementary Table 1: Predictors of EQ5D Index and EQ5D VAS Coefficients

EQ5D Index					EQ5D VAS		
Term	**Coef**	**SE Coef**	**p-value**		**Coef**	**SE Coef**	**P-Value**
Age ≤ 65 vs. > 65	0.0257	0.0123	0.036		3.94	1.02	<0.001
CRP ≤ 6.0 vs. > 6.0	-0.0695	0.0120	<0.001		-4.694	0.993	<0.001
BMI ≤ 27.5 vs. > 27.5	-0.0419	0.0123	0.001		-	-	-
Stroke (yes/no)	-0.1124	0.0211	<0.001		-6.16	1.75	<0.001
Heart failure (yes/no)	-0.1093	0.0308	<0.001				
Sex (female/male)	-0.0339	0.0124	0.006		-2.52	1.03	0.015
Cause of renal failure vs. Diabetes							
Hypertension	0.0886	0.0207	<0.001		6.54	1.69	<0.001
Glomerular	0.0796	0.0177	<0.001		3.52	1.46	0.016
Tubulointerstitial	0.0243	0.0223	0.275		1.76	1.84	0.340
Renovascular	0.0208	0.0248	0.401		0.01	2.05	0.994
Other	0.0661	0.0266	0.013		4.20	2.24	0.061
Polycystsic Kindey	0.1270	0.0274	<0.001		5.78	2.26	0.011
Unknown	0.0849	0.0218	<0.001		4.58	1.78	0.010

Supplementary Table 2: Predictors of PCS, MCS coefficients

KD QoL PCS					KD QoL MCS		
Term	Coef	SE Coef	P-value		Coef	SE Coef	P-Value
Age ≤ 65 vs. > 65	3.537	0.561	<0.001				
CRP ≤ 6.0 vs. > 6.0					-3.382	0.499	<0.001
BMI ≤ 27.5 vs. > 27.5					-1.915	0.511	<0.001
Myocardial infarction (yes/no)					-2.243	0.874	0.010
Hypertension (yes/no)	-1.330	0.634	0.036				
Stroke (yes/no)	-3.651	0.974	<0.001		-1.749	0.883	0.048
TSAT ≤ 20 vs. > 20	1.530	0.547	0.005				
Sex (female/male)	-1.201	0.574	0.037		-2.225	0.519	<0.001
Smoking former vs. current					0.743	0.866	0.391
Smoking never vs. current					2.094	0.790	0.008
Cause of renal failure vs. Diabetes							
Hypertension	1.600	0.944	0.090		3.037	0.849	<0.001
Glomerular	1.873	0.807	0.020		1.856	0.729	0.011
Tubulointerstitial	2.09	1.04	0.044		0.973	0.923	0.292
Renovascular	1.11	1.15	0.337		-0.22	1.02	0.829
Other	2.79	1.23	0.024		1.78	1.10	0.107
Polycystsic Kindey	3.44	1.25	0.006		2.56	1.13	0.023
Unknown	2.921	0.992	0.003		1.479	0.891	0.097

Supplementary Table 3: Predictors of burden of KD; Predictors of Symptoms of KD and predictors of effects

	Burden				Symptoms				Effects		
	Coef	SE Coef	P value		Coef	Se Coef	P Value		Coef	Ceof	P Value
Age ≤ 65 vs. > 65	5.495	0.903	<0.001		6.44	1.36	<0.001		11.11	1.09	<0.001
CRP ≤ 6.0 vs. > 6.0	-2.991	0.879	0.001		-3.82	1.32	0.004		-2.20	1.07	0.040
BMI ≤ 27.5 vs. > 27.5	-2.302	0.898	0.010						-2.47	1.09	0.024
Stroke (yes/no)					-6.21	2.33	0.008		-4.27	1.87	0.023
Gender (female/male)	-2.605	0.908	0.044		-2.75	1.38	0.046		-3.10	1.11	0.005
Smoking former vs. current	3.13	1.55	0.044								
Smoking never vs. current	4.23	1.4	0.003								
Cause of Renal Failure vs. Diabetes											
Hypertension	4.80	1.50	0.001		4.77	2.28	0.037		4.77	1.84	0.010
Glomerular	2.02	1.27	0.113		2.45	1.94	0.207		0.09	1.57	0.953
Tubulointerstitial	2.29	1.61	0.155		6.77	2.45	0.006		4.50	1.99	0.023
Renovascular	1.46	1.80	0.419		0.53	2.74	0.847		3.24	2.20	0.141
Other	5.15	1.94	0.008		5.41	2.96	0.067		4.36	2.38	0.067
Polycystsic Kindey	4.38	2.00	0.028		8.77	3.05	0.004		6.98	2.48	0.005
Unknown	3.48	1.57	0.027		6.13	2.37	0.010		5.09	1.93	0.008