Research Square

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First-year mortality in incident dialysis patients: results of the Peridialysis study

James Heaf (heaf@dadlnet.dk)
Zealand University Hospital
Maija Heiro
Turku University Hospital
Aivars Petersons
P. Stradins University Hospital
Baiba Vernere
P. Stradins University Hospital
Johan V Povlsen
Aarhus University Hospital
Anette Bagger Sørensen
Aarhus University Hospital
Naomi Clyne
Lund University and Skåne University Hospital
Inga Bumblyte
Lithuanian University of Health Sciences
Alanta Zilinskiene
Lithuanian University of Health Sciences
Else Randers
Viborg Regional Hospital
Niels Løkkegaard
Holbaek Hospital
Mai Rosenberg
Tartu University and University Hospital of Tartu
Stig Kjellevold
Vestfold Hospital
Jan Dominik Kampmann
Hospital of Southern Jutland
Björn Rogland
Kristianstad Hospital
Inger Lagreid
St. Olav University Hospital
Olof Heimburger

Karolinska Institutet

Bengt Lindholm

Karolinska Institutet

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Abstract

Background: Controversy surrounds which factors are important for predicting early mortality after dialysis initiation (DI). We investigated associations of predialysis course and circumstances affecting planning and execution of DI with mortality following DI.

Methods: Among 1580 patients participating in the *Peridialysis* study, a prospective study of causes and timing of DI, features of predialysis course, clinical and biochemical data at DI, incidence of unplanned suboptimal DI, contraindications to peritoneal dialysis (PD) or hemodialysis (HD), and modality preference, actual choice, and cause of modality choice were registered. Patients were followed for 12 months or until transplantation.

Results: First-year mortality was 20.2%. In addition to age and comorbid factors, independent factors predicting death were: clinical contraindications to PD or HD, a rapidly falling eGFR before DI, suboptimal DI, acidosis, high C-reactive protein, signs of overhydration (pulmonary stasis) and cerebral symptoms at DI while eGFR at DI was not. Among 1061 (67.2%) patients who could select dialysis modality based on personal choice, 654 (61.6%) chose PD, 368 (34.7%) center HD and 39 (3.7%) home HD. The 12-months survival did not differ significantly between patients receiving PD and in-center HD.

Conclusions: First-year mortality in incident dialysis patients was associated with high age, comorbidity, worsening of kidney failure and clinical symptoms, acidosis, inflammation, and suboptimal DI while eGFR at DI and dialysis modality did not appear as predictors. These findings support the view that choice of dialysis modality among patients who are able to make an informed decision can be based on patient preference.

Introduction

The survival in patients with end stage renal disease (ESRD) starting on dialysis therapy has improved during recent years but the mortality still remains high, especially during the initial months on dialysis therapy [1-4] . There are many potential biological factors contributing to the poor initial outcomes [5,6] . In incident hemodialysis (HD) patients, use of central venous catheter and hypoalbuminemia are associated with the highest early mortality risk [7]. In addition to biological factors, predialysis care and circumstances of dialysis initiation (DI), in particular suboptimal dialysis initiation are likely to play a role.

Most studies have showed initial lower mortality for patients treated with peritoneal dialysis (PD) compared to in-center HD [8-12]. There are plausible reasons why this difference may be causal. PD is associated with less hemodynamic stress, and a slower loss of residual renal function, a factor which is generally recognised to improve health and prognosis [13,14]. Hemodialysis is associated with a marked initial acceleration of mortality, particularly cardiovascular [15-17], that may be due to the unphysiological fluctuations in solutes and fluid and the cardiac strain of hemodialysis that increase the risk for sudden cardiac death, a common cause of death in dialysis patients [5,18,19]. On the other hand, studies comparing the mortality of patients on peritoneal dialysis (PD) versus hemodialysis (HD) are complicated

by the fact that patients are more likely to be treated with HD if they have multiple comorbidity and suboptimal DI, usually defined as unplanned DI in an in-patient setting using a temporary central venous catheter [20], and therefore statistical adjustments need to be performed. The fact that several studies failed to show a difference between PD and HD on initial mortality may suggest that insufficient corrections have been made in earlier studies for factors potentially influencing mortality [21-23].

Predialysis care is likely to be important and the existence of a multidisciplinary predialysis clinic is associated with reduced mortality [24-27]. Possible causality is speculative, putative factors being better patient attention to symptoms, improved dietary and therapeutic treatment [27] and reduced frequency of suboptimal DI.

Suboptimal DI is associated with increased mortality [7,28-32]. This may be causal, e.g. due to increased incidence of bacteremia compared to use of arteriovenous fistula (AVF) [33], but may just be a marker of the acute morbidity that often requires suboptimal DI.

Early referral to specialist nephrological care is associated with reduced mortality after DI. [34-39]. It is possible that this permits early dialysis planning with identification of patients who wish to have peritoneal dialysis, timely AVF placement for those who wish to have hemodialysis, and early identification of patients with rapid uremia progression. Rapid loss of renal function prior to DI is higher in HD patients than PD [40] and is related to increased mortality [41].

The “Peridialysis” study is a prospective, multi-center, international prospective observational study of the relevance of pre-dialysis renal care on causes and timing of dialysis initiation, modality choice and clinical outcomes [42-44] . The present study focuses on the relationships of the predialysis course, circumstances of DI, and choice of modality on short-term (1-year) mortality after DI.

Materials And Methods

This observational multinational multi-centre prospective study comprised 1619 ESRD patients who started dialysis over a 3-year period at 15 nephrology departments from seven Nordic and Baltic countries. The methodology of the “Peridialysis” project has been previously described [42-44]. All centers delivered both PD and in-centre HD; some also home-HD; all had a developed and working multidisciplinary pre-dialysis care team structure with nephrologists and experienced nurses; 13/15 centers also had access to a dietician, and 5/15 had access to social worker.

The commonest method of assessing residual renal function and guiding clinical treatment was estimated glomerular filtration rate (eGFR) as measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [45].

Patients

Patients included in this study were consecutive patients starting chronic dialysis therapy for end stage renal disease (ESRD) at the participating centers between January 1, 2015 and December 31, 2017. Five

centers had a shorter recruiting period.

A patient was considered as having ESRD at first dialysis if:

1. The patient was diagnosed as having ESRD according to the treating physician; this was the most used definition of ESRD.
2. The patient received dialysis treatment for >90 days.
3. If the doctor was in doubt whether the patient had acute or chronic renal failure, the patient was included retrospectively as soon as there was no doubt that the patient had chronic renal failure and ESRD.

The study protocol was approved by the ethical review boards in centers located in countries where according to the country´s regulations this was required. The study was approved by the Swedish Ethical Review Authority (Ref 2017/7), while in Denmark, due to the observational non-interventional design of the study using anonymized patient data, the study protocol was not considered to be eligible for ethical review. Informed consent - either written or verbal depending on the regulations in the different countries - was obtained from participants in all centers including those in Denmark, with the exception of Lithuania, where patient permission was waived by the ethics board (P2-BE-2-9/2014). The study is registered with Clinical Trials.gov, identifier NCT02488200. The Swedish approval was valid for all EU countries.

Methods

Patient clinical data

The following data were registered at DI: patient characteristics (age, sex, height, body weight, body mass index (BMI) and underlying renal diagnosis), selected comorbidities (previous myocardial infarction, heart failure, cardiac atherosclerosis, cerebrovascular disease, diabetes, peripheral atherosclerosis, previous cancer (except basocellular), chronic pulmonary disease, chronic liver disease, psychiatric disease, and “other chronic conditions”), previous renal transplantation, and dialysis access. Data on dialysis access was used to classify if the start of dialysis as optimal DI or suboptimal DI.

DI was classified as optimal if:

1. The access was an AVF or graft (AVG);
2. The access was a tunnelled vascular catheter as the patient’s permanent access due to a medical decision;
3. The access was a PD catheter, and PD was started >6 days after placement.

DI was classified as suboptimal if:

1. The access was a temporary vascular catheter;

2. The access was a tunnelled catheter, but a later AVF/AVG was planned;
3. The access was a PD catheter, and PD was started <6 days after placement.

Late referral was defined as referral to the specialist clinic <3 months before DI.

As pre-emptive transplants were often assessed and treated at other departments, patients receiving pre-emptive transplants were excluded from the study.

Modality choice was planned by shared decision making before DI or shortly thereafter. Primary causes of choice of dialysis modality choice included preference for PD (HD not possible); preference for HD (physical contraindication to PD); preference for HD (mental contraindication to PD); preference for HD (abdominal contraindication to PD); preference for HD (home dialysis modality not discussed); and other. The remaining patients could choose between PD, in-centre HD and home HD depending on their personal preferences. Changes in modality during the first year after DI were registered.

Patient biochemical data

The following biochemical data prior to or in conjunction with first dialysis were registered: blood hemoglobin, plasma concentrations of urea, creatinine, potassium, hydrogen carbonate (bicarbonate), albumin, C-reactive protein (CRP), total or ionized calcium, and phosphate. Most centers measured ionized calcium; for other centers, ionized calcium was assumed to be 50% of total calcium. Whenever available, plasma creatinine concentration and date of measurement were registered about three and six months before DI.

Rapid rate of loss of eGFR was defined as a fall of eGFR >1 ml/min/1.73m^2/month.

Reasons for dialysis initiation stated in questionnaire to physicians

Physicians gave details in an English language questionnaire of their reasons for prescribing chronic dialysis at DI. They could choose between several pre-stated clinical and/or biochemical reasons. Details of these have already been published. [42-44]. For the purposes of the present study, clinical symptoms were registered if they were the primary cause of DI. Life-threatening conditions were defined as presence of pulmonary stasis, dyspnea, cardiac symptoms, pericarditis, acidosis or hyperkalemia. Clinical reasons (rather than biochemical) were stated to be the primary cause of DI in 63% % of patients [42].

Statistics

Data are presented as mean ± standard deviation (SD) for normally distributed variables, median (interquartile range, IQR) for non-normally distributed variables, or as numbers and percentage. Parametric variables were compared using the Students t-test and MANOVA, and non-parametric variables using the Chi square, Mann-Whitney and Kruskal-Wallis tests.

Kaplan Meier and forward stepwise Cox proportional hazards analysis were performed to identify independent factors associated with mortality during the first year of dialysis. Patients were censored for lost-to-follow-up or transplantation.

Forward stepwise regression analysis was performed to identify independent associations with modality choice. Four models were analysed; all models included age, sex, comorbidity, plasma albumin and renal diagnoses, and in addition selected variables as follows: **"Predialysis" model** included predialysis variables: rate of eGFR change per month prior to DI, late referral and suboptimal DI. "**Biochemical" model** included selected biochemical variables at DI. **"Clinical" model** included those clinical problems that were stated as the primary cause of DI. **"Combined model"**, a final model that included all factors that were statistically significant in the previous three models.

A probability level of <0.05 was considered significant. Significance values were expressed as $p<0.05$, $p<0.01$, $p<0.001$.

Results

Altogether 1619 patients were recruited to the study; 39 patients were excluded due to insufficient basic data (n=10), lack of follow-up (n=12) or pre-emptive transplantation (n=17). The remaining 1580 patients (age 63.7 ±15.4 years; women 35.9%) were included in the present study. Clinical details at DI were available for 1544 (97.7%) patients and biochemical data in 1533 (97.0%) patients. The patient details are shown in **Table 1**. The eGFR at DI was on average 7.3 ±3.6, median 6.7 (IQR 5.0-8.5) ml/min/1.73m^2.

The mortality rate at 3- and 12- months was 7.0% and 20.2% respectively. There was no significant difference in mortality between the countries and regions involved in the study.

Age (but not sex), plasma albumin, most comorbidity conditions were highly correlated to mortality (see **Supplementary Table 1**). The most important comorbid conditions were heart failure and peripheral atherosclerosis (12-months mortality rate, 36.7% and 35.3%, respectively).

We analysed factors associated with mortality in four models. High age, comorbidity (with some exceptions; vide supra) and low plasma albumin were associated with increased mortality in most models. Other factors with significant associations with mortality in crude models are shown in **Table 2**. In the adjusted multivariate Predialysis model, glomerulonephritis and polycystic kidney disease were associated with lower mortality while suboptimal DI, rapid eGFR loss 3 to 0 months before DI, physical contraindication to PD, and contraindication to HD were associated with increased mortality risk. Patients with suboptimal DI and rapid eGFR had the highest mortality (**Fig. 1**). In the adjusted Biochemical model, acidosis, and CRP were associated with increased mortality while there was no relation to eGFR, hypokalemia or hyperkalemia at DI. In the adjusted Clinical model, focusing on clinical problems linked to the primary cause of DI, pulmonary stasis and cerebral symptoms were the only independent risk factors for death while polycystic kidney disease associated with lower mortality. Finally, in the Combined

model, only physical PD contraindication, unplanned DI and a raised CRP predicted death independently of age, albumin, and registered comorbidity (**Fig. 2**).

Among all 1580 patients, 1061 (67.2%) patients could select dialysis modality based on their personal choice and were differentiated prospectively from patients with contraindications to one or the other dialysis modality. Of these 1061 patients, 654 (61.6%) chose PD, 368 (34.7%) in-center HD and 39 (3.7%) home HD. Mortality for home HD patients was similar to the other two groups, but the number was too small for statistical analysis. 47 PD choice patients (7.6%) did not receive PD and 4 (0.1%) HD choice patients did not receive HD. The details of the remaining 971 patients starting on PD (n=607) or HD (n=364) are shown in **Table 3**. They were clinically similar, but PD patients had a lower incidence of late referral, unplanned DI and eGFR loss rate, and a higher eGFR at DI. There was no overall significant difference in mortality (**Fig. 3**). A subgroup analyses including patients who had a planned optimal DI gave similar results. The number of patients was too small to analyze the effects of age and DM.

Discussion

In our study, factors associated with one-year mortality after DI among 1580 incident dialysis patients participating in the Peridialysis study [42-44] were investigated in three models that - in addition to age, sex, comorbidity, plasma albumin and renal diagnoses - included data on predialysis course (“predialysis” model), biochemical parameters (“biochemical” model), and primary clinical cause of DI (“clinical” model). A fourth “combined model” that included all statistically significant factors in the three separate models (**Table 2**), showed that only high CRP, physical contraindications to PD, and suboptimal DI, were associated with increased risk of death within one year after DI, independent of high age, low serum albumin and comorbidity, whereas eGFR at DI was not related to mortality. These findings highlight the importance of suboptimal DI, a potentially modifiable factor, as a contributor to early mortality in patients starting on dialysis. In patients with a “free” choice of dialysis modality based on their personal preferences, PD and in-center HD led to broadly similar short-term outcomes. Our results thus support current recommendations that modality choice should be made according to patient preference rather than for medical reasons [46,47].

In a previous study of factors associated with suboptimal DI in the same population, we found that late referral and rapid eGFR loss were independent predictors of suboptimal DI and that patients with suboptimal DI were more uremic at DI as judged by eGFR, had more electrolyte disturbances over and above what would be expected from the level of eGFR, and had a higher CRP [43] (ref. CKJ suboptimal DI article 2020). In the present study, these factors, except for eGFR at DI and late referral, were independent predictors of increased mortality in one or more of the separate abovementioned multivariate models: physical PD contraindication, rapid eGFR loss, suboptimal dialysis, acidosis, raised CRP, cerebral problems, and pulmonary stasis. Thus, in the model focusing on factors involved in the predialysis course (“predialysis” model), physical contraindication to PD or HD and suboptimal DI associated with higher risk, while a renal diagnosis of polycystic kidney disease and glomerulonephritis were associated with lower risk. In the multivariate analysis focusing on biochemical parameters (“biochemical” model),

only elevated CRP and severe acidosis, associated with mortality, and in the model focusing on clinical causes of DI (“clinical” model), pulmonary problems, i.e., pulmonary stasis and cerebral problems (primarily coma) associated with increased risk while polycystic kidney disease associated with lower risk.

Some of these findings have previously been reported. Causal explanations of these associations are purely speculative. Physical PD contraindication can be regarded as a surrogate marker of comorbidity. One can imagine that an acute infection, e.g. pneumonia, could result in accelerated eGFR loss and suboptimal DI, the pneumonia being the primary cause of death. Rapid loss of renal function prior to DI has previously been associated with mortality [41,48] and could be expected to continue after DI. Residual renal function is associated with reduced mortality after DI, independently of total (renal and dialysis) Kt/V or creatinine clearance [49,50]. An alternative scenario emphasizes the pre-dialytic course, where rapid eGFR loss leads to delayed dialysis planning, with subsequent requirement for suboptimal DI in a clinical situation of severe uremia, pulmonary stasis and acute infection. Subsequent mortality would then be a consequence of poor clinical condition at DI and subsequent catheter-related complications.

Many studies have been published concerning the relative survival of PD and center HD patients including recent comprehensive reviews [47,51,52]. Most studies show a reduced mortality relative to HD during the early period after DI [8-10,53-56], but others an increased mortality [38,52,57,58]. Other studies have not found any difference [21,23,59]. PD seems to be advantageous for younger patients and non-diabetics. It has been suggested that the apparent early PD survival advantage is due to previous statistical analyses not correcting sufficiently for differences in patient clinical status, and that there are no major differences in mortality [21,22]. One major advantage of this study, compared to previous papers, is that patients were assessed before or at DI for suitability for HD and PD. Excluding unsuited patients will result in a more accurate assessment of the consequences of choosing in-center HD or PD. As previously described [40], PD patents had a slower rate of eGFR prior to DI and also had a higher eGFR at DI, but this did not affect the finding regarding mortality. Our results support the hypothesis that there are no major differences in short term prognosis for incident patients who were able to make a free choice based on their personal preference (**Fig. 3**).

This study has some weaknesses. Being an observational study, causal conclusions cannot be made. The number of patients is insufficient to demonstrate minor differences in mortality between HD and PD patients. The data were reported by physicians, who may have differed in their assessment of patient modality suitability.

In conclusion, first-year mortality in incident dialysis patients associated with high age, comorbidity, worsening of kidney failure, clinical symptoms, acidosis, inflammation, and suboptimal DI while eGFR at DI and dialysis modality did not appear as independent predictors. These findings highlight that suboptimal DI, a potentially modifiable factor, is a significant contributor to early mortality in patients starting on dialysis, indicating that predialysis care, early education and planning are warranted as it is possible that an intensive pre-dialytic program, with early access planning, and particular attention paid

to rapid eGFR loss, infectious complications and overhydration prophylaxis could reduce early mortality after DI. Our results that PD and in-center HD lead to broadly similar short-term outcomes, support current recommendations that modality choice should be based on patient preference rather than medical reasons only [46,47].

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethical review boards in centers located in countries where according to the country´s regulations this was required. The study was approved by the Swedish Ethical Review Authority (Ref 2017/7), while in Denmark, due to the observational non-interventional design of the study using anonymized patient data, the study protocol was not considered to be eligible for ethical review. Informed consent - either written or verbal depending on the regulations in the different countries - was obtained from participants in all centers including those in Denmark, with the exception of Lithuania, where patient permission was waived by the ethics board (P2-BE-2-9/2014). The study is registered with Clinical Trials.gov, identifier NCT02488200. The Swedish approval was valid for all EU countries.

Consent for publication

The authors consent for the paper to be published in BMC Nephrology.

Availability of data and materials

The data is available on Open Science Framework osf.io/3wh4g.[60]

Competing interests

Bengt Lindholm is employed by Baxter Healthcare at Baxter Novum, Karolinska Institutet. None of the other authors declare any conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Authors’ contributions

JGH: Protocol, statistics, data collection, manuscript preparation

MH: Protocol preparation, data collection, manuscript editing

AP: Protocol preparation, data collection, manuscript editing

BV: Data collection, manuscript editing

JVP: Protocol preparation, manuscript editing

ABS: Data collection, manuscript editing

NC: Protocol preparation, data collection, manuscript editing

IB: Data collection, manuscript editing

AZ: Data collection, manuscript editing

ER: Data collection, manuscript editing

NL: Data collection, manuscript editing

MR: Protocol preparation, data collection, manuscript editing

SK: Data collection, manuscript editing

JDK: Data collection, manuscript editing

BR: Protocol preparation, data collection, manuscript editing

IL: Protocol preparation, data collection, manuscript editing

OH: Protocol preparation, manuscript editing

BL: Protocol preparation, manuscript preparation

Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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References

1. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D *et al.*: **US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States.** *Am J Kidney Dis* 2020, **75:** A6-A7.
2. van WC, Manuel DG, Knoll G: **Survival trends in ESRD patients compared with the general population in the United States.** *Am J Kidney Dis* 2014, **63:** 491-499.
3. Pippias M, Jager KJ, Kramer A, Leivestad T, Sanchez MB, Caskey FJ *et al.*: **The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry.** *Nephrol Dial Transplant* 2016, **31:** 831-841.
4. Heaf J: **Current trends in European renal epidemiology.** *Clin Kidney J* 2017, **10:** 149-153.
5. McIntyre CW, Rosansky SJ: **Starting dialysis is dangerous: how do we balance the risk?** *Kidney Int* 2012, **82:** 382-387.
6. Molnar MZ, Ojo AO, Bunnapradist S, Kovesdy CP, Kalantar-Zadeh K: **Timing of dialysis initiation in transplant-naive and failed transplant patients.** *Nat Rev Nephrol* 2012, **8:** 284-292.
7. Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K: **Patterns and predictors of early mortality in incident hemodialysis patients: new insights.** *Am J Nephrol* 2012, **35:** 548-558.
8. Heaf JG, Wehberg S: **Relative survival of peritoneal dialysis and haemodialysis patients: effect of cohort and mode of dialysis initiation.** *PLoS One* 2014, **9:** e90119.
9. Weinhandl ED, Foley RN, Gilbertson DT, Arneson TJ, Snyder JJ, Collins AJ: **Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients.** *J Am Soc Nephrol* 2010, **21:** 499-506.
10. Liem YS, Wong JB, Hunink MG, de Charro FT, Winkelmayer WC: **Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands.** *Kidney Int* 2007, **71:** 153-158.
11. Waldum-Grevbo B, Leivestad T, Reisaeter AV, Os I: **Impact of initial dialysis modality on mortality: a propensity-matched study.** *BMC Nephrol* 2015, **16:** 179.
12. Marshall MR: **The benefit of early survival on PD versus HD-Why this is (still) very important.** *Perit Dial Int* 2020, 896860819895177.
13. Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA *et al.*: **Predictors of loss of residual renal function among new dialysis patients.** *J Am Soc Nephrol* 2000, **11:** 556-564.
14. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT: **Predictors of the rate of decline of residual renal function in incident dialysis patients.** *Kidney Int* 2002, **62:** 1046-1053.
15. Kalantar-Zadeh K, Kovesdy CP, Streja E, Rhee CM, Soohoo M, Chen JLT *et al.*: **Transition of care from pre-dialysis prelude to renal replacement therapy: the blueprints of emerging research in advanced chronic kidney disease.** *Nephrol Dial Transplant* 2017, **32:** ii91-ii98.
16. Robinson BM, Zhang J, Morgenstern H, Bradbury BD, Ng LJ, McCullough KP *et al.*: **Worldwide, mortality risk is high soon after initiation of hemodialysis.** *Kidney Int* 2014, **85:** 158-165.

17. Eckardt KU, Gillespie IA, Kronenberg F, Richards S, Stenvinkel P, Anker SD *et al.*: **High cardiovascular event rates occur within the first weeks of starting hemodialysis.** *Kidney Int* 2015, **88:** 1117-1125.
18. McIntyre CW: **Effects of hemodialysis on cardiac function.** *Kidney Int* 2009, **76:** 371-375.
19. Bleyer AJ, Russell GB, Satko SG: **Sudden and cardiac death rates in hemodialysis patients.** *Kidney Int* 1999, **55:** 1553-1559.
20. Mendelssohn DC, Malmberg C, Hamandi B: **An integrated review of "unplanned" dialysis initiation: reframing the terminology to "suboptimal" initiation.** *BMC Nephrol* 2009, **10:** 22.
21. Quinn RR, Hux JE, Oliver MJ, Austin PC, Tonelli M, Laupacis A: **Selection bias explains apparent differential mortality between dialysis modalities.** *J Am Soc Nephrol* 2011, **22:** 1534-1542.
22. Noordzij M, Jager KJ: **Survival comparisons between haemodialysis and peritoneal dialysis.** *Nephrol Dial Transplant* 2012, **27:** 3385-3387.
23. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E: **Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease.** *Arch Intern Med* 2011, **171:** 110-118.
24. Devins GM, Mendelssohn DC, Barre PE, Taub K, Binik YM: **Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up.** *Am J Kidney Dis* 2005, **46:** 1088-1098.
25. Lacson E Jr, Wang W, DeVries C, Leste K, Hakim RM, Lazarus M *et al.*: **Effects of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes.** *Am J Kidney Dis* 2011, **58:** 235-242.
26. Hemmelgarn BR, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Walsh M *et al.*: **Association between multidisciplinary care and survival for elderly patients with chronic kidney disease.** *J Am Soc Nephrol* 2007, **18:** 993-999.
27. Goldstein M, Yassa T, Dacouris N, McFarlane P: **Multidisciplinary predialysis care and morbidity and mortality of patients on dialysis.** *Am J Kidney Dis* 2004, **44:** 706-714.
28. Metcalfe W, Khan IH, Prescott GJ, Simpson K, Macleod AM: **Can we improve early mortality in patients receiving renal replacement therapy?** *Kidney Int* 2000, **57:** 2539-2545.
29. Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ *et al.*: **Associations between hemodialysis access type and clinical outcomes: a systematic review.** *J Am Soc Nephrol* 2013, **24:** 465-473.
30. Mendelssohn DC, Curtis B, Yeates K, Langlois S, MacRae JM, Semeniuk LM *et al.*: **Suboptimal initiation of dialysis with and without early referral to a nephrologist.** *Nephrol Dial Transplant* 2011, **26:** 2959-2965.
31. Chen YM, Wang YC, Hwang SJ, Lin SH, Wu KD: **Patterns of Dialysis Initiation Affect Outcomes of Incident Hemodialysis Patients.** *Nephron* 2016, **132:** 33-42.
32. Lorenzo V, Martn M, Rufino M, Hernandez D, Torres A, Ayus JC: **Predialysis nephrologic care and a functioning arteriovenous fistula at entry are associated with better survival in incident hemodialysis patients: an observational cohort study.** *Am J Kidney Dis* 2004, **43:** 999-1007.

33. Nelveg-Kristensen KE, Laier GH, Heaf JG: **Risk of death after first-time blood stream infection in incident dialysis patients with specific consideration on vascular access and comorbidity.** *BMC Infect Dis* 2018, **18:** 688.

34. Avorn J, Bohn RL, Levy E, Levin R, Owen WF, Jr., Winkelmayer WC *et al.*: **Nephrologist care and mortality in patients with chronic renal insufficiency.** *Arch Intern Med* 2002, **162:** 2002-2006.

35. Kessler M, Frimat L, Panescu V, Briancon S: **Impact of nephrology referral on early and midterm outcomes in ESRD: EPidemiologie de l'Insuffisance REnale chronique terminale en Lorraine (EPIREL): results of a 2-year, prospective, community-based study.** *Am J Kidney Dis* 2003, **42:** 474-485.

36. Chan MR, Dall AT, Fletcher KE, Lu N, Trivedi H: **Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis.** *Am J Med* 2007, **120:** 1063-1070.

37. Jungers P, Massy ZA, Nguyen-Khoa T, Choukroun G, Robino C, Fakhouri F *et al.*: **Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients.** *Nephrol Dial Transplant* 2001, **16:** 2357-2364.

38. Winkelmayer WC, Owen WF, Jr., Levin R, Avorn J: **A propensity analysis of late versus early nephrologist referral and mortality on dialysis.** *J Am Soc Nephrol* 2003, **14:** 486-492.

39. Huisman RM: **The deadly risk of late referral.** *Nephrol Dial Transplant* 2004, **19:** 2175-2180.

40. Maddux DW, Usvyat LA, Blanchard T, Jiao Y, otanamo P, van der Sande FM *et al.*: **Transition Period Clinical Trajectories for PD versus HD Starters .** *Perit Dial Int* 2019, **39:** 42-45.

41. Kovesdy CP, Naseer A, Sumida K, Molnar MZ, Potukuchi PK, Thomas F *et al.*: **Abrupt Decline in Kidney Function Precipitating Initiation of Chronic Renal Replacement Therapy.** *Kidney Int Rep* 2018, **3:** 602-609.

42. Heaf J, Petersons A, Vernere B, Heiro M, Povlsen JV, Sorensen AB *et al.*: **Why do physicians prescribe dialysis? A prospective questionnaire study.** *PLoS One* 2017, **12:** e0188309.

43. Heaf J, Heiro M, Petersons A, Vernere B, Povlsen JV, Sorensen AB *et al.*: **Suboptimal dialysis initiation is associated with comorbidities and uraemia progression rate but not with estimated glomerular filtration rate.** *Clin Kidney J* 2020, **13:** xxx.

44. Heaf J, Heiro M, Petersons A, Vernere B, Povlsen JV, Sorensen AB *et al.*: **Choice of dialysis modality among patients initiating dialysis: Results of the Peridialysis study.** *Clinical Kidney Journal* 2021, **16:** in press.

45. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, III, Feldman HI *et al.*: **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009, **150:** 604-612.

46. Mehrotra R: **Choice of dialysis modality.** *Kidney Int* 2011, **80:** 909-911.

47. Segall L, Nistor I, van BW, Brown EA, Heaf JG, Lindley E *et al.*: **Dialysis modality choice in elderly patients with end-stage renal disease: a narrative review of the available evidence.** *Nephrol Dial Transplant* 2017, **32:** 41-49.

48. Xie Y, Bowe B, Xian H, Balasubramanian S, Al-Aly Z: **Renal Function Trajectories in Patients with Prior Improved eGFR Slopes and Risk of Death.** *PLoS One* 2016, **11:** e0149283.

49. **Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group.** *J Am Soc Nephrol* 1996, **7:** 198-207.
50. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J *et al.*: **Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial.** *J Am Soc Nephrol* 2002, **13:** 1307-1320.
51. Xue J, Li H, Zhou Q, Wen S, Zhou Q, Chen W: **Comparison of peritoneal dialysis with hemodialysis on survival of diabetic patients with end-stage kidney disease: a meta-analysis of cohort studies.** *Ren Fail* 2019, **41:** 521-531.
52. Han SS, Park JY, Kang S, Kim KH, Ryu DR, Kim H *et al.*: **Dialysis Modality and Mortality in the Elderly: A Meta-Analysis.** *Clin J Am Soc Nephrol* 2015, **10:** 983-993.
53. Choi JY, Jang HM, Park J, Kim YS, Kang SW, Yang CW *et al.*: **Survival advantage of peritoneal dialysis relative to hemodialysis in the early period of incident dialysis patients: a nationwide prospective propensity-matched study in Korea.** *PLoS One* 2013, **8:** e84257.
54. van de Luijtgaarden MW, Noordzij M, Stel VS, Ravani P, Jarraya F, Collart F *et al.*: **Effects of comorbid and demographic factors on dialysis modality choice and related patient survival in Europe.** *Nephrol Dial Transplant* 2011, **26:** 2940-2947.
55. Lukowsky LR, Mehrotra R, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K: **Comparing mortality of peritoneal and hemodialysis patients in the first 2 years of dialysis therapy: a marginal structural model analysis.** *Clin J Am Soc Nephrol* 2013, **8:** 619-628.
56. Kumar VA, Sidell MA, Jones JP, Vonesh EF: **Survival of propensity matched incident peritoneal and hemodialysis patients in a United States health care system.** *Kidney Int* 2014, **86:** 1016-1022.
57. Chang JH, Sung JY, Ahn SY, Ko KP, Ro H, Jung JY *et al.*: **Hemodialysis leads to better survival in patients with diabetes or high comorbidity, compared to peritoneal dialysis.** *Tohoku J Exp Med* 2013, **229:** 271-277.
58. Couchoud C, Moranne O, Frimat L, Labeeuw M, Allot V, Stengel B: **Associations between comorbidities, treatment choice and outcome in the elderly with end-stage renal disease.** *Nephrol Dial Transplant* 2007, **22:** 3246-3254.
59. Yeates K, Zhu N, Vonesh E, Trpeski L, Blake P, Fenton S: **Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada.** *Nephrol Dial Transplant* 2012, **27:** 3568-3575.
60. Heaf, J **Peridialysis and Mortality.** OSF. 2021 osf.io/3wh4g.

Tables

Table 1. Patient details

	All	%
Total	1580	
Age (years)	63.7 ±15.4	
Female sex	568	35.9
Renal diagnosis		
Glomerulonephritis	283	17.9
Chronic interstitial nephritis	186	11.8
Polycystic kidney disease	105	6.6
Diabetic nephropathy	386	24.4
Hypertensive	301	19.1
Other	178	11.3
Unknown	141	8.9
Comorbidity		
None	426	27.0
Previous myocardial infarct	170	10.8
Heart failure	262	16.6
Cerebrovascular disease	188	11.9
Peripheral vascular disease	193	12.2
Diabetes mellitus	548	34.7
Cancer	261	16.5
Pulmonary disease	150	9.5
Hepatic disease	60	3.8
Previous kidney transplant	81	5.1
Psychiatric illness	67	4.2

Table 2. Factors showing significant associations with first-year all-cause mortality risk among 1580 patients starting dialysis in three separate models and a combined model including all factors with significant associations to mortality in the three separate models. All models were adjusted for age, serum albumin and comorbidity.

			Odds ratio (95% CI)		
	Number	Percent	Crude model	Multivariate models¤	
				Separate model	Combined model
Renal diagnosis				Predialysis model	
Polycystic disease	105	6.6	0.21 (0.09-0.50)[c]	0.39 (0.17-0.88)[a]	
Glomerulonephritis	283	17.9	0.38 (0.23-0.63)[c]	0.60 (0.40-0.89)[a]	
Predialysis course					
DGFR 6-3 months before DI >1 ml/min/1.73m^2/month	349	22.1	1.32 (1.00-1.74)[a]		
DGFR 3-0 months before DI >1 ml/min/1.73m^2/month	527	43.4	1.72 (1.33-2.22)[c]	1.41 (1.07-1.87)[a]	
Suboptimal DI	667	42.2	2.00 (1.60-2.51)[c]	1.53 (1.19-1.95)[c]	1.44 (1.12-1.85)[b]
Late referral (>3 months before DI)	310	21.1	1.49 (1.14-1.93)[b]		
Access (vs. AVF)					
Temporary CVC Access	448	28.4	2.66 (1.89-3.74)[c]		
Acute PD	70	4.4	2.17 (1.25-3.75)[b]		
Modality Choice (vs. HD as free choice)					
HD contraindicated	46	2.9	3.52 (2.05-	1.99 (1.22-3.25)[b]	

			6.05)[c]		
Physical PD contraindication	142	9.0	3.64 (2.47-5.35)[c]	2.20 (1.64-2.96)[c]	2.04 (1.51-2.74)[c]
PD not offered	106	6.7	1.73 (1.10-2.72)[a]		
Biochemical variables at dialysis initiation				**Biochemical model**	
eGFR (ml/min/1.73m^2)			0.91 (0.73-1.14)[NS]		
Hemoglobin ≥7 mmol/L	987	63.2	0.77 (0.62-0.97)[a]		
Urea ≥30 mmol/L	876	57.1	1.64 (1.29-2.10)[c]		
Bicarbonate ≥15 mmol/L	1018	86.8	0.56 (0.41-0.77)[c]	0.67 (0.48-0.94)[a]	
C-reactive protein 10-49 mg/L*	419	29.1	2.86 (2.13-3.86)[c]	2.28 (1.62-3.19)[c]	2.36 (1.74-3.18)[c]
C-reactive protein ≥50 mg/L*	315	21.9	4.22 (3.13-5.68)[c]	2.60 (1.81-3.73)[c]	2.63 (1.91-3.63)[c]
Ionized calcium ≥1.15 mmol/L	1222	81.4	0.62 (0.48-0.81)[c]		
Phosphate ≥2.0 mmol/L	654	1479	1.60 (1.27-2.03)[c]		
Primary clinical causes of dialysis initiation				**Clinical model**	
Polycystic disease	Ut supra	Ut supra	Ut supra	0.38 (0.16-0.92)[a]	

Life-threatening	300	19.4	1.94 (1.52-2.48)[c]	
Pulmonary stasis	126	8.2	2.10 (1.52-2.89)[c]	1.72 (1.23-2.41)[b]
Dyspnea	70	4.5	1.89 (1.24-2.90)[b]	
Edema	36	2.3	1.68 (1.18-2.40)[b]	
Cardiac symptoms	36	2.3	1.15 (0.57-2.32)[NS]	
Cerebral symptoms			2.88 (1.36-6.09)[b]	4.02 (2.16-9.87)[c]
Fatigue	293	19.0	0.63 (0.45-0.88)[b]	
Anorexia	388	25.1	0.34 (0.13-0.91)[a]	

[a]:p<0.05; [b]:p<0.01; [c]:p<0.001. [#]with some exceptions. ¤: age, comorbidity and albumin factors not shown. *vs. <10 mg/L. GFR: glomerular filtration rate; AVF: arteriovenous fistula; CVC: central venous catheter; PD peritoneal dialysis; HD: hemodialysis; NS: not significant

Table 3. Patient details and all-cause mortality risk of PD vs. HD among patients who could choose freely between in-center HD and PD based on their personal preferences and among patients with optimal dialysis initiation (DI)

	All		Optimal DI	
	PD	HD	PD	HD
	n=607	n=364	n=469	n=211
Patient characteristics				
Age (years)	62.9 ±15.7	62.4 ±15.6	63.3 ±15.1	64.1 ±15.4
Female sex, n(%)	212 (34.9%)	120 (33.0%)	166 (35.1%)	74 (35.1%)
Unplanned DI, n(%)	131 (21.5%)	153 (42%)[c]	0	0
Late referral, n(%)	60 (10.6%)	69 (20.4%)[c]	23 (5.2%)	11 (5.7%)
Plasma albumin (g/L)	34.2 ±6.1	33.7 ±6.8	35.0 ±5.6	35.2 ±5.8
Comorbidity number (mean)	0.90	0.95	0.83	0.98
Comorbidity number (median (IQR))	1 (0-1)	1 (0-2)	0 (0-1)	0 (0-2)
GFR fall 3 to 0 months before DI (ml/min/1.73m^2/month)	6.9 (2.4-14.0)	10.2 (4.9-19.7)[c]	6.1 (2.1-12.3)	7.6 (3.3-13.4)[a]
eGFR at DI (ml/min/1.73m^2)	7.6 ±3.4	6.7 ±2.8[c]	7.9 ±3.4	7.2 ±2.9[b]
Mortality (%)				
3-months (%)	3.0	3.9	3.0	2.4
12-months (%)	15.5	14.8	15.2	14.0
Mortality risk PD vs.HD (Odds ratio (95% CI)				
Crude model	1.13 (0.80-1.61)		0.92 (0.59-1.43)	
Adjusted Model*				
All patients	1.14 (0.78-1.61)		1.13 (0.73-1.76)	
Adjusted models for subgroups*				
No DM	1.39 (0.83-2.32)		0.82 (0.43-1.54)	
DM	0.90 (0.54-1.48)		0.98 (0.52-1.84)	
Age <65 years	0.60 (0.30-1.25)		1.64 (0.71-3.64)	
Age >65 years	1.37 (0.90-2.08)		0.67 (0.39-1.14)	

[a]:p<0.05; [b]:p<0.01; [c]:p<0.001. *Adjusted for significant comorbidity

Supplementary Table 1. Unadjusted odds ratios (95% confidence limits) for mortality for clinical variables

	Odds ratio
Age (decade)	1.46 (1.33-1.60)[c]
Female sex	1.01 (0.80-1.28)
Renal diagnosis	
Glomerulonephritis	0.46 (0.31-0.66)[b]
Chronic interstitial nephritis	1.29 (0.94-1.77)
Polycystic kidney disease	0.27 (0.12-0.60)[b]
Diabetic nephropathy	1.03 (0.79-1.33)
Hypertensive	1.01 (0.75-1.33)
Comorbidity	
Previous myocardial infarct	1.84 (1.37-2.47)[c]
Heart failure	2.52 (1.97-3.20)[c]
Other heart disease	1.34 (0.98-1.83)
All heart disease	2.27 (1.81-2.84)[c]
Cerebrovascular disease	1.68 (1.26-2.25)[c]
Peripheral vascular disease	2.15 (1.64-2.82)[c]
Diabetes mellitus	1.34 (1.07-1.69)[b]
Cancer	1.75 (1.35-2.27)[c]
Pulmonary disease	1.71 (1.24-2.36)[c]
Hepatic disease	1.61 (1.00-2.60)[a]
Previous kidney transplant	0.88 (0.51-1.50)
Psychiatric illness	1.47 (0.93-2.34

[a]:p<0.05; [b]:p<0.01; [c]:p<0.001.

Figures

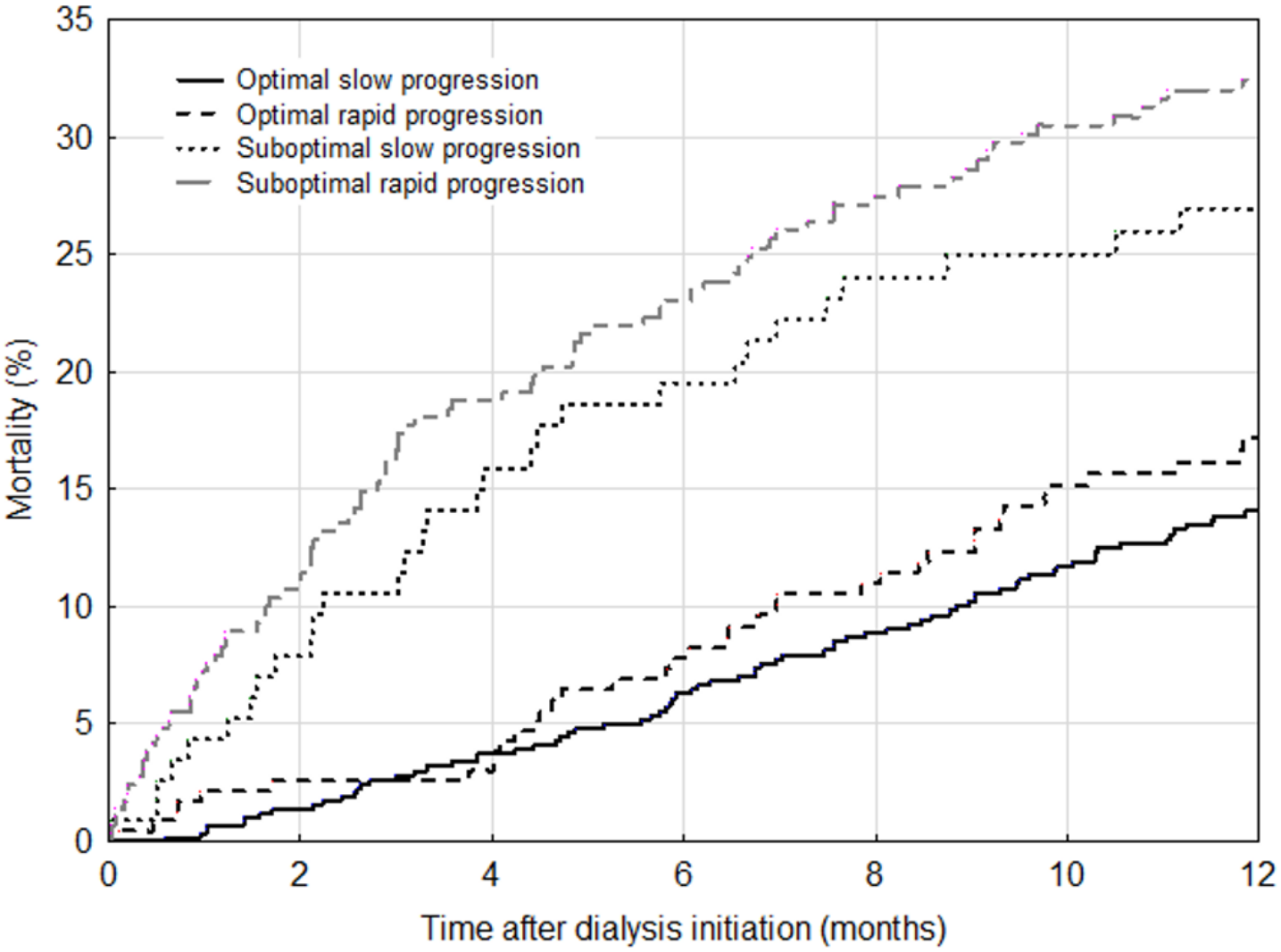

Figure 1

Relationship of mortality to optimal and suboptimal dialysis initiation with and without rapid loss of eGFR during three months prior to dialysis initiation.

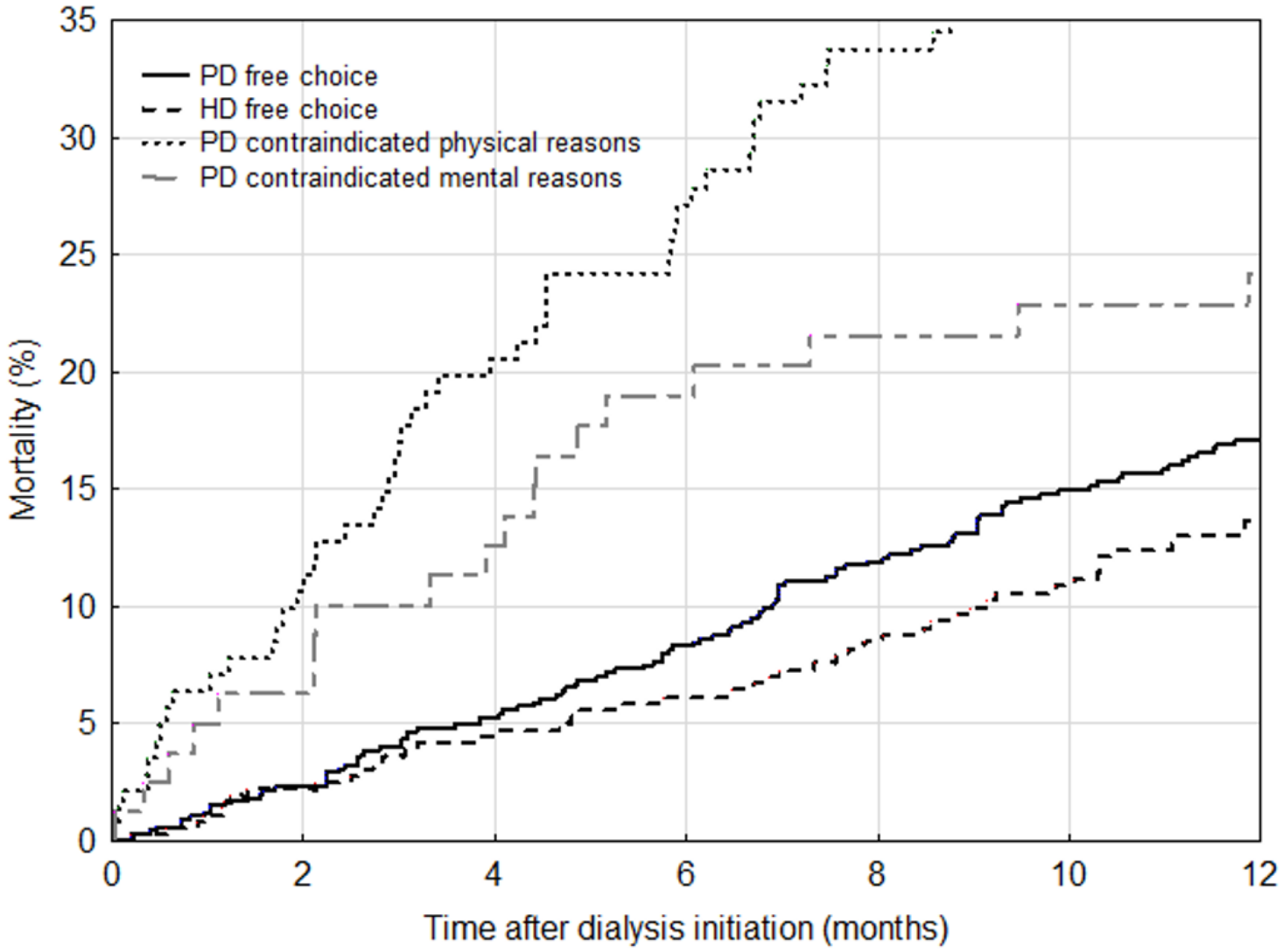

Figure 2

Relationship of mortality to selected reasons for modality choice: HD free choice; PD free choice; Physical PD contraindication; Mental PD contraindication. Intention-to-treat analysis

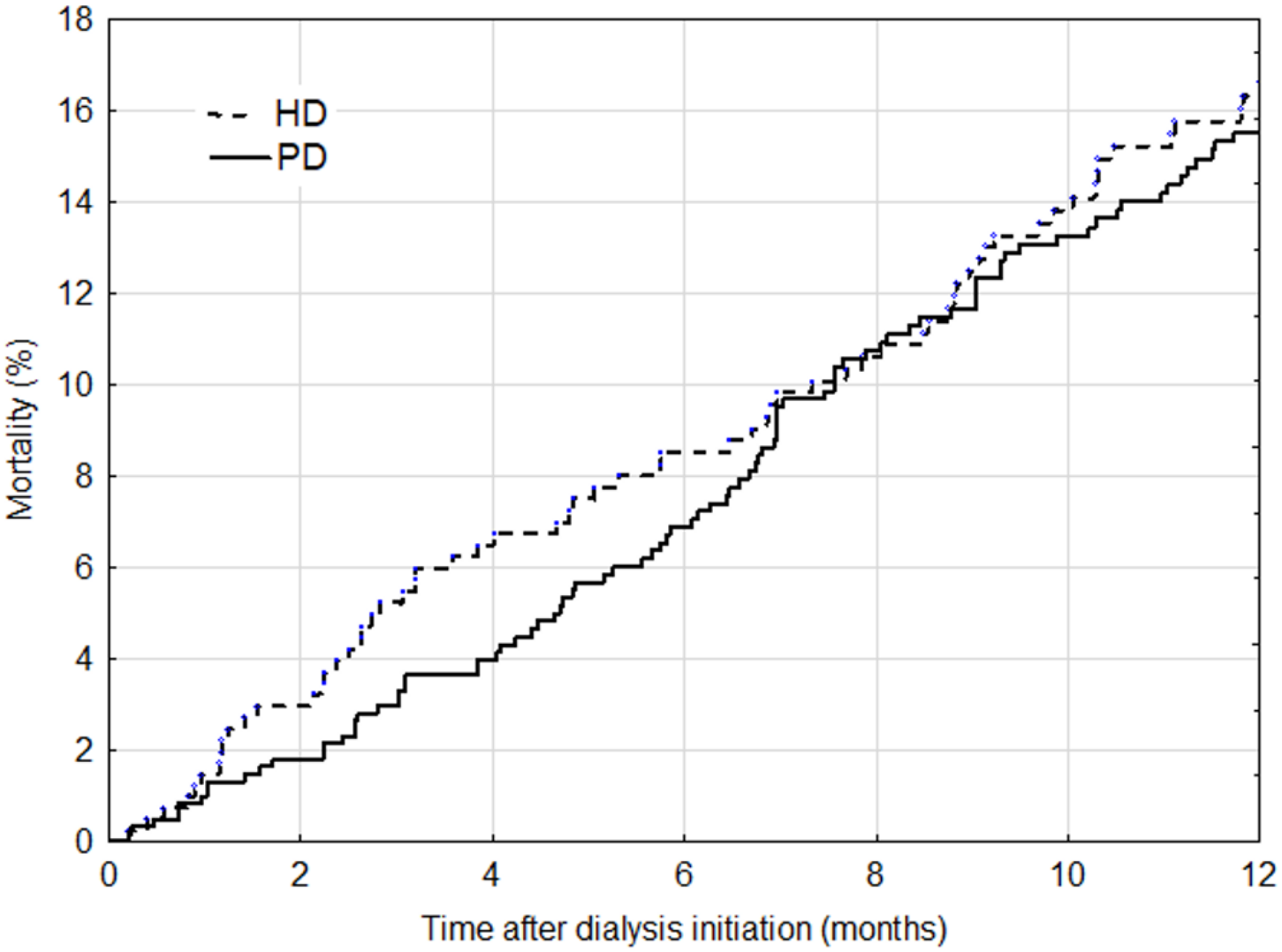

Figure 3

Relationship of mortality to free choice of modality. As-treated analysis.