Patient-centered care: facilitating home dialysis and improving health-related quality of life

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PATIENT-CENTERED CARE: FACILITATING HOME DIALYSIS AND IMPROVING HEALTH-RELATED QUALITY OF LIFE

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The secret of the care of the patient is in caring for the patient
- Dr. Francis W. Peabody

Voor mama

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Chapter 1

General introduction

Paragraph 5 of this introduction is in part adapted from:
Anna A. Bonenkamp, Maaike K. van Gelder, Alferso C. Abrahams, *et al*. Home haemodialysis in the Netherlands: State of the art. *The Netherlands Journal of Medicine 2018;76(4):144-57.*

General introduction

The number of patients with chronic kidney disease (CKD) and end stage kidney disease (ESKD) is continuing to rise globally.[1, 2] This worldwide growth in the number of patients is caused by both a rise in the prevalence *and* the incidence.[2] In developed countries, the prevalence is increasing as a result of enhanced dialysis survival[2, 3], while in undeveloped countries a remarkably growing number of patients suffer from CKD.[2] The increase in incidence has two main causes: first, the population is ageing and second, the number of patients suffering from diabetes mellitus and cardiovascular diseases - important risk factors for developing CKD - is growing.[1, 4] Furthermore, the disease-specific survival of patients with cardiac diseases and diabetes mellitus has increased. Therefore, patients have a higher life-time risk of developing CKD and ESKD in particular.[5, 6] Overall, the continuing growth in CKD and ESKD patients is a major global problem.

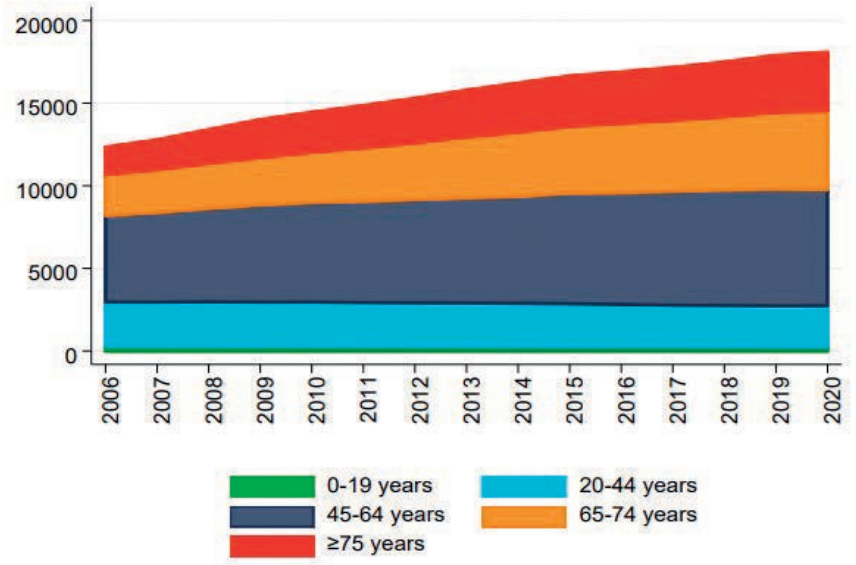


Figure 1. Prevalence of kidney replacement therapy by age categories adapted from RENINE annual report 2020. Available at: https://www.nefrovisie.nl/jaarrapportages/ Accessed: 23-02-2022.

In the Netherlands, the patient population being treated for ESKD has steadily increased over the past 15 years from 11,730 in 2005 to 18,071 in 2020. In the age

category over 65 years, a marked rise in prevalent patients is seen (Figure 1).[7] This is a result of a high age-specific incidence, i.e. the incidence in a specified age category divided by the general population in that age category. Compared to the age-specific incidence of patients <65 years, the age-specific incidence of elderly patients was 4-5 fold higher in the past two decades.[8] These findings show that with advanced age, comorbidities such as ESKD accumulate. Not only ESKD, but also other lifestyle diseases accumulate with age. The increase in older patients with diabetes mellitus is particularly striking.[9] Thus, the current population of patients with ESKD has changed; patients are older, have more comorbidities and will consequently be more frail. This developments, resulting in the growth of a vulnerable patient group, demand adjustment of our healthcare organization.

Home dialysis

ESKD is preferably treated with a kidney transplant, since it is associated with the highest survival.[10] However, as kidney donors are scarce, dialysis therapy remains a cornerstone in the management of ESKD. Dialysis may be performed in a dialysis centre, on average 3 times weekly for a 4 hour session, or at home. Home dialysis provides several advantages, including more independence, no travel time to the hospital and greater scheduling flexibility. Yet, the majority of patients is treated with in-centre haemodialysis (CHD).[11] At the end of 2020, there were 4,990 patients on CHD in the Netherlands, accounting for 80% of all dialysis patients.[12]

There are two home-based therapies to choose from, peritoneal dialysis (PD) and home haemodialysis (HHD). In PD, dialysis fluid enters the body through a permanent catheter in the abdominal cavity. Waste products in the peritoneal capillaries of the patient diffuse through the peritoneal membrane to the dialysis fluid. Excess body water is removed by osmotic ultrafiltration. After hours of dwelling time, the fluid filled with waste products and excess body water is drained into a waste bag and the cycle is repeated again. Home haemodialysis is essentially the same therapy as in-centre haemodialysis, yet only the location where the treatment is performed is different. In haemodialysis, the patient's blood exits the body through a vascular access into a dialyzer that consists of a synthetic semi-permeable membrane. In the dialyzer, waste products diffuse through this membrane to the dialysis fluid. In addition, excess body water is removed by hydrostatic ultrafiltration.

Home haemodialysis was the first home dialysis therapy to be introduced in 1961 by the Japanese doctor Yukihiko Nosé.[13] The reason to perform haemodialysis at home was primarily a practical consideration, since a proportion of the patients with ESKD could not be offered CHD due to capacity problems. The HHD incidence reached its global peak in 1970s, but soon decreased due to the introduction of PD, the expansion of CHD facilities, the increase of kidney transplantations and eventually, lack of experience of nephrologists.[14] Nowadays, only a small portion of home dialysis patients are treated with HHD. In the Netherlands, a total of 270 patients is treated with HHD, compared to 1,001 with PD.[12] The low use of HHD compared to PD can be explained by the complexity of the dialysis procedure, because patients are responsible for the dialysis machine set-up, self-cannulation and trouble-shooting. Nevertheless, HHD provides the perfect opportunity for prolonged or more frequent HD sessions. These intensive HD sessions are associated with improved survival, quality of life, blood pressure control and phosphate control.[15-17]

Peritoneal dialysis is the leading home-based dialysis therapy worldwide, but its use around the world is quite variable. Different governmental policies combined with financial incentives possibly play a role.[18] In Hong Kong, where a 'PD first' policy is adopted, >70% of dialysis patients are on PD compared to ≤ 20% in Australia, Canada and most European countries.[18] Remarkable is the contrast in recent developments: in Asia and the United States of America an increase in the number of PD patients is seen, whereas the number of PD patients has declined in several European countries, including the Netherlands.[18] For an overview of developments in European countries in recent years, see Appendix A. The use of PD is also quite variable among different regions within countries.[19, 20] In the Netherlands, the proportion of patients on home dialysis varies between 0 to 40% as shown in Figure 2.[8] Overall, from the perspective that majority of patients choose home dialysis after extensive treatment education[20, 21], the discrepancies among countries and within countries suggest that there is room for improvement in the uptake of home dialysis as a whole and PD in particular.

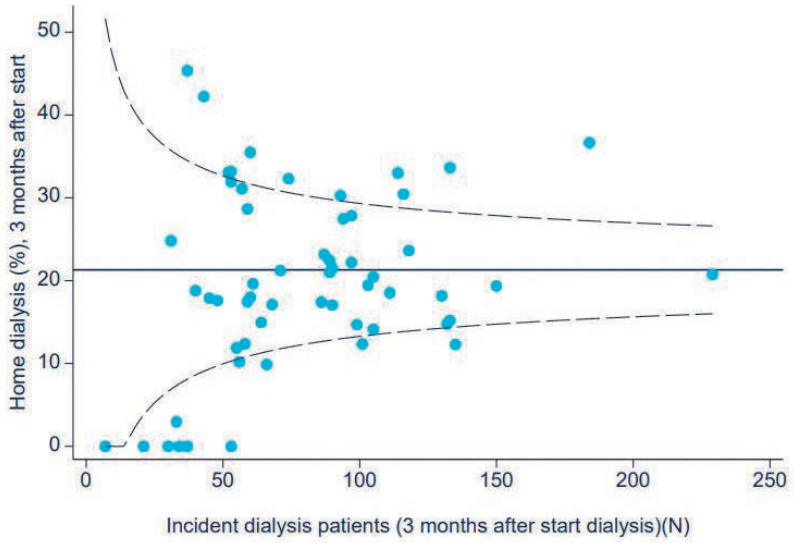


Figure 2. Funnel plot showing centre variation in percentage home dialysis at three months after start dialysis. Home dialysis includes peritoneal dialysis and home haemodialysis. Data is adjusted for age, sex, socioeconomic status, and primary kidney disease categories. Adapted from RENINE annual report 2020. Available at: https://www.nefrovisie.nl/jaarrapportages/ Accessed: 23-02-2022.

Multiple reasons for the decline in PD have been suggested. The decreasing number of *incident* PD patients is regarded the main problem [22], and has been attributed to multiple factors including the increasing number of patients that obtain a kidney transplant and the expansion of CHD facilities.[7, 22, 23] The latter occurred in the early 2000s as a result of governmental decision to allow dialysis in standalone centres rather than in hospitals only, initiated by an enormous shortage of CHD capacity leaving patients no choice but to opt for PD treatment.[7, 24] Other frequently mentioned reasons are the ageing of the dialysis population and the increasing number of diabetic patients starting dialysis.[22] The loss of *prevalent* PD patients due to a high rate of PD technique failure is considered another cause for the low number of PD patients. The reported incidence of PD technique failure within the first year ranges from 12.7% to 26.2%.[25] Identifying modifiable causes of technique failure could reverse the decline in the number of PD patients. These developments in both incidence and prevalence create a vicious circle: a decrease in the number of incident PD patients contributes to loss of experience of young nephrologists, which may increase technique failure rate and further prevent new uptake in PD.[26, 27]

Apart from more independence and flexibility, another important advantage is that home dialysis may be associated with lower costs.[28-32] Dialysis is a cost-consuming treatment. In the Netherlands, 0.1% of inhabitants have chronic kidney disease, accounting for 0.9% of the total healthcare spending in 2017.[33] Nearly half of these costs are spend on dialysis patients, representing a quarter of the total patients with chronic kidney disease.[34] Costs for CHD are the highest of all diseases within internal medicine, estimated at > 300 million. As an extreme example: average annual costs for a CHD patient are €50,000, while the costs for over 7000 diabetes mellitus patients with secondary complications are 43 million in total (on average €600 per patient annually).[34] Of course, these calculations are based upon healthcare claim costs from diagnosis-related group codes, not total costs per individual patient. For example, a study with Vektis data, which included costs of hospital admissions, medication and indirect non-medical costs such as transportation, showed that the costs for a dialysis patient are in reality between €77,566 and €105,833 per year.[28] The lowest costs were found for patients on continuous ambulatory peritoneal dialysis patients, a home dialysis treatment. Also in other previous economic evaluation studies home dialysis, including home hemodialysis, tended to be more cost-effective than CHD.[29-32] Home dialysis might thus be a sustainable option in a growing population of patients.

Health-Related Quality of Life

Despite major advances in kidney disease and kidney disease-related mortality [3], the survival of patients with ESKD is still considerably lower compared to patients without kidney disease. The unadjusted 5-year survival rate for patients on dialysis is 42.6%.[35] For a 45-year old patient starting dialysis, the remaining life expectancy is 10 years. For comparison, a 45-year old patient without kidney disease has an average remaining life expectancy of 35 years.[35] According to literature, there are no major differences in survival between home dialysis modalities (both PD and HHD) and CHD.[22, 36] Since a large European observational cohort study found that survival of patients starting on CHD or PD was similar (adjusted HR 0.91, 95% CI 0.88 – 0.95; PD vs CHD), mortality is no reason to favour CHD to a home dialysis modality.[22]

Due to the low survival of dialysis patients, it is important to make life with the burden of ESKD worthwhile. A life with dialysis is characterized by polypharmacy and frequent hospitalizations resulting in morbidity, and often a life-long dialysis dependency that requires a certain structure to everyday life.[37, 38] Thus, advantages and disadvantages of dialysis treatment modalities should be weighed for each individual

patient. A reason to favour home dialysis therapy is that it can offer more flexibility and autonomy than CHD. These features of home dialysis can likely contribute to less burden and improved quality of life for some patients.

The most well-known definition of quality of life is that from the World Health Organisation: '*individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*'.[39] Health-Related Quality of Life (HRQoL) thus not only consists of the physical health status affected by the disease, but rather of every aspect of life that is important to the patient. The key term 'individual perceptions' further stresses that differences are present in each individual's HRQoL. This emphasis on the individual is essential in understanding the concept of HRQoL. Means to objectively measure HRQoL are the use of self-reported questionnaires, HRQoL is thus a patient-reported outcome.

HRQoL is known to be low in patients with ESKD due to the marked burden of kidney disease; patients with ESKD on dialysis have a lower HRQoL compared to patients with chronic conditions such as diabetes mellitus and even malignancies.[40, 41] In recent years, HRQoL has received quite more attention, along with the interest for patient-centred care and individualized medicine. This has led to a paradigm shift from clinical outcomes - important to compare patient groups - to patient-reported outcomes – more important to the individual patient. In patient focus groups of both CHD and PD patients (including SONG-HD, SONG-PD and ICHOM), outcomes related to HRQoL - life participation, symptom burden and fatigue – were selected as core outcomes along some clinical outcomes – mortality, cardiovascular disease, technique survival.[42-45] These developments underscore the importance of improving HRQoL of dialysis patients.

The most commonly used generic questionnaires to measure HRQoL are the Short Form questionnaires.[46, 47] The advantage of these questionnaires is that they allow for comparison among different patient groups and the general population. A disadvantage is that they do not specifically map the burden of kidney disease and, therefore, important elements of HRQoL are missed. Therefore, also kidney disease specific HRQoL questionnaires exist, such as the Kidney Disease Quality of Life Instrument.[48] Disease burden may also be evaluated with a symptom questionnaire, for example with the Dialysis Symptom Index (DSI).[49]. It is conceptually assumed that a high symptom

burden causes a decline in functional status and in turn lower HRQoL.[50] (For an example of a generic and kidney disease specific symptom questionnaire, respectively Short Form 12 and Dialysis Symptom Index, see Appendix B.)

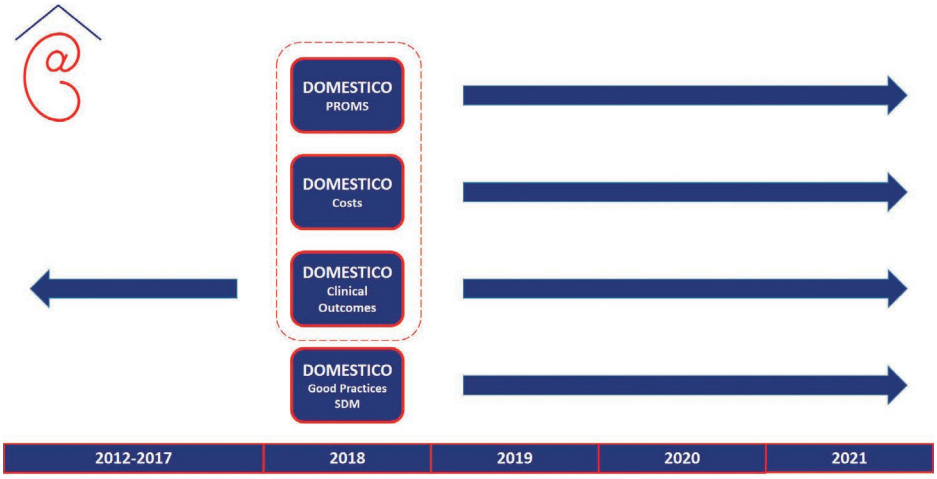
Although validated questionnaires exist and HRQoL is recognized as a core outcome, HRQoL is not frequently measured in daily practice.[51, 52] Accurate and frequent assessments can help to identify and address a high symptom burden[52], as well as facilitate patient-physician communication about HRQoL.[53] Previous studies showed that due to underrecognition *and* underreport of symptoms, such as depression and itch, patients often remained untreated.[54, 55] Additionally, early interventions such as re-education, home care worker support, dialysis schedules adjustments, and psychotherapy can help to enhance treatment modality satisfaction and treatment longevity.

DOMESTICO

The abovementioned poor quality of life and marked practice variation in proportion of home dialysis patients among centres were reasons to start the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO) in 2017. DOMESTICO consists of two multi-centre cohort studies and a implementation project (Figure 3). The retrospective multi-centre cohort study enrolled patients that started dialysis treatment between 1 January 2012 and 31 December 2016 from 37 Dutch dialysis centres, representing two thirds of all dialysis centres in the Netherlands. For each included home dialysis or nocturnal dialysis patient, one CHD patient was randomly selected. The aim of the retrospective DOMESTICO study was to evaluate modifiable factors in technique failure, and to compare outcomes between home dialysis and in-centre dialysis patients. In the prospective study, that started in December 2017, a total of 1600 patients starting dialysis will be followed for at least one year. A total of 56 dialysis centres participate in this study, all but one centres in the Netherlands and 2 from Belgium. The aim of this nationwide study is to compare quality of life, total costs and clinical outcomes between home dialysis and CHD patients. The implementation project aims to provide optimal education for all dialysis modalities, focusing on pre-dialysis education and good practices in dialysis care.

All original data presented in this manuscript originate from the Dutch kidney patient population, predominantly from the DOMESTICO studies. The Dutch patient population is unique in terms of kidney transplantation and dialysis access. The

Netherlands consistently ranks amongst the countries with the highest rates of (living) donor kidney transplantations worldwide, has a steady home haemodialysis rate and due to its small surface area, small distances of patient's residence to the hospital.[2, 11, 56]



Thesis outline

This thesis will contribute to the research surrounding home dialysis and HRQoL. In a growing and ageing patient population, home dialysis should obviously be considered as a sustainable kidney replacement therapy due to its possible cost-effectiveness. Therefore, identifying all patients eligible for home dialysis is crucial. From the same perspective enhancing technique survival should be an important goal. Because the dialysis population is characterized by low survival and high disease burden, HRQoL is the most important outcome, especially in an era with attention for patient-centred care. This thesis thus aims to investigate the following questions in dialysis patients:

- Which patient characteristics identify eligibility for home dialysis in the current dialysis population?
- What are modifiable causes of hospital admissions and technique failure (in PD patients)?
- Does treatment modality influence Health-Related Quality of Life?

The current dialysis population consists of more elderly patients then two decades ago. Therefore, time trends in the use of home dialysis for different age categories over the past 20 years are explored in **chapter 2**. Severe comorbidity is frequently perceived a contra-indication to receive home dialysis. **Chapter 3** examines the association between comorbidity and dialysis modality choice if corrected for age, BMI and differences between centres. Pre-dialysis education and programmes can help to aid patients in dialysis modality choice, and may also help the multidisciplinary team surrounding the patient. **Chapter 4** describes the findings from such a multidisciplinary pre-dialysis programme.

The second part of this thesis then focuses on PD technique survival. **Chapter 5** describes the hospitalization rate of PD patients compared to patients that receive HD with a multistate model. In addition, modifiable causes of hospitalization are sought that could contribute to the reduction of hospital admissions. **Chapter 6** then focuses on modifiable causes and risk factors of technique failure. Identifying modifiable causes and risk factors may provide important information to enhance technique survival of PD patients.

Part 3 concentrates on HRQoL, an important patient-reported outcome. **Chapter 7** systematically reviews the association between home dialysis and HRQoL of dialysis patients worldwide. **Chapter 8** examines the effect of a major pandemic, the COVID-19 pandemic, on the mental health of dialysis patients. **Chapter 9** describes the HRQoL of patients treated with a specific home based therapy, nocturnal home hemodialysis, in comparison to patients that obtained a kidney transplant.

Finally, the findings and relevance of this thesis are discussed in the **Discussion and future perspectives.** This part also contains the protocol of the prospective DOMESTICO study (**chapter 10**). The developments presented in this introduction led to the aims of this nationwide study, to investigate the HRQoL and cost-effectiveness of home dialysis in the current ageing dialysis population.

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Part I

Eligibility for home dialysis in the current dialysis population

Chapter 2

Trends in home dialysis use differ among age categories in past two decades: a Dutch registry study

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Abstract

Background: Although the number of patients with end stage kidney disease is growing, the number of patients who perform dialysis at home has decreased during the past two decades. The aim of this study was to explore time trends in the use of home dialysis in the Netherlands.

Methods: Dialysis episodes of patients who started dialysis treatment were studied using Dutch registry data (RENINE). The uptake of home dialysis between 1997 through 2016 was evaluated in time periods of 5 years. Home dialysis was defined as start with peritoneal dialysis or home haemodialysis, or transfer to either within 2 years of dialysis initiation. All analyses were stratified for age categories. Mixed model logistic regression analysis was used to adjust for clustering at patient level.

Results*:* A total of 33,340 dialysis episodes in 31,569 patients were evaluated. Mean age at dialysis initiation increased from 62.5±14.0 to 65.5±14.5 years in in-centre haemodialysis patients, whereas it increased from 51.9±15.1 to 62.5±14.6 years in home dialysis patients. In patients < 65 years, the uptake of home dialysis was significantly lower during each 5-year period compared to the previous period, whereas kidney transplantation occurred more often. In patients ≥ 65 years, incidence of home dialysis remained constant, whereas mortality decreased.

Conclusions: In patients < 65 years, the overall use of home dialysis declined consistently over the past 20 years. The age of home dialysis patients increased more rapidly than that of in-centre dialysis patients. These developments have a significant impact on the organization of home dialysis.

Introduction

Globally, the number of patients with chronic kidney disease (CKD) and end stage kidney disease (ESKD) is continuing to rise.[1, 2] This growth in prevalence of patients who need kidney replacement therapy (kidney transplantation or dialysis) causes a major economic and logistical burden to the healthcare system.[1, 2] The majority of patients is treated with in-centre haemodialysis (CHD), while the use of dialysis at home is low.[3] But home dialysis offers more flexibility and independence, which could improve quality of life.[4, 5] In addition, home dialysis might be more cost-effective than CHD.[6]

Another important development is global ageing, also resulting in the ageing of the dialysis population. A further contribution to this is that older patients are not often eligible for kidney transplantation. The ageing of the dialysis population might be a reason for the low use of home dialysis modalities.[7] In the past, home dialysis generally was performed by young, employed patients. However, nowadays young patients are frequently transplanted with kidneys from living donors.[8]

Consequently, in order to increase the use of home dialysis, it would be helpful to gain better understanding of the impact of age on the home dialysis use, for example to reduce the economic burden of a growing patient population. The aim of this study is to explore time trends in the use of home dialysis in the Netherlands. This country had a pronounced decline in home dialysis patients during the last two decades, and it consistently ranks amongst the countries with the highest rates of kidney transplantations worldwide.[3, 9, 10] Therefore, we studied the uptake of home dialysis between 1997-2016 in patients commencing dialysis treatment, stratified for age categories.

Methods

Study design

Anonymized registry data from the Dutch Renal Registry (RENINE) were used for this multicentre cohort study. RENINE collects treatment data of dialysis patients in all Dutch dialysis units; > 95% of all Dutch dialysis patients are registered in RENINE.[11] Kidney replacement therapies are registered as CHD, peritoneal dialysis

(PD), home haemodialysis (HD) or kidney transplantation. Modality and centre transfers are updated regularly. For this analysis, age at start of dialysis treatment, sex, dates of modality transfers, and information on recovery of kidney function, kidney transplantation, and death were provided. All patients provided informed consent for registration of the data and usage of data for conducting scientific research. Reporting of the study conforms to broad EQUATOR guidelines.[12, 13]

Study population

Dialysis episodes of patients who started *maintenance* dialysis treatment between 1-1-1997 through 31-12-2016 in the Netherlands were included, including dialysis episodes of patients who previously underwent kidney transplantation. Each dialysis episode was followed for 2 years, the last day of follow-up was 31-12-2018. A patient may have had multiple dialysis episodes during the study period and may thus be included more than once. Dialysis episodes instead of individual patients were chosen because we considered that a dialysis modality choice is made in each new dialysis episode, including in episodes of patients with a dialysis history. Dialysis episodes shorter than 90 days were excluded. In addition, dialysis episodes of patients < 20 years of age were excluded, since paediatric care is different from adult patient policy and this patient population is small.

Study outcomes

Primary outcome was start of home dialysis, i.e. PD and home HD. Both home dialysis at the beginning of the dialysis episode as well as a transfer to PD or home HD within 2 years of dialysis initiation were included. Subsequent switches after the start of home dialysis were ignored. A complete list of registry codes used to define study outcomes is provided in Appendix S1.

A relatively long transfer period of 2 years was chosen to also include *home HD* patients; in this registry study, the median time to HHD was 16 months [IQR 9 – 28] while the median time of transfer to PD was 4 months [IQR 2 – 12]. As in literature a shorter transfer period is more common[14], start of home dialysis within 12 months of dialysis initiation was also evaluated as a sensitivity analysis.

As secondary outcome, start of PD and start of home HD were analysed separately.

Statistical analysis

The age of incident patients was reported as mean with standard deviation (SD) and sex of incident patients as proportions.

Logistic regression was used to assess the uptake of home dialysis between 1997 through 2016. Calendar time at dialysis initiation was equally divided into 5-years periods: 1997-2001, 2002-2006, 2007-2011, and 2012-2016. The period 2002 to 2006 was set as reference category. During this period the incidence of CHD in the Netherlands peaked after opening of standalone dialysis centres following a governmental decision to allow dialysis treatment in satellite and independent centres.[15, 16] Follow-up time for each episode was maximum 2 years and censoring occurred at recovery of kidney function, kidney transplantation, or death (for corresponding codes, see Appendix S1). A logistic mixed model analysis was performed to adjust for clustering of dialysis episodes at a patient level. This model was additionally adjusted for sex, dialysis vintage, and transplantation history. Due to the interaction of age with the different time periods, analyses were stratified for the following age categories: 20-44 years, 45-64 years, 65-74 years, or ≥ 75 years.[17]

A competing risk model was used to estimate the cumulative incidence function (CIF) for start of home dialysis in incident patients with recovery of kidney function, kidney transplantations, and all-cause mortality as competing events.[18] The 2-year cumulative incidence is the proportion of the study population, that is incident dialysis patients, who develop the outcome of interest during this time before the occurrence of a competing event. Subsequently, CIFs were estimated for kidney transplantations and all-cause mortality. In these analyses, the other three outcomes were treated as competing events. The three curves were plotted simultaneously. The curve for all-cause mortality was plotted as 1 minus CIF.

To further explore the robustness of results, three sensitivity analyses were conducted as follows: (i) home dialysis was defined as start with home dialysis, or transfer to home dialysis within the *first* year after start dialysis - instead of within 2 years; (ii) only the first dialysis episode of patients were analysed, analysing patients instead of dialysis episodes and using logistic regression instead of mixed model logistic regression analysis; and (iii) only episodes of patients who were still treated with dialysis after two years were analysed. All incident dialysis episodes followed by recovery of kidney function (n=771), kidney transplant (n=4118), or death (n=7786) within 2 years were excluded, irrespective of dialysis treatment modality.

Overall, a p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics 25 (IBM) or STATA 14.

Results

A total of 33,340 chronic dialysis episodes between 1997 and 2016 fulfilled our inclusion criteria; these episodes belonged to 31,569 adult patients (Figure 1). Table 1 shows the characteristics of dialysis episodes and incident patients included in the study. Both the total number of dialysis episodes as the total number of incident patients increased from 1997 to 2016, whereas the total number of home dialysis episodes decreased (from 3,037 to 2,390). The total number of home HD was low, yet increased (from 67 to 253). The increase in the total number of incident patients was attributable to the increase in elderly patients: the number of patients aged ≥ 65 years increased from 2,921 to 4,889, whereas the number of patients aged 20-44 years decreased from 1,133 to 747.

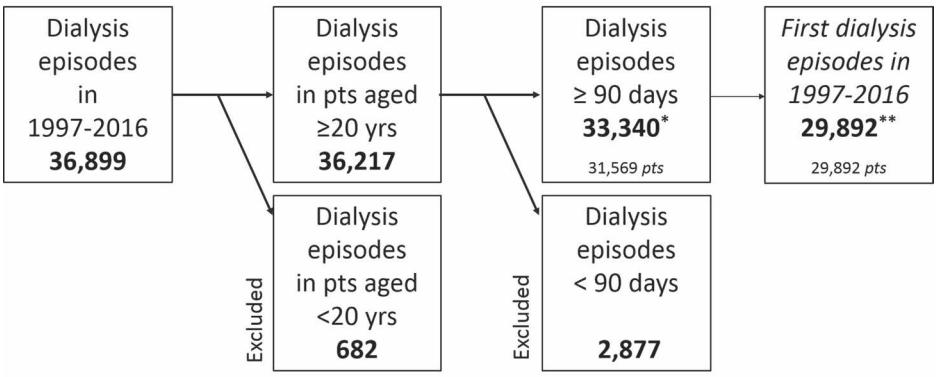


Figure 1. Flowchart of the study
* Main analysis
** Second sensitivity analysis

Table 1. Characteristics of dialysis episodes and incident patients of the study population, by time period

	1997-2001	2002-2006	2007-2011	2012-2016
Dialysis episodes				
Total number of dialysis episodes	7230	8107	9004	8999
Total number of home dialysis episodes *	3037	2668	2535	2390
Total number of PD episodes *	2980	2580	2412	2155
Total number of home HD episodes *#	67	98	131	253
Incident patients				
Total number of incident patients	6496	7329	8047	8020
Aged 20-44 years	1133	1025	863	747
Aged 45-64 years	2442	2480	2536	2384
Aged 65-74 years	1881	2132	2236	2439
Aged ≥ 75 years	1040	1692	2412	2450
Mean age at start dialysis (years ±SD)	59.6 ± 15.0	62.5 ± 14.8	64.9 ± 14.5	65.6 ± 14.1
Male (%)	3909 (60)	4487 (61)	5002 (62)	5009 (62)

*within 2 years of dialysis initiation
46 home haemodialysis episodes, were preceded by PD treatment

In Figure 2, the mean age in years at the start of a dialysis episode between 1997 and 2016 is shown. The age of home dialysis patients increased from 51.9±15.1 to 62.5±14.6 years during this period, while the age of CHD patients increased from 62.5±14.0 to 65.5±14.5 years.

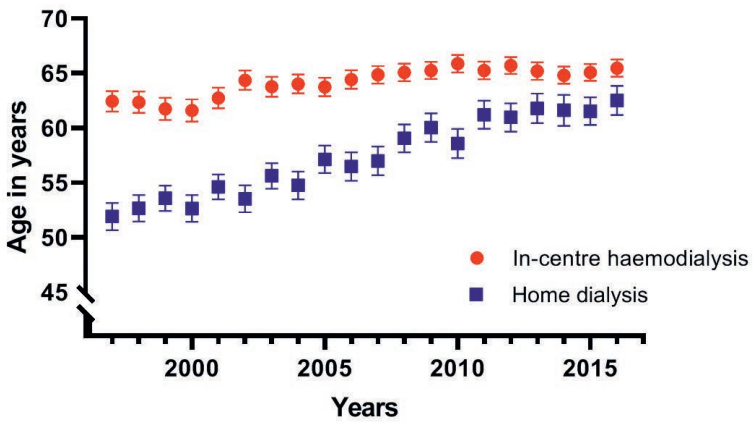


Figure 2. Mean age at start of a dialysis episode between 1997 and 2016. Mean age is presented with confidence intervals. Each dot represents a year from 1997 to 2016

Time trends in uptake of home dialysis

Table 2 shows the results of the logistic regression assessing the uptake of home dialysis in each time period for the four age categories, using 2002-2006 as the reference period since governmental policies introduced around this period incentivized the growth of dialysis centres.[15, 16] Table 2A shows the uptake of home dialysis within 2 years of dialysis initiation, and Table 2B shows the start of home dialysis within one year of dialysis initiation. During 1997-2001, for all age categories the uptake of home dialysis was significantly higher compared to the reference period (adjusted odds ratios (OR) ranging from 1.30 to 2.17, Table 2A). In the youngest two age categories, that is dialysis episodes of patients <65 years, the uptake of home dialysis was significantly lower in time periods 2007-2011 and 2012-2016 than for the period 2002-2006 (adjusted ORs ranging from 0.36 to 0.63). Each time period of 5 years was associated with a significantly lower uptake of home dialysis compared to the previous period in these age categories.

In the 65- to 74-year category, adjusted ORs in the time periods 2007-2011 and 2012-2016 were not significantly different from the reference period. In patients aged ≥ 75 years, the two most recent time periods were associated with a higher uptake of home dialysis (adjusted ORs 1.21 and 1.52 resp.) compared to the reference period. As findings were similar for the analyses with, respectively, a 2-year and a 1-year transfer period, all further analyses were performed with a transfer period of 2 years to allow for the longer transfer time of home HD.

Table 2. Uptake of home dialysis in *2 years* of dialysis initiation (A) and in the *first year* of dialysis initiation (B) (n=33,340), by time period and age category

		Time period						
		1997-2001 OR (95% CI)		2002-2006[a]	2007-2011 OR (95% CI)		2012-2016 OR (95% CI)	
		A	B		A	B	A	B
Age 20-44	*unadjusted*	2.24 (1.70 – 2.94)	2.44 (1.82 – 3.27)	1.0	0.52 (0.40 – 0.69)	0.49 (0.37 – 0.67)	0.34 (0.25 – 0.46)	0.32 (0.23 – 0.44)
	adjusted[b]	2.17 (1.66 – 2.84)	2.35 (1.77 – 3.13)	1.0	0.54 (0.42– 0.72)	0.53 (0.40 – 0.70)	0.36 (0.27 – 0.49)	0.35 (0.26 – 0.48)
Age 45-64	*unadjusted*	1.61 (1.35 – 1.92)	1.63 (1.37 – 1.95)	1.0	0.62 (0.52 – 0.74)	0.60 (0.50 – 0.71)	0.44 (0.36 – 0.53)	0.41 (0.34 – 0.50)
	adjusted[b]	1.60 (1.34 – 1.91)	1.62 (1.35 – 1.95)	1.0	0.63 (0.53 – 0.75)	0.60 (0.50 – 0.72)	0.43 (0.36 – 0.53)	0.41 (0.34 – 0.51)
Age 65-74	*unadjusted*	1.30 (1.14 – 1.49)	1.28 (1.12 – 1.47)	1.0	0.95 (0.84 – 1.09)	0.94 (0.82 – 1.08)	0.98 (0.86 – 1.11)	0.93 (0.82 – 1.06)
	adjusted[b]	1.30 (1.14 – 1.49)	1.28 (1.12 – 1.47)	1.0	0.95 (0.84 – 1.09)	0.94 (0.83 – 1.07)	0.98 (0.86 – 1.12)	0.94 (0.82 – 1.07)
Age above 75	*unadjusted*	1.35 (1.10 – 1.66)	1.37 (1.11 – 1.68)	1.0	1.22 (1.03 - 1.45)	1.21 (1.02 – 1.44)	1.54 (1.30 - 1.81)	1.50 (1.27 – 1.78)
	adjusted[b]	1.35 (1.10 – 1.67)	1.36 (1.11 – 1.68)	1.0	1.21 (1.02 - 1.44)	1.20 (1.01 – 1.43)	1.52 (1.29 - 1.80)	1.49 (1.25 – 1.76)

[a] time period 2002-2006 was regarded as reference period
[b] adjusted for sex, dialysis vintage, and transplantation history

Time trends in uptake of PD or home HD

The uptake of PD was quite similar to the overall uptake of home dialysis (Table 3). However in the 65-74 years category, the last time period was associated with a borderline significant lower uptake of PD (adjusted OR 0.89, 95% CI 0.78 – 1.01).

Table 3. Uptake of peritoneal dialysis within 2 years of dialysis initiation (n=33,340), by time period and age category

		Time period			
		1997-2001 OR (95% CI)	2002-2006 [a]	2007-2011 OR (95% CI)	2012-2016 OR (95% CI)
Age 20-44	*unadjusted*	2.41 (1.81 – 3.22)	1.0	0.46 (0.34 – 0.62)	0.26 (0.19 – 0.37)
	adjusted[b]	2.33 (1.75 – 3.11)	1.0	0.49 (0.36– 0.66)	0.28 (0.20 – 0.39)
Age 45-64	*unadjusted*	1.68 (1.40 – 2.01)	1.0	0.60 (0.50 – 0.72)	0.38 (0.31 – 0.46)
	adjusted[b]	1.67 (1.39 – 2.00)	1.0	0.60 (0.50 – 0.72)	0.37 (0.30 – 0.46)
Age 65-74	*unadjusted*	1.31 (1.15 – 1.50)	1.0	0.93 (0.81 – 1.06)	0.88 (0.78 – 1.01)
	adjusted[b]	1.31 (1.15 – 1.50)	1.0	0.93 (0.82 – 1.07)	0.89 (0.78 – 1.01)
Age above 75	*unadjusted*	1.36 (1.10 – 1.67)	1.0	1.22 (1.03 - 1.45)	1.40 (1.18 - 1.66)
	adjusted[b]	1.36 (1.10 – 1.67)	1.0	1.21 (1.02 - 1.44)	1.39 (1.17 - 1.64)

[a] time period 2002-2006 was regarded as reference period
[b] adjusted for sex, dialysis vintage, and transplantation history

After correction for sex, age, dialysis vintage, and transplantation history, the home HD use increased for each time period (Supplementary Table S1). The last time period had an adjusted OR of 3.57 (2.59 – 4.92). As the number of home HD episodes was too low, no stratification for age categories was performed.

Time trends in incidence of home dialysis

Figure 3 shows the results of a competing risk approach modelling the cumulative incidences for start of home dialysis and those for kidney transplantation and death following CHD within 2 years after dialysis initiation, categorized by time period and age group. Figure 3A shows that the 2-year incidence of home dialysis for patients aged 20-44 years decreased in subsequent time periods from 58% to 34%. Figure 3B shows that the 2-year incidence for patients aged 45-64 years also decreased from 45% to 29%. In patients aged 65-74 years, the 2-year incidence of home dialysis was 29% in time period 1997-2001 and remained 24% during the other time periods (Figure 3C). In patients aged ≥ 75 years, the 2-year incidence of home dialysis was low: 17% in the first, 14 % in the second, 16% in the third and 19% in the last time period (Figure 3D).

In the youngest age groups the 2-years incidence of kidney transplantation whilst on CHD increased considerably, from 7% to 30% in patients aged 20-44 years and from 5% to 16% in patients aged 45-64 years. In patients aged 65-74 years the incidence of kidney transplantation was 8% during the last time period, and in patients aged > 75 year, this incidence was almost nihil. In the time period 1997-2001, the 2-year incidence of home dialysis and kidney transplantations combined was 65% for patients aged 20-44 years, which was comparable with the combined incidence in the time period 2012-2016 in this age category. In patients aged 45-64 years, the combined 2-year incidence was 50% in 1997-2001 and 45% in 2012-2016. In patients aged 65-74 years, the 2-year incidences were 30% and 32% respectively.

The 2-year incidence of mortality on CHD decreased over the time periods for all age categories (Figure 3A-D). This phenomenon was most pronounced in older patients: the incidence of mortality decreased from 27% to 16% in patients aged 65-74 years and from 38% to 27% in patients aged ≥75 years. In addition, the proportion of patients that stayed on CHD increased from 43% to 52% in patients aged 65-74 years and from 44% to 53% in patients aged ≥75 years.

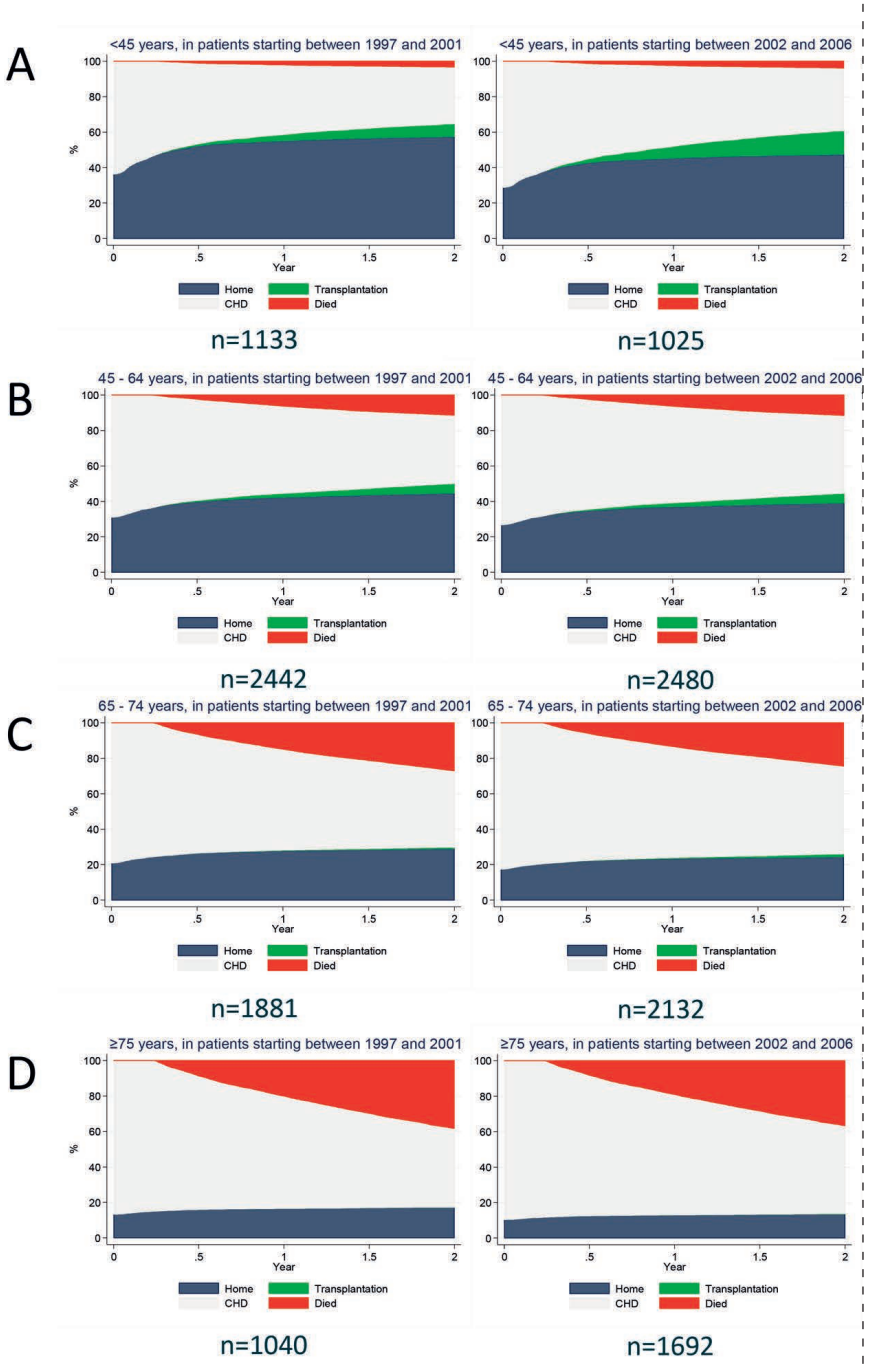
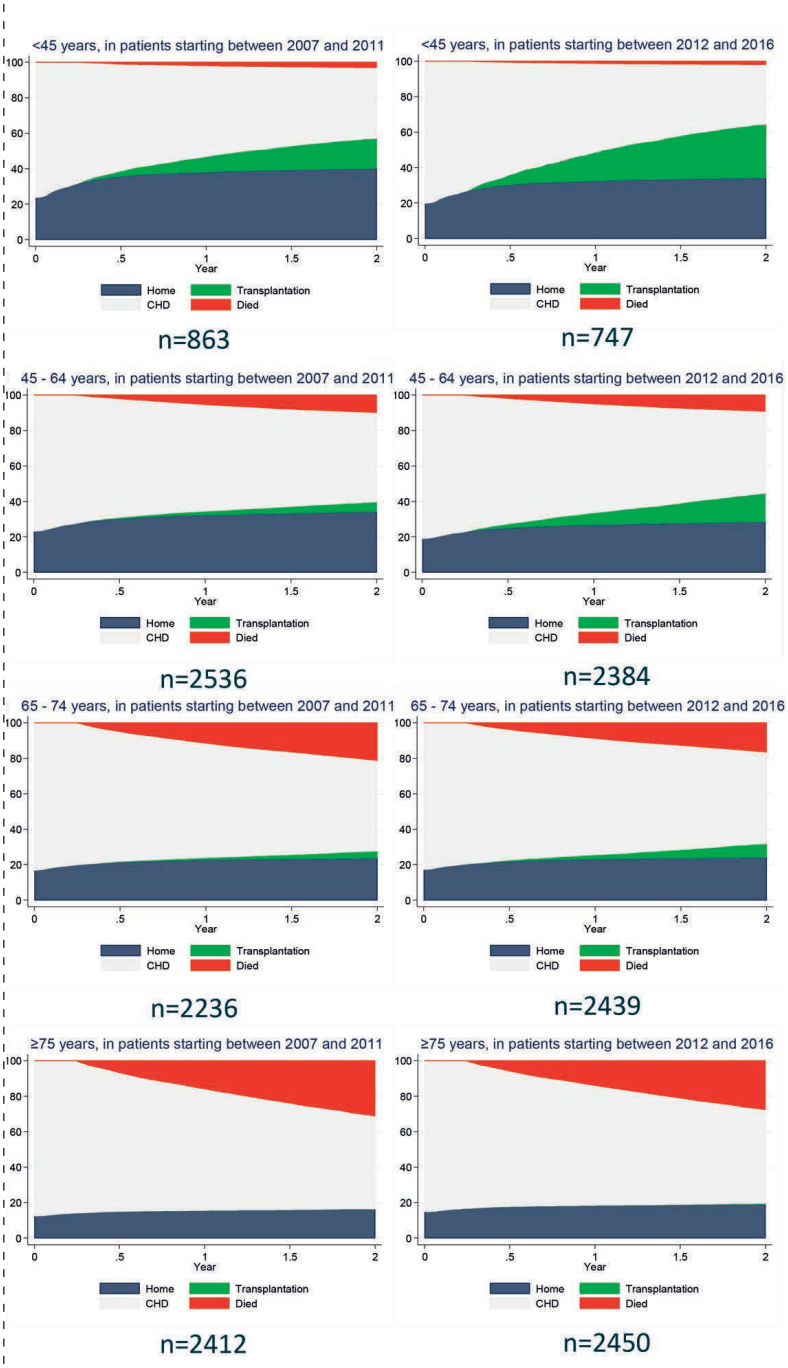


Figure 3. Cumulative 2 year incidences of home dialysis, kidney transplantation, CHD and



death in incident patients. A, 20-44 years; B, 45-64 years; C, 65-74 years; D, ≥ 75 years

Sensitivity analyses

Supplementary Table S2 shows the results of the sensitivity analysis of only first dialysis episodes between 1997-2016. A total of 29,892 patients were analysed. The uptake of home dialysis was still significantly lower in the last two time periods for patients < 65 years old, yet ORs tended to be higher if compared to the original analysis. The OR for home dialysis uptake in period 2012-2016 was 0.54 (95% CI 0.45-0.66) in patients aged 20-44 years and 0.59 (95% CI 0.52-0.66) in patients aged 45-64 years. In the third sensitivity analysis, only episodes of patients that were still on dialysis two years after dialysis initiation were evaluated, excluding episodes that ended with recovery of kidney function, kidney transplantation or death. A home dialysis episode was still defined according to the definition used in the original analysis, that is start or transfer to home dialysis within 2 years of dialysis initiation. The results of this analysis were similar to the results from the original analysis, except that in dialysis episodes of patients ≥ 75 years of age the uptake of home dialysis during the first time period was no longer significantly higher compared to the reference period (Supplementary Table S3).

Discussion

In this large cohort of Dutch patients, the home dialysis use in patients aged < 65 years declined over the time periods from 1997 to 2016. In these younger patients a considerable increase in the number of kidney transplants was seen. In contrast, the older population showed a constant home dialysis use over time for the patients 65-74 years of age and a significant increase for the patients above 75 years of age. As a result, the home dialysis population aged remarkably. In both elderly age groups, kidney transplantation was negligible, but a clear decrease in mortality was found in elderly patients starting dialysis. Most of the elderly patients remained on CHD over time. The predominantly used home-dialysis treatment in this cohort was PD. Although numbers are low, over time the home HD use increased.

Multiple factors possibly influenced the changes in the uptake of home dialysis. In the first time period, 1997-2001, the uptake of PD was quite high, in part explained by a shortage of CHD facilities. After a change in legislation regarding initiating a dialysis centre by the Dutch government in 1999, this capacity problem was resolved. Consequently, many new dialysis centres appeared and an increase in patients starting

CHD was observed in 2002.[15, 16] Apparently, such a policy change can have a major influence on the choice of dialysis modality within a population, as has also been reported in North America.[19, 20] In contrast, in Australia and China governmental initiatives to promote home dialysis have resulted in a stabilization or even an increase in the prevalence of home dialysis patients.[14, 21] In such large countries with extensive rural areas and great distance to the nearest dialysis centre home dialysis may be a favoured treatment.[21] Indeed, in China 20% of the total dialysis population is treated with PD, while in Australia 25% is treated with home dialysis.[21, 22] The small country of Hong Kong has even the highest percentage of home dialysis throughout the world, as 76% of dialysis patients are treated with PD, due to a three-decade PD-first policy adopted due to its cost-effectiveness.[23] Another country in which policy changes had a marked effect is the USA. In 2018, this country had a total of 12% of dialysis patients on a home-based therapy compared to 9% prior to differences in reimbursement.[24] Main reasons for changing the reimbursement were rising healthcare costs and improving healthcare efficiency.[21, 25] In Europe, the proportion varies from 7% in Greece to 30% in Scandinavian countries such as Finland.[3] In the latter a home first policy was adopted, partly due to a capacity problem but more importantly to provide individualized dialysis treatment which may be best achieved at home.[26] Overall, practices in these countries suggest that governmental policies to promote home dialysis are important and can have a large impact on uptake of home dialysis. In the present analysis, the initial decrease of home dialysis came to a halt in the time periods following 2002-2006 in the elderly patient groups, possibly due to dedication and initiatives of both nephrologists and nurses who stimulated home dialysis in these patients.

The average home dialysis patient aged significantly over a period of 20 years. First, this can be explained by the aging of the total dialysis population since more elderly patients started dialysis. Second, this can be explained by less younger patients starting home dialysis, since these patients are more often transplanted. This suggestion is supported by the fact that the CHD population has aged less than the home dialysis population and that we observed a clear increase in kidney transplantations after CHD initiation in patients under <75 years of age. This trend is in agreement with European data.[27]. One could claim that 'the home dialysis patient of 20 years ago obtains a kidney transplant at present'. Indeed, in the younger population the combined 2-year incidence of transplantation and home dialysis remained more or less the same over a period of 20 years.

In addition, a decrease in the 2-year incidence in mortality on CHD was found from 1997 to 2016, most pronounced in patients above 65 years of age. This is consistent with a recent study of the ERA-EDTA, contributing a 10-year reduction in mortality not solely to a better survival in the general population, but also to improvements in dialysis care.[28] As a consequence of the decreased mortality rates, more elderly patients are on long-term maintenance dialysis. The majority of these patients is treated with CHD; the 2-year incidence of home dialysis in most elderly patients (≥ 75 years) increased only slightly from 17% to 19%. The low incidence of home dialysis in the elderly patients might be explained by the notion that elderly patients are too frail to be treated with home dialysis.[7] However, the greater proportion of patients staying on CHD over time, could also suggest that more elderly patients would be able to start home dialysis if sufficiently assisted. Nevertheless, the aging of the dialysis population will have implications for the organization of predialysis education and home dialysis, as older patients may require additional support.

Over the past 15 years, several international initiatives were introduced to promote home dialysis, especially in elderly patients.[29] These initiatives include training of community-based home care workers to perform dialysis tasks at the patient's home, prolonging training time for the elderly patient and updating educating programs to enhance informed decision making.[30-32] Although we observed a 50% higher uptake of home dialysis in patients above 75 years of age, the overall use in these elderly patients remained low: the proportion increased from 14% in the reference period, that is 2002-2006, to 19% in the most recent time period. It should also be noted that the 2-year incidence for home dialysis was 17% in the time period prior to the governmental legislation. Thus, the abovementioned initiatives possibly helped to revive home dialysis after the governmental decision. In other countries a higher proportion of elderly patients is treated with home dialysis. Especially in Australia and New Zealand this proportion is quite high, 24% and 47% respectively, suggesting that it is possible for many elderly patients to perform home dialysis.[33] Incorporating more initiatives to promote home dialysis may allow more elderly patients to start home dialysis in the future.

The growing number of, especially elderly, dialysis patients puts pressure on healthcare expenses worldwide, since dialysis is an expensive treatment.[1, 2] Home dialysis might be a mean of relieving this financial burden, since especially continuous ambulatory PD is supposed to be more cost-effective.[6] Moreover, elderly patients may as well

benefit from home dialysis: they might obtain better quality of life and might be more satisfied with assisted PD than with CHD.[4, 34] However, home dialysis in elderly patients emphasizes the need for adaptation in organization of home dialysis care, yet total expenses, including those for home care workers, remains unknown. The results presented in this study have implications for further research, and underscore the need of cost-effectiveness studies in elderly patients.

The results of our study remained robust in three different sensitivity analyses, a strength of this study. Other strengths of this study include its large sample size and the inclusion of dialysis episodes of nearly all chronic dialysis patients in the Netherlands over 20 years. This enabled us to explore in detail the various shifts in kidney replacement therapy and in competing events, that is kidney transplantation and mortality, over time. However, registry data are also a limitation to this study. Not all potentially relevant confounders are registered in the registry; we were for example unable to explore the effect of a pre-dialysis education program.[35] Other patient-specific characteristics that are known to influence dialysis modality choice, such as comorbidities and acute start of dialysis, could also have changed the main results since these demographic characteristics have supposedly changed over time in the home dialysis population.[14, 30, 36] We evaluated shifts in kidney replacement therapy *after* dialysis initiation; the effect of pre-emptive kidney transplants is not evaluated in the present analysis.[11] Furthermore, not necessarily a limitation but noteworthy nevertheless, we presented the 2-year incidences of kidney transplantation and mortality for incident patients initiating CHD, not the kidney transplantation and mortality incidences for patients that initiated treatment with home dialysis.

Conclusions

From 1997 to 2016, the home dialysis use in patients aged <65 years declined sharply. This decrease can in part be explained by an increase in kidney transplantations. In incident patients above 65 years of age, the uptake of home dialysis remained stable, possibly explained by initiatives to promote home dialysis in the elderly. This study demonstrated that the home dialysis population has aged considerably, which was more pronounced than the ageing of the dialysis population in general.

Within a growing population with ESKD, sufficient resources to facilitate home dialysis must be offered to support this older patient population in their dialysis modality of choice.

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Supplementary material

Supplementary Table S1. Uptake of home haemodialysis within the first 2 years of dialysis initiation (n=33,340), by time period

	Time period			
	1997-2001 OR (95% CI)	2002-2006 [a]	2007-2011 OR (95% CI)	2012-2016 OR (95% CI)
unadjusted	0.72 (0.50 – 1.02)	1.0	1.26 (0.93 – 1.71)	2.90 (2.17 – 3.88)
adjusted[b]	0.63 (0.43 – 0.93)	1.0	1.36 (0.99 – 1.87)	3.57 (2.59 – 4.92)

[a] time period 2002-2006 was regarded as reference period
[b] adjusted for sex, age, dialysis vintage, and transplantation history

Supplementary Table S2. Sensitivity analysis: uptake of home dialysis in the first 2 years of dialysis initiation in patients with a first dialysis episode in 1997-2016 (n=29,892), by time period and age category

		Time period			
		1997-2001 OR (95% CI)	2002-2006 [a]	2007-2011 OR (95% CI)	2012-2016 OR (95% CI)
Age 20-44	*unadjusted*	1.63 (1.37 – 1.93)	1.0	0.71 (0.59 – 0.85)	0.54 (0.45 – 0.66)
	adjusted[b]	1.63 (1.37 – 1.93)	1.0	0.70 (0.59 – 0.84)	0.54 (0.45 – 0.66)
Age 45-64	*unadjusted*	1.30 (1.17 – 1.46)	1.0	0.80 (0.70 – 0.88)	0.59 (0.52 – 0.66)
	adjusted[b]	1.30 (1.17 – 1.46)	1.0	0.79 (0.70 – 0.88)	0.59 (0.52 – 0.66)
Age 65-74	*unadjusted*	1.30 (1.13 – 1.49)	1.0	0.96 (0.84 – 1.10)	0.99 (0.87 – 1.13)
	adjusted[b]	1.30 (1.14 – 1.50)	1.0	0.96 (0.84 – 1.10)	0.99 (0.86 – 1.13)
Age above 75	*unadjusted*	1.35 (1.10 – 1.66)	1.0	1.24 (1.05 – 1.48)	1.55 (1.31 – 1.84)
	adjusted[b]	1.36 (1.10 – 1.67)	1.0	1.24 (1.04 – 1.48)	1.54 (1.30 – 1.82)

[a] time period 2002-2006 was regarded as reference period
[b] adjusted for sex and transplantation history

Supplementary Table S3. Sensitivity analysis: uptake of home dialysis within the first 2 years of dialysis initiation in dialysis episodes with a dialysis duration of at least 2 years (n=20,665), by time period and age category

		Time period			
		1997-2001 OR (95% CI)	**2002-2006 [a]**	**2007-2011 OR (95% CI)**	**2012-2016 OR (95% CI)**
Age 20-44	*unadjusted*	2.05 (1.48 – 2.86)	1.0	0.45 (0.31 – 0.64)	0.37 (0.25 – 0.55)
	adjusted[b]	1.96 (1.43 – 2.68)	1.0	0.49 (0.35 – 0.68)	0.42 (0.29 – 0.61)
Age 45-64	*unadjusted*	1.72 (1.37 – 2.16)	1.0	0.59 (0.47 – 0.74)	0.40 (0.30 – 0.52)
	adjusted[b]	1.71 (1.36 – 2.15)	1.0	0.60 (0.48 – 0.75)	0.41 (0.31 – 0.52)
Age 65-74	*unadjusted*	1.42 (1.20 – 1.69)	1.0	0.95 (0.81 – 1.13)	0.88 (0.75 – 1.04)
	adjusted[b]	1.42 (1.20 – 1.68)	1.0	0.95 (0.81 – 1.12)	0.88 (0.75 – 1.04)
Age above 75	*unadjusted*	1.09 (0.82 – 1.45)	1.0	1.16 (0.93 – 1.44)	1.40 (1.13 – 1.73)
	adjusted[b]	1.09 (0.82 – 1.45)	1.0	1.16 (0.93 – 1.45)	1.40 (1.13 – 1.73)

[a] time period 2002-2006 was regarded as reference period
[b] adjusted for sex, dialysis vintage, and transplantation history

Appendix S1. Complete list of codes used to classify study outcomes and events during follow-up

VALUE = therap	Original code in registry	Defined as
	in-centre HD Including active in-centre HD and nocturnal in-centre HD	CHD
	Home HD	Home HD
	PD Including CAPD and APD	PD
	Kidney transplantation Including deceased donor kidney transplantation and living donor kidney transplantation	Kidney transplantation
	Lost to follow-up	Lost to follow-up
	Informed consent withdrawn	Lost to follow-up
	Recovery of kidney function	Recovery of kidney function
	Conservative treatment *In use from 2015*	Lost to follow-up
	Stop dialysis treatment and start palliative care	Death
	Death	Death

Chapter 3

Comorbidity is not associated with dialysis modality choice in patients with end-stage kidney disease

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Abstract

Background: Over the past years the proportion of home dialysis patients has decreased in the Netherlands. In addition, the home dialysis use varies significantly among centres. It is unclear whether this is the result of differences in comorbidity, other case mix factors or differently perceived barriers for home modalities by dialysis centres. Our aim was to investigate the association between comorbidity and dialysis modality choice.

Methods: The multi-centre DOMESTICO cohort study collected comorbidity data of patients who started dialysis in 35 Dutch centres from 2012 to 2016. Comorbidity was assessed by the Charlson comorbidity index. Home dialysis was defined as any peritoneal dialysis or home haemodialysis treatment during follow-up. Logistic regression analysis was used to assess the association between comorbidity and dialysis modality, with a mixed model approach to adjust for clustering of patients within dialysis centres. Other case mix factors, including age and body mass index, were included as confounders in the model.

Results: A total of 1358 patients were included, of whom 628 were treated with home dialysis. In crude mixed model analyses, the probability of receiving home dialysis was lower when comorbidity score was higher: having a high comorbidity score resulted in an odds ratio of 0.74 (95% CI 0.54-1.00, p-value 0.05) when compared to patients without comorbidities. After adjustments for age, sex, ethnic background, body mass index and dialysis vintage, there was no association between comorbidity and home dialysis.

Conclusion: Comorbidity was not significantly associated with home dialysis choice, after adjustment for several confounding factors including age and body mass index. Future studies should aim at unravelling the centre-specific characteristics that probably play a role in dialysis modality choice.

Introduction

The proportion of home dialysis patients has declined in several European countries, including the United Kingdom and the Netherlands.[1, 2] In the Netherlands, the proportion of prevalent home dialysis patients almost halved over 15 years: from 30% in 2003 to 18% in 2018.[3]

This decrease in home dialysis is often explained by the increasing number of patients with diabetes mellitus and cardiovascular disease.[1, 4-6] Patients have to be able to perform dialysis at home and as a result a high degree of comorbidity may be seen as a barrier to home dialysis. Indeed, peritoneal dialysis (PD) patients in older cohorts had fewer comorbidities than in-centre haemodialysis (CHD) patients.[7-12] Another perceived barrier is advanced age of patients with kidney failure, caused by ageing of the general population and by more kidney transplantations in younger patients.[1] In a registry study among different European countries, it was found that elderly patients and patients with various comorbidities were less likely to receive PD.[5]

However, in the proportion of patients treated with home dialysis, a large variation exists among countries and even among dialysis centres within a country.[3, 5, 13] In the Netherlands, with a nation-wide home dialysis prevalence around 20%, the proportion of home dialysis varies considerably from 0% to even 40%.[3] This variation could be explained by different characteristics of dialysis patients among centres, most importantly regarding comorbidity and age. However, this variation could also indicate different selection criteria for home dialysis among physicians. It remains unclear what the impact is of comorbidity on final dialysis modality choice.

The aim of this study is to investigate the association between comorbidity and type of dialysis treatment – home dialysis versus in-centre dialysis - in patients with end-stage kidney disease initiating dialysis between 2012-2017, accounting for centres' practice patterns.

Methods

Study design and patient population

The Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO) is a multi-centre retrospective cohort study investigating characteristics and outcomes of home and nocturnal dialysis patients, in comparison with in-centre dialysis patients. Eligible patients were adults who started maintenance dialysis treatment between 1 January 2012 and 1 January 2017, including those with graft failure. Patients who stopped dialysis or died within 30 days after dialysis initiation were excluded. In DOMESTICO, all patients who were treated with home dialysis (or nocturnal dialysis) during the study period were selected and CHD patients were randomly selected in a systematic manner. Patients were followed until kidney transplantation, wish to stop dialysis, death or study end on 1 January 2017. Local medical ethics committees of all participating dialysis centres approved the study.

Determinants

Comorbidity was assessed with Deyo's Charlson comorbidity index (CCI).[14] The adaption of Deyo *et al*., in which lymphoma and leukemia are scored under the condition 'malignancy', is most frequently used.[14, 15] The CCI was calculated from the presence of a total of 17 conditions with several assigned weights ranging from 1 to 6 (Supplementary Table S1).[14, 16] The total score in dialysis patients ranges from 2 to 29, as ESKD results in a CCI score of 2 points. The score was divided into three groups according to literature: a score of 2 reflecting no comorbidity (only ESKD), a score of 3-4 reflecting intermediate comorbidity, and a score of 5 or more points reflecting high comorbidity.[16]

In addition, the association of various single comorbidities with dialysis modality was evaluated. These comorbidities were: diabetes mellitus, ischemic heart disease, heart failure, cerebrovascular disease, any malignancy and chronic lung disease.

Data collection

All comorbidities were collected at dialysis initiation from patients' medical charts. Also age, sex, body mass index (BMI), ethnic background, cause of kidney failure, presence and duration of previous dialysis (i.e. dialysis vintage), and presence of previous transplantation were identified from patients' charts. BMI was divided into three groups according to the WHO classification: BMI < 25 kg/m^2, BMI 25 - 30

kg/m^2 (overweight), and BMI ≥ 30 kg/m^2 (obese). A high home dialysis volume was considered a marker for a successful home dialysis programme. Home dialysis centre size was thus defined based on the mean annual number of prevalent home dialysis patients according to registry data and subsequently dichotomized into <30 and ≥ 30 home dialysis patients.[17]

Outcome

In the present study, dialysis modality was defined as CHD (including nocturnal in-centre haemodialysis) or home dialysis, the latter including both PD and home haemodialysis (home HD). All patients who started with home dialysis or were ever treated with home dialysis during the follow-up were defined as home dialysis patients to reflect dialysis modality choice. If a patient was treated with both PD and home HD during the study period, the first episode of home treatment determined the category of home dialysis treatment.

Statistical analyses

All normally distributed continuous variables were reported as means with standard deviation (SD), non-normally continuous variables as median with interquartile range (IQR), and categorical variables as proportions. For examining differences between patients groups, t-tests, Mann-Whitney, and Chi-square tests were used where appropriate.

To assess the association between comorbidity and dialysis modality, logistic mixed model analysis was performed with CCI or single comorbidities as determinant. The assumption of linearity was validated and if violated, the CCI score was presented as categories. A mixed model - also known as multilevel model or hierarchical model - was chosen to account for the dependency of patients within a centre. This correction was performed by means of applying a random intercept for dialysis centre. Individual patients (level 1) were thus clustered within dialysis centres (level 2). The addition of a random slope was also tested, to allow for the association between comorbidity and dialysis modality to be different among dialysis centres. All analyses were corrected for age, sex, BMI, ethnic background, and dialysis vintage at study start. To investigate possible interaction of dialysis centres and case mix variables on the association between comorbidity and dialysis choice, interactions for home dialysis centre size, age, and BMI were investigated. In addition, important confounders were evaluated as individual risk factors as well. BMI was missing in 17% of the cases, therefore

weight and length were imputed with standard multiple imputation techniques using 10 repetitions and predictive mean matching (SPSS).[18]

Three sensitivity analyses were conducted, (i) using the Davies comorbidity score instead of the CCI (ii) including only patients with home dialysis as initial therapy and (iii) defining home dialysis as PD only, excluding all home HD patients.[19, 20] The latter was performed because the association between comorbidity and home dialysis could be different for the two individual types of home dialysis. Finally, the two types of home dialysis were analysed separately using a multinomial logistic regression, in which outcomes were CHD, PD, and home HD.

A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics version 26 (IBM Corp) or STATA 14 (StataCorp LP).

Results

A total of 1358 patients were included in this study, of whom 46% was treated with home dialysis during the study period: 41% was treated with PD (n=564) and 5% with home HD (n=64). Most home dialysis patients (72%) started home dialysis as initial therapy. Median follow-up time, i.e. inclusion in the study to end of the study (kidney transplantation, death, stop of dialysis or January 1st 2017), was 1.7 years (IQR 0.8 – 2.9). Baseline characteristics of the patients are described in Table 1.

Table 1. Characteristics of the 1358 included dialysis patients, divided by dialysis modality

	All patients n=1358	**Home dialysis n=628**	**In-center haemodialysis n=730**
Male sex, n (%)	832 (61)	390 (62)	442 (61)
Age (yr), mean ± SD	62.4 ± 15.7	61.6 ± 15.6	63.1 ± 15.8
Body mass index (kg/m^2), mean ± SD	26.8 ± 5.6	26.4 ± 5.1	27.2 ± 6.0
Ethnic background, n (%)			
Caucasian	805 (59)	403 (64)	402 (55)
Moroccan/Turkish	73 (5)	13 (2)	60 (8)
Asian	71 (5)	35 (6)	36 (5)
Afro-American	60 (4)	21 (3)	39 (5)
Unknown	330 (24)	146 (23)	184 (25)

Table 1. Characteristics of the 1358 included dialysis patients, divided by dialysis modality (continued)

	All patients n=1358	Home dialysis n=628	In-center haemodialysis n=730
ERA-EDTA code, n (%)			
Glomerulonephritis/pyelonephritis	261 (19)	125 (20)	136 (19)
Cystic kidney disease	78 (6)	39 (6)	39 (5)
Renovascular kidney disease	355 (26)	164 (26)	191 (26)
Diabetes mellitus	243 (18)	102 (16)	141 (19)
Other/unknown	421 (31)	198 (32)	223 (31)
Previous dialysis, n (%)	276 (20)	121 (19)	155 (21)
Dialysis vintage (mo), median [IQR][#]	29.4 [11.0 – 57.7]	17.7 [2.2 – 45.4]	38.4 [15.4 – 62.8]
Previous renal transplant, n (%)	241 (18)	92 (15)	149 (20)
Charlson comorbidity index, n (%)			
2 (no comorbidity)	409 (30)	202 (32)	207 (28)
3-4 (intermediate comorbidity score)	553 (41)	257 (41)	296 (41)
≥ 5 (high comorbidity score)	396 (29)	169 (27)	227 (31)
Davies comorbidity score, n (%)			
0 (no comorbidity)	398 (29)	194 (31)	204 (28)
1-2 (intermediate risk)	722 (53)	330 (53)	392 (54)
≥ 3 (high comorbidity score)	238 (18)	104 (17)	134 (18)
Diabetes Mellitus, n (%)	465 (34)	193 (31)	272 (37)
Ischaemic heart disease, n (%)	378 (28)	182 (29)	196 (27)
Heart failure, n (%)	149 (11)	83 (13)	66 (9)
Cerebrovascular disease, n (%)	187 (14)	84 (13)	103 (14)
Any malignancy, n (%)	192 (14)	81 (13)	111 (15)
Chronic lung disease, n (%)	159 (12)	67 (11)	92 (13)

[#] Dialysis vintage presented for patients with previous dialysis only.

The prevalence of comorbidity was: diabetes mellitus 34%, ischaemic heart disease 28%, heart failure 11%, cerebrovascular disease 14% and any malignancy 14%. Mean age at dialysis initiation was slightly higher in CHD patients compared to home dialysis patients (63.1 ± 15.8 vs. 61.6 ± 15.6 years, resp.). Patients receiving home dialysis were more likely to be Caucasian, had a shorter dialysis vintage at dialysis initiation, and less often a previous renal transplant. In Table 2, clinical characteristics of patients from small and large home dialysis centres are shown. No differences in

CCI, age and BMI were found between patients from small and large home dialysis centres.

Table 2. Characteristics of patients from small and large home dialysis centres

	Patients from centres with < 30 home dialysis patients N=535	Patients from centres with ≥ 30 home dialysis patients N=823	p-value
CCI of CHD patients, n (%)			
2 (no comorbidity)	94 (27)	113 (29)	0.45
3-4 (intermediate comorbidity score)	147 (43)	149 (38)	
≥ 5 (high comorbidity score)	101 (30)	126 (32)	
CCI of home dialysis patients, n (%)			
2 (no comorbidity)	69 (36)	133 (31)	0.24
3-4 (intermediate comorbidity score)	80 (41)	177 (41)	
≥ 5 (high comorbidity score)	44 (23)	125 (29)	
Mean age (± SD)	62.4 ± 15.0	62.4 ± 16.1	0.98
Mean BMI (± SD)	26.9 ± 5.7	26.7 ± 5.5	0.50

CCI, Charlson comorbidity index; CHD, in-centre haemodialysis; BMI, body mass index.

Association between comorbidity and dialysis modality

Table 3 shows the association between comorbidity and home dialysis as dialysis modality choice. CCI was analysed in categories, since the linearity assumption was violated. Intermediate comorbidity, i.e. 3-4 points, was not associated with home dialysis as modality choice (unadjusted OR 0.97, 95% CI 0.73 – 1.28). A high comorbidity score, i.e. a score of ≥ 5 points, was associated with a lower probability of receiving home dialysis (unadjusted OR 0.74, 95% CI 0.54 – 1.00, p-value 0.05). After adjustments for age, sex, BMI, ethnic background, and dialysis vintage, a higher comorbidity score was no longer associated with home dialysis (adjusted OR 0.88, 95% CI 0.63 – 1.23). Age and BMI were the most important confounders in the model, they induced the greatest change in the regression coefficient respectively 28% and 30%. The other confounders induced changes of less than 10%. Adding a random slope to the model with CCI as a continuous variable did not change our results, indicating that dialysis centre did not influence the association between CCI and

dialysis modality choice. This suggests that comorbidity was not weighted differently among centres.

Patients with heart failure (n=149) were more likely to receive home dialysis, even after adjustments for confounders (adjusted OR 1.60, 95% CI 1.09 – 2.37). Diabetic patients were less likely to receive home dialysis in the unadjusted analysis, but after correction for confounders this association lost significance (adjusted OR 0.83, 95% CI 0.64 – 1.08). Patients with ischaemic heart disease, cerebrovascular disease, malignancies or chronic lung disease were as likely to receive home dialysis as CHD. The Davies comorbidity score had also no association with home dialysis choice (Supplementary Table S2). Comparable results to the original analysis were also found in a sensitivity analysis that included only patients with home dialysis as initial therapy.

Table 3. Association of comorbidity and treatment with home dialysis, compared to in-centre haemodialysis

	Logistic mixed model regression analysis*					
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted[ł]	P-value	Odds ratio [95% CI] Adjusted[#]	P-value
Charlson comorbidity index						
CCI 2	REF	0.82	REF	0.73	REF	0.53
CCI 3-4	0.97 [0.73 – 1.28]	0.05	1.05 [0.78 – 1.41]	0.30	1.10 [0.82 – 1.49]	0.44
CCI ≥ 5	0.74 [0.54 – 1.00]		0.84 [0.61 – 1.17]		0.88 [0.63 – 1.23]	
At least 1 comorbidity	0.86 [0.67 – 1.12]	0.26	0.97 [0.74 – 1.27]	0.81	1.01 [0.77 – 1.33]	0.93
Diabetes Mellitus †	0.75 [0.59 – 0.97]	0.03	0.78 [0.61 – 1.01]	0.06	0.83 [0.64 – 1.08]	0.17
Ischaemic heart disease	1.08 [0.83 – 1.40]	0.57	1.17 [0.89 – 1.55]	0.26	1.23 [0.93 – 1.63]	0.15
Heart failure	1.47 [1.01 – 2.14]	0.05	1.54 [1.05 – 2.25]	0.03	1.60 [1.09 – 2.37]	0.02
Cerebrovascular disease	0.79 [0.57 – 1.11]	0.18	0.83 [0.59 – 1.17]	0.28	0.81 [0.57 – 1.15]	0.24
Any malignancy	0.91 [0.65 – 1.28]	0.58	0.92 [0.65 – 1.30]	0.65	0.89 [0.63 – 1.26]	0.50
Chronic lung disease	0.83 [0.58 – 1.21]	0.34	0.88 [0.61 – 1.29]	0.52	0.88 [0.60 – 1.29]	0.50

* Logistic mixed model regression analysis with dialysis centre as random intercept, with individual patients as first level.
ł Adjusted for age, sex, and BMI
Adjusted for age, sex, BMI, ethnic background, and dialysis vintage
† Adjusted for age, sex, ethnic background, and dialysis vintage.
CCI, Charlson comorbidity index; BMI, body mass index.

Interaction of dialysis centre, age and BMI on the association between comorbidity and dialysis modality

Home dialysis centre size and age were no interactions in the association between comorbidity and home dialysis choice (Supplementary Tables S3 and S4). However, obese patients (BMI ≥ 30 kg/m^2) with an intermediate or high comorbidity score were significantly less likely to receive home dialysis compared to obese patients without comorbidities, adjusted OR 0.40 (95% CI 0.18 – 0.86, p-value 0.02) for intermediate comorbidity score and adjusted OR 0.43 (95% CI 0.20 – 0.93) for high comorbidity score (Table 4). Patients with a BMI <25 kg/m^2 with an intermediate comorbidity score were significantly more likely to receive home dialysis compared to patients with a BMI <25 kg/m2 without comorbidities (adjusted OR 1.59, 95% CI 1.01 – 2.49, p-value 0.04).

Table 4. Interaction of BMI in the association between CCI and treatment with home dialysis, compared with in-centre haemodialysis

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
Patients with BMI <25 kg/m² *n = 493†*				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	1.37 [0.89 – 2.11]	0.15	1.59 [1.01 – 2.49]	0.04
CCI ≥ 5	1.03 [0.62 – 1.69]	0.92	1.22 [0.72 – 2.07]	0.46
Overweight patients (BMI 25 - 30 kg/m²) *n = 379†*				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	1.00 [0.61 – 1.64]	0.99	1.10 [0.66 – 1.83]	0.72
CCI ≥ 5	0.71 [0.41 – 1.24]	0.22	0.76 [0.43 – 1.35]	0.36
Obese patients (BMI ≥30 kg/m²) *n = 257†*				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	0.40 [0.19 – 0.86]	0.02	0.40 [0.18 – 0.86]	0.02
CCI ≥ 5	0.42 [0.20 – 0.88]	0.02	0.43 [0.20 – 0.93]	0.03

* Logistic mixed model analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for age, sex, ethnic background, and dialysis vintage
† A total of 1358 patients were analysed: for 229 patients imputed data for BMI were used.
BMI was divided according to the WHO classification: BMI <25 kg/m^2, BMI 25 - 30 kg/m^2 (overweight), and BMI ≥30 kg/m^2 (obese).
BMI, body mass index; CCI, Charlson comorbidity index.

Association between age or BMI and dialysis modality

Older age, analysed as an individual risk factor, was associated with a lower probability of receiving home dialysis both in unadjusted and adjusted analyses (Supplementary Table S5). Elderly patients (≥ 65 years of age) were less likely to receive home dialysis compared to patients younger than 65 years of age, adjusted OR 0.67 (95% CI 0.53 – 0.86, p-value 0.002). Also BMI, analysed as an individual risk factor, was associated with dialysis modality choice (Supplementary Table S6). Obese patients were less likely to receive home dialysis compared to patients with a BMI <25 kg/m2, adjusted OR 0.68 (95% CI 0.48 – 0.96, p-value 0.03)

Association between comorbidity and PD or HHD

A sensitivity analysis comparing PD with CHD, revealed similar results as the original analysis (Supplementary Table S7). Finally, the two types of home dialysis were analysed separately using a multinomial logistic regression, with CHD as reference treatment (Supplementary Table S8). A high comorbidity score of ≥5 was significantly associated with a lower probability of receiving peritoneal dialysis compared to CHD, with a crude OR of 0.74 (95% CI 0.55 - 0.98, p-value 0.04). After adjusting for confounders, the association lost significance (OR 0.83, 95% CI 0.61 – 1.14). The adjusted OR for a high comorbidity score and receiving home HD was 1.42 (95% CI 0.69 – 2.93).

Discussion

In this study, ESKD patients with a high comorbidity score measured by CCI were less likely to receive home dialysis as compared to CHD. However, when adjusted for confounders including age and BMI, we found no association between comorbidity and dialysis modality choice. In addition, no association was found with diabetes mellitus, ischaemic heart disease, malignancy and cerebrovascular disease. Patients with heart failure were more likely to receive home dialysis, while obese patients with comorbidities were more likely to receive CHD.

The association between comorbidities and PD as home dialysis modality has been investigated in different populations, including in the USA and Europe.[5, 7-9, 11, 12, 21, 22] Similar results were found in an older European cohort from 1998-2006, in which a high comorbidity score was highly associated with receiving CHD in unadjusted analyses yet almost lost significance in analyses adjusted only for age and sex.[5] However in their study, patients with malignancy and cerebrovascular disease were less likely to receive PD while patients with diabetes mellitus were more likely to receive PD (adjusted OR 1.09 (1.00 – 1.20)). In contrast, in another study, French patients with diabetes mellitus were more likely to receive CHD and patients with heart failure were more likely to receive PD, both similar to our results.[8] In studies from the USA, both heart failure and higher comorbidity scores were associated with a lower probability of receiving PD.[7, 9, 11] These studies however originate from before 2000, when the use of PD was historically low in the USA making comparisons with the current population difficult.[23, 24] Finally, in a study from Australia and New

Zealand, several comorbidities including diabetes mellitus were associated with a lower probability of receiving home dialysis.[22] Overall, these discrepancies among countries indicate that wide variation in selection of home dialysis exists and that comorbidity alone is not a justified contraindication for home dialysis.

In our study, both age and BMI were important confounders in the association between comorbidity and dialysis modality. Thus far, only few other studies corrected for both factors.[9, 21] In the French study of Couchoud *et al.*, only patients aged ≥ 75 years and single comorbidities were evaluated.[21] They found a positive association between heart failure and home dialysis (adjusted OR 1.8, 95% CI 1.5 – 2.3). The study of Stack *et al.* from USA, also evaluated single comorbidities only and was conducted prior to 2000.[9] Although few studies correct for age and BMI, increasing age is associated with a lower probability of receiving home dialysis in recent studies[5, 22, 25], as is obesity.[22] The often-reported association between comorbidity and dialysis modality may be largely explained by the confounding effect of age. The same may be true for BMI, as many conditions including cardiovascular disease are initiated by an unhealthy lifestyle.

Age should not be a barrier to receive home dialysis. Although elderly patients frequently have functional limitations and cognitive impairment that may limit the possibilities for self-care[26], this does not necessarily rule out a home-based treatment.[27] Assisted PD is an important and emerging treatment option for older dialysis patients with similar outcomes to CHD, such as mortality, hospitalisation rates, and health-related quality of life.[28-30] Moreover, PD provides ultrafiltration more slowly and is not associated with intradialytic hypotension frequently occurring in CHD, which is especially important in frail elderly patients.[31] Because of the considerable growth in the number of elderly dialysis patients, it is essential to consider home dialysis treatment as a feasible option for elderly patients.

Obese patients were less likely to receive home dialysis treatment in several studies.[8, 9, 22] It is possible that in obese patients CHD is preferred, due to the survival advantage known as the 'obesity paradox' in obese CHD patients that lacks in PD.[32] Another explanation may be that obesity (BMI >30 kg/m^2) in PD patients is associated with higher risk of leakage and PD-associated infections.[33-36] The latter could be related to the common co-existence of Diabetes Mellitus and lower socioeconomic status in obese patients, or it might be due to obese abominable folds.[34, 35] But, using extended

catheters or even pre-sternal catheters reduced this risk of infections in several studies.[37] Many nephrologists may consider obesity a contraindication for treatment with PD as PD can induce weight gain, but this issue is controversial.[31] Overall, obesity may not be considered an absolute contraindication for performing PD.

In keeping with findings of previous studies, our study identified that heart failure is associated with a higher probability of receiving home dialysis.[8, 21] PD is indeed suggested as ultrafiltration treatment in patients with diuretic-resistant heart failure.[38] In this seriously ill-group, percutaneous PD catheter insertion under local anaesthesia may be performed by interventional radiologists to avoid general anaesthesia.[37, 39] Since PD lacks the intradialytic hypotension known in CHD, it is a suitable treatment option in all patients with heart failure.[38]

Comorbidity alone does not explain the variation in percentage of home dialysis among centres. The present study results suggests that other factors in modality selection are weighted differently among centres. These factors likely include age and BMI, but since these factors were not different between centres with a high or low volume of home dialysis patients – considering a high volume a proxy for a successful home dialysis programme - other factors must also define dialysis modality choice. Indeed, in a French study analysing differences between centres in the use of PD, there was variation in PD use among regions but also huge variation in the evaluation of different patient characteristics.[8] The authors thus suggested that other regional practice patterns, such as the organisation of a home dialysis programme, play a role in modality selection. Ethier *et al.,* reporting on the ANZDATA registry and using a mixed model, stated that variation in the use of home dialysis among centres was associated more with centre factors, such as centre size and proportion of patients with a vascular access at dialysis initiation, than patient characteristics.[22] Also, logistic and financial factors form barriers for home dialysis and can be weighed differently by individual dialysis centres.[40-43] Further studies are needed to explore these centre-specific factors that might also influence dialysis modality selection.

The strengths of this study include the extensive statistical analyses and the definition of both determinant and outcome. The latter was defined as a start with or transfer to home dialysis during follow-up, reflecting dialysis modality choice. The determinant comorbidity was defined both in validated scores and in single comorbidities providing insight in the association from several points of view, especially heart failure was

positively associated with home dialysis. With mixed models, we corrected for centre differences in patient selection which has not often been performed in studies.[7, 22] However, we had a relatively small sample compared to others.[5, 8, 9, 21] Although CHD patients were randomly selected, the DOMESTICO study was not designed for the present research question and the population used might not represent a true reflection of modality selection. For this research question, it might have been better to match patients according to their total duration of follow-up. Due to the retrospective design of the study, we were unable to investigate causes of low use of home dialysis, but mere associations instead. Finally, CCI and Davies are developed for mortality predictions and not for dialysis modality choice. These scores might not adequately reflect the impact of comorbidity on dialysis modality choice, especially since the various single comorbidities had associations in different directions.

Notwithstanding these limitations, in this study comorbidity was not significantly associated with home dialysis choice if corrected for age, BMI and centre. Only obese patients with comorbidities were significantly less likely to receive home dialysis. Other factors than comorbidity possibly also influence dialysis modality choice. Differences in prevalence of obesity and age distribution, but probably also centre-specific factors may be related to the variation in the proportion of patients treated with home dialysis among centres. We suggest that future studies should focus on the centre-specific factors that determine dialysis modality selection.

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Supplementary material

Supplementary Table S1. Scoring of the Charlson comorbidity, as proposed by Deyo *et al.*[1]

Conditions	Points for Charlson comorbidity index
Myocardial infarction	1
Heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic lung disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes mellitus (without chronic complications)	1
Diabetes mellitus with chronic complications	2
Hemiplegia	2
Any malignancy including lymphoma and leukemia	2
End stage kidney disease	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
AIDS	6

Supplementary Table S2. Association of the Davies comorbidity score and treatment with home dialysis, compared with in-centre haemodialysis

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
Davies comorbidity score				
Davies 0	REF		REF	
Davies 1-2	0.90 [0.69 – 1.18]	0.45	1.04 [0.78 – 1.39]	0.80
Davies ≥ 3	0.78 [0.55 – 1.12]	0.19	0.96 [0.65 – 1.42]	0.83

* Logistic mixed model regression analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for age, sex, BMI, ethnic background, and dialysis vintage
BMI, body mass index.
The Davies comorbidity score was calculated from the presence of the following conditions, with a score ranging from 0 to 7: malignancy, ischaemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, and other significant pathology / life-threatening disease.[2, 3] The score was divided into three groups according to literature: 0 for patient with absent conditions, 1-2 conditions for intermediate comorbidity, and 3 or more conditions reflecting high comorbidity.[2]

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Supplementary Table S3 Interaction of centre size in the association between CCI and treatment with home dialysis, compared with in-centre haemodialysis

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
Small centre size < 30 patients n = 535				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	0.89 [0.56 – 1.42]	0.63	0.98 [0.61 – 1.59]	0.95
CCI ≥ 5	0.63 [0.37 – 1.07]	0.09	0.78 [0.45 – 1.36]	0.40
Large centre size ≥ 30 patients n = 823				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	1.01 [0.71 – 1.44]	0.60	1.17 [0.81 – 1.70]	0.40
CCI ≥ 5	0.79 [0.54 – 1.16]	0.23	0.93 [0.62 – 1.39]	0.72

* Logistic mixed model analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for age, sex, BMI, ethnic background, and dialysis vintage
CCI, Charlson comorbidity index; BMI, body mass index.

Supplementary Table S4 Interaction of age in the association between CCI and treatment with home dialysis, compared with in-centre haemodialysis

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
Younger patients <65 years of age n = 641				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	0.98 [0.67 – 1.45]	0.95	1.08 [0.72 – 1.60]	0.71
CCI ≥ 5	0.70 [0.44 – 1.11]	0.13	0.72 [0.45 – 1.18]	0.19
Older patients ≥ 65 years of age n = 717				
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3-4	1.07 [0.69 – 1.65]	0.77	1.08 [0.70 – 1.68]	0.73
CCI ≥ 5	0.87 [0.56 – 1.37]	0.56	0.95 [0.60 – 1.50]	0.82

* Logistic mixed model analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for age, sex, BMI, ethnic background, and dialysis vintage
CCI, Charlson comorbidity index; BMI, body mass index.

Supplementary Table S5 Association of AGE and treatment with home dialysis, compared with in-centre haemodialysis

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
Age				
<65 years of age	REF		REF	
≥ 65 years of age	0.76 [0.60 – 0.97]	0.02	0.67 [0.53 – 0.86]	0.002

* Logistic mixed model regression analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for sex and ethnic background

Supplementary Table S6 Association of BMI and treatment with home dialysis, compared with in-centre haemodialysis

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
BMI < 25 kg/m²	REF		REF	
BMI 25 - 30 kg/m²	0.81 [0.61 – 1.09]	0.17	0.80 [0.59 – 1.08]	0.14
BMI ≥ 30 kg/m²	0.63 [0.45 – 0.88]	0.006	0.68 [0.48 – 0.96]	0.03

* Logistic mixed model regression analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for age, sex, CCI, ethnic background, and dialysis vintage
BMI, body mass index; CCI, Charlson comorbidity index.

Supplementary Table S7. Association of comorbidity and treatment with peritoneal dialysis (n=564), compared to in-centre haemodialysis (n=730)

	Logistic mixed model regression analysis*			
	Odds ratio [95% CI] Crude	P-value	Odds ratio [95% CI] Adjusted#	P-value
Charlson comorbidity index				
CCI 2	REF		REF	
CCI 3 - 4	0.97 [0.72 – 1.29]	0.82	1.10 [0.81 – 1.51]	0.55
CCI ≥ 5	0.70 [0.51 – 0.97]	0.03	0.84 [0.59 – 1.20]	0.35
At least 1 comorbidity	0.85 [0.65 – 1.11]	0.22	1.00 [0.75 – 1.34]	0.98
Diabetes Mellitus †	0.77 [0.59 – 0.99]	0.04	0.86 [0.66 – 1.12]	0.27
Ischaemic heart disease	1.05 [0.80 – 1.37]	0.73	1.20 [0.89 – 1.61]	0.23
Heart failure	1.44 [0.98 – 2.11]	0.07	1.59 [1.06 – 2.38]	0.03
Cerebrovascular disease	0.80 [0.57 – 1.14]	0.22	0.83 [0.58 – 1.20]	0.32
Any malignancy	0.82 [0.58 – 1.18]	0.29	0.80 [0.55 – 1.15]	0.23
Chronic lung disease	0.84 [0.57 – 1.22]	0.36	0.86 [0.58 – 1.28]	0.45

* Logistic mixed model regression analysis with dialysis centre as random intercept, with individual patients as first level.
# Adjusted for age, sex, BMI, ethnic background, and dialysis vintage
† Adjusted for age, sex, ethnic background, and dialysis vintage
CCI, Charlson comorbidity index; BMI, body mass index.

Supplemental Table S8. Multinomial regression analysis of the association between Charlson comorbidity index and three dialysis modalities

	Multinominal regression analysis			
Dialysis modality	**Odds ratio [95% CI] Crude**	**P-value**	**Odds ratio [95% CI] Adjusted***	**P-value**
In-centre haemodialysis	REF		REF	
Peritoneal dialysis				
CCI 3 - 4	0.89 [0.68 – 1.16]	0.39	0.96 [0.73 – 1.27]	0.79
CCI ≥ 5	0.74 [0.55 – 0.98]	0.04	0.83 [0.61 – 1.14]	0.26
Home haemodialysis				
CCI 3 - 4	0.88 [0.47 – 1.65]	0.70	1.14 [0.58 – 2.25]	0.70
CCI ≥ 5	1.01 [0.53 – 1.93]	0.98	1.42 [0.69 – 2.93]	0.35

* Adjusted for age, sex, BMI, ethnic background, and dialysis vintage.
CCI, Charlson comorbidity index; BMI, body mass index.

Chapter 4

Key elements in selection of pre-dialysis patients for home dialysis

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Abstract

Background Most pre-dialysis patients are medically eligible for home dialysis, and home dialysis has several advantages over incentre dialysis. However, accurately selecting patients for home dialysis appears to be difficult, since uptake of home dialysis remains low. The aim of this study was to investigate which medical or psychosocial elements contribute most to the selection of patients eligible for home dialysis.

Methods All patients from a Dutch teaching hospital, who received treatment modality education and subsequently started dialysis treatment, were included. The pre-dialysis programme consisted of questionnaires for the patient, nephrologist and social worker, followed by an assessment of eligibility for home dialysis by a multidisciplinary team. Clinimetric assessment and logistic regression were used to identify domains and questions associated with home dialysis treatment.

Results A total of 135 patients were included, of whom 40 were treated with home dialysis and 95 with incentre haemodialysis. The key elements associated with long-term home dialysis treatment were part of the domains 'suitability of the housing', 'self-care', 'social support' and 'patient capacity', with adjusted odds ratios ranging from 0.13 for negative to 18.3 for positive associations.

Conclusion The assessment of contraindications by a nephrologist followed by the assessment of possibilities by a social worker or dialysis nurse who investigates four key elements, ideally during a home visit, and subsequent detailed education offered by specialized nurses is an optimal way to select patients for home dialysis.

Introduction

Home dialysis, that is, peritoneal dialysis (PD) or home haemodialysis (HD), offers more flexibility and independence than conventional incentre haemodialysis (CHD), whereas patient survival is comparable or better.[1-3] Therefore, it is not surprising that extensive pre-dialysis programmes lead to a preference for home dialysis in 70% of pre-dialysis patients.[4] Nevertheless, the percentage of patients treated with home dialysis is only about 9-11% throughout the world.[5, 6] An important barrier to uptake of home dialysis is limited pre-dialysis care.[7-11]

However, it remains uncertain which elements of pre-dialysis programmes influence a patient's treatment decision. Identifying key elements linked to long-term home dialysis treatment could help various centres to assess eligibility for home dialysis in more patients and to present home dialysis as a viable option among other kidney replacement therapies (KRT). Elements with a negative correlation for home dialysis can be addressed during treatment modality education. Therefore, the aim of this study was to assess which elements of a multidisciplinary structured pre-dialysis programme[12] contribute most to adequate selection of patients eligible for treatment with home dialysis.

Methods

Study population and design

All patients who had completed the pre-dialysis programme, were assessed for eligibility for home dialysis by both the nephrologist and the social worker and started dialysis between June 2013 and August 2018 in a large, non-academic teaching hospital in the Netherlands (Meander Medical Centre, Amersfoort, the Netherlands) were eligible for inclusion into this retrospective study. From 2013, this teaching hospital adopted a 'home first' policy, that resulted in adjusting the pre-dialysis programme. Prior to the implementation of this programme, the home dialysis rate was 18% as was noted in the article about the implementation.[12] All eligible patients had an eGFR of ≤15ml/min/1.73m^2 or Chronic Kidney Disease stage 4 with rapid deterioration of kidney function prior to referral to the pre-dialysis programme. The programme, that is, eligibility assessment for home dialysis and treatment modality education, was also offered to patients who had an unplanned start of dialysis, that is, acutely started

patients or so-called 'crash landers'. The study was approved by the Medical Research Ethics Committee of the VU University Medical Centre, Amsterdam.

Structured pre-dialysis programme

The structured pre-dialysis programme started with three questionnaires (provided as Supplementary material in Appendix A): for the patient (containing 31 questions), the social worker (20 questions), and the nephrologist (30 questions) of this patient (Figure 1).[12] The questionnaires were developed by Medworq project 'Gezonde Nieren (Healthy Kidneys)', aiming to collect as much relevant information as possible regarding patients and their possibilities for home dialysis. The patient's questionnaire consisted of questions about physical performance, daily activities, and the patient's social support system. The social worker's questionnaire consisted of questions about hygiene, availability of space in the patient's housing, and the capability of the patient and his family to perform dialysis at home. This questionnaire was ideally completed after the social worker performed a home visit. The nephrologist's questionnaire consisted of relative and absolute contra-indications to home dialysis and CHD, e.g. questions about non-compliance, multiple abdominal surgery, and morbid obesity for peritoneal dialysis and impossibility for a vascular access and severe heart failure for (home) HD. Both the social worker and the nephrologist assessed eligibility of all patients for home dialysis, based on the questionnaires. These eligibility assessments were not binding but a mere recommendation, that is, a patient who was judged by the nephrologist as not eligible for home dialysis might initiate home dialysis. The time necessary to fill in a questionnaire was expected to be about 25, 35, and 10 minutes for a patient, social worker and nephrologist respectively.

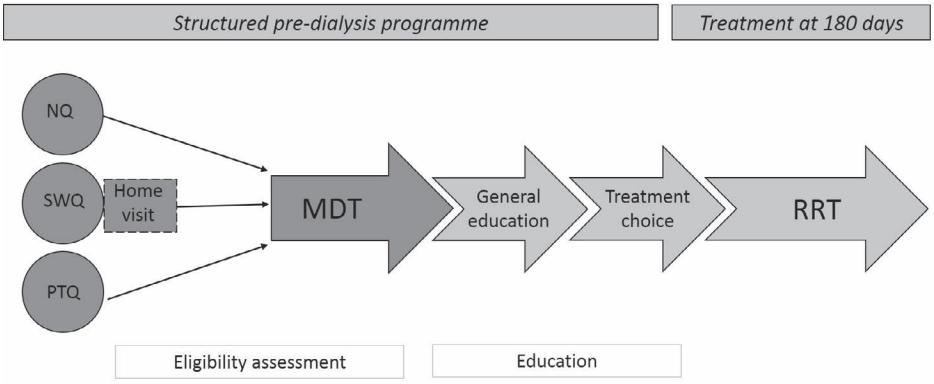

Figure 1. Overview of the structured pre-dialysis programme
NQ, nephrologist's questionnaire; SWQ, social worker's questionnaire; PTQ, patient's questionnaire; MDT, multidisciplinary team meeting; KRT, kidney replacement therapy (including conservative care).

Results of the three questionnaires and home visit were discussed during a Multi-Disciplinary Team (MDT) meeting (Figure 1), in which nephrologists, (pre-)dialysis nurses, and social workers were present. After this meeting the patient received education on all medically feasible treatment modalities by pre-dialysis nurses, including kidney transplantation and conservative care. Depending on the preferences of the patient and the health-care professionals, additional education was provided by transplant nurses and nurses specialized in home dialysis. After completing the education, the definitive choice for KRT was made by the patient, in consultation with his nephrologist. All health-care professionals involved in the pre-dialysis programme were thoroughly informed about the potential benefits of home dialysis at the start of the pre-dialysis programme.

Data collection

Baseline demographic data, eGFR according to chronic kidney disease epidemiology collaboration (CKD-EPI; ml/min/1,73m^2) and comorbidities were collected from patients' charts. Comorbidities were scored according to the Charlson comorbidity index.[13, 14] Social situation and education level were retrieved from the questionnaires. Higher level of education was classified as university or college attendance. Treatment modality was assessed from patients' charts.

Definition of outcome

Treatment modality was defined as the modality, that is, CHD or home dialysis, used at 180 days after dialysis initiation to reflect long-term use. Both (assisted) PD and home HD were considered as home dialysis. The time point of 180 days was chosen to ensure that patients who were eligible and willing to perform PD or home HD, but started for any reason with CHD, were identified as home dialysis patients. For example, patients presenting with acute kidney injury often start with CHD before switching to PD, and treatment with home HD is always preceded by CHD.

Statistical analysis

Continuous variables were reported as means with standard deviation (SD) or as medians with interquartile range (IQR), where appropriate. Categorical variables were presented as proportions. In general, a p-value of <0.05 was considered statistically significant.

Clinimetric properties of all questionnaires were evaluated by three independent researchers: two nephrologist-epidemiologists (FJvI. and BCvJ) and an investigator (AAB). The questions were analysed according to having a formative or reflective nature, and subsequently grouped within separate domains. Logistic regression analysis was performed to investigate the association between long-term home dialysis treatment and the questions within each domain. All questions within a domain with p-value <0.20 in univariable analysis were added to a multivariable model, to correct for correlation. The multivariable model was additionally adjusted for age and Charlson comorbidity index, where appropriate. All analyses were performed using SPSS Statistics 25 (Armonk New York: IBM Corp) or STATA® 14 (Texas: StataCorp LP).

Results

Patient characteristics

A total of 362 patients started the pre-dialysis programme (Figure 2). During the study period, 43 patients died or showed recovery of kidney function. A total of 66 out of 319 patients (21%) opted for conservative treatment. For 72 patients the questionnaires were incomplete. Furthermore, 41 patients had not commenced KRT by the end of

the study period and 71 patients obtained a pre-emptive kidney transplant (n=28, with a kidney transplant rate of 8%) or preferred conservative care (n=43, Figure 2).

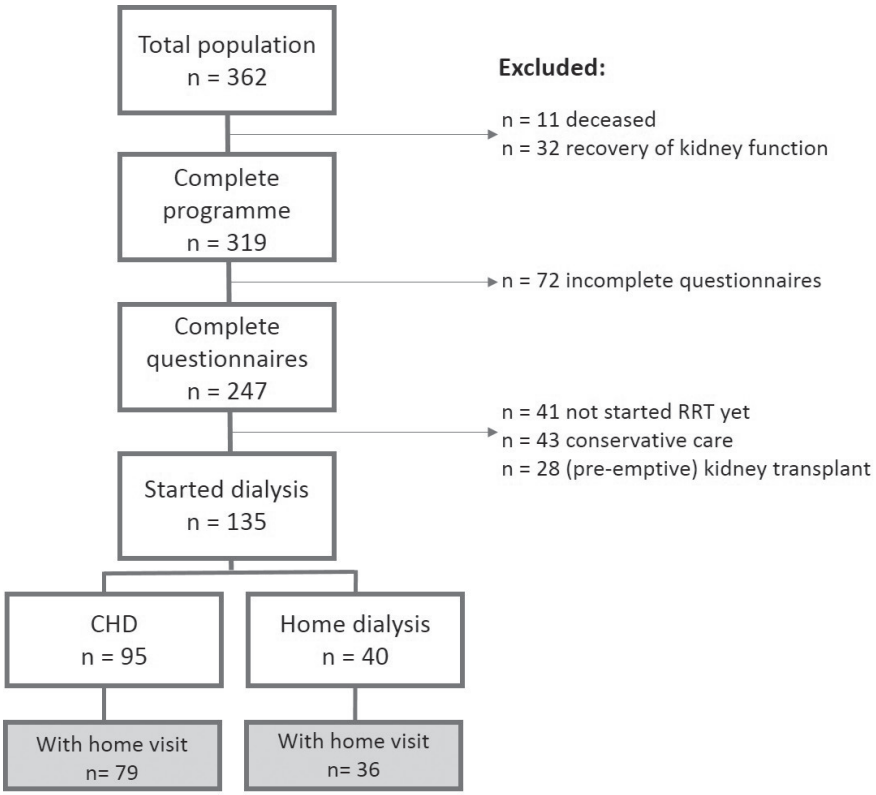

Figure 2. Flow chart of pre-dialysis program and subsequent renal replacement therapy
CHD, incentre haemodialysis.

The remaining 135 patients were included in the analysis, 85% of whom received a home visit. In 15% of patients, the social worker did not succeed in performing a home visit due to time constraints or because the patient did not consent to a home visit. Table 1 presents the characteristics of all included patients. More CHD patients lived alone and had congestive heart failure compared to home dialysis patients.

Table 1. Characteristics of the included patients

	All Patients n = 135	**Home Dialysis n = 40**	**CHD n = 95**
Demographics			
Male sex	85 (63)	22 (55)	63 (62)
Age (years)	66.8 ± 13.8	65.4 ± 14.6	67.5 ± 13.5
Living alone	61 (45)	14 (35)	47 (49)
Higher education	23 (24)	12 (30)	21 (22)
Employment	26 (19)	9 (23)	17 (18)
eGFR at start education*	12.4 ± 5.9	12.2 ± 3.6	12.5 ± 6.7
eGFR at start KRT*	8.2 ± 2.8	8.7 ± 3.0	8.0 ± 2.7
Comorbidities			
Charlson CI	4 [2-5]	4 [3-5]	4 [2-5]
Age-adjusted Charlson CI	6 [4-8]	6 [5-7]	6 [4-8]
Diabetes mellitus	54 (40)	16 (40)	38 (40)
Ischaemic heart disease	33 (24)	11 (28)	22 (23)
Congestive heart failure	12 (9)	1 (3)	11 (12)

Data are shown as n (%), mean ± standard deviation or median with interquartile range [IQR]. CHD, incentre haemodialysis; KRT, kidney replacement therapy; Charlson CI, Charlson Comorbidity Index; IQR, interquartile range.

* eGFR according to CKD-EPI creatinine equation in ml/min/1,73m^2

Preference of patients, health-care professionals and treatment decision

Of the 135 included patients, initial preferences at the start of the programme were: 58 patients preferred CHD (43%), 47 PD (35%), 11 home HD (8%), 5 pre-emptive kidney transplantation (4%), 3 conservative care (2%) and 11 did not have a preference (8%). The social workers considered the overall burden of home dialysis too high in 56 patients. The nephrologists considered previous abdominal surgery (8%), severe obesity (8%), large cystic kidneys (2%) and other reasons (3%) absolute contraindications for PD and no possibility for a vascular access (1%) a contraindication for home HD. These other reasons were intellectual disability, manic-depressive illness, or complete lack of self-sufficiency. For the final decision in the eligibility assessment, the nephrologist and social worker agreed on their eligibility assessment in 69% of patients. The nephrologist found that 8 patients were possibly ineligible for home dialysis, whereas the social worker found that home dialysis was a eligible option. In 34 patients, the nephrologist found that home dialysis could be an eligible option, whereas the social worker found these patients ineligible for home dialysis (Supplementary Table S1).

Dialysis treatment was initiated at a median of 5 months [IQR 0-11] after starting the programme, at a mean eGFR of 8.2 ml/min/1,73 m^2. At 180 days after start of dialysis, 95 patients were treated with CHD (70%), 34 with PD (25%), and 6 patients were treated with home HD (4%). The number of patients treated with home dialysis was comparable between acutely and non-acutely started patients (8 of 35 acutely (23%) vs. 32 of 100 non-acutely started patients (32%), p = 0.31). The rate of home dialysis in the total dialysis population, that is, including patients with incomplete questionnaires, was 29% (52/177), see Supplementary Figure S1.

Characteristics of Questionnaires

Assessment of face validity of the questionnaires, indicated that there was some overlap between the questionnaires regarding medical and housing parameters. Evaluation of the measurement model also indicated that the questions were predominantly formative (as opposed to reflective), meaning that the measured variables are considered to be the cause – and not a reflection - of the latent variable.[15] For example, the question about having enough space for the storage of supplies is a formative question, whereas a question on the consequences of home dialysis, e.g. having more time for education or work, would be a reflective question. In this context this implies that the questions for patient and social worker can be considered formative for, or having a causative

relation to, final eligibility for home dialysis. By clinimetric assessment, the questions of the questionnaires for the patient and social worker were classified into the seven domains: work, mental health, patient capacity, physical health, social support, self-care, and suitability of the housing (Figure 3). The questions from the nephrologists' questionnaire addressed assumed contra-indications for home dialysis; these were not considered as a domain but as a professional practice pattern.

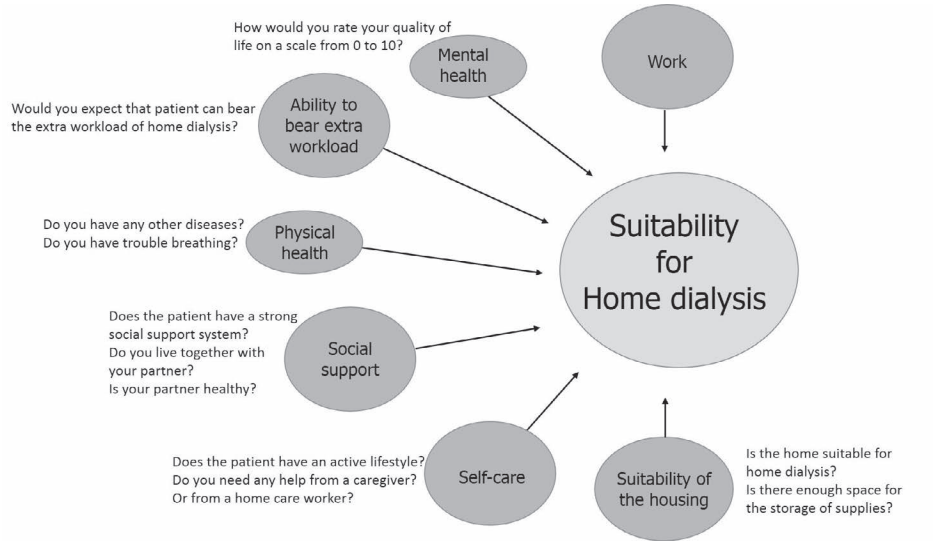

Figure 3. Domains within the patient's and social worker's questionnaires, with examples of the most discriminating questions.

Questionnaires: questions associated with home dialysis

The results of the associations between the different questions and long-term home dialysis treatment are depicted in Table 2. All questions that were associated with home dialysis in univariable analysis are shown. From the domain 'suitability of the housing' the general question 'Is the housing suitable for home dialysis' and 'Is there enough space available for dialysis supplies' were associated with home dialysis treatment, with an adjusted odds ratio (OR) of 9.34 (95% confidence interval (CI) 3.01 – 28.96) and 3.27 (95% CI 0.80 – 13.38, P 0.10) respectively. Not having an active lifestyle – domain 'self-care' - was associated with CHD treatment (adjusted OR 0.13, 95% CI 0.04 – 0.42). The question 'Does the patient have a strong social support system' from the corresponding domain was associated with home dialysis

(adjusted OR 4.86, 95% CI 1.87 – 12.60). The question 'Is the patient able to bear the extra workload of home dialysis' was also strongly associated with home dialysis (adjusted OR 18.60, 95% CI 3.11 – 111.21). Other questions did not show relevant associations with home dialysis after adjustment. Thus, the questions indicative of suitable housing, self-care, social support, and-patient capacity were most strongly associated with long-term home dialysis treatment.

Table 2. Association of questions with home dialysis at 180 days.

Domains	OR (95% CI) crude	p-value	OR (95% CI) adjusted*	p-value
Suitability of the housing				
Owner occupied home	2.06 (0.97 – 4.38)	0.06	1.07 (0.44 – 2.64)	0.88
Does the property have stairs?	1.78 (0.83 – 3.78)	0.14	1.42 (0.59 – 3.42)	0.44
Enough space available for dialysis machine	2.98 (1.37 – 6.49)	0.01	0.34 (0.08 – 1.51)	0.16
Enough space available for dialysis supplies	4.74 (2.03 – 11.04)	<0.001	3.27 (0.80 – 13.38)	0.10
The housing is suitable for home dialysis	9.33 (4.02 – 21.68)	<0.001	9.34 (3.01 – 28.96)	<0.001
Self-care				
Each hour of care by home care agency or caregiver	0.77 (0.61 – 0.97)	0.03	0.88 (0.71 – 1.08)	0.22
Each point on Katz scale#	2.31 (0.79 – 6.78)	0.13	1.14 (0.37 – 3.54)	0.82
The patient doesn't have an active lifestyle	0.10 (0.03 – 0.30)	<0.001	0.13 (0.04 – 0.42)	0.001
Social support				
Is your partner, with whom you live together, in good health?	2.28 (1.06 – 4.89)	0.04	1.76 (0.71 – 4.38)	0.23
Do you have people in the household to help you?	2.62 (0.99 – 6.90)	0.05	2.54 (0.71 – 9.04)	0.15
Does the patient have a strong social support system?	4.62 (1.86 – 11.46)	0.001	4.86 (1.87 – 12.60)	0.001
Physical health				
Do you have trouble breathing?	0.32 (0.09 – 1.17)	0.09	0.31 (0.08 – 1.12)	0.07
Do you have any other diseases?	2.11 (0.74 – 6.04)	0.16	2.66 (0.89 – 7.98)	0.08

Table 2. Association of questions with home dialysis at 180 days. (continued)

Domains	OR (95% CI) crude	p-value	OR (95% CI) adjusted*	p-value
Patient capacity				
Is the patient's understanding of their illness good?	1.38 (1.00 – 1.91)	0.05	0.99 (0.67 – 1.48)	0.96
Is the patient's mental health eligble for home dialysis?	6.87 (1.97 – 23.97)	0.002	0.71 (0.11 – 4.81)	0.73
Are there sufficient financial resources for home dialysis?	2.50 (0.69 – 9.11)	0.17	1.98 (0.47 – 8.39)	0.35
Is the patient able to bear the extra workload of home dialysis?	15.56 (4.49 – 54.01)	<0.001	18.60 (3.11 – 111.21)	0.001
Mental health				
How would you rate your quality of life on a scale from 0 to 10?	1.31 (0.92 – 1.85)	0.12	1.31 (0.92 – 1.85)	0.12

OR, Odds ratio; CI, confidence interval.
*Multivariable models were adjusted for other questions within the same domain; questions from the domains social support and physical health were additionally adjusted for age and Charlson comorbidity index.
This scale elaborates the independency in activities of daily life and ranges from 0 to 6, in which higher scores reflect a more independent patient (Ref. Katz S, JAMA 1963; 185:914-9).

Eligibility assessment by nephrologists and social workers and long-term dialysis treatment

The nephrologists classified 83 patients (61% of all dialysis patients) eligible for home dialysis of whom 37 patients actually were on home dialysis at 180 days, resulting in a positive predictive value (PPV) of 45%. In comparison, the social worker classified 57 patients (42% of all dialysis patients) eligible for home dialysis of whom 35 patients performed home dialysis at 180 days, resulting in a PPV of 61%. Both the nephrologist and the social worker regarded few true home dialysis patients initially ineligible for home dialysis (Supplementary Table S2 & S3).

Discussion

In this study on a pre-dialysis programme, we disentangled the value of different questions and characteristics that are commonly addressed during preparation for

dialysis care. We identified and quantified the value of questions that best predicted uptake of home dialysis following a eligibility assessment. We present 4 key questions on suitable housing, self-care, social support and patient capacity for optimal selection of patients for home dialysis. These elements should also be addressed in subsequent education, especially if the lack of these elements prevents home dialysis to be seen as treatment option.

This study arose from the observation of a significant increase in the proportion of home dialysis patients in a centre that adopted a structured pre-dialysis programme.[12] Within this programme, we sought those elements that had the highest association with-long-term home dialysis treatment. We discovered that a selected set of questions, in combination with information gathered during a home visit, is very efficient for selecting patients for home dialysis during pre-dialysis education. A barrier in the uptake of home dialysis is the feeling of lack of family support.[16, 17] In our analysis, the simple question 'Does the patient have a strong social support system?' appears to be a good selection question for home dialysis.

Offering adequate treatment modality education is an important process involving multidisciplinary input. It is of utmost importance that patients are provided information on all forms of KRT, including home dialysis, and choose the treatment that suits them best in a process of shared decision making. In clinical practice, negative associations with home dialysis unintendedly expressed by nephrologists or dialysis nurses may guide the patient's decision and form barriers to home dialysis.[18] By identifying elements of a patient's social and physical condition that most clearly distinguish long-term home dialysis treatment, our approach has the potential to increase the efficiency of the pre-dialysis decision process while ensuring a shared decision.

In our study, 80% of patients were medically eligible for home dialysis, compared to 76 – 87% in other studies.[7, 9] The nephrologists in the teaching hospital of this study considered some conditions, e.g. large polycystic kidneys and previous abdominal surgery absolute contra-indications for PD, yet many studies showed that in similar patients PD can be performed with necessary precautions.[19, 20] In a previous study, it was mentioned that significant variation in eligibility assessments among centres existed.[7] This practice variation in medical eligibility for home dialysis urges the need for more guidelines on contra-indications for home dialysis, especially in respect of the

increasing number of elderly patients with chronic kidney disease.[2] Elderly patients are often frail and more frequently have multiple comorbidities and thus might be considered ineligible for home dialysis treatment.[21] However, PD might be an excellent therapy option in elderly patients with for example hemodynamic instability.[20] Frail patients might need the assistance of caregivers or homecare workers, but with options for assisted PD home dialysis is also a feasible option for such patients.[22]

In the presented programme, three phases can be distinguished: the collection of information about the patient by nephrologist and the social worker and the general education session. Several studies suggest that a multi-step pre-dialysis programme is associated with a higher percentage of home dialysis patients. Shukla *et al.* 2017 found that a group education session followed by an individual session led to a steep increase in the number of patients starting home dialysis (38%).[4] Manns *et al.* 2005 randomized patients between standard education and an educational intervention including a group education session, combined with standard education. [23] They reported that patients in the intervention group opted for home dialysis and self-care haemodialysis significantly more often. Velasco *et al.* 2015 reported that the multicentre implementation of an education programme, consisting of an education session at home and multiple reflective sessions, resulted in a PD incidence of 48%, as opposed to the national-PD incidence of 15% in Spain.[24] Of interest, this was the only study of these 3 articles on multi-step pre-dialysis programmes, that reported the incidence rate of patients choosing conservative care. They reported a rate of 5%, while the incidence was 21% in our study. This underscores that our pre-dialysis programme provides optimal informed decision making on all KRT programs *and* conservative care.

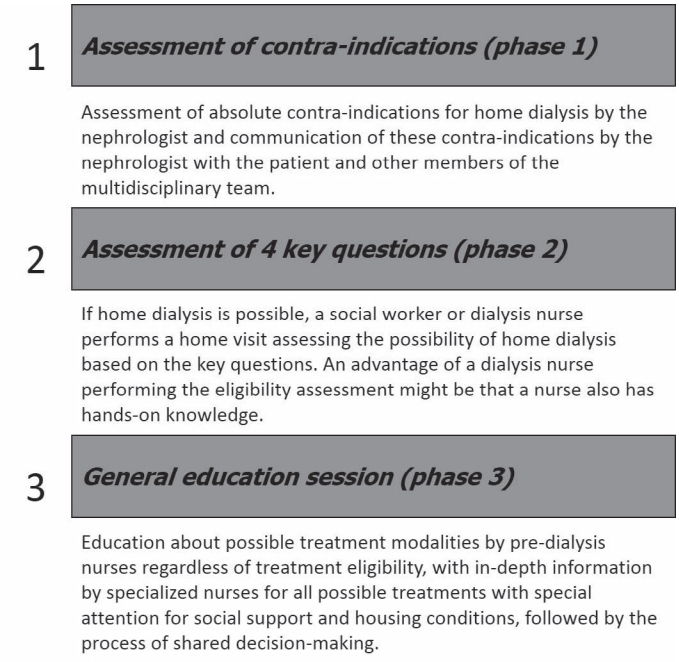

Figure 4. Proposed sequence in a structured pre-dialysis programme

To provide a practical workflow in pre-dialysis care, based on the experience collected in this study, one could adopt the following sequence of three-phase pre-dialysis programme (Figure 4). In this scenario, the professional knowledge of the nephrologist in assessing which patient *cannot* perform home dialysis for medical reasons is combined with the specific expertise of the social worker or dialysis nurse in determining which patient *can* perform home dialysis. We considered that a home visit was an important addition to this program to satisfactorily assess the suitability of housing for home dialysis. But a home visit might also help to inform and reassure the social system surrounding the patient. In a study evaluating treatment modality education at home, family members that were present demonstrated improved understanding of dialysis and experienced fewer concerns and fears.[25]

A limitation of this study is that data were collected during the implementation of a new structured pre-dialysis programme in a single centre and that our study analysed the elements of this programme retrospectively. Therefore, we were unable to examine the influence of different professionals on treatment decision nor the added value of a home visit instead of office consultations, whether verbal and non-verbal

communication played a role in the treatment decision and whether other related factors correlating with home dialysis not measured in the questionnaire affected the assessment of eligibility (residual confounding). The questionnaires used were not validated for construct validity or reliability. Also, we did not investigate whether it makes a difference which health care professional assesses the four key questions. However, as some questions are best answered during a home visit, we think that the home visit rather than the social worker should play a central role in a pre-dialysis programme. A home visit could not be performed in every patient, but as the home visit was performed in 85% of patients we believe that our conclusion about this part of pre-dialysis care is sufficiently well-founded.

Since certain questions involve a direct judgement by the social worker and are thus dependent on his expertise, a next step would be the validation of the key questions with assessments by other health professionals including dialysis nurses in external cohorts. Future studies might also specifically evaluate the effect of age and frailty on the treatment decision, as the number of elderly patients with chronic kidney disease increases.

The strength of this study includes the long follow-up period. Home dialysis was intentionally defined as a home modality at 180 days after start of dialysis, to enable inclusion of late home dialysis starters. This definition is likely a reflection of the long-term dialysis modality. At 180 days after dialysis initiation as compared to 90 days after dialysis initiation, we were able to select 2 extra home HD patients. In addition, another strength of this study includes using clinimetrics to reduce a large number of questions to 4 key elements that can be easily assessed during a pre-dialysis programme.

In conclusion, if there are no contraindications for home dialysis and a patient prefers this treatment, then a selection process including 4 key questions on suitable housing, self-care, social support, and patient capacity, if possible addressed during a home visit, is an optimal way to assess a patient's eligibility for home dialysis. This strategy helps to do justice to the wish of many patients to be treated, or in fact treat themselves, with a dialysis modality at home.

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Supplemental material

Appendix A1. Questionnaire Patient

Questions	Answer options
Are you in a relationship?	Y/N
Do you live together with your partner?	Y/N
Is your partner in good health, or is he/she limited in the activities that he/she can do?	*Good health/limited*
Do you have children?	Y/N
How many children do you have	*number*
Do you live together with your children?	Y/N
How many children still live at home?	*number*
Do you have siblings?	Y/N
Do you receive home care service?	Y/N
How many hours a week do you receive home care service?	*number*
Do you receive informal care from a caregiver?	Y/N
How many hours a week do you receive informal care from a caregiver?	*number*
Do you have people in the household to help you?	Y/N
Are you a homeowner?	Y/N
What type of home do you live in?	*house, apartment/flat, retirement condo, other*
If you live in an apartment, is there an elevator in the building?	Y/N
Does your property have stairs?	Y/N
What is your level of education?	*primary education, secondary education, further education, higher education*
Are you currently employed?	Y/N
How many hours do you work a week?	*number*
How would you rate your quality of life?	*Scale 1-10*
How would you rate your current health?	*Scale 1-10*
Do you have any other conditions/diseases besides your kidney failure?	Y/N
Do you feel like you have sufficient energy to do the things you want to do throughout the day?	Y/N
Do you have trouble breathing?	Y/N

Appendix A1. Questionnaire Patient (continued)

Questions	Answer options
The following questions belong to the KATZ-scale	*Scale 0-6*
BATHING	*Independence/dependence*
DRESSING	*Independence/dependence*
TOILETING	*Independence/dependence*
TRANSFERRING	*Independence/dependence*
CONTINENCE	*Independence/dependence*
FEEDING	*Independence/dependence*

Appendix A2. Questionnaire social worker

Questions	Answer options
Does the residence have enough space available for a dialysis machine/ equipment? (2 square meters)	Y/N
Does the residence have enough space available for the necessary (dialysis) supplies/materials? (1 cubic meter)	Y/N
Does the residence contain a residual current device?	Y/N
Are water supply and drainage systems present on the floor where dialysis may take place?	Y/N
Are the hygienic conditions in the residence sufficient for home dialysis?	Y/N
Have prior adaptations been made to the residence to aid in activities of daily living?	Y/N
Does the patient have an internet connection?	Y/N
Is the patient's residential housing suitable for home dialysis?	Y/N
What means of transport does the patient use for traveling?	*Patient drives car, public transport, patient transport*
Does the patient have an active lifestyle (do his/her daily activities make successful home dialysis likely)?	Y/N
Is the patient's understanding of their illness good?	Y/N
Does the patient have auditory or visual impairments that would hinder home dialysis?	Y/N
Does the patient's current physical health state allow for home dialysis?	Y/N
Have any major life events occurred in the patient's life in the past year?	Y/N
Does the patient's current mental health state allow for home dialysis?	Y/N
Are there sufficient financial resources (monetary or material) for home dialysis?	Y/N
Is the patient able to carry the burden of home dialysis?	Y/N
Can the patient's partner bear the extra burden of home dialysis?	Y/N

Appendix A2. Questionnaire social worker (continued)

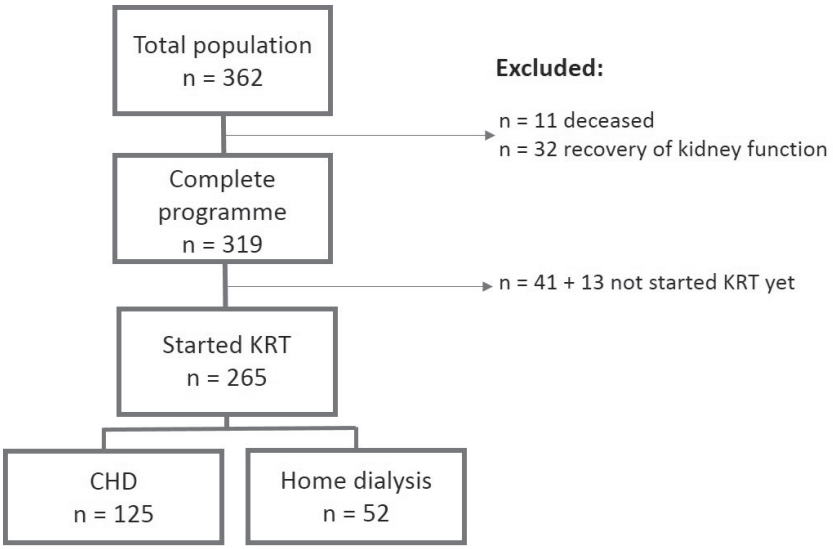
Questions	Answer options
Does the patient have a strong social support system, i.e. is the patient's social network supportive for home dialysis?	Y/N
Is the patient able to bear the extra workload of home dialysis, i.e. do the patient's personal and social circumstances allow for home dialysis?	Y/N

Appendix A3. Questionnaire nephrologist

Questions	Answer options
Does the patient want to be eligible for kidney replacement therapy?	Y/N
Is renal transplantation an option for this patient?	Y/N
Did the patient undergo abdominal surgery?	Y/N
Does the type of abdominal surgery constitute an absolute contraindication for peritoneal dialysis?	Y/N
Does the patient have an abdominal wall defect?	Y/N
Is it possible to correct the abdominal wall defect?	Y/N
Is the patient obese (BMI >30 kg/m2)?	Y/N
Is the patient morbidly obese (BMI >35 kg/m2)?	Y/N
Does the patient's weight constitute an absolute contraindication for peritoneal dialysis?	Y/N
Does the patient have severe Chronic Obstructive Pulmonary Disease (GOLD 3/4)?	Y/N
Does the patient's COPD (GOLD 3/4) constitute an absolute contraindication for peritoneal dialysis?	Y/N
Is there an active inflammatory process in the abdomen?	Y/N
Does this inflammatory process constitute an absolute contraindication for peritoneal dialysis?	Y/N
Does the patient have polycystic kidney disease?	Y/N
Are the polycystic kidneys large?	Y/N
Do the kidney cysts constitute an absolute contraindication for peritoneal dialysis?	Y/N
Are there other relative contraindications for peritoneal dialysis?	Y/N
Are there other absolute contraindications for peritoneal dialysis?	Y/N
Does the patient have heart failure?	Y/N
What is New York Heart Association (NYHA) Functional Classification of the patient's heart failure?	*Scale 1 - 4*
Is the patient's heart failure a reason to recommend peritoneal dialysis?	Y/N
Is it possible to place a AV fistula or graft?	Y/N

Appendix A3. Questionnaire nephrologist (continued)

Questions	Answer options
Is vascular access possible?	Y/N
Are there other relative contraindications for haemodialysis?	Y/N
Are there other absolute contraindications for haemodialysis?	Y/N
Does the patient exhibit non-cooperative behaviour that precludes home dialysis?	Y/N
Are there other relative contraindications for home dialysis?	Y/N
Are there other absolute contraindications for home dialysis?	Y/N
Are there other relative contraindications for in-centre haemodialysis?	Y/N
Are there other absolute contraindications for in-centre haemodialysis?	Y/N



Supplementary Figure 1. Flow-chart of the total number of patients that started dialysis following the structured pre-dialysis program
KRT, kidney replacement therapy

Supplemental Table 1. Final eligibility assessment of both nephrologist and social worker

	Social worker: eligible for home dialysis	Social worker: ineligible for home dialysis	TOTAL
Nephrologist: eligible for home dialysis	49	34	83
Nephrologist: ineligible for home dialysis	8	44	52
TOTAL	57	78	135

Supplemental Table 2. Eligibility assessment by the nephrologist compared to treatment at 180 days

	Treatment Home	Treatment CHD	TOTAL
Nephrologist: eligible for home dialysis	37	46	83
Nephrologist: ineligible for home dialysis	3	49	52
TOTAL	40	95	135

CHD, in-centre haemodialysis.

Supplemental Table 3. Eligibility assessment by the social worker compared to treatment at 180 days

	Treatment Home	Treatment CHD	TOTAL
Social worker: eligible for home dialysis	35	22	57
Social worker: ineligible for home dialysis	5	73	78
TOTAL	40	95	135

CHD, in-centre haemodialysis.

Part II

Enhancing technique survival of home dialysis

Chapter 5

Differences in hospitalization between peritoneal dialysis and haemodialysis patients

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Abstract

Background Dialysis is associated with frequent hospitalizations. Studies comparing hospitalizations between peritoneal dialysis (PD) and hemodialysis (HD) report conflicting results and mostly analyze data of patients that remain on their initial dialysis modality. This cohort study compares hospitalizations between PD and HD patients taking into account transitions between modalities.

Methods The retrospective Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes collected hospitalization data of patients who started dialysis between 2012 and 2017. Primary outcome was hospitalization rate, analyzed with a multi-state model that attributed each hospitalization to the current dialysis modality. Secondary outcomes were risk for first hospitalization, number of hospitalizations, number of hospital days per patient-year, and causes of hospitalizations.

Results In total, 695 patients (252 PD and 443 HD at 3 months) treated in 31 Dutch hospitals were included. The crude hospitalization rate for PD was 2.3 (±5.0) and for HD 1.4 (±3.2) hospitalizations per patient-year. The adjusted hazard ratio for hospitalization rate was 1.1 (95%CI 1.02-1.3) for PD compared to HD. The risk for first hospitalization was 1.3 times (95%CI 1.1-1.6) higher for PD compared to HD during the first year after dialysis initiation. The number of hospitalizations and number of hospital days per patient-year were significantly higher for PD. The most common causes of PD and HD hospitalizations were peritonitis (23%) and vascular access-related problems (33%), respectively.

Conclusion PD was associated with higher hospitalization rate, higher risk for first hospitalization, and higher number of hospitalizations compared to HD.

Introduction

Dialysis treatment for end-stage kidney disease (ESKD) is associated with high morbidity, frequently resulting in hospitalization.[1-4] The hospitalization rate of dialysis patients varies between 1.2 – 1.7 per patient-year, compared to 0.8 per patient-year for patients with a kidney transplant.[2, 5] Dialysis patients also have a higher risk of readmission, with a hazard ratio of 1.8 for readmission within one year compared to a control group of patients without kidney disease.[2, 6] Infections and cardiovascular diseases are the leading causes for hospitalization in dialysis patients.[2, 7, 8]

Hospitalization is an indirect measure of morbidity in dialysis patients, as well as a risk factor for mortality.[6, 9] Also, hospitalization negatively affects the quality of life and increases the costs of dialysis.[7, 10, 11] Hospitalization costs are one of the most expensive elements of dialysis treatment.[10-12] Therefore, prevention of hospitalization of dialysis patients is of utmost importance.

Differences in hospitalization between peritoneal dialysis (PD) and haemodialysis (HD) patients have been the subject of previous studies. However, there are several problems with these studies. First, they report conflicting results with studies describing an equal number and duration of hospital admissions for PD patients compared to HD patients[13-16], while other studies conclude that PD patients are more likely to be hospitalized.[3, 5, 17-21] Second, most studies do not take into account the time on dialysis, which also seems to affect hospitalization rates. The hospitalization rate for HD patients is highest during their first year of dialysis with a decrease thereafter, while PD patients experience an increase in hospitalization rate as their dialysis duration progresses, according to the 2018 report from the United States Renal Data System (USRDS).[2] Finally, and most importantly, most studies only analyse data from patients who remain on their initial dialysis modality or do not take transitions between dialysis modalities into account.[3, 13-15, 18, 19, 21] However, a transition from one dialysis modality to another, for example from PD to HD, occurs frequently in daily practice. Analysing only the data of patients who continue their original dialysis modality introduces selection bias in the results reported. Therefore, the aim of this study was to compare hospitalizations between incident PD and HD patients taking into account transitions between dialysis modalities and time on dialysis.

Methods

Study population

The Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO) is a multi-centre cohort study among dialysis patients in the Netherlands. For this analysis, retrospectively collected hospitalization data from a cohort of patients from 31 hospitals were used. Eligible patients were adults (≥ 18 years) who started dialysis treatment (i.e. PD or HD) between January 1, 2012 and January 1, 2017 with a minimum dialysis treatment duration of 3 months. Patients were allowed to have had previous kidney replacement therapy in the form of (dialysis followed by) kidney transplantation. Follow-up of patients was conducted until after kidney transplantation, a patient's wish to stop dialysis, death, or the end of the study period on January 1, 2017. The study was approved by local medical ethics committees of the participating dialysis centres.

Baseline characteristics

Baseline characteristics were collected at dialysis initiation. For the baseline data, patients were grouped according to their dialysis modality (i.e. PD or HD) at 3 months after dialysis initiation. Primary kidney disease was classified according to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) codes and categorized into: glomerulonephritis/pyelonephritis, cystic kidney disease, renovascular kidney disease, diabetes mellitus, and other/unknown.[22] Comorbidities were classified according to both the Charlson Comorbidity Index (CCI) and the Davies score.[23, 24] Kidney replacement therapy vintage and dialysis vintage were presented as the months that patients received kidney replacement therapy (i.e. kidney transplantation and dialysis combined) or dialysis alone in the past. Residual glomerular filtration rate was calculated as the creatinine clearance (ml/min), using creatinine measurements in blood and 24 hours urine collections. Patients were indicated as acute starters if they had never been under outpatient monitoring by a nephrologist prior to initiation of dialysis.

Hospitalization

Hospitalization was defined as a hospital admission with a minimum duration of 24 hours. The start and end dates of each hospitalization were recorded along with the reason using ICD-10 codes.[25] The primary outcome was hospitalization rate, which was defined as the number of hospitalizations per patient-year. Patient-years were

defined as the number of years a patient performed a dialysis modality within the study period.

Secondary outcomes were risk for first hospitalization, total number of hospitalizations per patient, number of hospital days per patient-year, and causes of hospitalization. Causes of hospitalization were grouped into the following categories: access-related (including vascular access infection, fistula operation, and PD catheter leakage, exchange or removal), peritonitis, fluid overload, cardiac disease (including myocardial ischemia or infarction, cardiac arrest or arrhythmia, cardiac failure, and hemorrhagic pericarditis), vascular disease (including pulmonary embolus, stroke, cerebrovascular hemorrhage, ruptured vascular aneurysm, mesenteric infarction, and peripheral vascular disease), non-dialysis related infection, gastrointestinal disease (excluding PD peritonitis), malignancy, transplantation, and other/unknown.

Statistical analysis

Baseline characteristics were presented as mean with standard deviation (SD), median with interquartile range (IQR) or as number with percentages. Groups were compared with a Chi-square test, an independent samples t-test or Mann–Whitney U test, where appropriate.

Since patients can transition between dialysis modalities over time (i.e. PD patients transition to HD or HD patients transition to PD), all analyses were performed with models that allow for such transitions. Hospitalization rate was analysed with a multi-state model with recurrent events, which attributed every hospitalization to the dialysis modality the patient performed at the time of admission. Patients who died were censored. The results of this model are presented with hazard ratios (HR).

The risk for first hospitalization was analysed with a Cox regression model with dialysis modality as time varying covariate. The proportional hazards assumption was tested and if it was violated, data were presented for two different time periods. Number of hospitalizations and number of hospital days per patient-year were analysed with negative binomial regression. The last two outcomes were analysed in a multilevel model, in which dialysis modality was the first level and the patient the second level. This analysis thus corrected for the dependency of both dialysis modalities within the same patient.

All analyses were adjusted for potential confounders. In the first model, adjustments were made for age and sex, in a second model data were also adjusted for CCI, dialysis vintage, and acute start of dialysis. Statistical analyses were conducted with IBM SPSS Statistics version 25 and R version 3.6.1.

Results

Baseline characteristics

The study cohort consisted of 695 dialysis patients, of whom 252 (36%) were receiving PD and 443 (64%) HD at 3 months after dialysis initiation. Baseline characteristics are presented in Table 1. Mean age was 63.0 (± 15.3) years for both groups, and the majority of patients were male. The comorbidity scores were similar between PD and HD patients. PD patients had a dialysis vintage of 16 months [IQR 9 – 41], whereas HD patients had a significantly longer dialysis vintage of 39 months [IQR 19 – 64]. PD patients less often had a previous kidney transplant compared to HD patients, 10% and 25% respectively (p<0.001). Only 4% of the PD patients had an acute start of dialysis, whereas 20% of HD patients did (p<0.001). Just over half of the patients performed PD themselves; the rest were assisted by a nurse or other caregiver at home.

Table 1. Baseline characteristics according to dialysis modality at 3 months.

Variable	Full sample n=695	PD n=252	HD n=443
Age (yr), mean ± SD	63.0 ± 15.3	63.1 ± 14.9	62.9 ± 15.6
Sex (male), n (%)	418 (60)	160 (64)	258 (58)
Ethnic background, n (%)			
Caucasian	395 (57)	149 (59)	246 (56)
Other	123 (18)	30 (12)	93 (21)
Unknown	177 (25)	73 (29)	104 (23)
Primary kidney disease, n (%)			
Glomerulonephritis/pyelonephritis	141 (20)	39 (16)	102 (23)
Cystic kidney disease	38 (6)	19 (8)	19 (4)
Renovascular kidney disease	193 (28)	71 (28)	122 (28)
Diabetes mellitus	119 (17)	49 (19)	70 (16)
Other/unknown	204 (29)	74 (29)	130 (29)
BMI (kg/m^2), mean ± SD	26.8 ± 5.5	26.6 ± 4.7	26.9 ± 6.0

Table 1. Baseline characteristics according to dialysis modality at 3 months. (continued)

Variable	Full sample n=695	PD n=252	HD n=443
Smoking, n (%)			
Yes	117 (17)	42 (17)	75 (17)
Quit	172 (25)	67 (27)	105 (24)
Unknown	103 (15)	36 (14)	67 (15)
CCI score, n (%)[a]			
2	208 (30)	84 (33)	124 (28)
3 – 4	281 (41)	97 (39)	184 (42)
≥ 5	204 (29)	71 (28)	133 (30)
Davies score, n (%)			
0	182 (26)	77 (31)	105 (24)
1 – 2	370 (53)	125 (50)	245 (56)
≥ 3	141 (20)	50 (20)	91 (21)
KRT vintage (months), median [IQR][b]	150 [64-212]	138 [44-181]	154 [69-230]
Dialysis vintage (months), median [IQR][c]	35 [15-58]	16 [9-41]	39 [19-64]
Previous transplant, n (%)	138 (20)	26 (10)	112 (25)
Residual GFR (ml/min), median [IQR]	7.8 [4.6-11.6]	9.5 [6.7-12.9]	6.6 [3.3-10.4]
Residual diuresis (ml/day), mean ± SD	1459 ± 841	1708 ± 743	1317 ± 862
Acute start of dialysis, n (%)	98 (14)	11 (4)	87 (20)

PD= peritoneal dialysis; HD= haemodialysis; SD=standard deviation; CCI= Charlson comorbidity index; KRT= kidney replacement therapy; IQR=interquartile range; GFR= glomerular filtration rate.
* Groups were compared with a Chi-square test, an independent samples t-test or Mann–Whitney U test, where appropriate.
a. By definition, dialysis patients have a minimum CCI score of 2.
b. KRT vintage was only calculated for the 159 patients (23%) who received previous kidney replacement therapy: 33 PD patients (13%) and 126 HD patients (28%)
c. Previous dialysis treatment was only calculated for the 148 patients (21%) who received dialysis before inclusion: 30 PD patients (12%) and 118 HD patients (27%)

Dialysis treatment and follow-up

The median dialysis duration for the entire study cohort was 22.0 months [IQR 11.1 – 36.4]. PD patients had a shorter dialysis duration [19.1 months , IQR 10.4 – 30.5] than HD patients [23.6 months, IQR 11.7 – 38.6] (p=0.001). Patients transitioned more often from PD to HD (33%), than from HD to PD (11%) (p<0.001).

Hospitalization rate

A total of 521 hospitalizations took place during PD, while 959 hospitalizations took place during HD. The crude hospitalization rate for PD was 2.3 (± 5.0) hospitalizations per patient-year and for HD 1.4 (± 3.2) hospitalizations per patient-year. Using a multi-state model, the adjusted HR for hospitalization rate was 1.1 (95% confidence interval (CI) 1.02 – 1.3) for PD compared to HD patients (Table 2).

Table 2. Comparison of hospitalization rate (hospitalizations per patient-year) and risk for first hospitalization.

Dialysis modality	Crude HR (95% CI)		Adjusted* HR (95% CI)		Adjusted** HR (95% CI)	
Hospitalizations per patient-year						
PD vs HD	1.1	(1.03 - 1.3)	1.1	(1.02 - 1.3)	1.1	(1.02 - 1.3)
Risk for first hospitalization during first year after dialysis initiation						
PD vs HD	1.3	(1.1 - 1.6)	1.3	(1.1 - 1.6)	1.3	(1.1 - 1.6)
Risk for first hospitalization ≥ 1 year after dialysis initiation						
PD vs HD	1.8	(1.4 - 2.5)	1.8	(1.4 - 2.5)	1.9	(1.4 - 2.5)

HR= hazard ratio; PD= peritoneal dialysis; HD= haemodialysis. The hospitalization rate was calculated with a multi-state model with recurrent events, which attributed every hospitalization to the dialysis modality the patient performed at the time of admission. The risk for first hospitalization was analysed with a Cox regression model with dialysis modality as time varying covariate.

* Adjusted for age and sex

** Adjusted for age, sex, Charlson Comorbidity Index, dialysis vintage, and acute start of dialysis

Risk for first hospitalization, number of hospitalizations, and number of hospital days per patient-year

Figure 1 shows the estimated cumulative incidence curves for the first hospitalization for PD and HD patients according to the Cox regression model. The model was adjusted for age, sex, CCI, dialysis vintage, and acute start of dialysis.

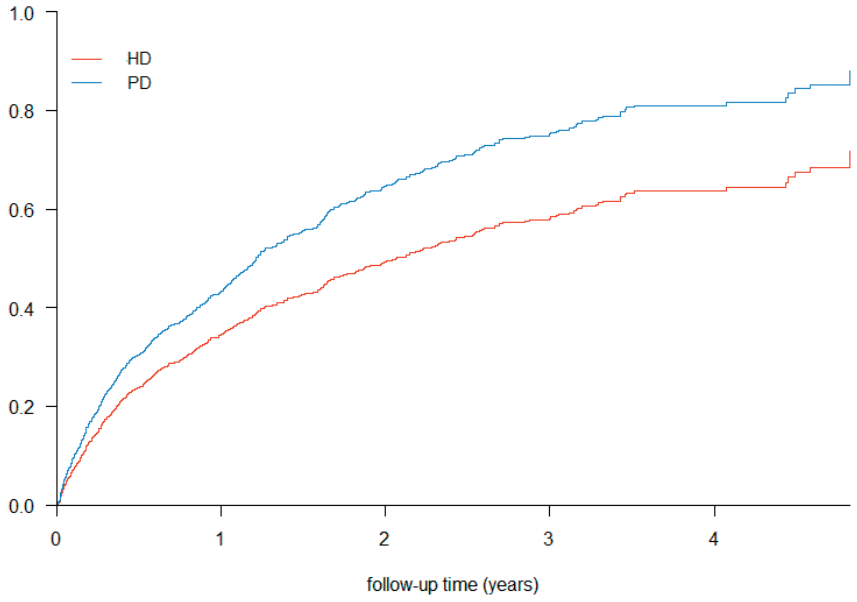

Figure 1. Risk for first hospitalization for PD and HD patients.

Estimated cumulative incidence curves for first hospitalization for PD and HD patients derived from a multi-state Cox regression model. Model is adjusted for age, sex, Charlson Comorbidity Index, dialysis vintage, and acute start of dialysis. PD= peritoneal dialysis; HD= haemodialysis.

Because the proportional hazards assumption was violated, HRs for risk for first hospitalization were calculated separately for the first year after dialysis initiation and for the period thereafter, conditional on having survived the first year. The adjusted HR for risk for first hospitalization during the first year was 1.3 (95% CI 1.1 – 1.6) for PD versus HD. For the period thereafter, the adjusted HR was 1.9 (95% CI 1.4 – 2.5) (Table 2).

The number of PD hospitalizations, corrected for the total PD duration, was significantly higher than the number of HD hospitalizations, corrected for the total HD duration (crude incidence rate ratio of PD relative to HD 1.3; 95% CI 1.1 – 1.6). Additional adjustments for age, sex, CCI, dialysis vintage, and acute start of dialysis resulted in a further increase in incidence rate ratio to 1.7 (95% CI 1.2 – 2.3) (Table 3).

The crude median number of hospital days per patient-year was 4.2 for PD patients [IQR 0 – 15.3] and 0.8 for HD patients [IQR 0 – 10.8]. The adjusted incidence rate ratio for number of hospital days per patient-year was 1.5 (95% CI 1.2 – 2.1) for PD compared to HD (Table 3).

Table 3. Comparison of number of hospitalizations and number of hospital days per patient-year.

Dialysis modality	Crude IRR (95% CI)		Adjusted* IRR (95% CI)		Adjusted** IRR (95% CI)	
Number of hospitalizations						
PD vs HD	1.3	(1.1-1.6)	1.7	(1.3-2.3)	1.7	(1.2-2.3)
Number of hospital days per patient-year						
PD vs HD	1.6	(1.2-2.1)	1.6	(1.2-2.1)	1.5	(1.2-2.1)

IRR= incidence rate ratio of PD relative to HD; PD= peritoneal dialysis; HD= haemodialysis.
* Adjusted for age and sex
** Adjusted for age, sex, Charlson Comorbidity Index, dialysis vintage, and acute start of dialysis

Causes

Causes of hospitalizations are presented in Table 4. The main cause for hospitalizations during PD treatment was peritonitis (23%), while the second most common cause were non-dialysis related infections (15%). The main cause for hospitalization during HD treatment was a vascular access-related reason (33%), such as a fistula operation or a dialysis access infection. The second most common cause for hospitalization during HD treatment were non-dialysis related infections (18%). For both PD and HD, hospitalizations for fluid overload were rare (2 – 3%).

Table 4. Causes of hospitalizations.

Causes	PD n=521	HD n=959
Access-related[a]	69 (13)	317 (33)
Peritonitis	117 (23)	N/A
Fluid overload	14 (3)	22 (2)
Cardiac disease[b]	57 (11)	87 (9)
Vascular disease[c]	28 (5)	50 (5)
Infection[d]	79 (15)	170 (18)
Gastrointestinal disease	46 (9)	94 (10)
Malignancy	9 (2)	25 (3)
Transplantation	13 (2)	25 (2)
Other / unknown	89 (17)	169 (18)

Data are presented as n (%). PD= peritoneal dialysis; HD= haemodialysis; N/A= not applicable.
Access-related includes vascular access infection, fistula operation, PD catheter leakage/exchange/removal.
Cardiac disease includes myocardial ischaemia/infarction, cardiac arrest/arrhythmia, cardiac failure, haemorrhagic pericarditis.
Vascular disease includes pulmonary embolus, stroke, cerebrovascular haemorrhage, ruptured vascular aneurysm, mesenteric infarction, peripheral arterial disease.
a. Non-dialysis related infections.

Discussion

In this retrospective cohort study among 695 dialysis patients, PD treatment was associated with a higher hospitalization rate, a higher risk for first hospitalization, a higher number of hospitalizations and a higher number of hospital days per patient-year compared to HD treatment, when hospitalizations were attributed to the dialysis modality the patient was receiving upon admission. In addition, PD hospitalizations were mainly caused by peritonitis, while vascular access-related reasons were the main causes for HD hospitalizations.

A higher PD hospitalization rate compared to HD is found in several other studies. Banshodani *et al.* retrospectively showed that emergency hospitalization rates for cardiovascular diseases and infectious diseases were significantly higher for 130 PD patients compared to 130 HD patients, with HRs of 2.70 (95% CI 1.53 – 4.77) and 4.16 (95% CI 2.59 – 6.68), respectively.[3, 21] Lafrance *et al.* also retrospectively showed

that infection-related hospitalization rates were significantly higher for PD patients compared to HD patients (HR 1.52, 95% CI 1.38 – 1.68).[18] Besides the fact that Banshodani *et al.* had a smaller study population than our study and Lafrance *et al.* investigated younger patients (HD 58.5 ± 16.4 years and PD 58.8 ± 14.5 years) during the period 2001 to 2007, both studies did not take transitions in dialysis modality into account. Banshodani *et al.* censored all patients who changed dialysis modality and Lafrance *et al.* attributed all hospitalizations of patients according to their dialysis modality at 90 days.[3, 18, 21] These studies defined patients according to a single dialysis modality, which does not do justice to daily practice at all.

That it is important to take transitions from and to different dialysis modalities into account is also shown in a study by Murphy *et al.*[17] In their prospective Canadian cohort, they showed that PD patients had a lower hospitalization rate (defined as the total number of hospitalization days relative to the survival of the patient) compared to HD patients (rate ratio 0.85, 95% CI 0.82 – 0.87) when hospitalizations were attributed to the dialysis modality at baseline, while they had a higher hospitalization rate (rate ratio 1.31, 95% CI 1.27 – 1.34) when hospitalizations were attributed to the dialysis modality at 3 months.[17] In addition, Murphy *et al.* performed an analysis in which hospitalizations were attributed to the dialysis modality the patient was receiving upon admission, which showed that PD treatment was associated with a higher hospitalization rate than HD treatment, with a rate ratio of 1.10 (95% CI 1.07 – 1.13).[17] This study advocated the use of treatment-received analyses in comparing hospitalization rates, which we did, instead of intention-to-treat analyses. However, our study defined hospitalization rate as the number of hospitalizations per patient-year, which is much more commonly used in studies, also investigated the risk for first hospitalization, and described a more recent study population.

In two Canadian cohorts, Quinn *et al.* and Oliver *et al.* used the number of hospitalization days per patient year for calculating their hospitalization rates. In their analyses with dialysis as time-varying covariate, they showed equal hospitalization rates for PD compared to HD (Quinn *et al.*: rate ratio 1.28, 95% CI 0.63 – 2.61. Oliver *et al.*: rate ratio 0.93, 95% CI 0.51 – 1.71).[8, 16] However, besides the fact that they used a different measure for hospitalization rate, which makes comparison with our study difficult, they did not investigate the risk for first hospitalization, and Oliver *et al.* only investigated patients on assisted PD. Several other studies showed that hospitalization rates of PD and HD patients are equal.[13-15, 19, 26] However, these studies

performed an intention-to-treat analysis by attributing hospitalizations of patients to their initial dialysis modality, which is not a valid analysis for the present research question, as argued above.

In our study, the main cause of PD hospitalizations was peritonitis, while HD hospitalizations were mainly vascular access-related. Also in a Japanese survey among 89,748 patients, these were most common causes for PD and HD hospitalizations.[20] Several other studies have identified infections and specifically peritonitis as an important cause for PD hospitalizations.[16, 18, 21, 27]

Apparently, PD patients have a higher risk for hospitalization than HD patients. This could be attributed to the dialysis modality per se, or could be the result of circumstantial factors. A possible explanation could be that the threshold for hospitalization is lower for PD than for HD patients. HD patients frequently visit the hospital for dialysis, in most cases at least three times a week for four hours. If, for example, they develop an infection, assessment and (start of) antibiotic treatment can easily be performed during the dialysis session in hospital. Moreover, the effect of the antibiotic treatment can be evaluated during the next scheduled dialysis session and adapted based on culture results. On the other hand, PD patients are treated at home and visit the hospital much less frequently. If they develop an infection, they must visit the hospital for evaluation. In addition, they have to attend the hospital again for evaluation of the treatment effect. It is conceivable that this need for frequent hospital visits could lead to a lower threshold for hospitalization in PD patients. Finally, we cannot exclude residual confounding as possible or additional explanation for finding a higher hospitalization risk in PD compared to HD.

To our knowledge, this is the first European study to describe several important hospitalization outcomes of PD and HD, taking into account transitions between dialysis modalities and thus properly showing the risk for hospitalization of the different dialysis modalities. Almost one-fifth of our population changed dialysis modality, underscoring that a model allowing this is superior to models evaluating hospitalizations on an intention-to-treat basis. Besides the fact that we used a multi-state model in a relatively large cohort of patients, we also describe a recent dialysis population, which is relevant because the composition of the dialysis population has changed in previous years, for example with respect to age.[28, 29] However, our study has some limitations. First, all types of admissions with a minimum duration of 24

hours were analyzed, possibly including admissions for PD training and vascular access procedures. Consequently, both PD and HD admissions might be overrated. Second, no center correction has been conducted, while the decision to admit a patient might differ between centers. Third, it should be noted that a very small number of hemodialysis patients were treated with home hemodialysis (n=45) and hospitalizations during this treatment (n=57) were counted among HD hospitalizations, which may have affected the results. Finally, the model we used, which allows transitions between dialysis modalities over time, was not compatible with competing risk regression models, whereas death should be considered a competing event. However, in our population, only 17 patients died without being hospitalised, while 140 patients died during or after at least one hospitalisation. Thus, we do believe that accounting for competing risks would not have altered our results.

In conclusion, our study shows that, when hospitalizations are attributed to the type of dialysis treatment upon admission, PD is associated with a higher hospitalization rate, a higher risk for first hospitalization, a higher number of hospitalizations and a higher number of hospital days per patient-year compared to HD. Since the PD hospitalizations were mainly caused by peritonitis, more attention to infection prevention is necessary for reducing the number of hospitalizations in the future.

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Chapter 6

Technique failure in peritoneal dialysis: modifiable causes and patient-specific risk factors

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Abstract

Background Technique survival is a core outcome for peritoneal dialysis (PD), according to SONG-PD. This study aimed to identify modifiable causes and risk factors of technique failure in a large Dutch cohort using standardized definitions.

Methods Patients who participated in the retrospective DOMESTICO cohort study and started PD between 2012 and 2016 were included, and followed until January 1st 2017. The primary outcome was technique failure, defined as transfer to in-center hemodialysis for ≥ 30 days or death. Death-censored technique failure was analyzed as secondary outcome. Cox regression models and competing risk models were used to assess the association between potential risk factors and technique failure.

Results A total of 695 patients were included, of whom 318 experienced technique failure during follow-up. Technique failure rate in the first year was 29%, while the death-censored technique failure rate was 23%. Infections were the most common modifiable cause for technique failure, accounting for 20% of all causes during the entire follow-up. Leakage and catheter problems were important causes within the first six months of PD treatment (both accounting for 15%). APD use was associated with a lower risk of technique failure (HR 0.66, 95% CI 0.53 – 0.83).

Conclusion Infections, leakage, and catheter problems were important modifiable causes for technique failure. As the first-year death-censored technique failure rate remains high, future studies should focus on infection prevention and catheter access to improve technique survival.

Introduction

Peritoneal dialysis (PD) is an established treatment for kidney failure, offering patients more flexibility and independence compared to in-center hemodialysis.[1, 2] Improving the technique survival of PD, i.e. preventing technique failure, remains a challenge despite advances in technique survival over the past decades.[3-5] In fact, technique survival was chosen as one of the five core outcomes for PD according to the Standardized Outcomes in Nephrology-Peritoneal Dialysis (SONG-PD) study.[6]

Identifying modifiable causes and risk factors of technique failure could contribute to develop strategies to improve PD technique survival. Previous research has identified causes and risk factors of technique failure during the first months of PD treatment.[7-9] Although technique failure after the first months of PD treatment is also relevant for the loss of prevalent PD patients, few studies have explored the various causes over an extended period of PD treatment.[10-12]

Moreover, comparing previous research on technique failure is hampered by the lack of standard definitions.[8] Technique failure is defined differently in almost every other study, especially in handling death as a cause of technique failure. Lan *et al.* therefore advocated the use of a standardized definition of technique failure, including both transfer to in-center hemodialysis (CHD) and death.[13] Few studies to date have used this standardized definition.[3, 7]

In addition, the characteristics of PD patients have changed over time and studies on technique failure in the current PD population are scarce. Therefore, this study aims to investigate the causes, risk factors, and center variation of PD technique failure in a recent Dutch cohort, all according to the standardized definitions.

Methods

Study design and research population

Patients were enrolled from the retrospective Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO), a multi-center cohort study in the Netherlands. In this study, 33 centers included PD patients, representing nearly two thirds of all dialysis centers in the Netherlands. Eligible patients were adults who

started PD between 1 January 2012 and 1 January 2017, and had a minimum PD treatment duration of 14 days. Patients who were previously treated with dialysis or kidney transplantation were also included. Patients who stopped dialysis or died within 30 days after dialysis initiation were excluded. Patients were followed until kidney transplantation, wish to stop dialysis, death or end of study period on 1 January 2017. Local medical ethics committees of all participating dialysis centers approved the study. Reporting of the study conforms to broad STROBE guidelines.[14]

Definition of PD technique failure

The primary outcome of this study was PD technique failure, defined as a transfer to CHD for ≥ 30 days, death on PD or death within 30 days after transfer to CHD, in accordance with the previously proposed standardized definition.[13] In patients with multiple episodes of technique failure, only the first episode of technique failure was analyzed. The following causes for technique failure were collected from the electronic patient charts: PD-related infections consisting of PD peritonitis and exit-site infections, catheter-related problems, clearance or ultrafiltration (UF) problems, peritoneal leakage, psychosocial problems, risk for or diagnosis of encapsulating peritoneal sclerosis (EPS), another reason, stop dialysis, and death.[15]

In addition, patients were stratified into an early and a late technique failure group. Early technique failure was defined as technique failure during the first 6 months after start of PD, and late technique failure was defined as technique failure that occurred more than 6 months after start of PD.[8, 9, 16]

Secondary outcomes were death-censored technique failure, death and permanent technique failure, the latter was defined as a transfer to CHD for ≥ 180 days, death on PD or death within 180 days after transfer to CHD.[13]

Covariates

Demographic, clinical, and dialysis-related data at dialysis initiation were collected from electronic patient charts. These included age, sex, ethnic background, employment status, smoking, body mass index (BMI), primary kidney disease, comorbid conditions, dialysis vintage, and kidney transplant history. PD modality, i.e. continuous ambulatory PD (CAPD) or automated PD (APD), was defined as the modality the patient used most of the time during follow-up. BMI was divided into three groups according to the WHO classification: BMI <25 kg/m^2, BMI 25 - 30 kg/m^2

(overweight), and BMI ≥30 (obese). Comorbid conditions were scored into three groups according to the Charlson Comorbidity Index (CCI): low (2 points, since patients with kidney failure by definition already have 2 points), intermediate (3-4 points), and severe comorbidity (≥5 points).[17] Causes of death, coded according to the ERA-EDTA coding system, were retrieved from the Dutch renal registry (RENINE).[18] For each participating center PD volume was calculated from data provided by RENINE, as mean annual number of prevalent patients, and divided into tertiles.[19] Variation in practice patterns were collected with an additional questionnaire that was send to the local investigators of the participating centers.

Statistical analysis

Baseline characteristics were expressed as number with percentages for categorical variables and as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Incidence of all-cause technique failure was presented as a Kaplan Meier curve. Cumulative incidence curves of cause-specific technique failure were calculated using a competing risk model.[20] Causes of early and late technique failure were shown as percentages.

To investigate the association between possible risk factors and technique failure, a cox regression model was conducted. This model was censored for kidney transplantation. BMI and PD modality were selected as potentially modifiable patient-specific risk factors according to literature.[3, 7, 9, 12, 16] Each potentially modifiable risk factor was adjusted for plausible predetermined confounders (age, sex, employment status, BMI, CCI, and center PD volume). The proportional hazard assumption was verified in the unadjusted models on the basis of Schoenfeld residuals and Kaplan Meier graphs. Several sensitivity analyses were conducted. First, a competing risk model was used to investigate the association between possible risk factors and technique failure in the presence of a competing event.[20] In such a model, a participant with the competing event (i.e. kidney transplantation) remains in the analysis. This model was also used to investigate the association between possible risk factors and death-censored technique failure, in which both kidney transplantation and death were competing events. Second, hypothesizing that PD modality at PD cessation might be different from PD modality used most of the time and be related to technique failure, in patients with technique failure the PD modality at PD cessation was used.

Finally, a funnel plot was constructed to evaluate the early technique failure rate of the participating centers, adjusted for age and sex. This is a graphical method to evaluate center performance with a reference standard, i.e. the overall early technique failure rate, and an indication of precision through control limits based on sample sizes.[21, 22] The early technique failure rate was chosen, because especially early failure is associated with catheter-related problems and thus possible modifiable causes.[8]

Missing confounders (maximum of 25% missing for BMI and CCI) were imputed using standard multiple imputation techniques in SPSS (10 repetitions and predictive mean matching). All analyses were performed using SPSS Statistics version 26 (IBM) or STATA 14 (StataCorp LP, College Station, TX). A p-value of < 0.05 was considered statistically significant.

Results

A total of 708 adult patients started PD treatment between 2012 and 2016 in the participating centers, of whom 13 patients were excluded since they had a total PD duration of less than 14 days. The study population thus consisted of 695 patients (See Flow diagram, Figure 1).

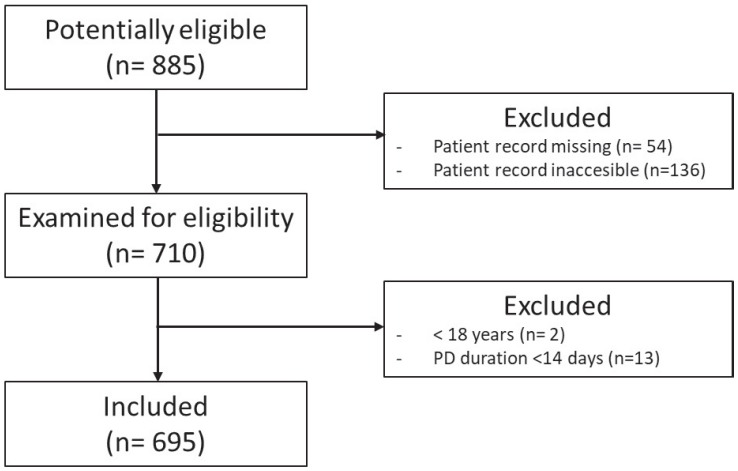

Figure 1. Flow chart of the patients included in the study

Baseline characteristics are presented in Table 1. Mean age at dialysis initiation was 62.9 ± 15.1 years and 27% of patients had a high CCI score indicating severe comorbidity. A history of previous dialysis was present in 15% of patients. APD was the predominantly used PD modality in 29% of patients with early technique failure and 53% of patients with late technique failure, reflecting common practice in the Netherlands to start PD therapy with CAPD. The median PD follow-up time for all patients was 13 months [IQR 6 – 22.2 months], with a minimum of 0 and a maximum of 59 months.

Table 1. Baseline characteristics of 695 patients treated with peritoneal dialysis

	All patients *n=695*	**Patients with technique failure** *n=318*	**Patients without technique failure** *n=377*	**p-value**
Age (yr), mean ± SD	62.9±15.1	64.8±14.8	61.4±15.1	0.003
Sex (male), n (%)	447 (64)	210 (66)	237 (63)	NS
Ethnic background, n (%)				NS
Caucasian	422 (61)	191 (60)	231 (61)	
Moroccan/Turkish	22 (3)	11 (4)	11 (3)	
Asian	39 (6)	15 (5)	24 (6)	
Afro-American	23 (3)	9 (3)	14 (4)	
Other/unknown	189 (27)	92 (29)	97 (26)	
Primary kidney disease, n (%)				NS
Glomerulonephritis	81 (12)	32 (10)	49 (13)	
Polycystic kidney disease	37 (5)	11 (4)	26 (7)	
Renovascular kidney disease	210 (30)	112 (35)	98 (26)	
Diabetes mellitus	123 (18)	58 (18)	65 (17)	
Other	183 (26)	84 (27)	99 (26)	
Unknown	61 (9)	21 (7)	40 (11)	
Employment status, n (%)	167 (28)	61 (22)	106 (32)	0.006
Current smoker, n (%)	111 (16)	52 (17)	59 (16)	NS
BMI (kg/m^2), mean ± SD	26.4±5.0	26.9±5.1	26.1±4.9	0.05
BMI, n (%)				NS
< 25 kg/m2	239 (46)	98 (42)	141 (49)	
25 – 30 kg/m2	177 (34)	85 (36)	92 (32)	
≥ 30 kg/m2	107 (20)	51 (22)	56 (19)	

Table 1. Baseline characteristics of 695 patients treated with peritoneal dialysis (continued)

	All patients *n=695*	Patients with technique failure *n=318*	Patients without technique failure *n=377*	p-value
Charlson comorbidity index, n (%)				
2 (low)*	168 (32)	58 (25)	110 (38)	0.001
3-4 (intermediate)	212 (41)	95 (41)	117 (40)	
≥5 (severe)	139 (27)	77 (33)	62 (21)	
Diabetes mellitus, n (%)	164 (32)	81 (35)	83 (29)	NS
Ischemic heart disease, n (%)	146 (28)	80 (35)	66 (23)	0.002
Heart failure, n (%)	69 (13)	38 (17)	31 (11)	NS
Vascular disease, n (%)	130 (23)	65 (26)	65 (21)	NS
History of dialysis at dialysis initiation, n (%)	103 (15)	39 (12)	64 (17)	NS
Dialysis vintage (months), median [IQR]	12 [1–36]	12 [4-37]	11 [1-33]	NS
History of kidney transplant at dialysis initiation, n (%)	73 (11)	29 (9)	44 (12)	NS
Kidney transplant (months), median [IQR]	120 [64-171]	99 [64-171]	135 [63-173]	NS
APD, n (%)	350 (50)	146 (46)	204 (54)	0.03

BMI, body mass index; APD, automated peritoneal dialysis; SD, standard deviation; IQR, interquartile range. Groups are defined according to the 30-day definition of technique failure.
* kidney failure alone represents a Charlson Comorbidity Index of 2 points

Incidence of technique failure

A total of 318 patients developed technique failure during the study, of whom 22 patients experienced a recurrent episode of technique failure. The PD patients experienced a mean of 0.36 episodes of technique failure per person–year of follow-up. The 1- and 2-year technique failure rates were 29% and 52% respectively (Figure 2A). The median time to technique failure was 1.85 years. Patients with technique failure were older, had higher comorbidity scores, were more likely to have ischemic heart disease, and were more frequently treated with CAPD (Table 1). A total of 202 patients developed death-censored technique failure during the study (0.24 episodes of death-censored technique failure per person-year). The 1- and 2-year death-censored technique failure rates were 23% and 35% respectively (Figure 2B). The median time to death-censored technique failure was 3.58 years.

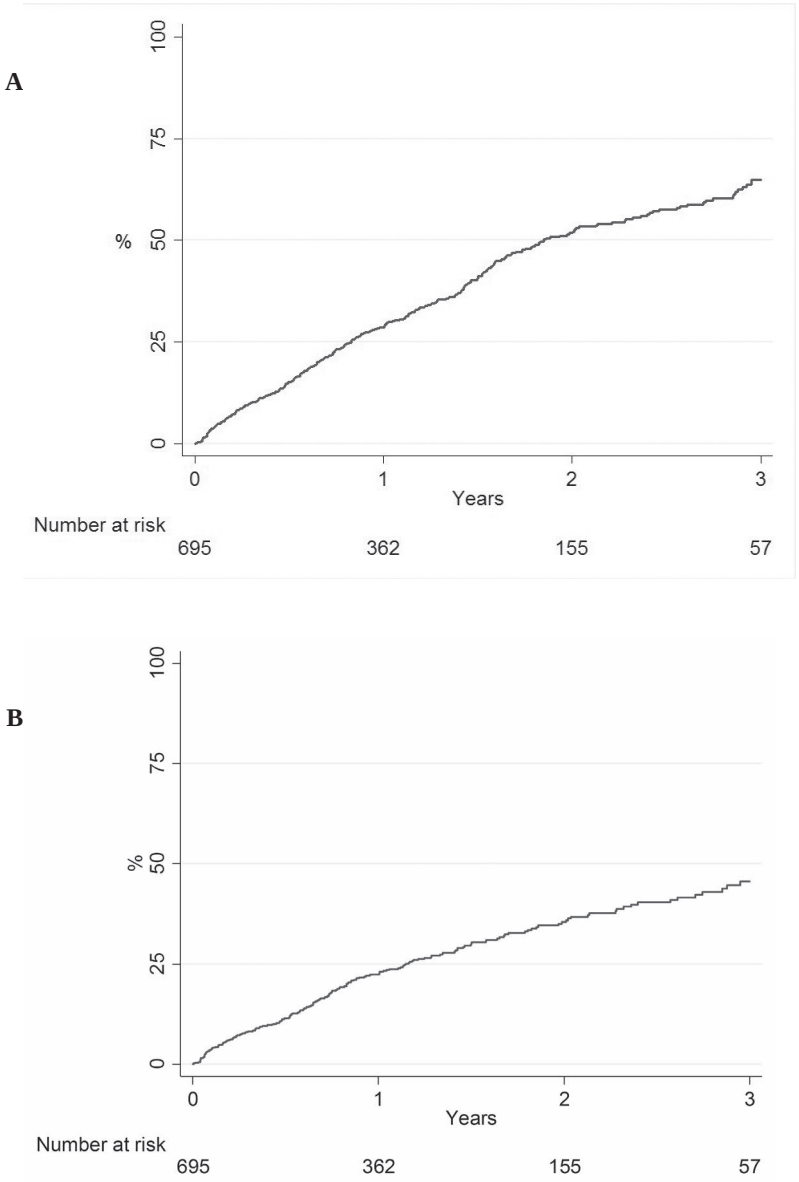

Figure 2. Technique failure, as a composite outcome (with transfer to CHD or death) (A) and as death-censored technique failure (B)**.** Technique failure was defined as a transfer to CHD for ≥ 30 days, death on PD or death within 30 days after transfer to CHD. First day of receiving CHD was the date assigned as technique failure.

Causes of technique failure

Figure 3 shows that death was the most common cause of technique failure, followed by PD-related infections (20%). The other causes of technique failure occurred in about 10% or less than 10% of the patients who experienced technique failure. The predominant causes for death were cardiovascular disease (28%), infections other than PD peritonitis (15%) and malignancies (13%). None of the deaths were attributable to a PD peritonitis.

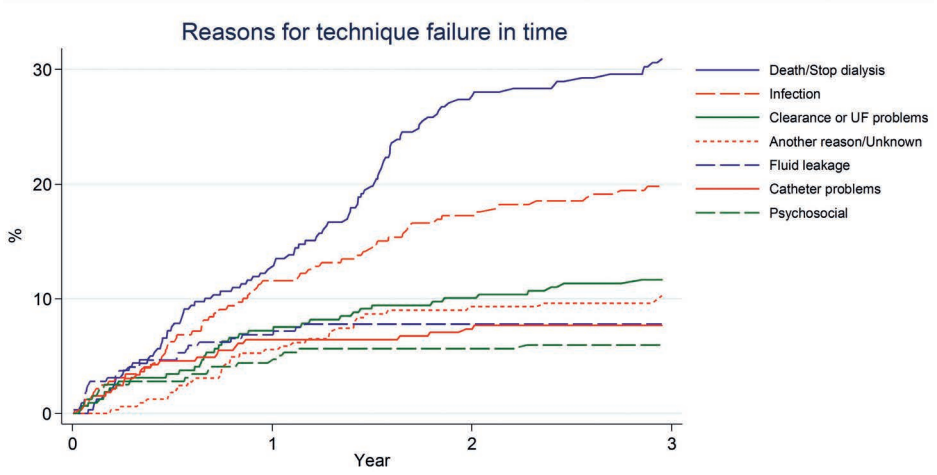

Figure 3. Cumulative incidence of different causes for technique failure
Shows the occurrence of different causes for technique failure over time in a population of patients with technique failure (n=318, 100%). UF, ultrafiltration.

Figure 4 shows the different causes of early (i.e. during the first 6 months after start of PD) and late (i.e. more than 6 months after start of PD) technique failure. A total of 99 patients developed early technique failure, and 219 patients developed late technique failure. Catheter-related problems were the cause of early technique failure in 15% of patients, whereas this was the cause of late technique failure in only 5% of patients. Similarly, PD fluid leakage was the cause in 15% and 5%, respectively. Infections and clearance problems were a major cause of both early and late technique failure; infections were in 20% of patients the cause of technique failure and clearance problems in 11–12% of patients. EPS was a cause of technique failure in less than 1% of patients. The group of 'other reasons' included (temporary) discontinuations of PD due to major (abdominal) surgery with hospitalization.

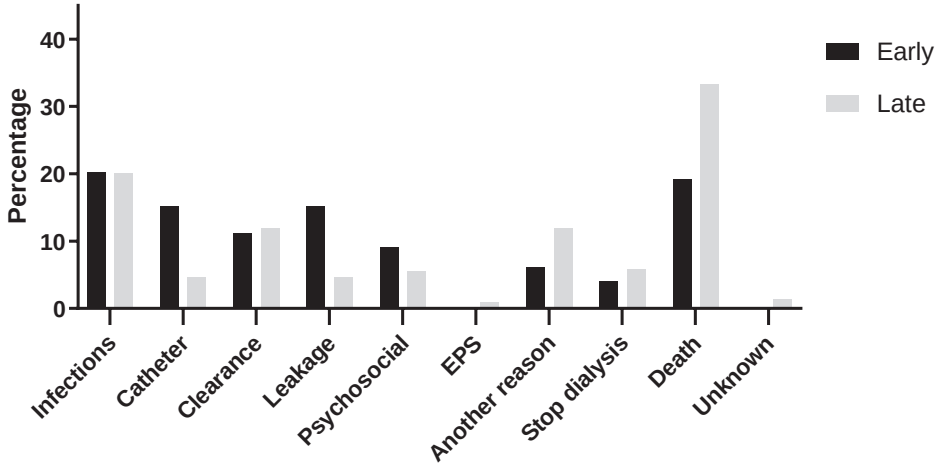

Figure 4. Comparison of causes of early and late technique failure
Early PD technique failure is defined as occurrence of technique failure in the first 6 months after start of PD (n=99). Late PD technique failure is defined as occurrence of technique failure more than 6 months after start of PD (n=219). EPS, encapsulating peritoneal sclerosis.

Risk factors

The patient-specific risk factors sex, age, employment status and BMI were not associated with technique failure (Table 2). APD compared to CAPD was associated with a reduced risk of technique failure (adjusted hazard ratio (HR) 0.66 (95% Confidence Interval (CI) 0.53 – 0.83). The patient-specific risk factors for death-censored technique failure were similar to those for technique failure including death in the definition (Supplementary Table S1); only APD was associated with a reduced risk of death-censored technique failure (adjusted HR 0.60, 95% CI 0.46 – 0.80). In addition, APD use was not associated with death as a separate outcome while age was associated with death (Supplementary Table S2).

Table 2. Patient-specific risk factors associated with technique failure in a Cox regression model

Risk factors	Crude HR (95% CI)	p-value	Adjusted model 1 HR (95% CI)	p-value	Adjusted model 2 HR (95% CI)	p-value
Male sex	1.15 (0.91 – 1.45)	0.24				
Age (10-year)	1.05 (0.97 – 1.13)	0.25				
Employed	0.80 (0.60 – 1.07)	0.13				
CCI						
low	Reference					
intermediate	1.41 (1.02 – 1.96)	0.04				
severe	1.81 (1.29 – 2.55)	0.001				
PD volume						
< 15 patients	Reference					
15-25 patients	1.05 (0.68 – 1.63)	0.83				
>25 patients	0.81 (0.53 – 1.24)	0.33				
BMI						
< 25 kg/m^2	Reference		Reference			
25 – 30 kg/m^2	1.21 (0.91 – 1.62)	0.20	1.17 (0.87 – 1.58)	0.31		
≥ 30 kg/m^2	1.21 (0.86 – 1.69)	0.28	1.23 (0.88 – 1.71)	0.22		
APD (vs CAPD)	0.66 (0.53 – 0.83)	<0.001	0.67 (0.54 – 0.84)	<0.001	0.66 (0.53 – 0.83)	<0.001

*M*odel 1 is adjusted for age and sex
Model 2 is adjusted for age, sex, employment status, BMI, CCI, and center PD volume
In this cox regression model both pre-selected potentially modifiable risk factors, BMI and PD modality, and all determinants used for adjustments are shown. HR, hazard ratio; BMI, body mass index; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCI, Charlson Comorbidity index.

The sensitivity analysis in which the association between patient-specific risk factors and technique failure was investigated with a competing risk model, showed similar results for these associations as the original analyses (Supplementary Table S3). In a sensitivity analysis using PD modality at PD cessation, similar results were found (for APD compared to CAPD, adjusted HR 0.60 (95% CI 0.47 – 0.75)).

Center variation in technique failure

All centers used icodextrin and antibiotic prophylaxis during PD catheter insertion (Supplementary Table S4). Most centers used neutral pH low glucose degradation products (GDP) solutions (91%) and exit site antibiotic prophylaxis (79%). The initial antibiotic regimen for peritonitis varied across centers and antifungal prophylaxis during antibiotic therapy was provided only in 6% of centers.

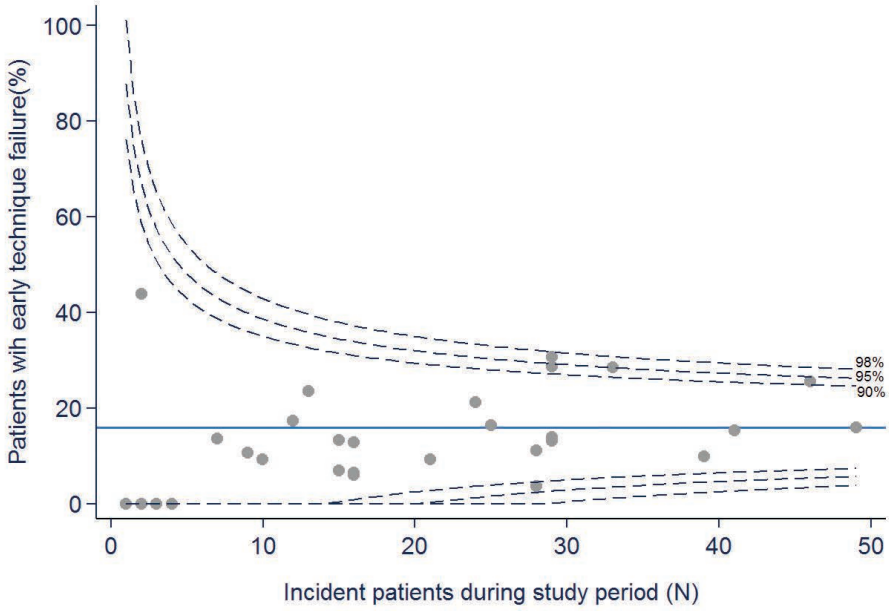

Figure 5. Funnel plot of early technique failure in incident study patients
Each circle represents the early technique failure rate for a participating center (n=31). Rates are adjusted for age and sex. The overall early technique failure rate is used as a reference (blue). The 90%, 95%, and 98% control limits are provided as dotted lines. Using the 95% control limit, one center with 29 incidents patients during the study period had a significantly higher early technique failure rate and performed worse than expected.

The center variation in technique failure rate is shown in Figure 5. The overall early technique failure rate, shown as the reference standard, was 16%, which is the total number of patients with early technique failure divided by the total number of PD patients from all centers that were not lost to follow-up at 6 months (due to transplantation or study end, *n* = 73). Most centers had an early technique failure rate around the overall rate of 16%. Four centers had a higher rate, of which only one center was outside the 95% control limits of the reference standard.

Permanent technique failure

A total of 254 patients developed permanent technique failure during the study: i.e. at 180 days after transfer to CHD they had not returned to PD (0.26 episodes of permanent technique failure per person-year). The 1- and 2-year permanent technique failure rate was 22% and 43% respectively (Supplementary Figure S1). The median time to permanent technique failure was 2.7 years. The most common cause of permanent technique failure was death, followed by infections. A total of 72 patients developed early permanent technique failure and 182 patients developed late permanent technique failure. Again, early technique failure was associated with catheter-related problems and leakage, while infection and clearance problems were important causes for both early and late technique failure (Supplementary Figure S2 and Supplementary Table S5).

Discussion

In this cohort of 695 Dutch patients who were treated with PD between 2012 and 2017, the technique failure rate within the first year of PD treatment was 29%. Death was the most common cause of technique failure. Death-censored technique failure rate at 1 year was 23%. In 20% of patients with technique failure, infections were a possible modifiable cause. In addition, early technique failure was frequently caused by catheter-related problems and leakage (both accounting for 15%). We found that APD use had a protective effect on technique failure.

Only few studies to date have used the standardized technique failure definition as proposed by L*an et al.*[3, 7, 13] See *et al.*, reporting on Australian patients that started PD between 2000 and 2014, also used the standardized 30-day definition and found a first year technique failure rate of 26%.[7] In an older study by Descoeudres *et al.*, not using

the standard definition but a similar definition of technique failure including death by any cause, the technique failure rate at 1 year was 25%.[23] The technique failure rate in our study is thus comparable to other studies that included death as a cause for technique failure. Death was the most common cause for technique failure during the entire follow-up, as would be expected in a study on dialysis patients since mortality rates of both PD and CHD patients are high.[24] Yet the death-censored technique failure rate was still high. This, in addition to the decline of the number of PD patients in the Netherlands, underscores the need to find modifiable causes for technique failure.

In recent decades, significant advances in PD treatment have declined the overall rate of technique failure.[3-5] Boyer *et al.* state that this is, in addition to improved patient survival, attributable to less infection-related technique failure.[5] Nevertheless, infections were still an important cause of technique failure - both in early and late technique failure - indicating that prevention of infections is pivotal in technique survival. Recommendations for the prevention of peritonitis from the ISPD, including exit-site prophylaxis and antibiotic prophylaxis during PD catheter insertion, were generally well followed by participating centers especially if compared to international data from PDOPPS.[25-27] In a recent study by PDOPPS, antibiotic prophylaxis during PD catheter insertion was indeed associated with a lower peritonitis risk.[28] On the other hand, most centers in the Netherlands did not use antifungal prophylaxis during antibiotic therapy although prophylaxis was associated with a significant risk reduction of fungal peritonitis in a systematic review.[29] According to the results of PDOPPS antifungal prophylaxis was also variably used across countries, the lowest in Japan (8% of facilities) and the highest in Australia (89%).[27] So a greater reduction in infections may be possible if all centers would adhere to current guidelines.

The ISPD guidelines refrain from recommending a specific antibiotic regimen for peritonitis based on a Cochrane systematic review due to lack of superiority.[25, 30] As a result, the initial antibiotic regimen varied across centers. Of note, one third of all centers used a combination with glycopeptides, possibly based on a systematic review in which glycopeptides were proven most effective in combination with ceftazidim.[31] Also in PDOPPS a variable use of vancomycin across countries has been reported.[27] However, because evidence for antibiotic regimens including glycopeptides remain weak[30], future clinical trials may evaluate good practices from single centers. Examples are temporary discontinuation of PD without removing the catheter (peritoneal rest) combined with intravenous meropenem and meropenem intracatheter as lock (Mero-

PerRest protocol) in case of enteric peritonitis and the treatment with amphotericin B catheter lock for salvage of the PD catheter in case of *Candida* peritonitis.[32, 33]

Catheter-related problems have been identified as an important cause of early technique failure in previous studies.[10, 23] In this study, we identified leakage as another important cause of early technique failure. This underscores the need for a multidisciplinary team with sufficient experience in catheter care and insertion.[34] In a study from Australia and New Zealand, small center volume - possibly indicative of low center experience - was associated with technique failure due to mechanical complications.[3] A striking variation in PD catheter survival among different centers in the UK suggests differences in access protocols.[15] Still, previous studies have not yielded results that could lead to recommendations for the preferred use of a catheter delivery technique or specific PD catheter type.[34, 35] The workgroup PD catheter access of PDOPPS hypothesize that standardized protocols for catheter insertion will be associated with a reduction of technique failure, the results of this working group are thus eagerly awaited.[15]

A possible other reduction in technique failure might be the increased interest in assisted PD due to the ageing dialysis population.[36] Within this demographic shift, assistance during PD treatment is a mean to provide home dialysis to elderly patients that may be unable to perform PD themselves due to frailty or physical impairments. In a recent study, family-assisted PD was associated with lower risk on catheter-related technique failure.[37] The authors hypothesized that involving family members in dialysis treatment may lead to better adherence to diet restrictions resulting in less constipation. Of note, in this study also a lower risk on technique failure due to clearance problems was found in both family assisted and nurse-assisted PD. The nurse or family member supervising the treatment likely ameliorates the patient's adherence to dialysis prescriptions.[37] Clearance problems, in our report the main cause of death-censored technique failure following infections, may thus also be perceived as a modifiable cause for technique failure. These aforementioned modifiable causes – infections, leakage, catheter-related problems and clearance problems - accounted for 48% of technique failure within our cohort, hence, quality improvements aimed at these causes can have a major impact on technique survival.

APD use had a protective effect on death-censored technique failure in our analysis, even after adjustments for age and comorbidity. In recent literature conflicting results have been presented: APD use was associated with an adjusted lower technique

failure rate and higher patient survival in one study[38], while in other studies APD use was associated with a higher risk of technique failure.[3, 7] There may be a link with infections, since CAPD use was associated with a higher rate of peritonitis in recent studies.[28, 39] Also in the only two randomized controlled trials to date - although originating from <2000 - higher peritonitis rates with CAPD use were found.[40, 41] This association with peritonitis might be due to better adaptation of therapy to patient needs, as the authors of a recent study suggest[39], or to fewer connections between catheter and dialysis bags when using APD instead of CAPD and thus less risk of breaching hygiene measures. Although the suggestion of fewer connections resulting in less infections is disputed[25], new devices that assists the patient are hypothesized to reduce infection risk.[42] APD might also be used more often by patients themselves than for assisted PD[37], which could explain the protective effect since self-care may be associated with a lower peritonitis rate.[43, 44] However, the association between APD use and technique failure may also reflect long-term PD treatment, as patients with early technique failure may not be able to transfer to APD (in other words: confounding by indication). In the Netherlands, most patients start PD treatment with CAPD to familiarize themselves with performing exchanges by hand prior to a transfer to APD. The reason for the protective effect of APD is thus uncertain, therefore the choice for APD or CAPD should ideally be based on patient preference.[25]

In a previous study from the Netherlands by Huisman *et al.*, smaller centers with on average less than 20 PD patients had a significantly higher risk of technique failure than larger centers.[45] The association between center volume and technique failure however likely reflects center experience.[16] Indeed, others confirmed that in larger centers technique failure due to modifiable causes, i.e. infections, catheter - and ultrafiltration problems, were less common.[46] Guillouët *et al.* found that center volume and patients characteristics alone could not fully explain the center effect on technique failure. They suggested that factors of center experience such as patient education and nephrologist's views on home dialysis play an important role in technique failure.[16] Contributing to this, we showed that the early technique failure rate – often caused by infections, leakage and catheter-related problems – was similar across all centers and was not related to the number of incident study patients. This probably indicates that it is not the center volume itself that matters, but the experience within a center and having a dedicated team.

In this study, technique failure consisted of a composite outcome of death and transfer to CHD, in accordance with the standardized definition.[13] Death is an objective measure but transfer to CHD is subjective; often a choice is made by the nephrologist to discontinue treatment and this decision will be weighed differently by each nephrologist. A considerable proportion of the causes of technique failure may have been modifiable, i.e. infections, leakage and catheter problems, since practice variation exists in peritonitis rate and in the treatment of infections and access.[27, 39] Because the definition of technique failure partly consists of the decision to discontinue PD, studies on infection prevention and catheter access such as the PDOPPS will help to increase technique survival.[15]

Strengths of this study include the use of the standardized definitions of technique failure, including the death-censored and permanent definition, the analysis of causes of both early and late technique failure, the use of a patient cohort reflecting current practice patterns and extensive adjustments for confounders. In addition, most studies were conducted on registry data whereas our cohort study enabled to identify the causes of technique failure in more detail. Yet, the study sample of this analysis was relatively small and the study was conducted in a single country. The study duration of this study was a respectable 5 years, yet the median follow-up duration was 13 months. As a result, the proportion of technique failure after 1 year should be interpreted with caution.

In conclusion, in this multi-center Dutch study of PD patients PD-related infections, leakage and catheter problems were important modifiable causes for technique failure. As almost a quarter of patients experience death-censored technique failure within the first year, future studies should emphasize on prevention of infections and PD catheter access problems to improve technique survival.

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Supplemental material

Supplementary Table S1. Patient-specific risk factors associated with death-censored technique failure in a competing risk analysis

Risk factors	Crude SHR (95% CI)	p-value	Adjusted model 1 SHR (95% CI)	p-value	Adjusted model 2 SHR (95% CI)	p-value
Male sex	1.14 (0.86 – 1.53)	0.36				
Age (10 year)	0.94 (0.86 – 1.03)	0.16				
Employed	1.07 (0.78 – 1.47)	0.69				
CCI						
low	Reference					
intermediate	1.15 (0.79 – 1.68)	0.47				
severe	1.13 (0.74 – 1.74)	0.57				
BMI						
< 25 kg/m^2	Reference		Reference			
25 – 30 kg/m^2	1.14 (0.80 – 1.62)	0.47	1.16 (0.82 – 1.63)	0.41		
≥ 30 kg/m^2	0.88 (0.57 – 1.37)	0.58	1.01 (0.67 – 1.52)	0.97		
APD (vs CAPD)	0.64 (0.49 – 0.84)	0.001	0.62 (0.47 – 0.81)	0.001	0.60 (0.46 – 0.80)	<0.001

Model 1 is adjusted for age and sex
Model 2 is adjusted for age, sex, employment status, BMI, CCI, and center PD volume
SHR, subdistribution hazard ratio; BMI, body mass index; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCI, Charlson Comorbidity index.

Supplementary Table S2. Patient-specific risk factors associated with death in a Cox regression model

Risk factors	Crude HR (95% CI)	p-value	Adjusted model 1 HR (95% CI)	p-value	Adjusted model 2 HR (95% CI)	p-value
Male sex	1.14 (0.78 – 1.67)	0.51				
Age (10 year)	1.40 (1.20 – 1.63)	<0.001				
Employed	0.34 (0.18 – 0.66)	0.001				
CCI						
low	Reference					
intermediate	2.41 (1.24 – 4.67)	0.009				
severe	4.27 (2.22 – 8.19)	<0.001				
BMI						
< 25 kg/m^2	Reference		Reference			
25 – 30 kg/m^2	1.33 (0.79 – 2.23)	0.28	1.16 (0.68 – 1.97)	0.59		
≥ 30 kg/m^2	1.92 (1.12 – 3.30)	0.02	1.62 (0.97 – 2.71)	0.07		
APD (vs CAPD)	0.74 (0.52 – 1.07)	0.11	0.83 (0.57 – 1.20)	0.32	0.87 (0.59 – 1.27)	0.46

Model 1 is adjusted for age and sex
Model 2 is adjusted for age, sex, employment status, BMI, CCI, and center PD volume
HR, hazard ratio; BMI, body mass index; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCI, Charlson Comorbidity index.

Supplementary Table S3. Patient-specific risk factors associated with technique failure in a competing risk analysis

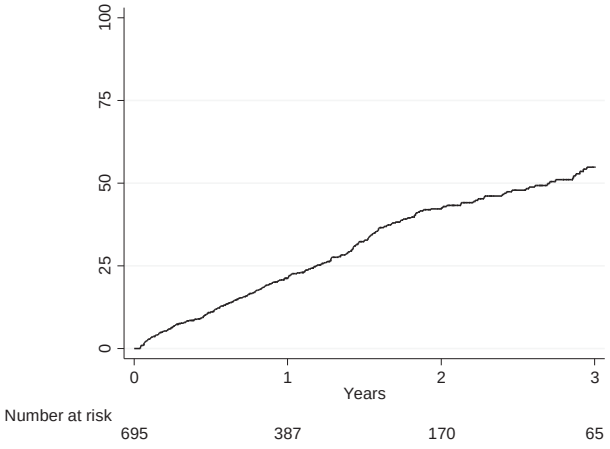
Risk factors	Crude SHR (95% CI)	p-value	Adjusted model 1 SHR (95% CI)	p-value	Adjusted model 2 SHR (95% CI)	p-value
Male sex	1.16 (0.93 - 1.46)	0.20				
Age (10 year)	1.11 (1.03 - 1.20)	0.009				
Employed	0.67 (0.51 – 0.89)	0.006				
CCI						
low	Reference					
intermediate	1.54 (1.11 – 2.15)	0.01				
severe	2.10 (1.49 – 2.95)	<0.001				
BMI						
< 25 kg/m^2	Reference		Reference			
25 – 30 kg/m^2	1.20 (0.90 – 1.61)	0.21	1.14 (0.84 – 1.54)	0.40		
≥ 30 kg/m^2	1.23 (0.89 – 1.71)	0.20	1.22 (0.89 – 1.68)	0.21		
APD (vs CAPD)	0.63 (0.51 – 0.79)	<0.001	0.65 (0.52 – 0.81)	<0.001	0.65 (0.52 – 0.81)	<0.001

Model 1 is adjusted for age and sex
Model 2 is adjusted for age, sex, employment status, BMI, CCI, and center PD volume
SHR, subdistribution hazard ratio; BMI, body mass index; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CCI, Charlson Comorbidity index.

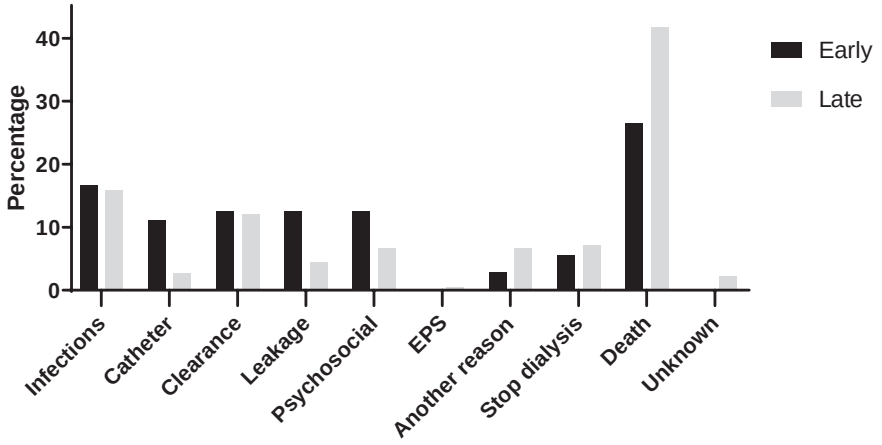
Supplementary Table S4. Center characteristics

	N (%)
Center type	
Academic	8 (24)
non-academic	25 (76)
PD solution	
Conventional	3 (9)
neutral pH low GDP	30 (91)
Icodextrin	33 (100)
Exit site antibiotic prophylaxis	26 (79)
Antibiotic prophylaxis during PD catheter insertion	33 (100)
Antifungal prophylaxis during antibiotic therapy	2 (6)
PD volume	
< 15 patients	6 (18)
15-25 patients	12 (36)
≥ 26 patients	15 (45)
HHD volume	
< 5 patients	12 (36)
5-10 patients	13 (39)
≥ 11 patients	8 (24)

PD, peritoneal dialysis; GDP, glucose degradation products; HHD, home hemodialysis.



Supplementary Figure S1. Permanent technique failure
Permanent technique failure was defined as a transfer to CHD for ≥ 180 days, death on PD or death within 180 days after transfer to CHD.(1)



Supplementary Figure S2. Comparison of causes of early and late permanent technique failure
Early PD technique failure is defined as occurrence of permanent technique failure in the first 6 months after start of PD (n=72). Late technique failure is defined as occurrence of permanent technique failure more than 6 months after start of PD (n=182).

Supplementary Table S5. Causes of technique failure by definition

	30 day definition = technique failure ***n = 318***	**180-day definition = permanent technique failure** ***n = 254***
Infections	64 (20%)	41 (16%)
Catheter problems	25 (8%)	13 (5%)
Clearance	37 (12%)	31 (12%)
Leakage	25 (8%)	17 (7%)
Psychosocial	21 (7%)	21 (8%)
EPS	2 (1%)	1 (0%)
Another reason	32 (10%)	14 (6%)
Stop dialysis	17 (5%)	17 (7%)
Death	92 (29%)	95 (37%)
Unknown	3 (1%)	4 (2%)

Technique failure according to the 30-day definition was defined as a transfer to CHD for ≥ 30 days, death on PD or death within 30 days after transfer to CHD.
Permanent technique failure according to the 180-day definition was defined as a transfer to CHD for ≥ 180 days, death on PD or death within 180 days after transfer to CHD.
All were in accordance with the standardized definition as proposed by Lan *et al.*[1]

1. Lan PG, Clayton PA, Johnson DW, McDonald SP, Borlace M, Badve SV, *et al.* Duration of Hemodialysis Following Peritoneal Dialysis Cessation in Australia and New Zealand: Proposal for a Standardized Definition of Technique Failure. Perit Dial Int. 2016;36(6):623-30.

Part III

Shift towards Health-Related Quality of Life

Chapter 7

Health-Related Quality of Life in home dialysis patients compared to in-center hemodialysis patients: a systematic review and meta-analysis

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Abstract

Rationale & Objective Dialysis patients judge Health-Related Quality of Life (HRQoL) as an essential outcome. Remarkably, little is known about HRQoL differences between home dialysis and in-center hemodialysis (HD) patients across the world.

Study design Systematic review and meta-analysis.

Setting & Study populations Search strategies were performed on the Cochrane Library, Pubmed, and Embase databases between 2007 and 2019. Home dialysis was defined as both peritoneal dialysis and home hemodialysis.

Selection criteria for studies Randomized controlled trials and observational studies that compared HRQoL in home dialysis patients versus in-center HD patients.

Data extraction The data extracted by two authors included: HRQOL scores of different questionnaires, dialysis modality, and subcontinent.

Analytical approach Data was pooled using a random-effects model and results were expressed as standardized mean difference (SMD) with 95% confidence intervals. Heterogeneity was explored using subgroup analyses.

Results Forty-six articles reporting on 41 study populations were identified. Most studies were cross-sectional in design (90%), conducted on PD patients (95%), and used the 12-item or 36-item Short-Form Health Survey questionnaires (83%). More than half of the studies showed moderate or high risk of bias. Pooled analysis of 4,158 home dialysis patients and 7,854 in-center HD patients showed marginally better physical HRQoL score in home dialysis patients compared to in-center HD patients (SMD 0.14, 95%CI 0.04 to 0.24), although heterogeneity was high (I^2>80%). In a subgroup analysis, Western European home dialysis patients had higher physical HRQoL score (SMD 0.39, 95%CI 0.17 to 0.61) compared to in-center HD, while home dialysis patients from Latin America had a lower physical score (SMD -0.20, 95%CI -0.28 to -0.12) compared to in-center HD. Mental HRQoL showed no difference in all analyses.

Limitations No randomized controlled trials were found and high heterogeneity among studies existed.

Conclusions Although pooled data showed a marginally better physical HRQoL for home dialysis patients, the quality of design of the included studies was poor. Large prospective studies with adequate adjustments for confounders are necessary to establish whether home dialysis results in better HRQoL.
PROSPERO 95985

Summary

Health-Related Quality of Life (HRQoL) is an essential outcome for dialysis patients. However, little is known about differences across the world between HRQoL of home dialysis patients versus in-center hemodialysis patients. A systematic review was conducted, which yielded 46 articles. Subsequently, a meta-analysis showed that home dialysis patients have marginally better physical HRQoL compared to in-center hemodialysis patients. In a subgroup analysis, Western European home dialysis patients had a higher physical score, while home dialysis patients from Latin America had a lower physical score. Mental HRQoL showed no difference. However, the quality of design of the included studies was poor, so large prospective studies are necessary to establish whether home dialysis results in better HRQoL.

Introduction

End Stage Kidney Disease (ESKD) is associated with poor survival. Patients starting on dialysis have a median five-year survival rate of only 45%.[1] Observational studies comparing patients performing home dialysis, mostly peritoneal dialysis (PD), with in-center hemodialysis (ICHD) show comparable survival between groups.[2-4] Therefore, these survival studies will not help patients in choosing a dialysis modality.

Counterintuitive to what some clinicians assume, patients with ESRD consider quality of life far more important than survival.[5-10] Many patients experience dialysis as a heavy burden; they even have poorer Health-Related Quality of Life (HRQoL) than patients with diabetes or malignancies.[11,12] Patients also indicate HRQoL aspects as important research topics.[13,14] This has affected the research performed in the medical field during the last decade, with focus shifting from clinical outcomes to patient reported outcomes.[15,16] Indeed, the number of articles reporting HRQoL in dialysis patients has multiplied over the last 10 years.

Reducing the impact of ESKD and its treatment on daily life could potentially improve HRQoL. Performing dialysis at home, instead of being treated with ICHD, has the advantage of more independence and flexibility during the day.[17-20] Moreover, due to the possibility of self-care and fewer hospital visits with home based therapies, patients are able to return to work and to engage in daily social activities.[18,21-23] Home hemodialysis (HHD) enables intensifying the dialysis regime, allowing a reduction in medication burden.[24] All the aforementioned factors could contribute to an improvement of HRQoL.

Many cross-sectional and some cohort studies from different regions across the world have reported on HRQoL of home dialysis patients in comparison to ICHD patients. Interpretation of these studies are hampered by a large variety in type of questionnaire used and applied study design.[25-27] In addition, as these studies are conducted in different countries, disparity exists in study populations since the percentage of patients on home dialysis varies across the world. This difference in practice patterns, together with a difference in local cultures, are suggested to influence HRQoL.[28] Investigators of 'The Dialysis Outcomes and Practice Patterns Study' found different HRQoL scores between ICHD patients across Japan, Europe, and the United States, after adjustment for several confounders including comorbidities.[28] Due to inequalities

among studies, it is difficult to determine whether home dialysis patients have a better HRQoL. Differences in HRQoL of home dialysis patients and ICHD patients should be interpreted in relation to the country of residence.

Hence, a systematic review and meta-analysis was conducted to summarize and evaluate the available studies on HRQoL between home dialysis and ICHD patients, with a special focus on differences across the world.

Methods

Search strategy and selection criteria

The Cochrane Library, Pubmed, and Embase databases were searched for relevant articles using all synonyms and abbreviations of the terms 'dialysis' and 'quality of life' (Table S1). The search was limited to publications during the last 10 years, since the perception of quality of life in patients treated with dialysis changed over time, for example by improved metabolic control over the years.[29] After removing the duplicates, two authors (AB and AE) independently performed screening of titles and abstracts according to predetermined in- and exclusion criteria. All articles comparing the HRQoL of adult (i.e. ≥ 18 yr.) home dialysis patients with HRQoL of ICHD patients were included. Articles other than randomized controlled trials (RCTs) and observational studies were excluded, such as validation and reliability studies on quality of life questionnaires. In addition, articles in a language other than English were excluded.

The remaining articles were read full text by two authors (AB and AE) and screened for additional references. All articles assessing HRQoL, by applying worldwide most commonly used questionnaires,[30] were included (see Table S2). The full text articles were also checked for outdated patient data (data collected before 2007), which was reason for exclusion, and missing HRQoL scores. When no quantitative scores were reported for home dialysis and ICHD patients, the authors were emailed. If they provided the quantitative data, the article was subsequently included in the critical appraisal. Final inclusion was based on consensus between the two authors (AB and AE). In case they failed to reach consensus, a third author (TH) was asked for an opinion that was decisive. The selection process is summarized in Figure 1.

Data extraction

Data extraction was performed and checked by two authors (AB and AE). The included studies were structured according to the dialysis modality, country and subcontinent of conductance, number of participants with characteristics (age, dialysis vintage, and gender), and type of HRQoL questionnaire used. From all studies, HRQoL scores were extracted and evaluated. If no standard deviation (SD) was reported, it was calculated (e.g. from interquartile range (IQR), confidence interval (CI), or standard error) or substituted from another study with similar characteristics.[31] Subcontinents were classified according to the regional boards of the International Society of Nephrology.[32]

For the meta-analysis, the Physical Component Summary (PCS) was used as score for the physical domain and the Mental Component Summary (MCS) for the mental domain. If the summary scores of the Short Form (SF) were not available, the physical functioning score or the mental health score were used respectively. If the World Health Organization Quality of Life (WHOQOL)-BREF was assessed, the physical health score was used for the physical domain and the psychological health score for the mental domain. If the EuroQol-5D (EQ-5D) was reported, the visual analogue scale (VAS) was used for the analysis.

Risk of Bias assessment

After full text screening, articles eligible for critical appraisal were independently appraised by two authors (AB and AE) using criteria based on the Critical Appraisal Skills Programme Cohort Study checklist and the Newcastle-Ottawa Scale.[33,34] The following criteria were assessed: study design, patient selection, comparability of patients between groups, accurate measurement of outcome, correction for confounding, duration of follow-up, selective reporting, and conflict of interest (details are provided in Table S3). They were scored as + (low risk of bias), - (high risk of bias) or unclear (?) based on consensus between the two authors (AB and AE). In case of disagreement a third opinion (BJ) was decisive. After completing the critical appraisal, the corresponding authors of the articles were contacted if any uncertainty remained (i.e. criteria scored as unclear). Any given comment was taken into account for the final critical appraisal.

Analytical approach

With the extracted HRQoL scores a meta-analysis was performed. Heterogeneity, both in clinical characteristics (e.g. variability in patients) and methodological aspects

(i.e. design, and risk of bias), was explored by visual inspection and quantified by an I^2 above 75%.[35] Significant heterogeneity was expected, due to the use of different types of HRQoL questionnaires and differences between countries regarding practice patterns and accessibility for home dialysis leading to differences between patient populations.[28] Therefore, standardized mean difference (SMD) of HRQoL scores and a random effects model were used.

The following subgroup analyses were performed: different subcontinents and subgroups of studies according to overall risk of bias (as scored by authors: low, moderate, or high). When appropriate, type of home dialysis (PD or HHD) was compared to ICHD. Additional analyses were conducted for the following subgroups: type of questionnaire used, different age categories (<45 years, 45 – 60 years, >60 years), and dialysis vintage (<36 months vs. ≥ 36 months). Finally, a sensitivity analysis was conducted that excluded articles for which the SD was calculated or substituted. All analyses were performed with Stata/SE 14.1 for Windows.

Protocol and registration

This systematic review was registered in PROSPERO, the International prospective register of systematic reviews. The study protocol can be retrieved from the PROSPERO website (https://www.crd.york.ac.uk/prospero/) using the registration number 95985.

Results

Study selection

The initial literature search was performed on the 21st of November 2017 and was last updated in January 2019. The final search yielded 1,647 articles, after removal of duplicates. Subsequently, articles were excluded based on title and abstract, according to previously determined in- and exclusion criteria. Systematic reviews that were among these articles were checked for references before they were excluded.[21,25,26,30,36-46] This resulted in one article; however its data collection was performed before 2007 and therefore was excluded.[47]

The full-text of the remaining 80 articles were retrieved and assessed for eligibility. A total of 35 articles were excluded due to the following reasons: comparison group other than ICHD,[48-50] groups were not separately presented,[51-55] unspecified HRQoL

questionnaire,[56-59] HRQoL data exclusively presented in graphs,[60-62] unclear calculation of HRQoL scores,[63,64] and outdated population data (data collected before 2007).[65-80] The studies of Garg[17] (FHN trials) and Jardine[81] (ACTIVE dialysis trial) were excluded since they focused on frequent hemodialysis which was not exclusively performed at home. The remaining 45 articles were screened for additional references, resulting in 1 article that was evaluated and included (Figure 1).[82]

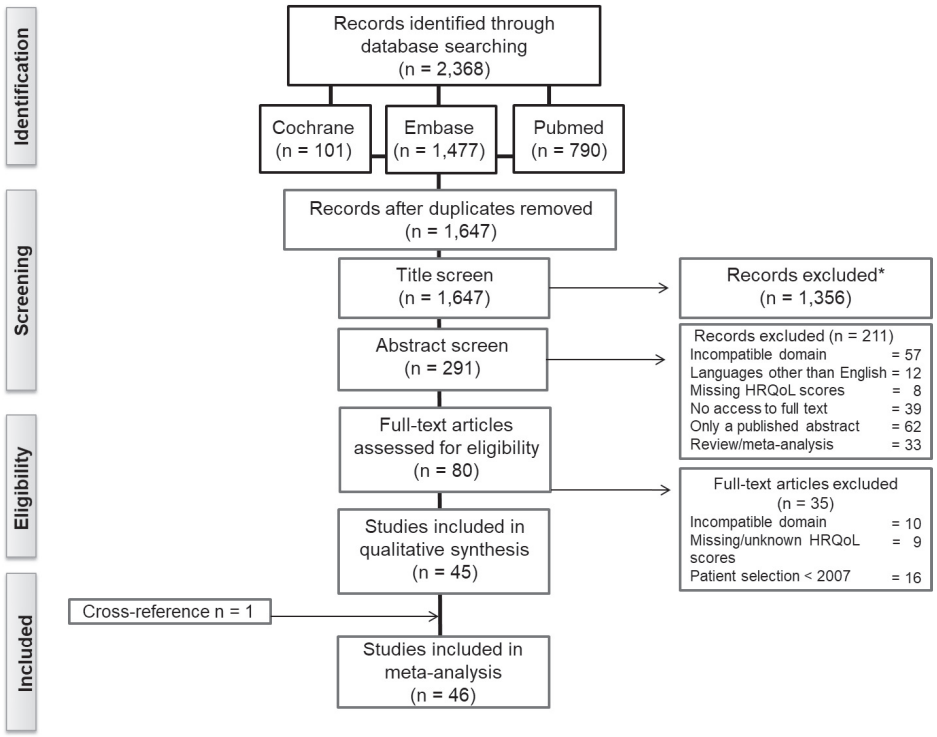

Figure 1. Selection flow diagram.
HRQoL, Health-Related Quality of Life.
* Exclusion criteria: Articles describing data older than 10 years, case-reports, congress abstracts, editorials, language other than English, letters, opinion papers, reviews, validation and reliability studies on quality of life questionnaires.

A total of 46 articles was eligible for critical appraisal.[82-127] The following articles presented overlapping patient data and were appraised as one: Bujang and Liu,[91,92] Chkhotua and Maglakelidze,[94,95] Griva and Yang,[103,104] 2 articles by Kontodimopoulos,[111,112] and 2 articles by Theofilou,[120,121] leaving 41 studies for analysis.

Study characteristics

The characteristics of the included studies are described in Table 1. Most of the studies (32%) were conducted in Western Europe, followed by Asia (27%). From the 41 studies included, only 3 compared the HRQoL of HHD patients with ICHD patients,[82,123,124] while the remaining focused on the comparison PD versus ICHD. The predominantly used questionnaire was the SF, either as a separate questionnaire or as part of the KDQOL (83%).

Mean age of the home dialysis population was 55.9 ± 13.8 years, while the ICHD patients where slightly younger (mean age 54.8 ± 14.1 years). There was a difference in dialysis vintage between both groups with a median of 34.1 months for home dialysis patients (IQR 22.8 - 43.4) and 56.9 months for ICHD patients (IQR 31.0-77.2). The majority (55%) of the total dialysis population was male. One study was conducted in females only.[87] Half of the home dialysis population was male (range 27-90%) compared to 57% of the ICHD population (range 44%-85%). In the included studies there were no RCTs of ICHD versus home dialysis. Furthermore, most studies had a cross-sectional design, comparing prevalent patients on ICHD with prevalent home dialysis patients.

It should be noted that 4 studies were observational cohort studies with a longitudinal follow-up. Da Silva-Gane *et al.* assessed HRQoL of dialysis patients every 3 months until 12 months after dialysis initiation.[97] Baseline PCS scores were lower in ICHD patients. However, after a median follow-up period of 14.7 months HRQoL between dialysis modalities was equal. As the follow-up results of PD and ICHD patients are not shown in the article, in the following meta-analysis only baseline data of this study could be used.

Table 1. Study characteristics of 41 studies

Author, year	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ ICHD)	Age, years (SD) (home/ ICHD)	Dialysis vintage, months (SD) (home/ICHD)	HRQoL questionnaire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclu-sion
Al Wakeel, 2012	PD	Saudi Arabia, Middle East	100 / 100	51.0 (13.5) / 47.5 (13.8)	34.1 (26.9) / 77.2 (75.5)	KDQOL	47.7 (23.6) / 53.1 (32.0)	61.9 (13.5) / 50.5 (14.8)	Favors PD
Alvares, 2012	PD	Brazil, Latin America	788 / 1,621	55.6 (15.3) / 48.9 (14.5)	39.7 (42.5) / 53.9 (55.1)	SF	41.0 (9.4) / 43.0 (9.6)	44.7 (8.0) / 44.6 (7.6)	Favors ICHD
Atapour, 2016	PD	Iran, Middle East	46 / 46	51.0 (12.5) / 47.8 (10.6)	18.8 (13.7) / 24.4 (14.8)	SF	60.5 (10.4) / 56.2 (10.3)	55.7 (7.1) / 55.1 (6.2)	Favors PD
Barata, 2015	PD	Portugal, Western Europe	31 / 94	N /A	N/A	WHOQOL-BREF	61.7 (12.7) / 43.7 (13.9)	56.1 (11.4) / 46.0 (12.2)	Favors PD
Basok, 2009	PD	Turkey, Eastern Europe	21 / 24	45.2 (8.9) / 43.1 (12.4)	N/A	SF	43.2 (9.8) / 47.4 (10.2)	44.5 (10.9) / 50.2 (12.6)	N/A
Baykan, 2012	PD	Turkey, Eastern Europe	41 / 42	40.6 (11.9) / 49.1 (12.0)	N/A	SF	53.2 (7.6) / 47.0 (9.2)	45.2 (6.7) / 42.2 (6.7)	N/A
Borowiak, 2009	PD	Poland, Eastern Europe	50 / 50	58.9 (13.2) / 59.6 (13.4)	N/A	EQ-5D VAS**	55.3 (21.7)/ 53.2 (16.2)	55.3 (21.7)/ 53.2 (16.2)	Equal
Brown, 2010	PD	UK, Western Europe	70 / 70	73.1 (5.5) / 73.4 (5.1)	30.5 (28.3) / 31.4 (26.5)	SF	36.0 (12.1) / 34.3 (9.7)	55.0 (8.4) / 51.3 (12.9)	Favors PD
Bujang, 2015 and **Liu**, 2014	PD	Malaysia, Asia	539 / 793	52.8 (15.4) / 55.5 (15.3)	45.6 (37.2) / 91.2 (74.4)	WHOQOL-BREF	55.5 (15.5) / 56.6 (16.1)	60.2 (16.0) / 59.6 (17.3)	Favors PD
Chen, 2017	PD	China, Asia	103 / 253	63.1 (12.7) / 56.6 (12.1)	N/A	KDQOL	40.3 (12.0) / 37.4 (12.6)	50.3 (10.0) / 51.0 (10.3)	Favors PD

Table 1. Study characteristics of 41 studies (continued)

Author, year	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ ICHD)	Age, years (SD) (home/ ICHD)	Dialysis vintage, months (SD) (home/ICHD)	HRQoL questionnaire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclu-sion
Chkhotua, 2011 and **Maglakelidze** 2011	PD	Georgia, Eastern Europe	43 / 120	N /A	N/A	SF	55.7 (52.2) / 56.9 (53.4)	47.5 (47.9) / 49.9 (51.4)	Equal
Czyzewski, 2014	PD	Poland, Eastern Europe	30 / 40	N /A	39.6 / 78.0	KDQOL	37.5 (10.6) / 34.7 (7.4)	49.9 (7.0) / 43.7 (11.1)	Equal
Da Silva-Gane, 2012	PD	UK, Western Europe	44 / 80	48.0 (15.6) / 60.6 (14.9)	N/A	SF	30.1 (6.5) / 25.2 (8.8)	45.9 (10.6) / 47.6 (10.7)	Favors PD
De Fijter, 2018	PD	The Netherlands, Western Europe	33 / 42	66.0 (14.0) / 66.0 (11.0)	16 / 27	KDQOL	43.0 (20.0) / 35.0 (21.0)	56.0 (24.0) / 49.0 (20.0)	Favors PD
Fructuoso, 2011	PD	Portugal, Western Europe	14 / 37	38.9 (13.3) / 67.3 (14.9)	22.8 (15.6) / 73.2 (78.0)	KDQOL	44.9 (5.6) / 35.9 (9.0)	46.2 (10.2) / 42.6 (12.6)	Favors PD
Garcia-Llana, 2013	PD	Spain, Western Europe	31 / 30	47.9 (15.9) / 60.6 (16.7)	31.4 (28.6) / 56.9 (81.7)	SF	39.4 (8.7) / 34.3 (8.7)	49.8 (11.5) / 47.1 (10.7)	Favors PD
Ginieri-Coccossis, 2008	PD	Greece, Western Europe	48 / 41	64.1 (10.4) / 65.3 (8.4)	43.4 (24.0) / 49.8 (30.8)	WHOQOL-BREF	13.5 (2.8) / 12.4 (3.8)	13.2 (3.2) / 12.9 (3.5)	Favors PD
Goncalves, 2015	PD	Brazil, Latin America	116 / 222	58 (13.9) / 54.4 (15.2)	N/A	KDQOL	45.8 / 52.8	44.3 / 56.6	Favors ICHD
Griva, 2014 and **Yang**, 2015	PD	Singapore, Asia	266 / 236	59.3 (12.5) / 54.4 (10.6)	42.6 (39.4) / 76.4 (66.5)	KDQOL	37.1 (9.7) / 38.9 (9.6)	46.6 (11.2) / 46.3 (10.4)	Favors ICHD
Günalay, 2018	PD	Turkey, Eastern Europe	10 / 50	52.4 (15.1) / 50.0 (18.9)	38.5 (14.2) / 53.5 (48.3)	EQ-5D VAS**	58.1 (13.1) / 66.7 (22.3)	58.1 (13.1) / 66.7 (22.3)	Equal

Table 1. Study characteristics of 41 studies (continued)

Author, year	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ ICHD)	Age, years (SD) (home/ ICHD)	Dialysis vintage, months (SD) (home/ICHD)	HRQoL questionnaire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclu-sion
Ibrahim, 2011	PD	Malaysia, Asia	91 / 183	N / A	N/A	SF	74.6 / 68.4	77.1 / 70.9	Favors PD
Ikonomou, 2015	PD	Greece, Western Europe	39 / 90	58.0 (16.0) / 57.9 (13.8)	N/A	SF	42.4 (10.0) / 40.7 (11.3)	52.3 (9.1) / 49.3 (10.3)	Equal
Iyasere, 2016	PD	UK, Western Europe	129 / 122	76.0 / 75.0	22.0 / 27.5	SF	33.0/ 31.7	49.3 / 50.8	Equal
Kang, 2017	PD	Korea, Asia	366 / 1,250	54.1 (11.9) / 56.4 (13.2)	63.6 (46.8) / 61.2 (55.2)	KDQOL	58.5 (23.0) / 61.9 (21.2)	55.5 (24.9) / 59.8 (21.2)	Favors ICHD
Kim, 2013	PD	Korea, Asia	65 / 172	N/A	N/A	KDQOL	38.7 (9.0) / 39.3 (9.7)	44.8 (6.4) / 44.6 (7.0)	Favors PD
Kontodimo-poulos, 2008 and 2009	PD	Greece, Western Europe	65 / 642	58.7 (12.9) / 58.1 (14.9)	63.6 (67.2) / 74.4 (68.4)	SF	49.2 (30.7) / 49.2 (30.6)	53.0 (26.1) / 55.1 (22.7)	Equal
Nakayama, 2015	PD	Japan, Asia	102 / 77	62.5 (12.0) / 63.5 (12.4)	N/A	SF	25.4 (25.3) / 32.1 (20.6)	45.6 (12.1) / 46.1 (10.5)	N/A
Neumann, 2018	PD	Germany, Western Europe	153 / 200	59.0 (15.4) / 59.8 (16.0)	N/A	SF	Baseline 38.3 (9.8) / 39.9 (10.8) 12 months 35.4 (11.6) / 37.9 (11.5)	Baseline 52.1 (9.4) / 52.1 (10.0) 12 months 45.8 (10.6) / 46.1 (11.6)	Equal

Table 1. Study characteristics of 41 studies (continued)

Author, year	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ ICHD)	Age, years (SD) (home/ ICHD)	Dialysis vintage, months (SD) (home/ICHD)	HRQoL questionnaire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclu-sion
Okpechi, 2013	PD	South Africa, Africa	26 / 56	36.0 (6.1) / 38.6 (10.5)	14.5 (11.6) / 49.8 (71.5)	KDQOL	67.5 (27.5) / 65.4 (53.1)	75.0 (23.5) / 74.6 (21.0)	Equal
Ören, 2013	PD	Turkey, Eastern Europe	125 / 175	46.4 (14.6) / 47.6 (15.3)	45.4 (34.8) / 94.4 (60.0)	SF	58.4 (25.9) / 48.6 (26.5)	63.3 (18.9) / 57.0 (19.8)	Favors PD
Painter, 2012	HHD	USA, North America	10 / 13	42.6 (12.4) / 45.5 (10.4)	33.8 (44.3) / 28.5 (21.2)	KDQOL	Baseline 45.3 (11.3) / 48.8 (10.0) 6 months 49.6 (9.1) / 48.4 (7.4)	Baseline 48.1 (14.6) / 51.1 (9.1) 6 months 48.9 (12.6) / 51.7 (9.6)	Favors HHD
Ramos, 2015	PD	Brazil, Latin America	60 / 257	56.5 (15.3) / 57.9 (15.9)	N/A	SF	51.3 (27.8) / 53.5 (29.7)	71.7 (20.4) / 68.7 (22.6)	Equal
Ruiz de Alegría - Fernández de Retana, 2013	PD	Spain, Western Europe	45 / 53	50.8 (13.3) / 52.3 (13.1)	N/A	SF	3 months 42.6 (8.9) / 40.8 (8.9) 6 months 40.6 (9.8) / 42.2 (9.7) 12 months 43.9 (9.8) / 39.9 (9.7)	3 months 50.5 (13.0) / 46.3 (13.4) 6 months 50.3 (11.6) / 49.3 (11.6) 12 months 50.5 (11.6) / 49.6 (11.6)	N/A
Tannor, 2017	PD	South Africa, Africa	48 / 58	36.1 (10.7) / 42.8 (9.8)	26.4 / 72.0	KDQOL	55.5 (21.7) / 54.7 (19.4)	62.7 (19.7) / 68.6 (17.9)	Equal

Table 1. Study characteristics of 41 studies (continued)

Author, year	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ ICHD)	Age, years (SD) (home/ ICHD)	Dialysis vintage, months (SD) (home/ICHD)	HRQoL questionnaire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclu-sion
Theofilou, 2011 and 2013	PD	Greece, Western Europe	60 / 84	64.3 (12.5) / 58.1 (16.1)	38.4 (24.0) / 87.6 (85.2)	WHOQOL-BREF	13.7 (3.0) / 12.7 (3.7)	13.4 (3.1) / 13.3 (3.7)	Favors PD
Turkmen, 2012	PD	Turkey, Eastern Europe	64 / 90	52.4 (15.3) / 55.0 (15.7)	19.8 (14.3) / 22.7 (13.1)	SF	47.6 (18.5) / 59.4 (20.7)	41.7 (17.2) / 63.9 (20.6)	Favors ICHD
Watanabe, 2014	HHD	Japan, Asia	46 / 34	54.0 (8.3) / 57.1 (7.6)	76.8 (68.4) / 88.8 (99.6)	KDQOL	48.7 (9.2) / 37.1 (12.9)	51.2 (8.9) / 49.6 (6.2)	Favors HHD
Wright[a], 2015	HHD	USA, North America	22 / 29	N/A	N/A	KDQOL	40.4 (12.7) / 42.8 (9.8)	50.6 (9.4) / 50.4 (10.0)	Equal
Wright[b], 2015	PD	USA, North America	26 / 29	N/A	N/A	KDQOL	43.2 (8.8) / 42.8 (9.8)	51.1 (8.2) / 50.4 (10.0)	Equal
Wu, 2013	PD	China, Asia	93 / 97	54.5 (15.5) / 58.3 (17.5)	25.5 / 31.0	SF	34.0 (11.9) / 30.5 (14.5)	41.3 (10.0) / 38.5 (12.0)	Equal
Ying, 2014	PD	Malaysia, Asia	73 / 147	N/A	N/A	SF	60.2 (21.9) / 49.6 (20.2)	67.1 (19.4) / 58.0 (20.3)	Favors PD
Yongsiri, 2014	PD	Thailand, Asia	26 / 34	53.0 (14.4) / 61.1 (15.5)	N/A	WHOQOL-BREF	3.0 (0.9) / 2.9 (0.8)	3.7 (0.7) / 3.7 (0.6)	Equal

Table 1. Study characteristics of 41 studies (continued)

Author, year	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ ICHD)	Age, years (SD) (home/ ICHD)	Dialysis vintage, months (SD) (home/ICHD)	HRQoL questionnaire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclu-sion
TOTAL	N/A	N/A	4,158 7,854	55.9 (13.8) 54.8 (14.1)	34.1[#] (22.8-43.4) 56.9[#] (31.0-77.2)	N/A	N/A	N/A	N/A

PD, peritoneal dialysis; HHD, home hemodialysis; UK, United Kingdom; USA, United States of America; ICHD, in-center hemodialysis; SD, standard deviation; N/A, not applicable or not available; HRQoL, Health-Related Quality of Life; KDQOL, Kidney Disease Quality Of Life instrument; SF, Short Form; EQ-5D VAS, EuroQol-5D Visual Analogue Scale; WHOQOL-BREF, World Health Organization Quality of Life-BREF.

[a, b] Wright *et al.* included 3 patient populations: HHD, PD, and ICHD

* The regional boards of the International Society of Nephrology were used for the classification of countries into subcontinents

** EQ-5D VAS score was used as a surrogate for both physical score and mental score

[#] Median with interquartile range

The study by Neumann *et al*. investigated the change in social networks and social support, and their association with HRQoL, of dialysis patients over a 12 month period.[114] The PCS and MCS scores of PD and ICHD patients decreased equally during follow-up. The follow-up HRQoL scores at 12 months were used in this meta-analysis. The study by Painter *et al*. examined exercise capacity after modality switch from ICHD to HHD, yet also assessed HRQoL.[82] Modality switch was associated with a significant improvement in physical HRQoL scores after 6 months. The follow-up HRQoL scores at 6 months were used in this meta-analysis. The study by Ruiz de Alegría - Fernández de Retana *et al*. related coping mechanisms to HRQoL.[118] SF-36 questionnaires were collected at 3, 6, and 12 months after dialysis initiation. Separate HRQoL scores for PD and ICHD were obtained from the author. These unpublished data showed improvement in MCS for ICHD patients, but PCS remained the same in both groups. HRQoL scores 12 months after initiation of dialysis treatment were used in this meta-analysis.

Risk of Bias assessment

The results of the critical appraisal are presented in Table S4. Seventeen of the 41 studies were assessed as having an overall low risk of bias. There was a general lack of adequate presentation of patient characteristics, with 6 studies presenting baseline data without separation by dialysis modality[86,106,110,126] or no baseline data at all.[95,96] Few studies adequately adjusted HRQoL scores for confounding between groups.[84,97,98,108,109,114] Apart from adjustment for confounders, also a stratified analysis was considered as a low risk of bias. HRQoL, as a patient reported outcome measure, should be self-reported or assessed by a trained research-assistant.[128] For 8 studies it was unknown whether the professional performing the interview was trained to assess HRQoL, leading to potential bias in outcome assessment.[89,99,102,106,115,116,120,126]

Meta-analysis

The included studies for the meta-analysis compared HRQoL for a total of 4,158 home dialysis patients with 7,854 ICHD patients. The study by Wright *et al*. compared two home dialysis populations (HHD and PD) with ICHD patients and is presented twice in the meta-analysis.[124]

Although heterogeneity was high, HRQoL on the physical domain was marginally better in home dialysis patients compared to ICHD patients with a SMD of 0.14

(95% CI 0.04 to 0.24). The HRQoL on the mental domain was equal between the two groups (SMD 0.06, 95% CI -0.03 to 0.15).

A comparison among subcontinents showed that patients on home dialysis in Western Europe had higher physical HRQoL scores compared to ICHD patients (SMD 0.39, 95% CI 0.17 to 0.61), whereas patients on home dialysis from Latin America had lower physical HRQoL scores (SMD -0.20, 95% CI -0.28 to -0.12) (Figure 2A). The HRQoL on the mental domain showed no difference among the subcontinents (Figure 2B).

If studies were divided according to overall level of bias, an increased risk of bias was associated with an increase in SMD in physical HRQoL (high risk of bias: SMD 0.26, 95% CI -0.01 to 0.52) (Figure 3A). For the mental domain, there was no difference among the different levels of bias (Figure 3B). The subgroup analysis regarding type of home dialysis (PD or HHD) provided no additional insights, recognizing that only 3 studies focused on HHD (data not shown). Heterogeneity remained after all subgroup analyses. Additional analyses regarding type of questionnaire used, different age categories, and dialysis vintage did not alter results nor influenced heterogeneity (Figures S1A, S1B, S2A, and S2B).

The SD for the HRQoL scores in 5 studies had to be calculated, if sufficient data were available,[95,98,108] or substituted.[102,106] Also, WHOQOL-BREF scores in 2 studies were transformed into a 100-scale.[101,121] To further explore the robustness of data, sensitivity analysis was performed which did not change the aforementioned results.

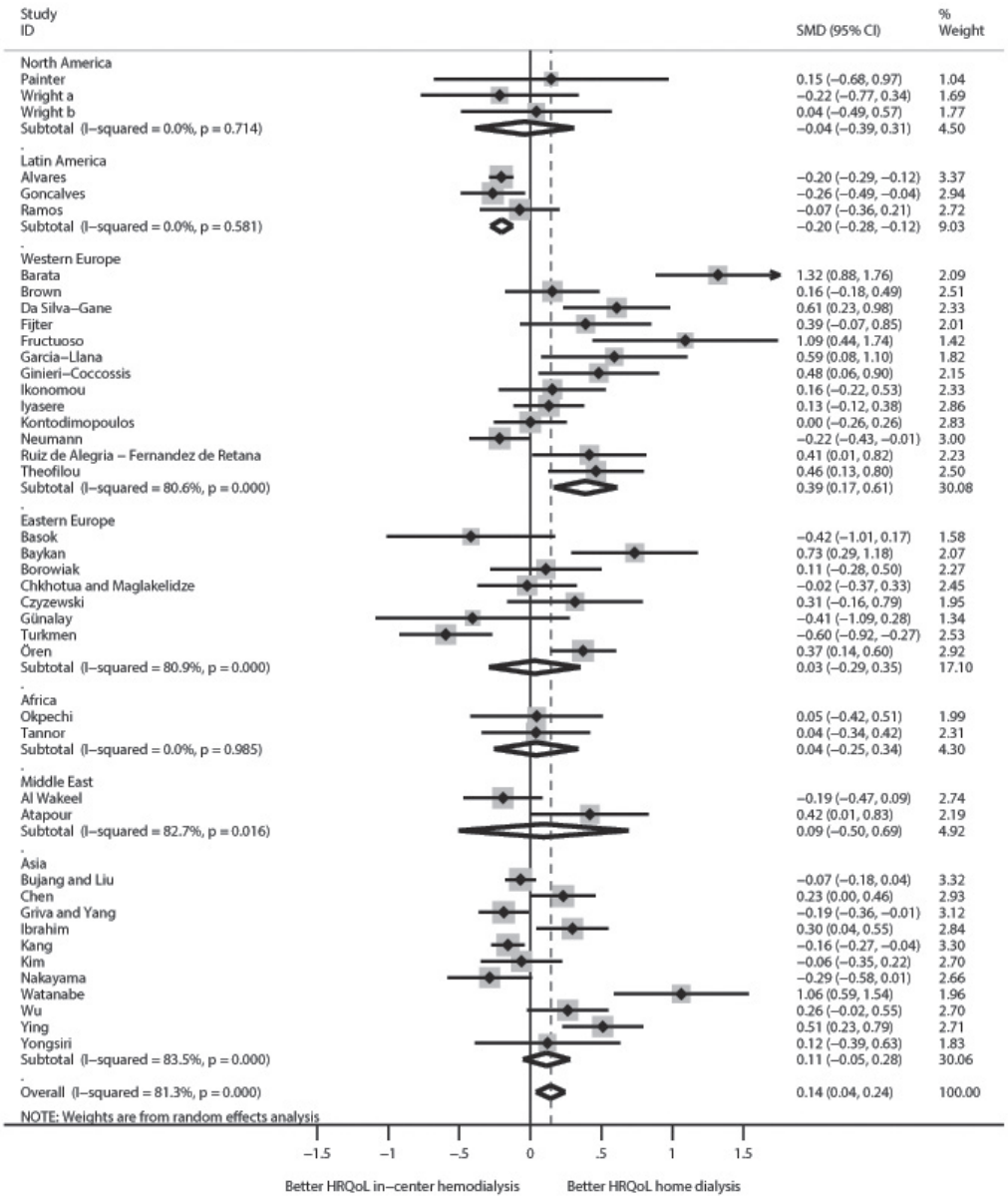

Figure 2A. Meta-analysis of Physical Health-Related Quality of Life among subcontinents. SMD, standardized mean difference; 95% CI, 95% confidence interval; HRQoL, Health-Related Quality of Life.

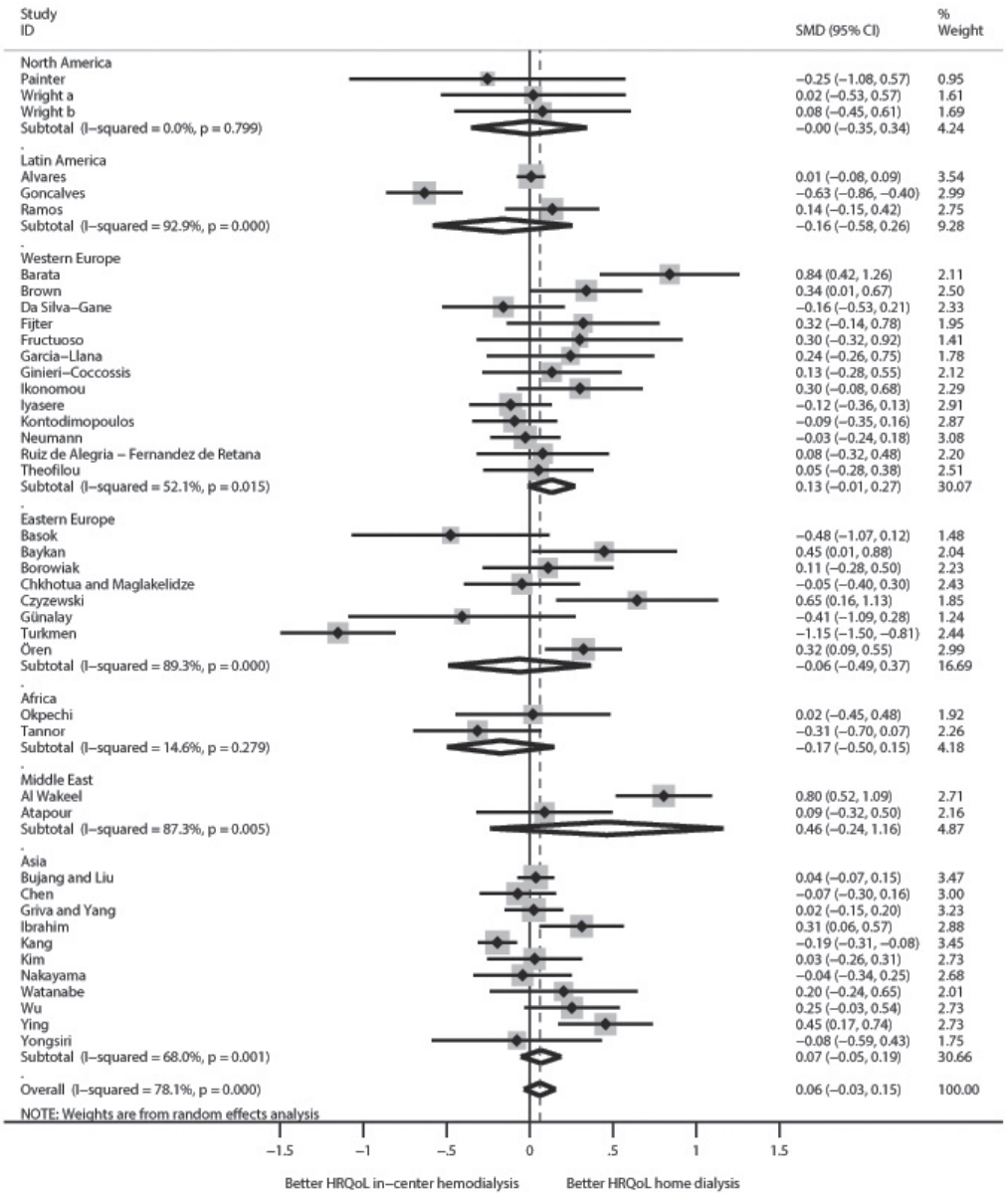

Figure 2B. Meta-analysis of Mental Health-Related Quality of Life among subcontinents. SMD, standardized mean difference; 95% CI, 95% confidence interval; HRQoL, Health-Related Quality of Life.

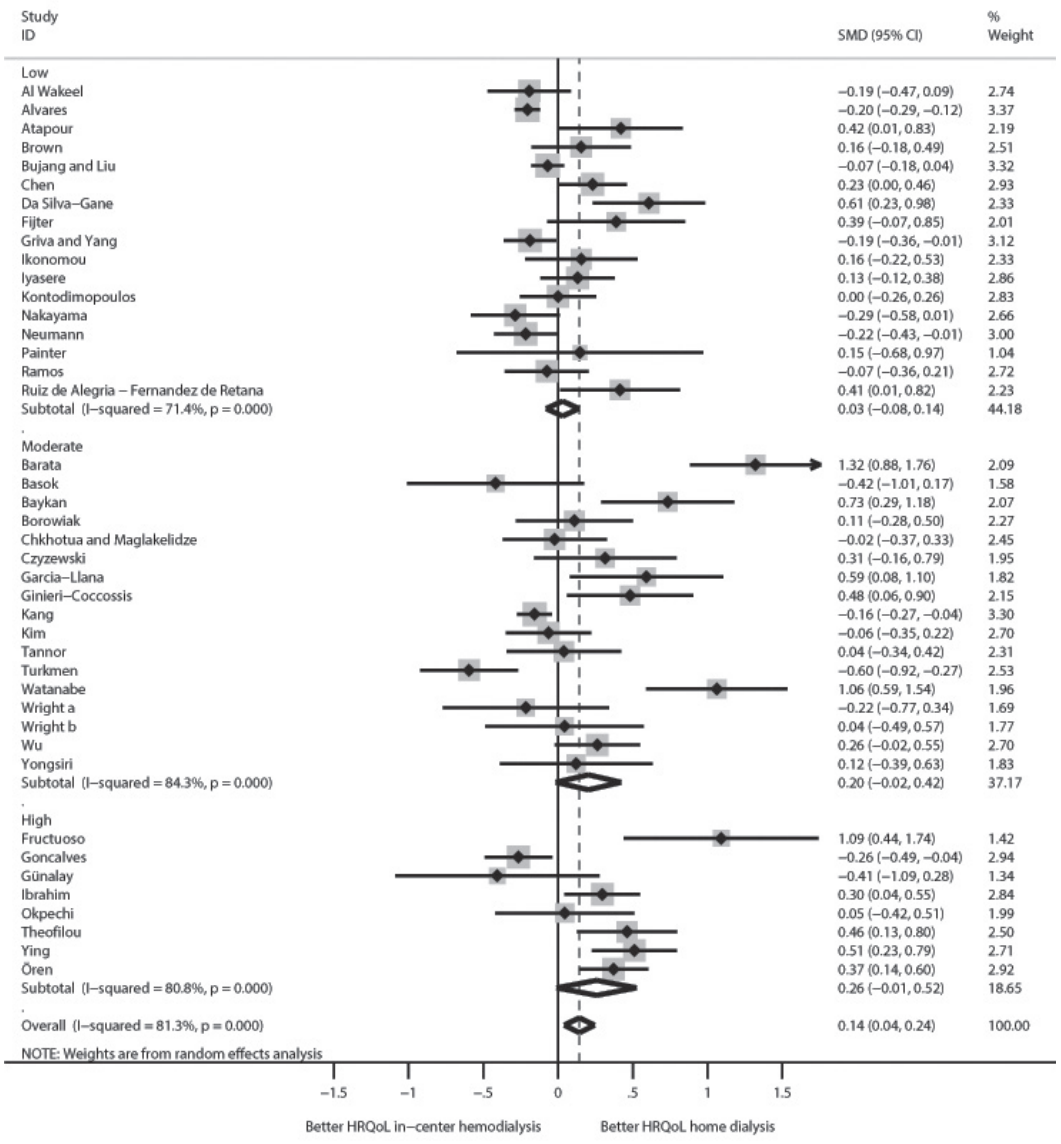

Figure 3A. Meta-analysis of Physical Health-Related Quality of Life among level of bias. SMD, standardized mean difference; 95% CI, 95% confidence interval; HRQoL, Health-Related Quality of Life.

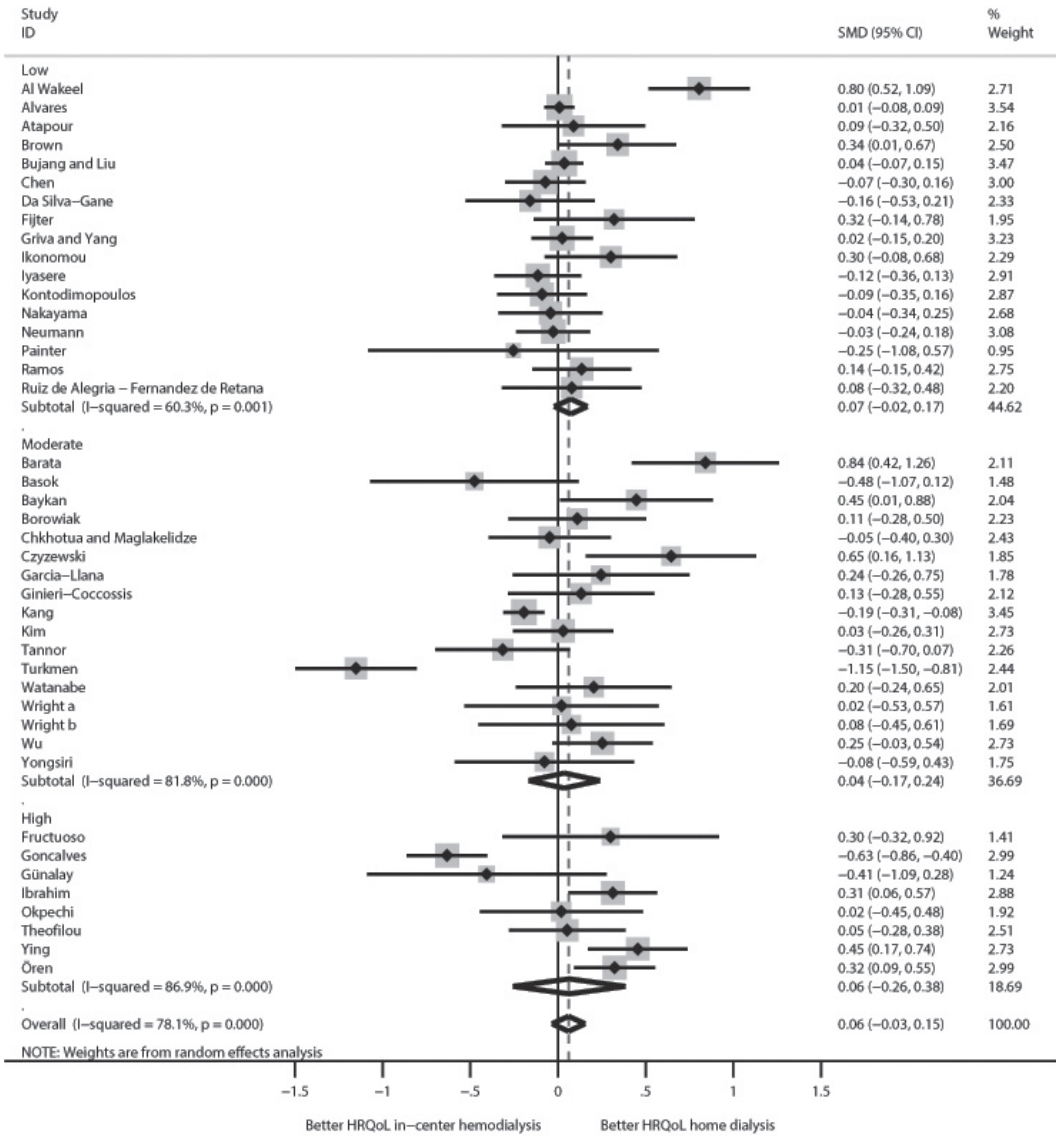

Figure 3B. Meta-analysis of Mental Health-Related Quality of Life among level of bias. SMD, standardized mean difference; 95% CI, 95% confidence interval; HRQoL, Health-Related Quality of Life.

Discussion

This meta-analysis shows a better physical HRQoL for patients treated with a form of home dialysis compared to ICHD patients, while the mental HRQoL is comparable between these two patient groups. However, higher physical HRQoL scores in home dialysis patients were only found in Western Europe. Home dialysis patients from Latin America were found to have poorer physical HRQoL compared to ICHD patients. No studies were conducted in Oceania or Russia and only a few in Africa and the Middle East, hampering the comparison regarding HRQoL in the dialysis population worldwide. Furthermore, it should be noted that included studies were generally low in quality and showed high heterogeneity. Therefore, the conclusion regarding better HRQoL of home dialysis patients compared to ICHD patients lacks the necessary robustness.

The finding that home dialysis patients from Western Europe had better physical HRQoL compared to ICHD patients, could be explained by the fact that PD patients from some of the Western European studies were younger due to practice patterns, suggestive for confounding by indication.[97,99,100] Although most studies performed statistical adjustments of their analyses, important residual confounding between these patient groups might still be present. In contrast to West-European home dialysis patients, those from Latin America were found to have a poorer physical HRQoL. However, these results could also be subject to confounding by indication since in Brazil, the country where these studies were conducted, it is common practice to perform PD only if patients are not eligible for ICHD.[84] Brazilian ICHD patients may be healthier and therefore physically in a better condition than PD patients in general.[84,102] This was emphasized by Ramos *et al.* as in this study, PD and ICHD patients were more comparable and physical HRQoL scores were found to be equal.[117]

The differences in HRQoL of dialysis patients across the world could also be explained by differences in access to dialysis. Liyanage *et al.* modelled inaccessibility among countries and estimated that at least 47% and at most 73% of the world population has no access to renal replacement therapy (RRT). In Latin America, up to 52% of ESKD patients have no access to dialysis, while Africa and Asia have the highest inaccessibility rates, 83% and 91% respectively.[129] In South-Africa more than half of the patients in need for RRT cannot be treated.[130,131] Due to limited resources, prolonged maintenance dialysis is not applied and only patients suitable for transplantation are

eligible for RRT. As a result, the elderly or unemployed and patients with diabetes or drug abuse are hardly accepted for dialysis treatment.[130,131] In India, less than 10% of patients start RRT and yet more than two-thirds cease dialysis treatment due to financial problems, often within 3 months. Most dialysis facilities belong to private hospitals and although PD has gained popularity, due to financial restrictions both home dialysis and ICHD are reserved for the rich minority.[132] In most countries of North and South Asia dialysis care is publicly funded, as is most common in the rest of the world, whereas only 31% of countries in Southeast Asia provide free publicly funded dialysis care.[133] Particularly patients from low income countries worldwide depend on private funding.[133,134] In high income countries inaccessibility is very low, with a maximum of 30%, in comparison to 98% in low income countries.[129,135] Due to these accessibility issues, the dialysis patients from high income countries (e.g. Western Europe) substantially differ from patients worldwide, which could influence HRQoL scores importantly.

This meta-analysis also underscores the effect of bias in HRQoL. A high risk of bias was associated with better HRQoL in favor of home dialysis if compared to studies with low risk of bias. Remarkably, in all studies with a high risk of bias HRQoL questionnaires were not completed by patients themselves, yet were administered by researchers for whom it was unclear whether they had been trained. In the manual of the Short Form it is stated that the questionnaire should be completed by the patient alone, prior to any contact with the clinician, to avoid influencing the patient and reduce risk of socially desirable answers.[128] Hood *et al.* has found that assessment by an interviewer is a potential risk of significant bias.[136] The aforementioned conclusion is confirmed by the results of this meta-analysis.

No RCTs with randomization between home and in-center dialysis were found in the literature search, as previous experiences have learned that a patient's choice between home dialysis and ICHD is too fundamental to let it be determined by fate.[20,137] In this meta-analysis most studies had a cross-sectional design and did not adjust for confounding even though populations were not comparable at baseline. However, patients performing home dialysis are principally different from ICHD patients. Therefore, in cross-sectional studies the observed associations are less likely to be causative. Korevaar *et al.* showed that patients starting home dialysis had higher HRQoL scores than ICHD patients even in adjusted analysis[138], while Manns *et al.* reported that *choosing* home dialysis improved HRQoL even prior to initiation of

home dialysis.[139] The prospective studies in this meta-analysis had a follow-up period of 6 to 12 months. However, it might take longer for patients to return to social activities and work, two factors suggested to be of major influence on HRQoL.[18,21-23] Therefore, prospective studies with at least one year of follow-up will be necessary to provide a valid assessment of HRQoL of home dialysis patients.

Unfortunately, few studies reported on disease specific domains, whereas dialysis modality possibly has a greater impact on specific complaints or domains than on generic physical and mental HRQoL scores.[140,141] Future studies should also incorporate disease specific domains as outcome measure.

The most important limitation of this meta-analysis is the high heterogeneity among studies. High heterogeneity remained despite several subgroup analyses, emphasizing the clinical and methodological diversity among studies. Yet, this systematic review and meta-analysis provides a detailed overview of current literature on HRQoL of home dialysis patients across the world, while previous reviews were unable to provide such a detailed insight.[25-27] Another limitation was that only three studies focused on HHD, illustrating the knowledge gap regarding this modality.

In conclusion, although pooled data in this meta-analysis shows a marginally better physical HRQoL for home dialysis patients; the quality of design of the included studies is poor and large heterogeneity among studies exist. Therefore, no definitive conclusions on HRQoL of patients treated with home dialysis can be drawn. Large prospective studies with adequate follow-up and adjustments for confounders are necessary to evaluate HRQoL of home dialysis patients.

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Supplementary material

Supplementary table S1. Search strings for Cochrane, Embase, and Pubmed databases

Database	Search
Cochrane	(((hemodialys*:ab,ti,kw OR haemodialys*:ab,ti,kw OR "hemo-dialys*":ab,ti,kw OR "haemo-dialys*":ab,ti,kw OR "renal dialys*":ab,ti,kw OR "dialysis modalit*":ab,ti,kw OR "artificial kidney*":ab,ti,kw) AND (home:ab,ti,kw OR homebased:ab,ti,kw)) OR "peritoneal dialys*":ab,ti,kw OR "peritoneum dialys*":ab,ti,kw) AND ("patient reported outcome":ab,ti,kw or "life qualit*":ab,ti,kw or "quality of life":ab,ti,kw or qol:ab,ti,kw or hrql:ab,ti,kw or hrqol:ab,ti,kw or "SF 36":ab,ti,kw or SF36:ab,ti,kw or "SF 12":ab,ti,kw or SF12:ab,ti,kw or "short form 36":ab,ti,kw or "short form 12":ab,ti,kw or "EQ 5D*":ab,ti,kw or EQ5D*:ab,ti,kw or "Quality Adjusted Life":ab,ti,kw or QALY:ab,ti,kw or QALYs:ab,ti,kw or QALE:ab,ti,kw) *Search dates from 1 January 2007 until 1 January 2019*
Embase	('peritoneal dialysis'/exp OR 'home dialysis'/exp OR ('hemodialysis'/de OR 'artificial kidney'/exp OR hemodialys*:ab,ti OR haemodialys*:ab,ti OR 'hemo-dialys*':ab,ti OR 'haemo-dialys*':ab,ti OR 'renal dialys*':ab,ti OR (dialysis NEAR/3 modalit*):ab,ti OR 'artificial kidney*':ab,ti AND (home:ab,ti OR homebased:ab,ti)) OR 'peritoneal dialys*':ab,ti OR (peritoneum NEAR/3 dialys*):ab,ti) AND ('patient-reported outcome'/exp OR 'quality of life'/exp OR 'patient reported outcome':ab,ti OR life AND qualit*:ab,ti OR 'quality of life':ab,ti OR qol:ab,ti OR hrql:ab,ti OR hrqol:ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'sf 12':ab,ti OR sf12:ab,ti OR 'short form 36':ab,ti OR 'short form 12':ab,ti OR 'eq 5d*':ab,ti OR eq5d*:ab,ti OR 'quality adjusted life':ab,ti OR qaly:ab,ti OR qalys:ab,ti OR qale:ab,ti) *Search dates from 1 January 2007 until 1 January 2019*
Pubmed	("Peritoneal Dialysis"[Mesh] OR "Hemodialysis, Home"[Mesh] OR (("Renal Dialysis"[Mesh:noexp] OR "Kidneys, Artificial"[Mesh] OR hemodialys*[tiab] OR haemodialys*[tiab] OR hemo-dialys*[tiab] OR haemo-dialys*[tiab] OR renal dialys*[tiab] OR dialysis modalit*[tiab] OR artificial kidney*[tiab]) AND (home[tiab] OR homebased[tiab])) OR peritoneal dialys*[tiab] OR peritoneum dialys*[tiab]) AND ("Patient Reported Outcome Measures"[Mesh] OR "Quality of Life"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "patient reported outcome"[tiab] OR life qualit*[tiab] OR "quality of life"[tiab] OR qol[tiab] OR hrql[tiab] OR hrqol[tiab] OR SF 36[tiab] OR SF36[tiab] OR SF 12[tiab] OR SF12[tiab] OR short form 36[tiab] OR short form 12[tiab] OR EQ 5D*[tiab] OR EQ5D*[tiab] OR Quality Adjusted Life[tiab] OR QALY[tiab] OR QALYs[tiab] OR QALE[tiab]) *Search dates from 21 November 2007 until 1 January 2019*

Supplementary table S2. HRQoL questionnaires

Questionnaire	Content
Short Form (SF)	The long version of the SF (SF-36) consists of eight domains: Physical functioning, Role-physical, Bodily pain, General health, Vitality, Social function, Role-emotional, and Mental health.[1] These domains are summarized in the Physical Component Summary (PCS) and Mental Component Summary (MCS). The shorter version of the SF (SF-12) only reports the PCS and MCS.[2] The SF questionnaires are the most widely used.[3]
Kidney Disease Quality Of Life Instrument (KDQOL)	The long version of the KDQOL (KDQOL-SF) consist of the SF-36 questionnaire and the following kidney disease specific domains: Symptoms, Effects of kidney disease, Burden of kidney disease, Work status, Cognitive function, Quality of social interaction, Sexual function, Sleep, Social support, Dialysis staff encouragement, and Patient satisfaction.[4] The short version of the KDQOL (KDQOL-36) consists of the SF-12 and the first three kidney disease specific domains (Symptoms, Effects of kidney disease, and Burden of kidney disease).
EuroQol-5D (EQ-5D)	The EuroQol-5D (EQ-5D) is a short questionnaire that can be used to calculate quality adjusted life years (QALYs) and reports on the following domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D is widely used in cost-effectiveness research.[5]
World Health Organization Quality of Life (WHOQOL-BREF)	The World Health Organization Quality of Life (WHOQOL) has developed the WHOQOL-BREF questionnaire which measures four domains (physical health, psychological, social relationships, and environment) and an overall assessment of quality of life and general health.[6]

1. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: Manual and Interpretation Guide. Boston, MA: The Health Institute, New England Medical Center; 1993.
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5. Versteegh MM, Vermeulen KM, Evers SMAA, *et al.* Dutch Tariff for the Five-Level Version of EQ-5D. Value in Health. 2016;19:343-352.
6. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF Quality Of Life Assessment. Psychological Medicine. 1998;28:551-558.

Supplementary table S3. Criteria used in Risk of Bias assessment

Criteria	+	?	-
Design	+ RCT or cohort study		- cross-sectional study
Patient selection	+ clear description setting and selection process, selection criteria mentioned and response ≥70%	? insufficient data to estimate risk of bias	- no clear description setting and selection process, selection criteria not mentioned and response <70%
Comparability	+ matched controls or comparable baseline for age, comorbidities, dialysis vintage	? insufficient data to estimate risk of bias	- non-matched or non-comparable groups
Outcome	+ self-reported HRQoL or trained interviewer	? insufficient data to estimate risk of bias	- no clear protocol for interview or administering questionnaire
Confounding	+ Adjusted analyses or stratified presentation in results	? insufficient data to estimate risk of bias	- confounding factors not mentioned or only as part of discussion
Follow-up	+ follow-up >6 months and <30% loss in the first year, with non-selective reasons	N/A not applicable	- follow-up <6 months and >30% loss in the first year
Selective reporting	+ all pre-defined HRQoL scores in protocol or methods section are reported	? insufficient data to estimate risk of bias	- not all pre-defined scores are reported
Overall (risk of bias)	low: ≥4 plus signs in above mentioned elements	moderate: 3 plus signs in above mentioned elements or 1-2 plus signs with ≥1 question mark	high: ≤2 plus signs in above mentioned elements
Conflict of interest	+ mentioned, non-conflicted	? not-mentioned	- mentioned and conflicted

Supplementary table S4. Critical appraisal of 41 studies

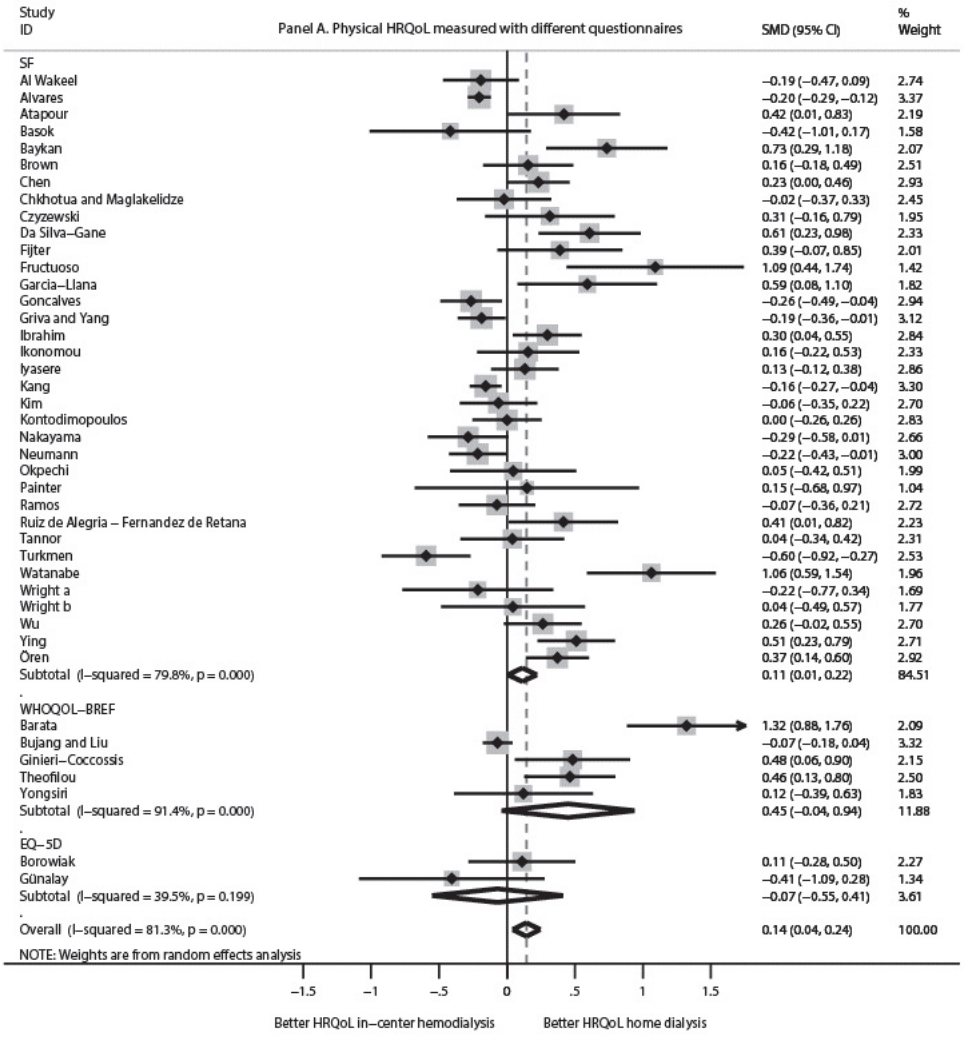
Author, year	Design	Patient selection	Comparability	Outcome	Confounding	Follow-up	Selective reporting	Overall Risk of Bias	Conflict of interest
Al Wakeel, 2012	-	+	?	+	+	N/A	+	Low	?
Alvares, 2012	-	+	-	+	+	N/A	+	Low	+
Atapour, 2016	-	+	+	?	+	N/A	+	Low	?
Barata, 2015	-	?	?	?	-	N/A	?	Moderate	?
Basok, 2009	-	?	?	+	-	N/A	+	Moderate	?
Baykan, 2012	-	?	?	?	-	N/A	+	Moderate	+
Borowiak, 2009	-	?	?	-	?	N/A	+	Moderate	?
Brown, 2010	-	+	+	+	+	N/A	+	Low	-
Bujang, 2015 and **Liu**, 2014	-	+	+	+	-	N/A	+	Low	+
Chen, 2017	-	+	?	+	+	N/A	+	Low	+
Chkhotua, 2011 and **Maglakelidze**, 2011	-	?	?	+	-	N/A	-	Moderate	?
Czyzewski, 2014	-	?	?	+	-	N/A	-	Moderate	?
Da Silva-Gane, 2012	+	+	-	+	+	+	-	Low	+
De Fijter, 2018	-	+	-	+	+	N/A	+	Low	+
Fructuoso, 2011	-	?	-	-	+	N/A	+	High	?
Garcia-Llana, 2013	-	+	-	+	?	N/A	+	Moderate	-
Ginieri-Coccossis, 2008	-	?	+	+	-	N/A	+	Moderate	+
Goncalves, 2015	-	?	?	-	-	N/A	-	High	?

Supplementary table S4. Critical appraisal of 41 studies (continued)

Author, year	Design	Patient selection	Comparability	Outcome	Confounding	Follow-up	Selective reporting	Overall Risk of Bias	Conflict of interest
Griva, 2014 and **Yang**, 2015	-	+	-	+	+	N/A	+	Low	+
Günalay, 2018	-	?	-	?	-	N/A	+	High	?
Ibrahim, 2011	-	+	?	-	-	N/A	?	High	?
Ikonomou, 2015	-	+	?	+	+	N/A	+	Low	+
Iyasere, 2016	-	+	+	+	+	N/A	+	Low	-
Kang, 2017	-	?	+	?	+	N/A	+	Moderate	+
Kim, 2013	-	+	?	+	?	N/A	-	Moderate	?
Kontodimopoulos, 2008 and 2009	-	+	+	+	+	N/A	+	Low	?
Nakayama, 2015	-	+	+	+	-	N/A	+	Low	-
Neumann, 2018	+	?	+	+	+	+	+	Low	+
Okpechi, 2013	-	-	-	-	-	N/A	+	High	?
Ören, 2013	-	+	-	-	+	N/A	-	High	?
Painter, 2012	+	+	+	+	-	+	+	Low	+
Ramos, 2015	-	+	+	+	+	N/A	+	Low	?
Ruiz de Alegria - Fernandez de Retana, 2013	+	+	+	+	+	+	-	Low	+
Tannor, 2017	-	+	-	+	-	N/A	+	Moderate	+
Theofilou, 2011 and 2013	-	+	?	-	-	N/A	?	High	?

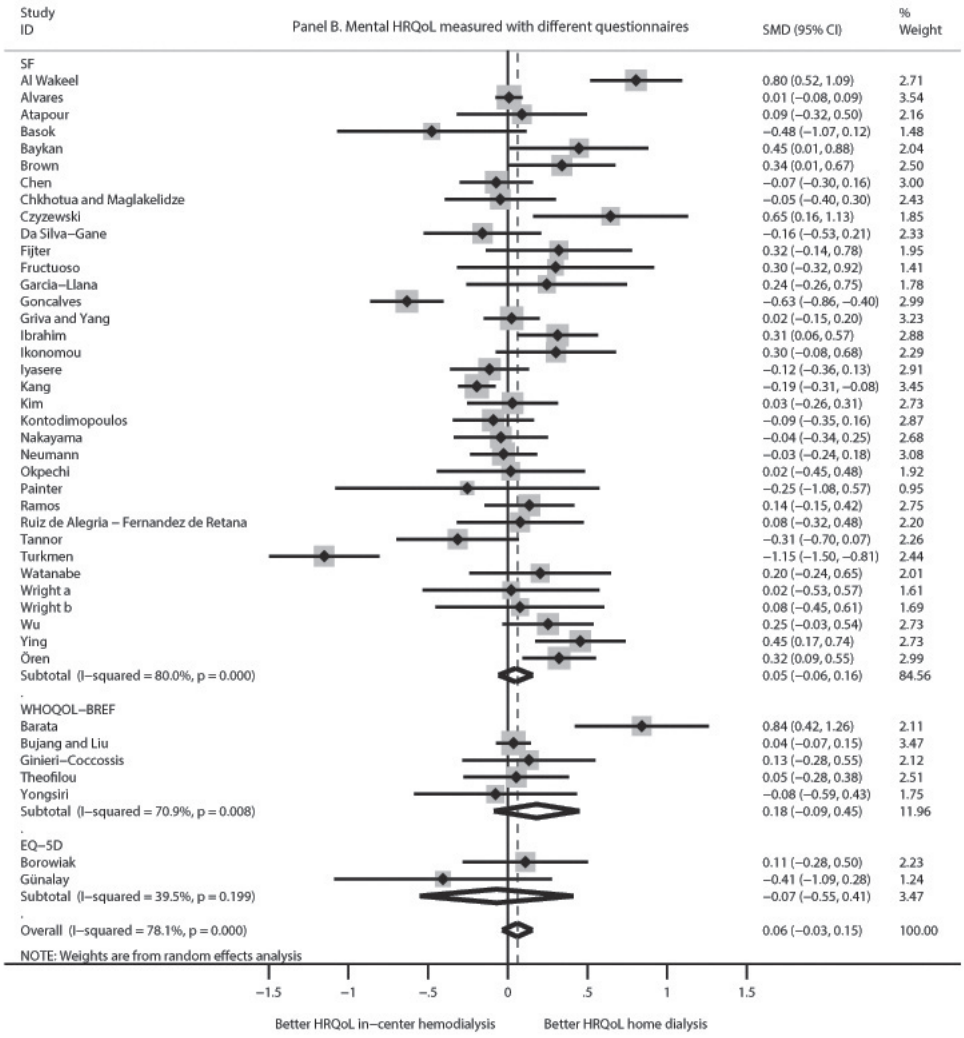
Supplementary table S4. Critical appraisal of 41 studies (continued)

Author, year	Design	Patient selection	Comparability	Outcome	Confounding	Follow-up	Selective reporting	Overall Risk of Bias	Conflict of interest
Turkmen, 2012	-	+	+	?	-	N/A	-	Moderate	+
Watanabe, 2014	-	?	+	+	-	N/A	+	Moderate	+
Wright, 2015	-	+	?	+	-	N/A	+	Moderate	+
Wu, 2013	-	?	+	+	-	N/A	+	Moderate	+
Ying, 2014	-	+	?	-	-	N/A	-	High	?
Yongsiri, 2014	-	?	+	?	-	N/A	+	Moderate	+



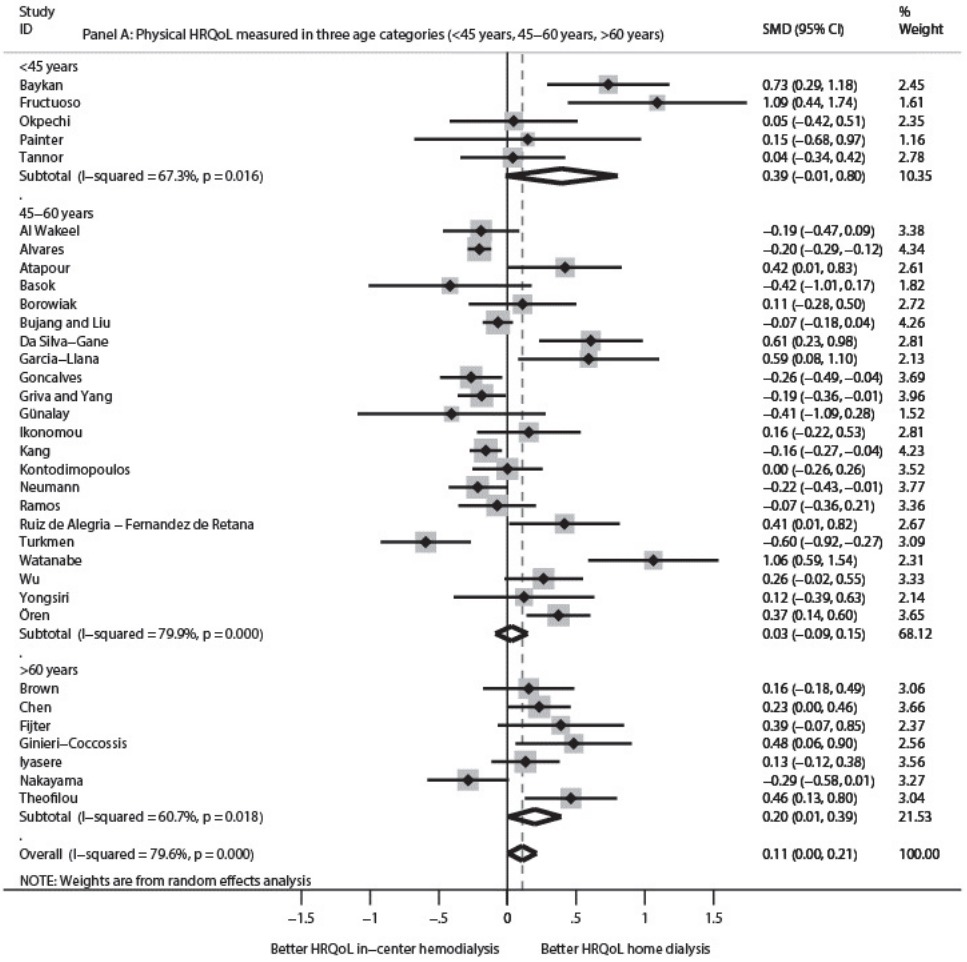
Legend: SMD, standardized mean difference; 95% CI, 95% confidence interval; SF, Short Form (including KDQOL); WHOQOL–BREF, World Health Organization Quality of Life–BREF; EQ–5D, EuroQol–5D; HRQoL, Health–Related Quality of Life.

Supplementary figure S1A. Meta-analysis of Health-Related Quality of Life in different questionnaires.



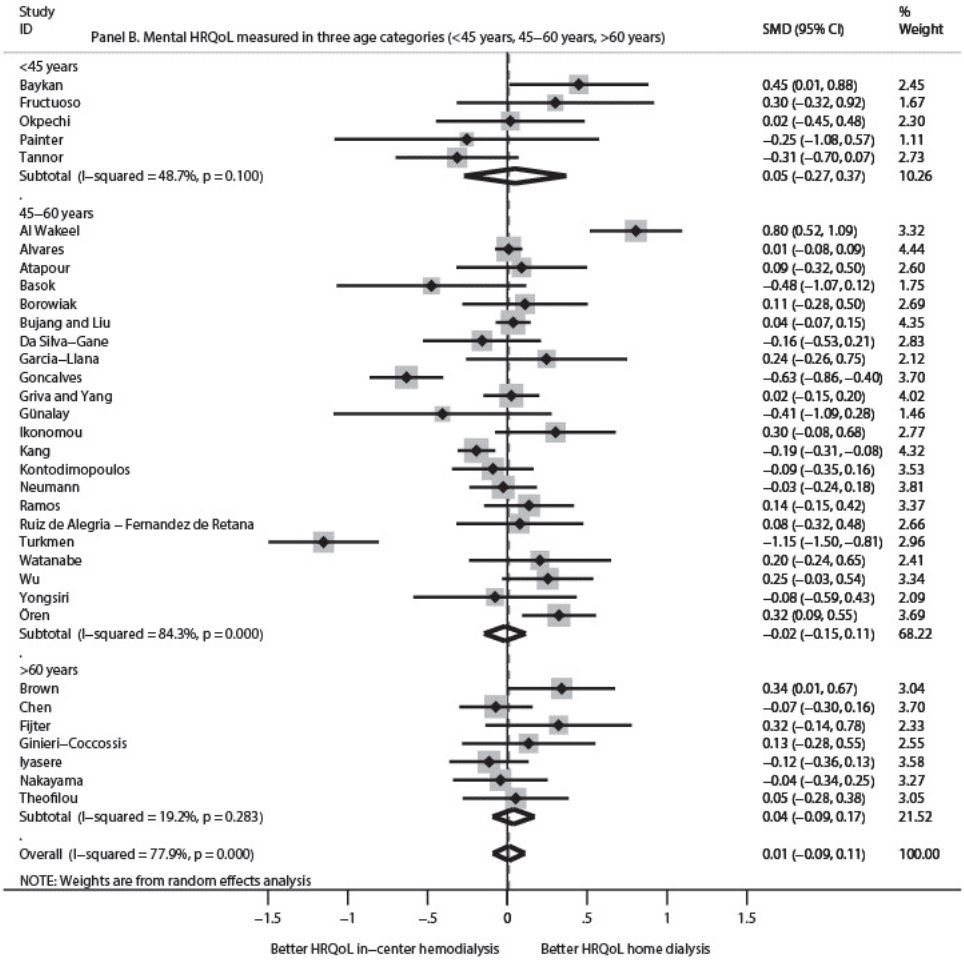
Legend: SMD, standardized mean difference; 95% CI, 95% confidence interval; SF, Short Form (including KDQOL); WHOQOL–BREF, World Health Organization Quality of Life–BREF; EQ–5D, EuroQol–5D; HRQoL, Health–Related Quality of Life.

Supplementary figure S1B. Meta-analysis of Health-Related Quality of Life in different questionnaires.



Legend: SMD, standardized mean difference; 95% CI, 95% confidence interval; HRQoL, Health–Related Quality of Life.

Supplementary figure S2A. Meta-analysis of Health-Related Quality of Life in different age categories.



Legend: SMD, standardized mean difference; 95% CI, 95% confidence interval; HRQoL, Health–Related Quality of Life.

Supplementary figure S2B. Meta-analysis of Health-Related Quality of Life in different age categories.

Chapter 8

The impact of COVID-19 on the mental health of dialysis patients

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Abstract

Background Studies have shown increased anxiety, depression, and stress levels among different populations during the coronavirus disease 2019 (COVID-19) pandemic. However, the impact of the pandemic on the mental health of dialysis patients remains unknown. The aim of this study was to investigate the mental health of dialysis patients during the COVID-19 pandemic compared to the period preceding the pandemic.

Methods Data originate from the ongoing multicentre observational Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes. Patients who filled in a Health-Related Quality of Life (HRQoL) questionnaire during the pandemic and six to three months prior were included. The mean difference in Mental Component Summary (MCS) score of the Short Form 12 was analysed with multilevel linear regression. A McNemar test was used to compare presence of mental health-related symptoms during and prior to the COVID-19 pandemic.

Results A total of 177 patients were included. The mean MCS score prior to COVID-19 was 48.08 ± 10.15, and 49.00 ± 10.04 during the COVID-19 pandemic. The adjusted mean MCS score was 0.93 point (95% CI -0.57 to 2.42) higher during the COVID-19 pandemic than during the period prior to the pandemic. Furthermore, no difference in the presence of the following mental health-related symptoms was found during the COVID-19 pandemic: feeling anxious, feeling sad, worrying, feeling nervous, trouble falling asleep, and trouble staying asleep.

Conclusions The mental health of dialysis patients appears to be unaffected by the COVID-19 pandemic. Dialysis patients may be better able to cope with the pandemic, since they have high resilience and are less impacted by social distancing measures.

Introduction

The coronavirus disease 2019 (COVID-19) outbreak that started in China rapidly spread across the globe, with major consequences for health and the healthcare system. Currently, the estimated number of infections worldwide is 66 million and the estimated number of deaths 1.5 million.[1] In the Netherlands, the first COVID-19 patient was diagnosed on February 27th, 2020.[2] In response, the Dutch government announced drastic measures; they obliged social distancing including working from home and closing all educational institutions, restaurants, cultural and sporting facilities, to limit further spread of the virus.

The current COVID-19 outbreak has been shown to increase levels of anxiety, depression, and stress among the general population.[3–5] In patients with Alzheimer's disease and immunodeficiency, COVID-19 also resulted in higher anxiety levels and a higher risk of developing depression.[6,7] Moreover, patients with chronic conditions had an increased risk of developing sleeping disorders.[8] Patients with end-stage kidney disease (ESKD) who are treated with dialysis have a higher risk of a severe clinical course of COVID-19 and worse outcome.[9] The knowledge that they have a higher risk of infection, can become more seriously ill and have a higher mortality risk might result in symptoms like feeling anxious, feeling sad, worrying, feeling nervous and sleeping problems. Moreover, the psychological well-being of dialysis patients may also be affected by fear among fellow patients and healthcare professionals. However, data regarding the impact of the COVID-19 pandemic on the mental health of dialysis patients are lacking. The aim of this study was to investigate the mental health of dialysis patients during the COVID-19 pandemic compared to the period preceding the pandemic.

Methods

Study population and design

To compare the mental health of dialysis patients prior to the COVID-19 pandemic with a period during the COVID-19 pandemic, data were used from the ongoing Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO, Netherlands Trial Register identifier: NL6519).[10] In this nationwide, prospective, observational study Health-Related Quality of Life (HRQoL) of home dialysis, i.e.

peritoneal dialysis and home haemodialysis, patients is compared with HRQoL of in-centre haemodialysis patients. All adult patients that started chronic dialysis were potentially eligible and all included patients provided written informed consent. The first patient was recruited in December 2017 and the end of the inclusion period is expected in 2021. HRQoL, and other patient-reported outcomes such as symptom burden, were measured with questionnaires.

For the present study, patients were included if they had completed a questionnaire during the COVID-19 pandemic, defined as the period between February 27th and July 1st, 2020, and a questionnaire 6 months prior to the COVID-19 pandemic. When the questionnaire administered 6 months prior to the COVID-19 pandemic was not available, the questionnaire administered 3 months prior to the COVID-19 pandemic was used.

Outcome parameters

The primary outcome parameter was mental health, assessed with the Mental Component Summary (MCS) score of the 12-item Short Form (SF-12) health survey. The MCS was calculated using standard algorithms, meaning that a healthy individual scores 50 points on a scale of 0-100 with a standard deviation of 10 points.[11,12] Higher scores of the MCS reflect better HRQoL.[11] The secondary outcome parameters were the Physical Component Summary (PCS) score of the SF-12, and the presence and severity of mental health-related symptoms assessed with the Dialysis Symptom Index (DSI).[11,13] These symptoms included feeling anxious, feeling sad, worrying, feeling nervous, trouble falling asleep, and trouble staying asleep. A 5-point Likert scale, ranging from 'not at all bothersome' to 'very bothersome', was used to evaluate the severity of these 6 symptoms.[13]

Data collection

The following sociodemographic and clinical data were collected at study baseline: sex, age, primary kidney disease, living situation (alone, with partner, or in a nursing home), level of education, work status, history of comorbidities, recent start, dialysis modality (in-centre haemodialysis, peritoneal dialysis, or home haemodialysis), and acute start at dialysis initiation. Primary kidney disease was classified according to the codes of the ERA-EDTA. A higher level of education includes university colleges and university of applied sciences. Comorbidity was scored according to the Charlson comorbidity index.[14] Recent start of dialysis was defined as start of dialysis 6 months

prior to the COVID-19 pandemic. Acute start of dialysis was defined as an unplanned start of dialysis with no previous consultation of a nephrologist.

In addition, the questionnaires were reviewed to check whether participants had written comments related to COVID-19.

Statistical analysis

All normally distributed continuous variables are presented as mean with standard deviation (SD), non-normally distributed variables as median with interquartile range (IQR), and categorical variables as proportion.

Multilevel linear regression was used to assess the overall association between the COVID-19 pandemic and MCS or PCS score. The multilevel model was used to adjust for correlation of repeated observations within a patient. Both crude and adjusted analyses were performed. Adjusted models were corrected for sex, age, Charlson comorbidity index, higher educational level, dialysis modality, and recent start of dialysis.

A McNemar test was used to compare the presence of mental health-related symptoms prior to the COVID-19 pandemic with the period during the COVID-19 pandemic. A Wilcoxon signed-rank test was used to compare the severity of mental health-related symptoms prior to the COVID-19 pandemic with the period during the COVID-19 pandemic. In addition, the severity scores of the 6 mental health-related symptoms were added up to an overall symptom severity score ranging from 0 to 30, in which a severity score of 30 meant that in all mental health-related symptoms the maximum severity score was reported.[13,15]

Missing values of SF-12 items and confounders were imputed with standard multiple imputation techniques using 10 repetitions and predictive mean matching (SPSS).[16] A difference of 3 points on the MCS and PCS was considered clinically relevant and a p-value of <0.05 was considered statistically significant.[17,18] All analyses were performed using SPSS Statistics version 26 (IBM) or STATA 14.

Results

A total of 177 patients were included, of whom 125 patients had filled in a questionnaire 6 months prior to the COVID-19 pandemic and 52 had filled in a questionnaire 3 months prior to the COVID-19 pandemic. The majority of patients (87%) had filled in their questionnaires completely. Patient characteristics are depicted in Table 1. The majority (63%) was male, the mean age of the study population was 64.9 ± 11.5 years and 61% started dialysis 3 to 6 months prior to the COVID-19 pandemic. Only 1% of the study population was infected with SARS-CoV-2.

Table 1. Patient Characteristics

Characteristics	Patients (n=177)
Sex, male, n (%)	112 (63)
Age, mean (SD), years	64.9 ± 11.5
Primary kidney disease, n (%)	
Glomerulonephritis/pyelonephritis	27 (21)
Cystic kidney disease	12 (9)
Renovascular kidney disease	28 (21)
Diabetes mellitus	24 (18)
Other/unknown	41 (31)
Living situation, n (%)	
Alone	49 (31)
With partner	95 (60)
In nursing home	4 (3)
Higher education, n (%)	34 (21)
Employed, n (%)	27 (16)
Charlson comorbidity index, median [IQR]	4 [2-5]
Recent start of dialysis, n (%)	107 (61)
Dialysis modality at dialysis initiation, n (%)	
In-centre haemodialysis	132 (75)
Peritoneal dialysis	43 (25)
Home haemodialysis	2 (1)
Acute start of dialysis, n (%)	25 (14)
Infected with SARS-CoV-2, n (%)	2 (1)

The MCS score was 48.08 ± 10.15 prior to the COVID-19 pandemic and 49.00 ± 10.04 during the COVID-19 pandemic (Figure 1A). The mean MCS score was 0.91 point (95% CI -0.59 to 2.41, *p*-value 0.2) higher during the COVID-19 pandemic than prior to the COVID-19 pandemic (Table 2). Adjustment for multiple confounders did not change this result.

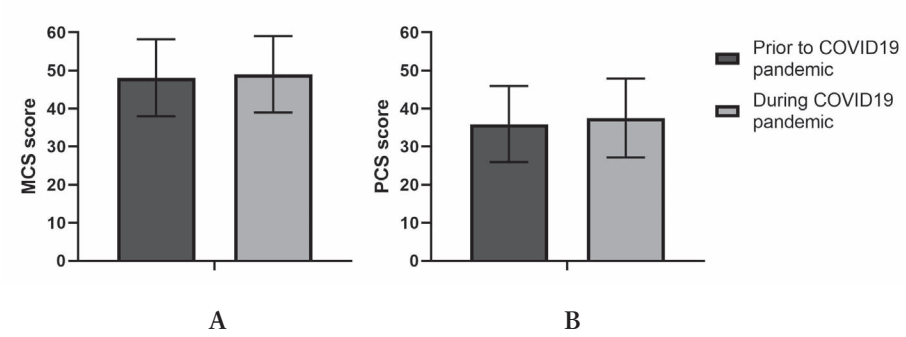

Figure 1. Mental Component Summary score (A) and Physical Component Summary score (B) prior and during COVID-19 pandemic
MCS, Mental Component Summary; PCS, Physical Component Summary.

The PCS score was 35.92 ± 9.99 prior to the COVID-19 pandemic and 37.52 ± 10.38 during the COVID-19 pandemic (Figure 1B). The mean PCS score was 1.63 point (95% CI 0.28 to 2.99, *p*-value 0.02) higher during the COVID-19 pandemic than prior to the COVID-19 pandemic (Table 2). Adjustment for multiple confounders did not change this result.

Table 2. Linear regression of Health-Related Quality of Life score during COVID-19 pandemic

	Regression Coefficient (95% CI)		
	Crude	**Adjusted***	**Adjusted****
MCS change during COVID-19	0.91 (-0.59 to 2.41)	0.91 (-0.59 to 2.41)	0.93 (-0.57 to 2.42)
PCS change during COVID-19	1.63 (0.28 to 2.99)	1.63 (0.28 to 2.98)	1.64 (0.28 to 2.99)

MCS, Mental Component Summary; PCS, Physical Component Summary.
* Adjusted for age and sex
** Adjusted for age, sex, Charlson comorbidity index, higher educational level, dialysis modality, and recent start of dialysis

As depicted in figure 2, patients on dialysis reported frequently that they were feeling sad (33% vs 35%), were worrying (35% vs 36%), had trouble falling asleep (37% vs 39%) and had trouble staying asleep (53% vs 51%). For all mental health-related symptoms, there was no significant difference in presence prior to the COVID-19 pandemic compared to the period during the COVID-19 pandemic.

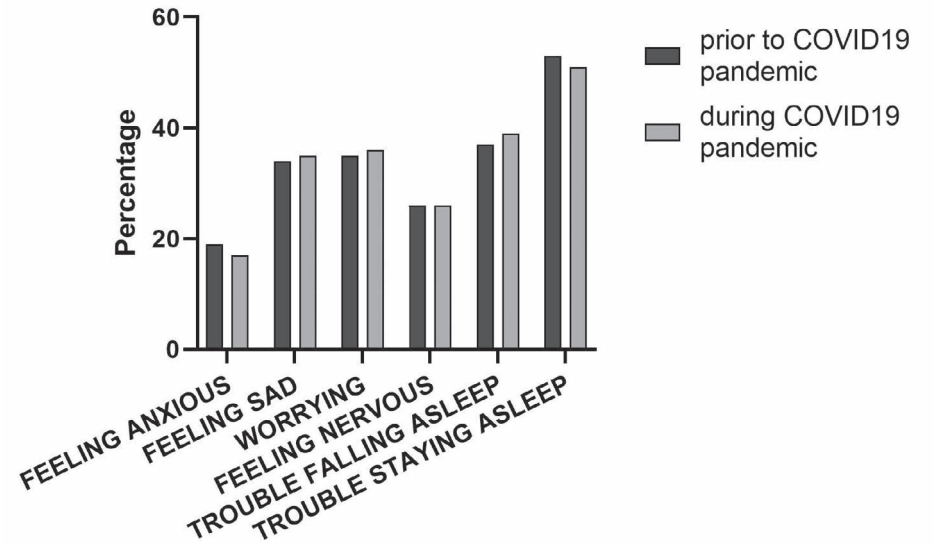

Figure 2. Presence of mental health-related symptoms prior and during COVID-19 pandemic

Also, no difference was found regarding the total number of mental health-related symptoms: 74% of patients reported at least 1 symptom prior to the COVID-19 pandemic compared to 72% of patients during the COVID-19 pandemic while 7% of patients reported all 6 symptoms prior the COVID-19 pandemic compared to 6% of patients during the COVID-19 pandemic.

The severity of mental health-related symptoms was not significantly higher during the COVID-19 pandemic (Supplementary Figure 1). In addition, the total symptom severity score (ranging from 0-30) was not different between the two time periods (4 [IQR 0 - 8] prior to the pandemic vs 4 [IQR 0 - 9] during the COVID-19 pandemic).

Finally, a few patients wrote comments on the questionnaire concerning the COVID-19 pandemic. Patients commented that the COVID-19 pandemic had a huge impact on everyday life and that more help by informal caregivers was needed. For example, a patient wrote '*this corona period also affects our daily life. Due to my health condition, we have tried to avoid all threats. The domestic help is no longer coming and grocery shopping has been done by our children.*' Another patient wrote '*Daily life has changed quite a bit due to corona. I stay indoors as much as possible*'. Few patients also noted that they felt isolated, '*Loneliness because of corona. I am unable to receive visitors and all other activities have been discontinued.*'

Discussion

This study showed that the COVID-19 pandemic did not affect the self-reported mental health of dialysis patients, as measured with HRQoL and symptom questionnaires. Dialysis patients did not report a higher burden or a higher severity of mental health-related symptoms such as feeling anxious, feeling sad, worrying, feeling nervous, trouble falling asleep, and trouble staying asleep.

A possible explanation for our findings could be that dialysis patients already suffer greatly from their kidney disease and treatment, which could limit the impact of the COVID-19 pandemic. Dialysis has a major impact on the mental health of dialysis patients resulting in a lower HRQoL than patients with other chronic illnesses such as malignancies.[19,20] Mittal *et al.* found that patients with kidney disease had a 2.68 point lower MCS score compared to the general population, whereas patients with malignancies had a 0.31 lower MCS score compared to the general population.[20] In addition, dialysis patients have to deal with fluid restrictions, polypharmacy, and frequent hospital visits. As a result, dialysis patients have to adjust their everyday life for they encounter all these difficulties and adversities. As such, they have developed coping mechanisms in order to maintain satisfactory mental health. This ability to adapt is called resilience in literature and is often described as 'a measure of successful stress-coping ability'.[21] Resilience includes having a positive perception, accepting a burdensome situation, and being motivated to overcome various difficulties.[22] In a Spanish study, a higher level of resilience was associated with higher HRQoL scores.[23] The importance of resilience for both haemodialysis and peritoneal dialysis patients to overcome the burden of dialysis has been emphasized in multiple studies.[24–26] In one of these studies the resilience of dialysis patients was quantified with a frequently used resilience scale. They found a score of 82.4 in dialysis patients, comparable to the general population (80.4) and reasonably higher than among patients visiting a general practitioner (71.8).[21,24] Dialysis patients may have a high level of resilience compared to primary care patients, as they have learned to adapt over time to bear the burden of dialysis and their disease in general, which could explain their ability to deal better with different stressors such as the COVID-19 pandemic.

The large amount of unemployed dialysis patients in our population may also explain why the COVID-19 pandemic did not seem to affect mental health. A study showed that people who are unemployed had higher mental distress in general, but did not

experience an increase of mental distress during the COVID-19 pandemic as assessed with the 12-item General Health Questionnaire (change score –0.48 (95% CI –1.55 to 0.60).[27] Whereas people who are employed during the COVID-19 pandemic experienced an increase in mental distress compared to the period before COVID-19 (change score 0.63 (95% CI 0.20 to 1.06).[27,28] In our population only 16% was employed, which is consistent with clinical practice as many dialysis patients are unemployed.

The third possible explanation for our results could be that 75% of our study population received in-centre haemodialysis, which might diminish mental problems that could have developed as a result of the national social isolation. Support from fellow patients, nurses, and health care professionals can contribute to a reduced sense of loneliness. Moreover, dialysis patients usually participate less in everyday activities than age-matched healthy individuals or even kidney transplant patients due to the nature of the dialysis treatment.[29] The regular visits to the hospital for dialysis treatments consumes an important part of the patient's time, with less time for social activities, work or travelling. Dialysis patients will be affected less by national policy measures such as social distancing since they experience fewer major changes in everyday life. In addition, in-centre haemodialysis patients might experience a sense of safety during their hospital visits that further limits the effect of the COVID-19 pandemic on mental health. In the Netherlands, many precautionary measures were taken at dialysis centres, such as screening for fever/complaints at entry for all patients, distance of 1.5 m whenever possible between people and wearing of face masks for dialysis patients, dialysis nurses and physicians early in the course of the pandemic. Also, dialysis patients that attended the hospital for haemodialysis sessions were able to obtain adequate information concerning COVID-19 directly from their health care professionals. In a Chinese study it was found that more information about the disease contributed to less anxiety levels.[4]

It should be noted that some dialysis patients did express feelings of loneliness due to social isolation in the additional comments of the questionnaire. Because of their vulnerability they were being extra careful to protect themselves; informal caregivers took over many tasks for the patients so that they could avoid contact with others as much as possible. In a national survey among the general Dutch population, more than half of the participants indicated moderate or severe feelings of loneliness from April to June 2020. Nonetheless, they found that concerns among the general Dutch

population began to subside around the end of March 2020.[30] At this point the number of newly reported corona cases also began to decline. Compared to other countries in Europe including France, the United Kingdom and Italy, the number of newly reported COVID-19 patients and deaths was lower in the Netherlands, which could be a final explanation of the results in our study.[31]

The results of our study are in line with a recent study in the United Kingdom, which showed that the COVID-19 pandemic did not affect the mental health of patients with chronic illnesses as assessed with a generic HRQoL questionnaire (change score in the GHQ-12 0.40 (95% CI −0.30 to 1.09).[27] Contradictory, an online survey among 1.210 Chinese people found higher levels of stress, depression, and anxiety among those with a history of chronic illnesses.[4] Another study conducted in Northern Spain also showed higher levels of stress, depression, and anxiety among those with a history of chronic illnesses.[5] Unfortunately, none of all these studies have specified the participants' diseases, making a good comparison with our study population difficult. Also, in two studies no comparison with a historic control group or a pre-COVID-19 assessment of mental health was performed.[4,5]

To our knowledge, this is the first study investigating whether the COVID-19 pandemic affects the mental health of dialysis patients. Strengths of this study include the use of validated self-reported HRQoL and symptom questionnaires and the use of an existing prospective and nationwide cohort of dialysis patients (DOMESTICO) for analysis. Moreover, the number of patients in our study would have been sufficient to detect a significant difference in SF-12 composite scores between time periods as small of 2.17, whereas a difference of 3 is defined clinically relevant in literature.[17,18] We calculated in our sample size that a total of 123 patients was sufficient to detect a 3 point difference between time points (α=0.05, β=0.10). In our study, we had a 97% power to detect such a clinically relevant difference. A limitation of our study might be that the MCS score of the SF-12 questionnaire is not sensitive enough to detect differences over time in individuals, i.e. that the MCS score has limited responsiveness.[32] To overcome this issue, we also used the DSI which provides more detailed information about the mental health of the patients. Another limitation might be that the chosen period of the COVID-19 pandemic was too short to demonstrate an association with mental health. The COVID-19 virus is still spreading and its effect on the economy is currently unclear. Therefore, if the pandemic lasts longer, a negative impact on mental health may still be revealed.

In conclusion, the mental health of dialysis patients assessed with SF-12 and DSI appears to be unaffected during the first wave of the COVID-19 pandemic. This could be explained by higher resilience, more unemployment among dialysis patients, less impact of social distancing on the dialysis population, strict precautionary measures and perceived support from health care professionals, which may all contribute to better coping with the COVID-19 pandemic. However, a second peak of COVID-19 is expected and the economic burden of the pandemic has yet to be discovered. Therefore, it is important to continue paying attention to the concerns and needs of our dialysis population.

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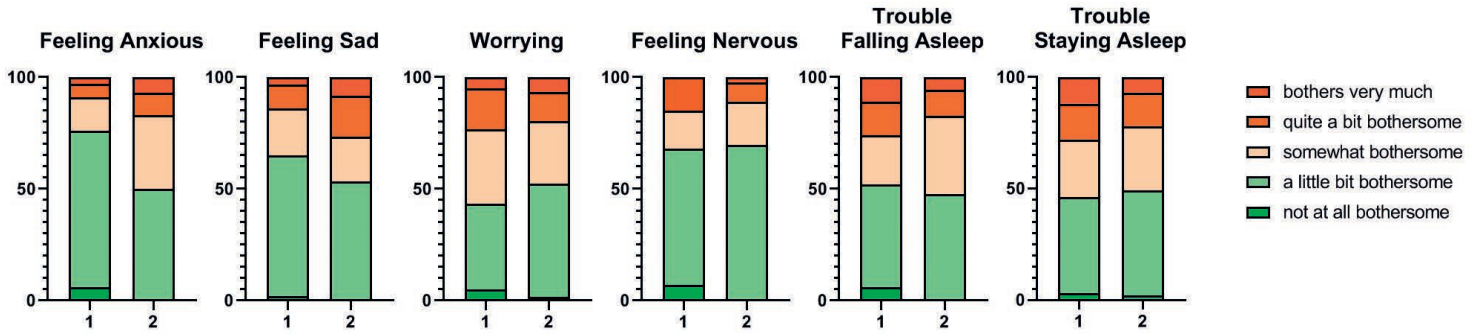
Supplemental material



Supplementary Figure 1. Severity of mental health-related symptoms prior and during COVID-19 pandemic
1; period prior to COVID-19 pandemic. 2; period during COVID-19 pandemic.

Chapter 9

Health-Related Quality of Life compared between kidney transplantation and nocturnal hemodialysis

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Abstract

Background Health-Related Quality of Life (HRQoL) is an important outcome measure in patients with end-stage renal disease. HRQoL is assumed to improve with kidney transplantation and also with nocturnal hemodialysis compared to conventional hemodialysis. However, there is no evidence regarding HRQoL to support the optimal treatment choice for patients on nocturnal hemodialysis who hesitate opting for transplantation. We therefore compared HRQoL between patients who were treated with kidney transplantation or nocturnal hemodialysis for one year.

Methods We assessed HQRoL using the Kidney Disease Quality of Life–Short Form questionnaire in a cross-sectional sample of patients who were treated with kidney transplantation *(n=41)* or nocturnal hemodialysis *(n=31)* for one year. All patients on nocturnal hemodialysis were transplantation candidates. Using linear regression, we compared HRQoL between kidney transplantation and nocturnal hemodialysis, and adjusted for age, sex, dialysis duration, cardiovascular disease, and presence of residual urine production.

Results At one year follow-up, mean age of the study population was 54 ±13 years, and median dialysis duration was 3.2 (IQR 2.1–5.0) years. Kidney transplantation was associated with significantly higher HRQoL on the domain *effects* compared to nocturnal hemodialysis (adjusted difference 12.0 points, 95% CI 3.9; 20.1). There were potentially clinically relevant differences between kidney transplantation and nocturnal hemodialysis on the domains *burden* (adjusted difference 11.1 points, 95% CI -2.6; 24.8), *social support* (adjusted difference 6.2, 95% CI -6.6; 19.1), and the physical composite score (adjusted difference 3.0, 95% CI -2.0; 8.1), but these were not significant.

Conclusion After kidney transplantation, HRQoL is especially higher on the domain "effects of kidney disease" compared to nocturnal hemodialysis. This can be useful when counseling patients on nocturnal hemodialysis who may opt for transplantation.

Introduction

Health-Related Quality of Life (HRQoL) is an important indicator of well-being in patients with end-stage renal disease and is associated with survival and clinical outcomes.[1-4] Compared to the general population, patients with end-stage renal disease have severely diminished HRQoL, by some deemed even lower than in diseases such as congestive heart failure, chronic lung disease or cancer.[5]

The preferred treatment for end-stage renal disease is kidney transplantation, which is associated with improved HRQoL and survival.[6] However, because of the limited availability of donor kidneys and because of transplant failure, many patients have to remain on dialysis.

An alternative to conventional dialysis modalities is frequent nocturnal hemodialysis. With this treatment, patients dialyze almost daily and twice as long (7–8 hours), generally at home. Thus, this treatment removes fluid more slowly and clears more solutes such as urea and phosphate.[7] Nocturnal hemodialysis may hence improve intermediate outcomes[8, 9] and possibly even survival, although mortality data remain inconsistent.[10, 11] By dialyzing at night, patients save time during the day, and nocturnal hemodialysis has thus been reported to improve HRQoL[12-14] to such an extent that some patients may even choose to forgo transplantation.[15]

How clinicians should deal with this reluctance toward transplantation is unclear. Currently, there is no evidence to support the optimal treatment choice for these patients, particularly not regarding patient-reported outcome measures. To fill this gap, we compared HRQoL measured with the Kidney Disease Quality of Life—Short Form (KDQOL-SF) between kidney transplant recipients and transplantation-eligible patients treated with nocturnal hemodialysis.

Methods

Study population

We analyzed a cross-sectional cohort from the ongoing NOCTx study (NCT00950573), a prospective cohort study designed to compare progression of coronary artery calcification between kidney transplant recipients, patients on frequent nocturnal

home hemodialysis, and patients on chronic peritoneal dialysis or conventional hemodialysis. Patients were eligible when aged between 18 and 75 years and were candidates for transplantation when on dialysis. All study participants gave written informed consent. NOCTx excluded patients with a life expectancy <3 months, pre-emptive transplantation, or non-adherence to dialysis regimens. NOCTx has been approved by the Medical Ethics Committee of the University Medical Center Utrecht and is conducted in accordance with the Declaration of Helsinki.

Between December 2009 and February 2016, NOCTx included 54 kidney transplant recipients and 39 patients on nocturnal hemodialysis who were referred for study participation to the University Medical Center of Utrecht, the Netherlands. For the present analyses, we included all kidney transplant recipients (*n=41*) and patients on nocturnal hemodialysis (*n=31*) who had one-year follow-up data. Most patients with a kidney transplant and on nocturnal hemodialysis entered NOCTx 2–3 months after switching to their respective treatment; thus, data from before switching were not available in these patients. We therefore analyzed data cross-sectionally after one year of treatment.

Treatment characteristics

Patients received treatment according to guidelines by the attending nephrologists. Kidney transplant recipients were treated in two tertiary centers, where standard immunosuppressant regimens consisted of a calcineurin inhibitor (tacrolimus), mycophenolate mofetil, and prednisone in tapering doses. Patients on nocturnal hemodialysis were trained and monitored in two dialysis centers that offered specialized training programs for nocturnal home hemodialysis. Patients dialyzed ≥ 4 x 8 hours per week at home, on a single needle, with a lower effective blood flow (150–220 mL/min), lower dialysate flow (300 mL/min), and a somewhat lower bicarbonate concentration compared to conventional hemodialysis, which was adjusted depending on laboratory results. Unfractionated heparin was used as anticoagulation.

Health-Related Quality of Life

We assessed HRQoL with the validated KDQOL-SF version 1.2.[16] The KDQOL-SF consists of a general part and a disease-specific part. The general part, the Short Form with 36 questions (SF-36) version 1[17], consists of eight domains that can be summarized in two scores. These summary scores are designed to reflect the general population in the United States when the means are 50 with a standard deviation of

10 points for physical functioning (physical composite score) and mental functioning (mental composite score).[18] The composite scores were obtained from 12 questions in the SF-36 (PCS-12 and MCS-12).[1] The disease-specific part of the KDQOL-SF consists of 44 kidney disease-targeted questions, grouped in 12 domains. We focused on the domains *symptoms of kidney disease*, *effects of kidney disease*, *burden of kidney disease*, *cognitive function*, *quality of social interaction*, *sexual function*, *sleep*, *social support* and *overall health*. We did not evaluate the domains *work status*, *patient satisfaction* and *dialysis staff encouragement* in this study. The domains are scored from 0 to 100, with higher scores indicating better quality of life. Explanations of the disease-specific domains are available as Table 1 (adapted from Carmichael *et al*.[19]).

Table 1. Explanation of the Kidney Disease Quality of Life-Short Form (KDQOL-SF) kidney disease-specific domains.

Domains	Interpretation	
	Low score	High score
Symptoms of kidney disease	Extremely bothered by dialysis-related symptoms such as muscle cramps, pruritus, anorexia, and/or access problems	Not at all bothered
Effect of kidney disease on daily life	Extremely bothered by fluid and dietary restriction, by an inability to travel, and dependency on doctors	Not at all bothered
Burden of kidney disease	Extremely bothered by the time consumed by dialysis, its intrusiveness, and degree burden on family	Not at all bothered
Cognitive function	Affected all of the time by inability to concentrate, confused, with poor reaction time	Not at all affected
Quality of social interaction	Continual irritation and failure to get along with people with virtual isolation	No problems, socially interactive
Sexual function	Experiencing severe problems with enjoyment and arousal	No problems
Sleep	Very poor sleep with daytime somnolence	No problems with sleep
Social support	Very dissatisfied	Satisfied with level of social support
Overall health	Rates health as worst possible	Rates health as best possible

Adapted from Carmichael *et al*.[19]

Other variables

At time of questionnaire completion, study personnel recorded demographical and clinical parameters (pre-dialysis blood pressure and post-dialysis weight averaged from routine measurements during 3 hemodialysis sessions or 2 outpatient visits for kidney transplant recipients) and laboratory parameters (total calcium, phosphate, parathyroid hormone, total cholesterol, albumin, hemoglobin, and C-reactive protein) routinely measured at local treatment facilities. Study personnel assessed presence of comorbidities by chart review, and assessed residual urine production with the most recent 24h-urine collection, which we classified as present (≥100mL/24u) or absent. Smoking status, oral anticoagulant use, and educational level were self-reported.

We defined diabetes mellitus as use of oral anti-diabetic medication or insulin therapy, and cardiovascular disease as any history of angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, stroke, intermittent claudication, peripheral artery angioplasty or bypass grafting. We defined higher education as any tertiary education. We estimated glomerular filtration rate with the Chronic Kidney Disease-Epidemiology Collaboration equation 2009 for kidney transplant recipients.

Statistical Analyses

We reported data as number (proportion) for categorical data, mean ±standard deviation for normally distributed variables, and median (interquartile range [IQR]) for non-normally distributed variables. We presented patient characteristics and HRQoL by renal replacement therapy. We compared categorical data with chi-squared tests, normally distributed variables with t-tests, and non-normally distributed variables with Mann-Whitney-U tests.

We used multiple linear regression analyses to examine the associations between renal replacement therapy and HRQoL. We regarded 5-point differences clinically relevant in the disease-specific domains, and 3-point differences clinically relevant in the composite scores.[17, 18] We adjusted stepwise for potential confounders age (years), sex, educational level (high/low), dialysis duration (years), presence of diabetes mellitus, cardiovascular disease, and presence of residual urine production (≥100mL/24u or absent), and kept them in the model when coefficients changed >10%. In the final model, we adjusted for age, sex, dialysis duration, cardiovascular disease, and presence of residual urine production.

We reported regression coefficients with 95% confidence intervals (CI). We considered P-values ≤ 0.05 (two-tailed) statistically significant, did not attempt imputation for missing values, and performed all analyses with R 3.4.1.[20]

Results

Study population

The mean age of the study population *(n=72)* was 54 ±13 years, 50 (69%) were male, median dialysis duration was 38 (IQR 25–60) months, and 17 (24%) had a history of cardiovascular disease. There were no significant differences in demographics or medical history between the kidney transplant recipients (*n=41*) and patients on nocturnal hemodialysis (*n=31*), but kidney transplant recipients had significantly lower phosphate levels and higher hemoglobin levels (Table 2). Kidney transplant recipients had an estimated glomerular filtration rate of 54.8 ±15.7 mL/min, while patients on nocturnal hemodialysis had median 0 (IQR 0–250) mL/day residual urine production. Patients on nocturnal hemodialysis dialyzed 38.3 ±7.2 hours per week in 4.8 ±0.8 sessions per week.

Table 2. Characteristics of the 72 kidney transplant recipients and patients on nocturnal hemodialysis at one year of follow-up.

	Kidney transplantation (n = 41)	**Nocturnal hemodialysis (n = 31)**	***P-value***
Demographics			
Age (yr)	54.0 ±13.8	53.9 ±12.5	0.97
Male (%)	31 (75)	19 (62)	0.29
Body mass index (kg/m2)	25.5 ±4.2	26.5 ±5.2	0.37
Systolic blood pressure (mmHg)	132 ±14	139 ±20	0.11
Diastolic blood pressure (mmHg)	80 ±10	75 ±12	0.12
Current smoker (%)	6 (15)	6 (19)	0.83
Oral anticoagulant use (%)	5 (13)	2 (7)	0.66
Higher education (%)	11 (28)	8 (26)	0.99
Medical history			
Dialysis duration (mo)	28 (24–58)	39 (28–66)	0.12
End-stage renal disease duration (mo)	28 (25–62)	39 (28–94)	0.15

Table 2. Characteristics of the 72 kidney transplant recipients and patients on nocturnal hemodialysis at one year of follow-up. (continued)

	Kidney transplantation (n = 41)	**Nocturnal hemodialysis (n = 31)**	***P-value***
Cause of end-stage renal disease (%)			0.23
Glomerulonephritis	9 (22)	11 (36)	
Interstitial nephritis	1 (2)	0 (0)	
Cystic kidney disease	14 (34)	5 (16)	
Renovascular	9 (22)	3 (10)	
Diabetes mellitus	1 (2)	2 (7)	
Other	3 (7)	5 (16)	
Unknown	4 (10)	5 (16)	
Comorbidities (%)			
Diabetes mellitus	3 (7)	4 (13)	0.70
Prior cardiovascular disease	7 (17)	10 (32)	0.22
Laboratory parameters			
Calcium (mmol/L)	2.41 ±0.10	2.37 ±0.20	0.30
Phosphate (mmol/L)	0.88 ±0.21	1.42 ±0.39	<0.001
Parathyroid hormone (pmol/L)	8.5 (6.4–12.0)	13.8 (7.6–22.8)	0.14
Cholesterol (mmol/L)	5.0 ±1.1	4.6 ±1.0	0.26
Albumin (g/L)	42.4 ±3.1	42.4 ±3.1	0.95
Hemoglobin (mmol/L)	8.9 ±1.0	7.0 ±0.8	<0.001
C-reactive protein (mg/L)	3.0 (2.0–8.3)	5.0 (3.0–10.0)	0.29

Results are presented as mean ±standard deviation, median (interquartile range), or number (proportion).

The current sample comprised 77% of all kidney transplant recipients and patients on nocturnal hemodialysis who entered NOCTx *(n=93)*. Seven kidney transplant recipients (3 were lost to follow-up, 2 withdrew consent, 2 died) and 7 patients on nocturnal hemodialysis (3 received a transplant, 2 withdrew consent, 1 was lost to follow-up, 1 died) did not complete follow-up at one year, while 6 kidney transplant recipients and 1 patient on nocturnal hemodialysis did not complete quality of life questionnaires at the one-year follow-up. Their mean age (*n=21*) was 49 ±14 years (P=0.15 versus study population), 12 (57%) were male (P=0.43 versus study population), median dialysis duration was 65 (IQR 42–84) months (P=0.03 versus study population), and 4 (19%) had a history of cardiovascular disease (P=0.89 versus

study population). Kidney transplant recipients were not more likely to complete follow-up than patients on nocturnal hemodialysis (P=0.88).

Health-Related Quality of Life at one year of treatment

The quality of life questionnaires were generally well-completed. In the following scales, one or more questionnaire items were missing resulting in a missing score: *sexual function* (5 respondents, 7%), SF-12 items (physical and mental composite scores; 2 respondents, 3%), *symptoms of kidney disease*, *effects of kidney disease*, *burden of kidney disease*, and *overall health* (1 respondent each, 1%).

Overall, kidney transplant recipients had numerically higher scores on the kidney disease-specific domains of HRQoL and the physical composite score compared to patients on nocturnal hemodialysis (Figure 1). Kidney transplant recipients scored significantly higher on the domain "effects of kidney disease" compared to patients on nocturnal hemodialysis, both in crude and adjusted analyses (Table 3). There were no significant differences on the other kidney disease-specific domains or the composite scores in both crude and adjusted analyses. When adjusted for age, sex, dialysis duration, cardiovascular disease, and residual urine production, kidney transplant recipients had potentially clinically relevant higher scores on the domains *burden of kidney disease*, *social support*, and the physical composite score compared to nocturnal hemodialysis, but these differences were not significant.

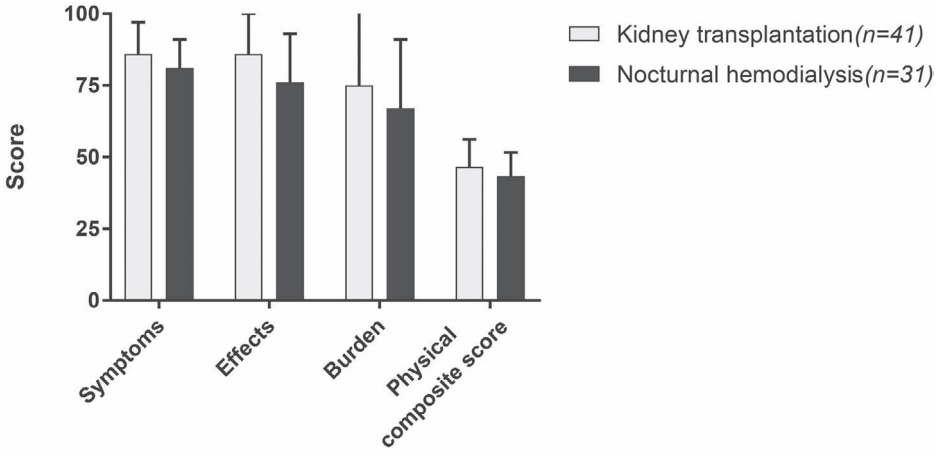

Figure 1. Disease-specific Health-Related Quality of Life scores and physical composite scores in the 72 kidney transplant recipients and patients on nocturnal hemodialysis.
Mean HRQoL scores on the disease-specific domains *symptoms*, effects, *burden of kidney disease*, and the physical composite scores as bar charts in the 72 kidney transplant recipients and patients on nocturnal hemodialysis. We presented 95% confidence intervals alongside the bars. Mean scores for kidney transplantation and nocturnal hemodialysis: "symptoms" 86 and 81; "effects" 86 and 76; "burden" 75 and 67; physical composite score 47 and 43 points, respectively.

Table 3. Health-Related Quality of Life scores and differences in scores between the 72 kidney transplant recipients and patients on nocturnal hemodialysis at one year of follow-up.

	Kidney transplantation (n = 41)	**Nocturnal hemodialysis (n = 31)**	***Crude difference (95% CI)***	***Adjusted* difference (95% CI)***
Kidney disease-related quality of life				
Symptoms of kidney disease	86 ±11	81 ±10	-5.7 (-10.7; -0.7)	-4.6 (-10.6; 1.3)
Effects of kidney disease	86 ±14	76 ±17	-9.8 (-16.9; -2.6)	-12.0 (-20.1; -3.9)
Burden of kidney disease	75 ±27	67 ±24	-8.0 (-20.1; 4.1)	-11.1 (-24.8; 2.6)
Cognitive function	81 ±19	78 ±18	-2.5 (-11.3; 6.3)	-4.3 (-14.2; 5.6)
Quality of social interaction	79 ±15	77 ±14	-1.3 (-8.3; 5.8)	1.4 (-6.7; 9.5)
Sexual function	72 ±30	64 ±33	-7.8 (-23.1; 7.5)	-2.0 (-19.1; 15.0)
Sleep	66 ±23	63 ±16	-2.8 (-12.3; 6.8)	-3.3 (-14.5; 8.0)
Social support	87 ±21	82 ±25	-4.7 (-15.5; 6.0)	-6.2 (-19.1; 6.6)
Overall health	70 ±16	65 ±17	-4.3 (-12.3; 3.6)	-4.9 (-14.1; 4.3)
SF-12 composite scores				
Physical composite score	47 ±10	43 ±8	-3.4 (-7.7; 0.9)	-3.0 (-8.1; 2.0)
Mental composite score	51 ±10	52 ±11	0.6 (-4.2; 5.5)	1.2 (-4.4; 6.8)

Abbreviations: SF-12: short form-12 items. Scores are presented as mean ±standard deviation, and differences with 95% confidence intervals.
*Adjusted for age (years), sex (male/female), dialysis duration (years), cardiovascular disease, and presence of residual urine production (≥100mL/24u or absent).

Discussion

To our knowledge, this is the first study to compare HRQoL between kidney transplantation and nocturnal hemodialysis, demonstrating that kidney transplantation is associated with significantly higher quality of life on the domain *effects of kidney disease* compared to nocturnal hemodialysis. In addition, kidney transplant recipients

have potentially clinically relevant higher quality of life on the domains *burden of kidney disease*, *social support*, and the physical composite score, although not significantly higher in this study. Together, these findings suggest that HRQoL is generally better after kidney transplantation than on treatment with nocturnal hemodialysis.

The differences in HRQoL are the most evident on the domain *effects of kidney disease*. As this domain involves the restraints patients experience regarding their diet, ability to travel, and dependency on doctors, it is explainable that kidney transplant recipients score higher on this domain. After all, kidney transplant recipients are freer in terms of diet and travel than any patient on dialysis. Besides this domain, kidney transplant recipients have numerically higher adjusted scores on the domains *burden of kidney disease*, *social support*, and the physical composite score. Although not *statistically significant*, these differences may be *clinically relevant*.[21] The original KDQOL-SF manual reads that 5-point differences are clinically relevant regarding the disease-specific domains, and 3-point differences regarding the composite scores[17, 18], which has been adopted by others.[22, 23] Notably, a 3-point difference in the composite scores is associated with a mortality risk of approximately 6.0%.[2, 3, 24] Given the size and consistent direction of these differences, we consider them relevant, even though they do not reach statistical significance with the current sample size.

In our experience, some patients treated with nocturnal hemodialysis decline kidney transplantation and prefer to stay on treatment with nocturnal hemodialysis. The current findings suggest that kidney transplantation - in which quality of life is known to improve[25-27] - is a more favorable treatment option regarding HRQoL for transplantation-eligible patients on nocturnal hemodialysis, although individual outcomes may differ importantly.

For patients that are unlikely to receive a kidney transplant (e.g. HLA-sensitized patients), potential benefits of nocturnal hemodialysis remain relevant, such as an improvement of quality of life. Importantly, HRQoL has been shown to improve after conversion to nocturnal hemodialysis from conventional hemodialysis in several observational studies[12, 14] and on selected domains in a randomized trial.[28] This is despite the fact that nocturnal hemodialysis is performed almost daily and requires considerable patient involvement. Notably, patients on nocturnal hemodialysis in our cohort have somewhat higher HRQoL scores compared to North-American

cohorts[12, 13, 29], which may be because all patients were transplantation candidates in our study. Remarkably, nocturnal hemodialysis does not seem to deteriorate sleep quality: patients on nocturnal hemodialysis have similar scores on the domain *sleep* to kidney transplant recipients in our study.

The results of this study should be interpreted within the context of some limitations. First, our study is not powered to demonstrate significance of all potentially relevant differences in kidney disease-specific HRQoL domains. For example, we would have needed 161 patients per group to show significance of an 8-point difference (as currently found) in the disease-specific domain *burden of kidney disease*. Second, the current data are cross-sectional after one year of treatment with kidney transplantation or nocturnal hemodialysis. A before/after comparison of HRQoL was not possible as patients were included in this study shortly after they had started treatment with either kidney transplantation or nocturnal hemodialysis. Third, we do not know the reasons why individual patients converted to nocturnal hemodialysis – there may have been patient selection. As noted in previous studies, healthier and more motivated patients may have been preferentially selected for nocturnal hemodialysis[30], which could influence HRQoL. Also, the current data are observational, although it should be noted that randomization to kidney transplantation would be unethical.

Our study has several strengths. First, questionnaire response rate in this study is high (91%) as compared to large studies on patients on hemodialysis.[1, 2] The responders' demographic characteristics are largely similar to that of non-responders; therefore, we consider our findings generalizable to patients on nocturnal hemodialysis who may opt for kidney transplantation. Second, we focus on kidney disease-specific domains of HRQoL alongside the physical and mental composite scores, which increases the ability to detect more specific differences in patients' well-being. Finally, this study has only included patients on nocturnal hemodialysis who were transplantation candidates; simultaneously, no kidney transplant recipients had been transplanted pre-emptively, i.e. all recipients had a history of dialysis treatment. Both of these inclusion criteria enable valid comparisons between the treatment groups.

In conclusion, HRQoL is higher after kidney transplantation especially on the domain *effects of kidney disease* compared to nocturnal hemodialysis. This can be useful when counseling patients on nocturnal hemodialysis who may opt for transplantation.

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Supplemental material

Extra Supplemental table 1. Crude differences in Health-Related Quality of Life between kidney transplantation and dialysis at one year of follow-up.

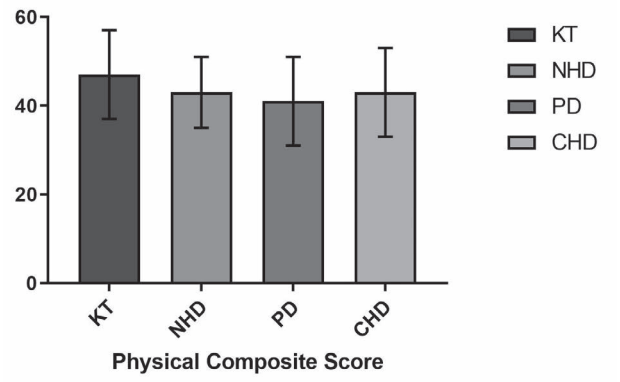
	KT (n = 41)	NHD (n = 31)		PD (n = 18)		CHD (n = 25)	
		B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Kidney disease-related quality of life							
Symptoms of kidney disease	*	-5.7 (-12.1; 0.7)	0.08	-8.6 (-16.2; -1.1)	**0.03**	-5.7 (-12.6; 1.2)	0.10
Effects of kidney disease	*	-9.8 (-17.5; -2.1)	**0.01**	-13.6 (-22.7; -4.5)	**<0.01**	-16.3 (-24.5; -8.1)	**<0.001**
Burden of kidney disease	*	-8.0 (-20.4; 4.4)	0.20	-16.5 (-31.2; -1.8)	**0.03**	-21.8 (-35.0; -8.6)	**0.001**
Work status	*	-11.3 (-31.8; 9.3)	0.28	-6.2 (-30.6; 18.1)	0.61	-7.1 (-29.0; 14.8)	0.52
Cognitive function	*	-2.5 (-10.9; 5.8)	0.55	5.1 (-4.8; 15.1)	0.31	-0.3 (-9.2; 8.7)	0.95
Quality of social interaction	*	-1.3 (-8.3; 5.7)	0.72	2.0 (-6.2; 10.3)	0.63	1.6 (-5.9; 9.0)	0.68
Sexual function	*	-7.8 (-24.6; 9.0)	0.36	-12.7 (-32.9; 7.5)	0.22	-13.4 (-33.6; 6.7)	0.19
Sleep	*	-2.8 (-12.1; 6.6)	0.56	-1.2 (-12.3; 9.9)	0.83	-1.7 (-11.6; 8.3)	0.74
Social support	*	-4.7 (-16.2; 6.8)	0.41	-7.4 (-21.0; 6.3)	0.29	-19.0 (-31.3; -6.7)	**<0.01**
Overall health	*	-4.3 (-12.1; 3.4)	0.27	-10.1 (-19.2; -0.9)	**0.03**	-7.1 (-15.3; 1.1)	0.09
SF-12 composite scores							
Physical composite score	*	-3.4 (-7.9; 1.1)	0.14	-5.9 (-11.4; -0.3)	**0.04**	-3.5 (-8.8; 1.7)	0.19
Mental composite score	*	0.6 (-3.7; 5.0)	0.77	2.7 (-2.7; 8.1)	0.32	-0.3 (-5.4; 4.8)	0.92

*Reference group.
Abbreviations: KT: kidney transplantation; NHD: nocturnal hemodialysis; PD: peritoneal dialysis; CHD: conventional hemodialysis; 95% CI: 95% confidence interval; SF-12: short form-12 items.

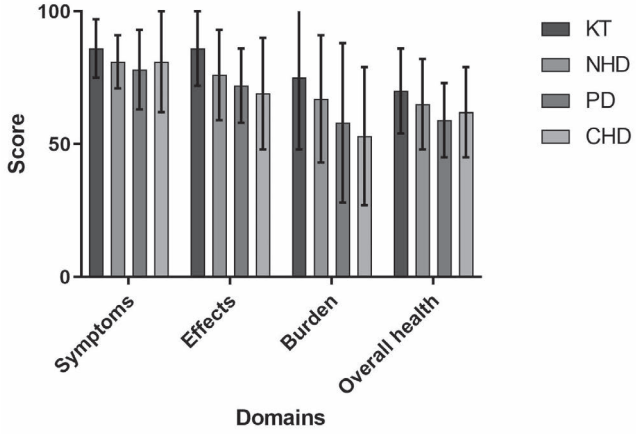
Extra Supplemental table 2. Adjusted* differences in Health-Related Quality of Life between kidney transplant recipients *(n=41)* and patients on nocturnal hemodialysis *(n=31)*, peritoneal dialysis *(n=18)* and conventional hemodialysis *(n=25)*.

	KT (n = 41)	NHD (n = 31)	PD (n = 18)	CHD (n = 25)
		B (95% CI)	B (95% CI)	B (95% CI)
Kidney disease-related quality of life				
Symptoms of kidney disease	*	-6.1 (-13.0; 0.8)	-10.9 (-20.1; -1.8)	-6.8 (-15.3; 1.6)
Effects of kidney disease	*	-10.7 (-18.9; -2.6)	-14.4 (-25.3; -3.5)	-17.5 (-27.4; -7.7)
Burden of kidney disease	*	-10.7 (-23.9; 2.4)	-22.2 (-39.7; -4.7)	-27.7 (-43.6; -11.8)
Cognitive function	*	-3.5 (-12.3; 5.3)	1.4 (-10.4; 13.2)	-1.9 (-12.6; 8.9)
Quality of social interaction	*	0.2 (-7.1; 7.4)	2.9 (-6.9; 12.6)	5.0 (-3.8; 13.9)
Sexual function	*	-7.2 (-25.0; 10.6)	-13.0 (-37.2; 11.2)	-10.7 (-34.2; 12.7)
Sleep	*	-2.9 (-12.8; 7.1)	-2.1 (-15.4; 11.2)	-1.8 (-13.8; 10.2)
Social support	*	-6.2 (-18.4; 6.0)	-8.2 (-24.6; 8.1)	-21.9 (-36.7; -7.1)
Overall health	*	-4.5 (-12.7; 3.8)	-10.5 (-21.5; 0.5)	-6.8 (-16.8; 3.2)
SF-12 composite scores				
Physical composite score	*	-4.7 (-9.6; 0.1)	-9.3 (-16.0; -2.6)	-6.2 (-12.5; 0.2)
Mental composite score	*	0.1 (-4.6; 4.8)	2.1 (-4.4; 8.7)	-1.5 (-7.7; 4.7)

Regression coefficients (B) are to be interpreted as the absolute differences in quality of life scores. Reference: kidney transplantation.
SF-12: short form-12 items.
*Adjusted for age (years), sex (male/female), dialysis duration (years), and presence of residual urine production (≥100mL/24u or absent)



Extra Supplemental Figure S1. Bar charts to present Health-Related Quality of Life on the Physical Component score in kidney transplant, nocturnal hemodialysis, peritoneal dialysis and hemodialysis patients. 95% confidence intervals are presented alongside bars.



Extra Supplemental Figure S2. Bar charts to present Health-Related Quality of Life on the disease-specific domains *symptoms, effects, burden of kidney disease,* and *overall health* in kidney transplant, nocturnal hemodialysis, peritoneal dialysis and hemodialysis patients. 95% confidence intervals are presented alongside bars.

Part IV

Discussion and future perspectives

Chapter 10

Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO): rationale and design

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Abstract

Background More than 6200 End Stage Kidney Disease patients in the Netherlands are dependent on dialysis, either performed at home or in a dialysis centre. Visiting a dialysis centre three times a week is considered a large burden by many patients. However, recent data regarding the effects of dialysis at home on quality of life, clinical outcomes, and costs compared with in-centre haemodialysis are lacking.

Methods The Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO) is a nationwide, prospective, observational cohort study that will include adult patients starting with a form of dialysis. Health-Related Quality of Life, as the primary outcome, clinical outcomes and costs, as secondary outcomes, will be measured every 3-6 months in patients on home dialysis, and compared with a control group consisting of in-centre haemodialysis patients. During a 3-year period 800 home dialysis patients (600 peritoneal dialysis and 200 home haemodialysis patients) and a comparison group of 800 in-centre haemodialysis patients will be included from 53 Dutch dialysis centres (covering 96% of Dutch centres) and 1 Belgian dialysis centre (covering 4% of Flemish centres).

Discussion DOMESTICO will prospectively investigate the effect of home dialysis therapies on Health-Related Quality of Life, clinical outcomes and costs, in comparison with in-centre haemodialysis. The findings of this study are expected to ameliorate the shared decision-making process and give more guidance to healthcare professionals, in particular to assess which type of patients may benefit most from home dialysis.

Trial registration The DOMESTICO study is registered with the National Trial Register on https://www.trialregister.nl/trial/6519 (number: NL6519, date of registration: 22 August 2017) and the Central Committee on Research Involving Human Subjects (CCMO) (number: NL63277.029.17).

Background

In the Netherlands, over 6200 patients with End Stage Kidney Disease (ESKD) are dependent on dialysis, and over the past 15 years, the number of dialysis patients has increased by more than 20%.[1-3] The burden of dialysis is high and the Health-Related Quality of Life (HRQoL), which is presently considered to be the most important outcome parameter in dialysis patients, is much worse than that of healthy people.[4] As patient survival is poor, with a median five-year survival rate of only 45%, optimising HRQoL is of great importance for this growing group of patients.[5,6]

Besides its impact on HRQoL, dialysis is also an expensive treatment. In the Netherlands, the estimated costs are approximately 570 million euro per year (639 million US dollars) and are still increasing.[Personal communications, G.A. De Wit, National Institute for Public Health and the Environment, 2019] This makes dialysis by far the highest cost-consuming treatment in internal medicine, not only calculated per individual patient, but also if total treatment costs are taken into account.[7]

Home dialysis has a potential positive effect on HRQoL because it offers flexibility to patients and greater freedom.[8] Moreover, home dialysis is possibly a more cost-effective therapy if less nursing staff is needed, when patients perform their treatment autonomously or with help of an informal caregiver. Despite these potential advantages, currently more than 80% of dialysis patients are treated with in-centre haemodialysis (ICHD). Furthermore, the percentage of patients treated with home dialysis is steadily decreasing in the Netherlands, from 32% in 2002 to 18% in 2018. This decline is mainly attributable to a reduction in the number of patients performing peritoneal dialysis (PD), the main home based therapy, with 1,519 PD patients (30% of total dialysis patients) in 2002 versus 894 PD patients (14% of total dialysis patients) in 2018.[1]

Available evidence regarding the effects of home dialysis compared with ICHD on HRQoL, a Patient Reported Outcome (PRO), is limited. Most studies have a cross-sectional design and lack adequate correction for confounding among dialysis groups.[9-38] Also, the characteristics of patients starting with some kind of home dialysis treatment have changed remarkably over the past years. Previously, those patients were typically young, working people with little comorbidities, whereas during the last years the general home dialysis population is older and often suffers

from multiple comorbidities.[2] This could influence clinical outcomes such as mortality and hospitalisation rate. Finally, there are limited data available regarding the cost-effectiveness of home dialysis.

To investigate the effect of home dialysis on HRQoL, clinical outcomes, and costs, the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO) has been initiated. The aim of this study is to compare HRQoL, clinical outcomes, and cost-effectiveness of home dialysis with ICHD. The hypothesis is that home dialysis is associated with better HRQoL, at least comparable clinical outcomes and lower costs, compared to ICHD.

Methods

Study design

DOMESTICO is a nationwide, prospective, observational cohort study comparing home dialysis with ICHD. The maximum follow-up period of the study is 48 months. At present, 53 Dutch dialysis centres (covering 96% of Dutch centres) and 1 Belgian dialysis centre have agreed to recruit patients (Figure 1). The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Study population

All patients, aged 18 years and older, with ESKD that start with a form of dialysis in the participating centres, between December 2017 and December 2020, are eligible for this study. These patients are allowed to have a history of renal replacement therapy (RRT), however they have to (re)start dialysis during the study period for example due to kidney transplant failure (with or without previous dialysis). All these patients are defined as 'incident patients'. Prevalent dialysis patients, and patients with a life expectancy shorter than 3 months or an expected kidney transplantation within 3 months, are excluded. Patients have to provide written informed consent before participating in the study.

Figure 1. Participating centres
The red dots indicate the participating centres: 53 Dutch dialysis centres (covering 96% of Dutch centres) and 1 Belgian dialysis centre.

Inclusion

Patients are included in the period within four weeks before to four weeks after start of dialysis. If patients are missed for inclusion within this timeframe (for example, due to acute start of dialysis), they can be included at 3 months (± 2 weeks) after start of dialysis. Start of dialysis is defined as the first PD session performed at (a nursing) home (excluding PD-training) or, in case of ICHD, the first haemodialysis session performed in a centre (excluding continuous RRT).

The first patient was included in December 2017 and the study has currently started in 45 centres with 338 participating patients (Figure 2).

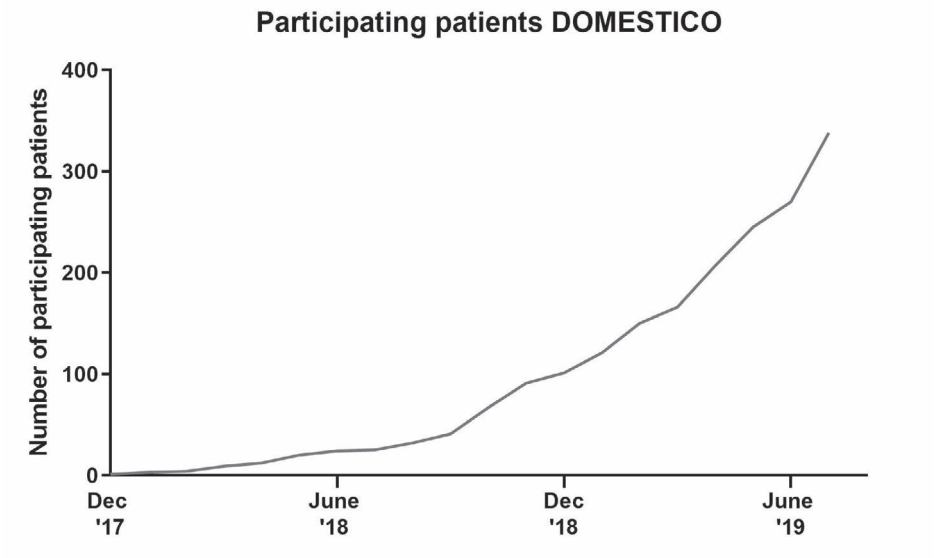

Figure 2. Participating patients

(Early) termination

For each participating patient, the study ends on 20 December 2021. Early study termination occurs if the patient withdraws from the study or stops dialysis treatment. Reasons to stop dialysis include kidney transplantation, recovery of kidney function, the wish to stop dialysis, or death.

Outcomes

Primary outcome parameter

The primary outcome parameter is the patient's HRQoL, a PRO, determined with the 12-item Short Form (SF-12) health survey.[39] The Dialysis Symptom Index (DSI) was added to the SF-12, to also assess symptom burden – also a PRO. Both questionnaires were carefully selected as recommended Patient Reported Outcome Measures (PROMs) in nephrological care by the Dutch Kidney Patients Association, the Dutch Federation for Nephrology, Nefrovisie (the Dutch Quality Institute for Nephrology), and Leiden University Medical Center.[41,42]

The SF-12 is the shorter version of the Short Form-36 (SF-36), one of the most widely used surveys to assess HRQoL.[43,44] The SF-36 consists of eight domains: Physical

functioning, Role-physical, Bodily pain, General health, Vitality, Social function, Role-emotional and Mental health. These domains are summarised in the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. In the SF-12 these summary scores are calculated from the 12 most important questions (explaining ~90% variance) of the SF-36 questionnaire.[39,45] As the average difference in summary scores between SF-36 and SF-12 is quite small, for time-efficiency reasons, the SF-12 can be used reliably in cohort studies.[46]

The DSI consists of 30 questions evaluating the severity of symptoms relevant to dialysis and ESKD patients (Table 1). Patients report the level of burden of specific symptoms on a 5-point Likert scale, options range from 'not at all bothersome' to 'very bothersome'.[40]

Table 1. Items Dialysis Symptom Index

1. Constipation	**16.** Chest pain
2. Nausea	**17.** Headache
3. Vomiting	**18.** Muscle soreness
4. Diarrhoea	**19.** Difficulty concentrating
5. Decreased appetite	**20.** Dry skin
6. Muscle cramps	**21.** Itching
7. Swelling in legs	**22.** Worrying
8. Shortness of breath	**23.** Feeling nervous
9. Lightheadedness or dizziness	**24.** Trouble falling asleep
10. Restless legs or difficulty keeping legs still	**25.** Trouble staying asleep
11. Numbness or tingling in feet	**26.** Feeling irritable
12. Feeling tired or lack of energy	**27.** Feeling sad
13. Cough	**28.** Feeling anxious
14. Dry mouth	**29.** Decreased interest in sex
15. Bone or joint pain	**30.** Difficulty becoming sexually aroused

Secondary outcome parameters

Secondary outcome parameters are hospitalisation, mortality, other clinical parameters, costs, and technique failure.

The cause of each hospitalisation episode will be categorised into the following categories (using ICD-10 codes)[47]:

Cardiac (including myocardial ischaemia/infarction, cardiac arrest/arrhythmia, cardiac failure, fluid overload/pulmonary edema, haemorrhagic pericarditis);

- Vascular disease (including pulmonary embolus, stroke, cerebrovascular haemorrhage, ruptured vascular aneurysm, mesenteric infarction, peripheral arterial disease);
- Infection, non-dialysis related (including bacteraemia/sepsis, cardiac infection, HIV, osteomyelitis, respiratory infection, urinary tract infection);
- Dialysis related (including dialysis access infection, peritonitis, PD catheter leakage/exchange/removal, fistula operation, renal fluid overload, bleeding);
- Malignancy;
- Bleeding, non-dialysis related (including intracranial bleeding, gastro-intestinal bleeding, other causes of bleeding);
- Other causes.

Mortality will be categorised into the following categories (using ERA-EDTA codes)[48]:

- Sudden death 'with unknown cause';
- Cardiac (including myocardial ischaemia/infarction, cardiac arrest/arrhythmia, cardiac failure, fluid overload/pulmonary edema, haemorrhagic pericarditis);
- Vascular (including pulmonary embolus, stroke, cerebrovascular haemorrhage, ruptured vascular aneurysm, mesenteric infarction, peripheral arterial disease);
- Infectious, dialysis related (including dialysis access infection, peritonitis);
- Infectious, non-dialysis related (including bacteraemia/sepsis, cardiac infection, HIV, osteomyelitis, respiratory infection, urinary tract infection);
- Malignancy;
- Bleeding (including dialysis related bleeding, intracranial bleeding, gastro-intestinal bleeding, other causes of bleeding);
- Overall deterioration in clinical condition/stopping dialysis;
- Other causes.

Besides hospitalisation and mortality, several clinical parameters will be recorded including blood pressure and use of antihypertensive drugs, haemoglobin and use of erythropoiesis-stimulating agents, phosphate levels and use of phosphate binders, vascular access parameters, and nutritional status.

Direct healthcare costs, patient costs, and costs with regard to productivity losses will be assessed with a subset of questions from the Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire (iPCQ) and the iMTA Medical Cost Questionnaire (iMCQ).[49,50] To capture all health care costs for the population under research a small number of disease specific services are added to the standard iMCQ, e.g. home dialysis. Given the fact that many patients need substantial help from close relatives, also use of informal care by patients will be assessed. The costs related to the healthcare consumption, the dialysis procedures, the diagnostic tests and (over-the-counter) medication will be derived from the patient's medical chart during the study. Unit costs will be derived from the Dutch manual for costing studies.[51]

To further examine cost-effectiveness, the EuroQol-5D-5L (EQ-5D-5L) questionnaire will be used. The EQ-5D-5L measures HRQoL on the following 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has 5 levels of functioning, ranging from 'no problems' to 'extreme problems'. The EQ-5D-5L also contains a visual analogue scale on which the current health state can be indicated. The EQ-5D scores can be used to calculate utilities, which describe HRQoL on a scale from 0 (dead) to 1 (perfect health). Utilities can be combined with survival to calculate quality adjusted life years (QALYs). As outcome measure for cost-effectiveness, the costs per additional QALY will be analysed.[52,53]

All participating patients will also receive a self-management screening questionnaire (SeMaS) at baseline, in order to investigate whether self-management can predict a successful home dialysis treatment. This questionnaire shows the abilities and possible barriers for self-management by asking questions about the burden of disease, locus of control, self-efficacy, social support, coping style, anxiety, depression, and skills.[54,55]

Table 2 provides an overview of the moments when participating patients will fill in the aforementioned questionnaires.

Finally, technique failure rate of home dialysis, defined by a composite outcome of death or transfer to ICHD, will be assessed. Both a 30-days and a 180-days definition of technique failure will be used according to the minimum number of days the patient received ICHD after cessation of home dialysis.[56] Permanent technique failure is defined by death or transfer to ICHD (using the 180-days definition), or cessation of dialysis. Death-censored technique failure will be reported separately. Transfer

to kidney transplantation is not considered to be technique failure and will also be reported separately.[56]

Table 2. Overview questionnaires

Visit	SF-12 and DSI	iPCQ and iMCQ	EQ-5D-5L	SeMaS
Baseline	X	X	X	X
At 3 and 6 months	X	X	X	
At 9 months and every 6 months thereafter		X		
At 12 months and every 6 months thereafter	X	X	X	

SF-12: Short Form-12; DSI: Dialysis Symptom Index; iPCQ: Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire; iMCQ: iMTA Medical Cost Questionnaire; SeMaS: self-management screening questionnaire

Data collection

All study outcomes, except the SeMaS, will be assessed at baseline, after 3 months, 6 months, and thereafter every 6 months until end of follow-up or end of the study (Table 2).

Data will be registered in case report forms (CRF). IBM Data Collection will be used as CRF. The database is developed by Nefrovisie and follows the principles of Good Clinical Practice (i.e. it has an audit trail, possibility for electronic signing, direct validation of inserted data, authorisation per form and user). Nefrovisie will also host the database for the duration of the study. The database will be archived for future research during 15 years after termination of the study.

Statistical analysis

All statistical analyses will be performed using statistical software such as SPSS and Stata.

Univariable and multivariable regression analysis will be conducted. In case of repeated measures, multilevel analysis or generalised estimating equations will be applied. Possible confounders determined a priori are age, gender, marital status, level of education, work status, cause of renal failure, prior RRT with dialysis vintage, comorbidities, albumin, body mass index, and protein energy wasting. Cumulative incidence of hospitalisation, mortality, and technique failure will be reported in

Kaplan Meier curves. In case of missing data, multiple imputation techniques will be used to impute the missing values where appropriate.

Overall costs will be compared across the treatment groups and 95% confidence intervals will be estimated using bootstrapping techniques. The cost-effectiveness of different dialysis modalities will be determined using a state transition model. This model captures the changes in treatment modality, including transplantation, over time. The results of the DOMESTICO study will be used as input parameters for this model.

Sample size calculation

For the primary outcome HRQoL, obtained with the SF-12, a sample size of 350 patients is required. To obtain a clinically relevant difference between groups of 3 points in the SF-12 summary scores, after a median of 12 months follow-up, 175 patients per group are needed (assumed standard deviation = 10 points, $\alpha = 0.05$, $\beta = 0.20$).[46,57-59]

However, for the EQ-5D-5L, an important component for the secondary outcome cost-effectiveness, a sample size of 1400 patients (700 patients per group) is needed. A difference of 0.03 - 0.07 points between groups after a mean follow-up of 12 months is considered clinically relevant.[44,60,61] The standard deviation in dialysis groups ranges from 0.1 to 0.22.[62,63] Assuming a common standard deviation of 0.20 and the lowest, still clinically relevant score, a total of 1400 patients (700 patients per group) will be sufficient to detect a difference of 0.03 points in the EQ-5D-5L score between groups ($\alpha = 0.05$, $\beta = 0.20$).

When approximately 10% loss to follow up is taken into account, a group of 800 home dialysis patients and a comparison group of 800 ICHD patients has to be included in order to have sufficient power to analyse both outcomes. Since the ratio between PD patients and home haemodialysis (HHD) patients in the Netherlands is expected to be 3:1 in future years, the home dialysis group will consist of 600 PD and 200 HHD patients.

Discussion

Dialysis has a great impact on the HRQoL of ESKD patients and dialysis is a very expensive treatment. More than 80% of Dutch dialysis patients are treated with ICHD although home dialysis could result in a better HRQoL and could be more cost effective. Therefore, we initiated the DOMESTICO study, which will investigate the effects of home dialysis on HRQoL in relation to clinical outcomes and costs, in comparison with ICHD. This nationwide cohort study will include 1600 incident dialysis patients over a period of 3 years. At time of submission of this manuscript, 338 patients have been included.

Although a randomised controlled trial (RCT) would yield the ultimate answer to our research question, this is not in accordance with the concept of shared decision making. A patient's choice between home dialysis and ICHD is considered too fundamental, to let it be determined by chance. Indeed, an RCT in the Netherlands comparing PD with ICHD conducted in the past, stopped early due to poor patient recruitment; only 38 patients consented to be randomly assigned to either PD or ICHD.[64] Hence, DOMESTICO is designed as a prospective, observational cohort study collecting extensive parameters to correct for confounding by indication.

The results of this study will be of great importance for future ESKD patients when choosing a treatment, as HRQoL is increasingly acknowledged by clinicians and patients as an important aspect in the decision-making process. In addition, the results with respect to clinical outcomes will ameliorate the shared decision-making process. Finally, the data could give more guidance to healthcare professionals, in particular to assess which type of patients may benefit most from home dialysis.

List of abbreviations

CCMO: Central Committee on Research Involving Human Subjects
CRF: case report forms
DOMESTICO: Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes
DSI: Dialysis Symptom Index
EQ-5D-5L: EuroQol-5D-5L
ESKD: End Stage Kidney Disease
HHD: home haemodialysis
HRQoL: Health-Related Quality of Life
ICHD: in-centre haemodialysis
iMTA: Institute for Medical Technology Assessment
iMCQ: iMTA Medical Cost Questionnaire
iPCQ: iMTA Productivity Cost Questionnaire
MCS: Mental Component Summary
PCS: Physical Component Summary
PD: peritoneal dialysis
PRO: Patient Reported Outcome
PROM: Patient Reported Outcome Measure
QALY: quality adjusted life year
RCT: randomised controlled trial
RRT: renal replacement therapy
SeMaS: self-management screening questionnaire
SF: Short Form

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Chapter 11

Summary and general discussion

Worldwide, home dialysis is utilized significantly less often than in-centre haemodialysis (CHD) with few exceptions.[1, 2] This is remarkable, as home dialysis - both peritoneal dialysis (PD) and home haemodialysis (HHD) - is associated with similar survival as CHD and with more independence and greater scheduling flexibility than CHD.[3] Previously, home dialysis was mostly performed by younger patients. However, more elderly patients are currently receiving home dialysis, because the Netherlands and other developed countries are facing an ageing population (**Chapter 2**).[4-6] This development urges the need to organize care for the current elderly dialysis population and to prioritize Health-Related Quality of Life (HRQoL) – rather than survival - as an important outcome. This thesis aimed to re-evaluate home dialysis eligibility, technique survival and HRQoL in the context of this demographic shift. In this final chapter, the main findings of this thesis will be placed in a broader perspective and recommendations for future research will be made.

Part I – Eligibility for home dialysis in the current dialysis population

More patients in the current patient population might be eligible for home dialysis, than receive this dialysis modality at present (20% of the dialysis population is treated with either PD or HHD). In previous studies, it was estimated that >80% of patients are eligible for home dialysis.[7-9] When patients are given comprehensive education, over 60% of patients chose a home dialysis modality including those who are older.[9, 10] Using Dutch registry data, we found that the current home dialysis population is ageing due to both an increase in kidney transplantation in younger patients and an increase in the absolute number of elderly patients (**Chapter 2**). The relative cumulative incidence of home dialysis, however, remained more or less the same for patients aged 65-74 (ranging from 29 to 25% over 20 years' time) and above 75 (ranging from 17 to 19%).

The high absolute numbers of elderly patients facing dialysis require adaptions in the organization of pre-dialysis education and dialysis care, while the constant relative numbers require further consideration. Since over 50% of elderly patients opt for PD[9], more elderly people may initiate home dialysis if they are offered home dialysis as treatment option. Compared to the Netherlands, Canada has a comparable proportion of elderly patients on PD (19%).[11] Yet in the greater Toronto area, the uptake of PD was statistically different in regions with and without home care support (47% to 37% resp.), indicating that sufficient home care support is a key factor in implementing home dialysis to elderly patients.[9] In other countries, such as in Australia and New

Zealand, the proportion of elderly people on home dialysis (both PD and HHD) is much higher than in the Netherlands (resp. 24 and 47%).[12] In these countries, home dialysis might be favoured due to long travel distances. As a result mobile buses providing HD services were quite popular.[13] Nevertheless, these data suggest that a higher proportion of older patients might be eligible to receive home dialysis.

An important reason to favor home dialysis in the elderly is the high flexibility in dialysis schedules of home dialysis, which can be a major advantage for elderly and frail patients.[13] Other important advantages of home dialysis that may be important to the elderly patient are related to haemodynamics. PD is associated with better cardiovascular stability during dialysis - due to the slow removal of molecules, while intensive HD is associated with better blood pressure control.[14-16] Assisted PD and HHD can be safely offered to elderly patients. Previous studies indicated that among elderly patients on assisted PD compared to self-care PD mortality and technique failure rates are similar.[17, 18] A French study found that assisted PD patients had worse survival, but this finding was possibly due to differences in frailty between the groups.[19] Home care assistance in elderly dialysis patients is thus a viable option. As a result, the most important barrier for elderly patients who cannot perform self-care due to functional limitations, is the lack of home support.[9, 13] Other challenges in the elderly population are the development of PD leakage due to weak abdominal muscles in PD and the occurrence of falls due to intradialytic hypotension in HHD.[13]

Both age and comorbidity are frequent reported barriers to home dialysis.[20] Due to improved treatments in cardiac disease and diabetes, patients with severe comorbidities are currently surviving long enough to reach End Stage Kidney Disease (ESKD) and the start of dialysis. Patients initiating dialysis appear to have more comorbidities than patients with several solid tumours.[21] The results in this regard are striking: dialysis patients have a high prevalence of hypertension (81%), diabetes mellitus (54%), cardiovascular disease (41%) and heart failure (37%), compared to respectively a maximum of 54%, 29%, 21% and 8% in patients with solid tumours.[21] Many nephrologists may perceive severe comorbidity as a barrier to initiate home dialysis, despite options to provide support. Yet, using data from the retrospective DOMESTICO study we found that patients with high comorbidity scores were as likely to start home dialysis as CHD, if corrected for confounding factors including BMI and age (**Chapter 3**). Obese patients with high comorbidity scores were however significantly less likely to receive home dialysis. The presented results suggest that BMI

and age play a more important role in dialysis modality initiation than comorbidity, even though both factors are no absolute contraindications for initiating home dialysis.[14] Of note, we found no difference in average BMI and age among centres, while the proportion of home dialysis varies considerably in the Netherlands. These insights might imply that dialysis modality initiation depends not only on patient characteristics, but also on the weighting of these characteristics by the dialysis centre, i.e. by practice policies. In addition, other centre-specific characteristics unrelated to patient characteristics, such as staff shortage, insufficient training in home dialysis for young nephrologists or reimbursement, might play a role in the decision not to start home dialysis. Indeed, in previous studies it was suggested that factors such as regional health policies, small centre-size and offering limited dialysis treatment options determine the variance in home dialysis use.[22, 23] Although centres should ideally offer both home and in-centre dialysis, both night and daytime dialysis, extended hours dialysis *and* home dialysis assistance, providing all these options is often not feasible within one centre. More regional collaboration among dialysis centres would facilitate providing all different dialysis treatment options to patients.

It is difficult to determine upfront which patients will benefit from receiving home dialysis. A home visit prior to initiating dialysis modality and pre-dialysis education, helps to identify patients with suitable housing (**Chapter 4**). In this chapter, we describe the results of an implementation project on patient selection. We found that suitable housing had a significant association with long-term home dialysis treatment. In our opinion, this determinant is best assessed during a home visit. Moreover, the health personnel involved in this project acknowledged that the home visit was the most important addition to the pre-dialysis programme. The social worker, who performed the home visit, had a valuable role in patient selection. It should be recognized that the specificity of the social worker's assessment was significantly higher than the nephrologist's assessment, indicating that the social worker was particularly capable of selecting patients *unsuitable* for home dialysis. In addition to suitable housing, we found that a strong social support system, an active lifestyle and being able to balance burden and capacity were other key determinants of whether patients received home dialysis. In previous research, lack of social support has indeed been identified as an important barrier to home dialysis.[24] We believe that involving family members in decision making, may help to improve family support for home dialysis. A home visit might also be the perfect opportunity for such treatment education. In a study on treatment education at home, family members present during education sessions

demonstrated improved understanding of dialysis and experienced fewer concerns and distress.[25] We would recommend considering a home visit as part of a pre-dialysis programme, for the various reasons presented above. Another important feature of the presented implementation project, was the success of the 'home dialysis first' policy. It has been reported that such a policy, results in more patients receiving home dialysis.[26, 27]

Although in this thesis home dialysis consistently refers to both PD and HHD, as is concomitant with literature, it is important to consider that both modalities are completely different therapies. The main similarity between these therapies is the advantages of scheduling flexibility and autonomy that are associated with a treatment at home. The dialysis tasks of both therapies are very different and require different degrees of patient empowerment. Therefore, PD patients and HHD patients are not likely equal to each other. Throughout this thesis, sensitivity analyses were performed to acknowledge the important difference in patient populations. In **chapter 2**, for example, we found that the home haemodialysis use increased over time as compared to a decline of the overall home dialysis incidence. However in most chapters, including in the systematic review of **chapter 7**, we had to conclude that the sample size of HHD patients was too small to draw conclusions on this patient group. Thus, most data provided in this thesis concerns PD patients.

Part II – Enhancing technique survival of peritoneal dialysis

Among patients on dialysis, five-year survival rates are below 50%.[28] For comparison, the survival rate of patients with solid tumours including breast and colorectal cancer is higher than that of patients treated with dialysis.[21] As previously stated, being treated with dialysis is associated with a high prevalence of comorbidity.[21] As a result, dialysis patients are once to twice annually admitted to the hospital.[4] Using data of the retrospective DOMESTICO study, we demonstrated that the risk for hospital admission is higher in PD patients compared to haemodialysis patients (**Chapter 5**). This may indicate a difference between treatments, but could also be explained by circumstantial factors. For example, patients treated at home may be more likely to be admitted to the hospital to receive treatment for infections and fluid overload, than patients seen thrice weekly on the dialysis ward where treatment can be intensively monitored on an outpatient basis. Another important finding of this study was that PD patients were most frequently hospitalized for peritonitis, which is in keeping

with findings of previous studies.[29-32] More attention to prevention of PD-associated infections is necessary for reducing the number of hospitalizations in the future.

PD-related infections consisting of PD peritonitis and exit-site infections were a major cause of PD technique failure (**Chapter 6**). In this chapter, we present the causes and risk factors of PD technique failure, the primary outcome, in the retrospective DOMESTICO study. In accordance with previous research, we showed that the highest risk of PD technique failure is noted in the first year of PD treatment.[33] Few studies however studied the reasons of technique failure, especially over an extended period.[34-36] We found that infections were the most important cause of early technique failure. Other important causes for specifically early technique failure in DOMESTICO were PD fluid leakage and catheter problems. Infections and PD catheter problems can be considered modifiable causes of technique failure, and major barriers to long-term PD treatment if insufficiently addressed. We also found that ultrafiltration failure was the cause for technique failure (early and late combined) in less than 10%. This is in line with previous reports[34, 37, 38], further indicating the possible reversibility of technique failure. Successful long-term treatment with PD thus depends on the prevention of technique failure, i.e. the prevention of PD infections and catheter problems.

There is at present no consensus on antibiotic regimens in PD peritonitis.[39] In fact, many recommendations from PD guidelines are based on level C evidence.[39-41] Current study groups, including PDOPPS, are evaluating evidence for antibiotic regimens and PD catheter access.[42] Yet, also experiences from single centres are contributing to this evidence, for example from our study group.[43, 44] Leakage and catheter problems are thus other modifiable causes of technique failure. For example, incorrect implementation technique or too early PD initiation are known causes for early leakage.[40] The recommended period between PD catheter implementation and PD initiation is two weeks.[40] On the other hand, in urgent PD, the catheter is used within 3 days with small dialysate volumes.[45] These examples indicate that the success of the therapy depends on knowledge and experience of the physician.

Another important finding in the DOMESTICO study that should be emphasized is that death was the leading cause of both early and late technique failure. The mortality rate of PD patients is identical to the rate in CHD patients, as already stated in the first paragraph.[3] Thus high mortality is an expected result of the disease and *not* the result of the dialysis modality. This is important to consider when comparing research

on CHD and PD patients, since technique failure is an outcome solely reported in research on home dialysis patients. CHD patients do not usually transit from CHD to PD, thus technique failure on CHD results in death. Hence, mortality is the reported outcome in research on CHD patients, while in studies on home dialysis patients both mortality and technique failure (including death) are reported outcomes. Accordingly, to optimize transparency of home dialysis studies it is important to report technique failure according to the standardized definition, death-censored technique failure *and* mortality.

A large number of studies have investigated risk factors for technique failure. Both demographic and patient characteristics, such as diabetes mellitus, cardiovascular disease and residual GFR, and centre characteristics, such as small centre size, are associated with early technique failure.[34, 37, 38] In DOMESTICO however, we demonstrated that centre size was not associated with technique failure rate as shown in a funnel plot (**Chapter 6**). Funnel plots are a graphical method to compare performance indicators among health care providers. The important feature in funnel plots is the use of control limits, that are based upon the sample sizes of individual hospitals. Funnel plots are superior to league tables ranking health-care providers, because they are easy to interpret and identify outliers instead of implying the existence of ranking.[46, 47] In addition, funnel plots can be adjusted for important confounders. Our funnel plot was adjusted for both age and sex, but not for other case-mix variables such as comorbidity. Another important limitation of our study is that some centres only provided few patients, resulting in broad control limits. Despite these limitations, we believe that the funnel plot indicates that centre size is not causally related to technique failure and that size is a mere proxy for a successful home dialysis program. We suggest that dedication and organization play the most important role in technique survival.

Part III – Shift towards Health-Related Quality of Life

Progress in technology notwithstanding, traditionally important outcomes are disappointing in dialysis patients: survival is low, hospital admissions are frequent and the technique failure rate is high. HRQoL is becoming an increasingly important outcome in ESKD patients, who consider HRQoL a core outcome alongside more traditional outcomes.[48-51] This is not surprising, as the burden of living with ESKD negatively affects HRQoL. The low HRQoL of dialysis patients as compared with HRQoL of the general population and patients with other chronic diseases such as

malignancies and diabetes mellitus[52, 53], implies the need to identify interventions to improve HRQoL. Lower levels of HRQoL or mental health-related factors are also associated with traditional outcomes, both mortality and frequent hospitalization.[54-56] The postulated mechanism behind this association might be that lower HRQoL leads to non-adherence to therapy. Non-adherence likely results in hospital admissions and eventually could lead to death.[57, 58] Elaborating on this, HRQoL may also be linked to technique failure by the same mechanism. Sufficient coping is crucial for home-based therapies, because home dialysis patients need a certain ability to perform self-care. Insufficient coping, for example through feelings of anxiety, may contribute to technique failure.[59] These factors are more modifiable than risk factors such as comorbidity and may therefore have significant impact on improvement of technique survival. Although both the emerging interest in HRQoL and its association with traditional outcomes emphasize the importance of HRQoL as an important outcome measure, few studies on home dialysis report HRQoL as outcome. Less than 4% of randomized trials on PD patients described results from HRQoL questionnaires.[60]

In our systematic review and meta-analysis of forty-six articles reporting on HRQoL in 41 study populations, we found marginally higher HRQoL scores for home dialysis patients across the world (**Chapter 7**). Since the overall quality of included studies was poor and few longitudinal studies exist, the results should be interpreted with caution. The few recent longitudinal studies that have been performed report conflicting results.[61-64] For example one study showed a decline in HRQoL in both incident CHD and PD patients over time[62], while another study found that HRQoL improved after a transfer from CHD to home haemodialysis.[63] No randomized controlled trials (RCTs) were included in this meta-analysis, since no recent RCTs on HRQoL of home and CHD patients have been performed. To date, there have been few RCTs on home dialysis and CHD, because recruitment in these studies is challenging due to patients preferring one of the modalities.[65, 66] This may be illustrated by the experiences from the NECOSAD study group: while 773 incident dialysis patients were eligible, only 38 patients could be randomized in this trial.[66]

Another important limitation of the presented meta-analysis is that most studies, even half of the included longitudinal studies, included prevalent patients. Using prevalent patients makes comparability among study populations challenging, since HRQoL tends to decline over time and dialysis vintage thus is an important confounder.[67] An important bias introduced in studies with prevalent patients is survival bias,

since patients with higher HRQoL scores may survive and then be able to transit to home dialysis. In other words, these difficulties in observational studies highlight the importance of longitudinal studies on HRQoL of incident home dialysis.

The following example from a nocturnal HD trial further stresses the importance of longitudinal studies: in a study randomising patients between nocturnal home haemodialysis and CHD, no difference was found between the change in HRQoL scores of both groups after randomization.[68] However, when pre-randomisation scores were used as baseline, i.e. when the patient was still unaware of treatment choice, the general HRQoL of nocturnal home haemodialysis patients did improve over time.[68] This example shows that treatment choice alone, even prior to dialysis initiation, can effect HRQoL. Another important finding in this trial was that the kidney disease specific domains 'effects of kidney disease' and 'burden of kidney disease' were significantly higher in nocturnal HHD patients, in which a higher score indicates a more favourable HRQoL. This example also highlights the additional value of disease-specific HRQoL domains, i.e. 'burden of kidney disease' or a questionnaire addressing symptom burden, compared to general HRQoL measures.

In the NOCTx study, one-year follow-up HRQoL data were used for the reason presented in the previous paragraph. Baseline in this study was 2 to 3 months after transfer to nocturnal HD or obtaining a kidney transplant. The primary aim in the NOCTx study was to prospectively measure progression of arterial calcification in nocturnal haemodialysis patients and in kidney transplant patients, hence baseline results were collected 2-3 months after treatment initiation to allow for stabilization of laboratory data and treatment modality. In **chapter 9**, we present the results of the secondary outcome, HRQoL as measured with the Kidney Disease Quality of Life Instrument (KDQOL-SF), of 75 patients with 1-year follow-up data. General HRQoL did not demonstrate a statistically significant difference between nocturnal haemodialysis and kidney transplantation, although clinically relevant changes in the physical component score and kidney-disease specific domains were observed in favor of kidney transplantation. Only the domain 'effects of kidney disease' was associated with a significantly lower score in incident nocturnal HD patients compared to incident kidney transplant patients, implicating less favorable HRQoL for nocturnal HD patients. A kidney transplant for transplantation-eligible patients should always be the preferred therapy, both in terms of traditional outcomes and HRQoL, as our study suggests. Yet, for patients ineligible for kidney transplantation, nocturnal HD

may have potential advantages compared to other dialysis modalities. Nocturnal HD patients may be more free in diet restrictions and in the ability to work or travel due to nightly HD regimens. Intensive HD regimens, such as nocturnal HHD, are associated with higher survival rates compared to CHD.[69-71] The hypothesized mechanism of improved survival from intensive HD regimens is that these regimens lead to better solute and fluid removal[15], resulting in better blood pressure, phosphate control and nutritional status and thus in turn reducing morbidity and mortality.[16] These mechanisms likely also contribute to improved HRQoL when patients switch to nocturnal HD.[72-74] The extra supplemental tables of the manuscript indeed showed that some kidney-disease specific domains of nocturnal patients were higher than in CHD patients, consistent with previous reports on nocturnal HD and CHD.[72, 73] The CHD group in the NOCTx study were all transplantation-eligible patients, making them fairly more comparable to the group of incident kidney transplant and nocturnal HD patients then CHD patients in general. These tables were however omitted from the final article on request of the editor, because the CHD group consisted of prevalent patients. Nevertheless, these results might be useful when counselling on dialysis modality choice in patients who are ineligible for kidney transplantation.

This thesis was written during a worldwide and memorable pandemic, that of COVID-19. Therefore, it was indispensable to investigate the effect of this major pandemic on the main outcome parameter of this thesis within the studied population. In **chapter 8**, data from the ongoing prospective DOMESTICO study were used; eligible patients had HRQoL scores both before and during the COVID-19 pandemic. Mental health was assessed using both the Short Form-12, i.e. general HRQoL, and mental health-related symptoms of the Dialysis Symptom Index. We found that the mental health of dialysis patients was unaffected by the major pandemic; no difference was found in either the Mental Component Summary and in the presence of specific symptoms during the COVID-19 pandemic. We hypothesize that major life events do not effect dialysis patients due to their high resilience. This is striking, as the COVID-19 pandemic negatively impacted the mental health of patients with many other chronic diseases, such as malignancies and Alzheimer's disease.[75, 76] Another explanation for the presented results, also stated in the original article, is that the majority of the studied patients were treated with CHD and thus had frequent social contact with healthcare professionals despite social distancing. Social distancing negatively affects important mental health-related outcomes such as depression and social anxiety, as stated in a recent review.[77] This is important to consider, since this is unlikely to be

the last outbreak in human history, and the current COVID-19 pandemic resulted in an increased interest in home dialysis.[78] Sufficient support from the health care professionals, for example provided by eHealth, to maintain social connection and quality of care is then needed.

HRQoL as a core outcome fits better in the paradigm shift towards patient-centred care then traditional outcomes such as survival. Patient-centred care focusses on finding the treatment that suits the patient best, instead of finding the treatment with the best clinical outcomes. Since there are few major differences in clinical outcomes between dialysis modalities, a focus on patient-centred care is especially valuable in ESKD. With the shift towards patient-centred care, understanding patient-reported outcomes such as HRQoL is pivotal for an in-depth conversation with the patient about dialysis modality choice. There are several examples in the context of kidney disease showing the focus on patient-centred care. Examples include renewed interest in abandoning traditional thrice-weekly regimens by also offering nocturnal dialysis or incremental dialysis, and thus individualizing treatment according to patient needs.[79, 80] As another example, several centres are providing extra support in the home to safely conduct dialysis, such as assisted PD or providing home haemodialysis by a dialysis nurse. However, probably the intriguing examples are the initiatives of single centres. To illustrate, an example from Bravis hospital, a centre that also offers haemodialysis at the general practitioner's practice, the so-called *dialysis hub*, thus bringing dialysis to patients without burdening them with long travel.[81] Another example: offering nocturnal haemodialysis within the safe surrounding of a dialysis centre but with private sleeping rooms (Diapriva Dialysis Centre). The latter examples, including the example in **chapter 4**, may be exemplified as 'good practices', i.e. as practices initiated by health care professionals with high success within their centre but lacking an evidence-based foundation.[82]

One of the principles of patient-centred care is shared decision making. In my opinion, shared decision making should be achieved by listening carefully to the patient's beliefs, providing information by a multidisciplinary team and offering all treatment options, not necessarily the available or feasible options. Only then one can make an informed decision. In European surveys, 25-39% of patients reported that they were not informed about any treatment modality options.[83, 84] In higher income countries, a substantial proportion of patients were not informed about PD (16%) and HHD (27%).[83] The presented examples of incomplete treatment modality education are obviously are barrier to home dialysis. While the nephrologist reported that he never

made the decision without consulting the patient[85], 10% of CHD patients felt the doctor decided for them compared to 1,5% of patients on home dialysis.[83] This might be the result of patients simply being unable to remember the decision on treatment modality (recall bias). However, due to the difference between CHD and home dialysis patients, this phenomenon might also be the result of implicit persuasion, i.e. unintentionally steering patients towards the treatment that seems to suit best. Steering behaviour is frequently observed in oncology[86], but has recently also been recognized in treatment modality consultations in nephrology.[87] Selectively presenting treatment options, advantages and disadvantages is common, and could lead to less involvement of the patient in the treatment modality decision.[87]

Discussing treatment modality options in ESKD, also means fully considering the patient's social system. As mentioned earlier in this thesis, life-long dialysis dependency requires a certain structure to everyday-life not only to the patient but also to the patient's social system, especially spouses and children. Since family members are frequently also carers to the patient, especially elderly patients, it is important to include informal caregivers in the treatment modality decision. The treatment modality decision is thus never a decision by one person, but should be team-made. An informed treatment modality decision will eventually lead to treatment satisfaction and thus higher HRQoL scores. The decision may sometimes be an unexpected choice for the clinician (personal experience). During this research project, I met a young employed man with small children. Although he started on PD, he eventually opted for CHD because he did not want his home to turn into a hospital.

Part IV - Future perspectives and conclusions

Although home dialysis has been associated with similar survival, its impact on HRQoL and cost-effectiveness in especially elderly patients require further elucidation. The prospective DOMESTICO study will investigate the effect of home dialysis therapies on HRQoL, cost-effectiveness and clinical outcomes, compared to CHD in the current dialysis population (**Chapter 10**). Several patient-reported outcome measures are being used, including the Short-Form 12 to measure generic HRQoL and the Dialysis Symptom Index to measure symptom burden. Symptom burden is related to the concept of HRQoL, according to the model of Wilson & Cleary: a high symptom burden causes a decline in functional status and in turn lower HRQoL.[88] The DOMESTICO study will also include some interesting secondary outcomes, such as caregiver burden and productivity losses, that are still knowledge gaps.

As previously stated, HRQoL is an important outcome to dialysis patients.[48-51] HRQoL is however still a non-traditional outcome in clinical practice, because it only recently gained its role as a core outcome in research.[48, 49] Even though establishing a core outcome set is intended to enhance shared decision making and quality of care, patient-reported outcome measures are not frequently used in daily practice. Dialysis patients have low HRQoL and high symptom burden, but due to underreporting not all symptoms are adequately treated.[89] It is therefore pivotal, that health care workers integrate HRQoL and symptom questionnaires into everyday care. One way to achieve this is to routinely apply those questionnaires in clinical practice.[90] Introducing patient-reported outcomes within the dialysis registry in the Netherlands, i.e. by the means of the PROMS-NL (both Short Form-12 and Dialysis Symptom Index) of Nefrovisie, is a good example of this.[91] Subsequently, data on HRQoL and especially symptoms should be used to relieve symptom burden, which is best achieved if all health care workers perceive benefits from collecting data on patient-reported outcomes. It is important that the entire multi-disciplinary team values patient-reported outcomes and understands their interpretation, to relieve the workload associated with collecting questionnaires and avoid survey fatigue among patients through good motivation. In a study from the UK concerning routinely measuring HRQoL and symptom questionnaires, difficulty in understanding questionnaire results by health professionals was a barrier to integrating questionnaires in everyday care. This resulted in the study team providing workshops to discuss the interpretation of results.[89] Likewise in our own prospective study, the inclusion rate and questionnaire collection seem to be associated with the feedback provided by the nephrologist to the patient and the endeavor of the entire health care team involved. Future studies should therefore focus on 'good practices' of integrating questionnaires into everyday care. Another important direction for future studies is whether management of symptoms has an effect on HRQoL.

Cost-effectiveness is the other important outcome in the prospective DOMESTICO study. Most economic evaluation studies to date, have used health insurance claims to compare costs between various dialysis modalities.[92-94] These studies suggest that home dialysis is associated with lower costs. Also a recent Dutch study performed with Vektis data concluded that CAPD was associated with the lowest costs, including also indirect non-medical costs such as transportation.[92] Still this study did not include all costs to estimate cost-effectiveness, most importantly indirect non-medical costs related to productivity losses were unknown while these costs can be rather important

in dialysis patients.[95] Productivity costs are best described as '*costs associated with production loss and replacement costs due to illness, disability and death of productive persons*'.[96] A large proportion of dialysis patients are unemployed. This may be partly due to disability of the disease, but also by difficulty to combine the thrice-weekly regimen of CHD with a paid job schedule. As a result, employed patients frequently opt for home dialysis. If more patients receive home dialysis, more patients might be able to go back to work and thus contribute to reducing production losses. In the current aging population this may seem of less importance, but it is important to consider that elderly patients frequently need informal caregivers to support them with dialysis-related tasks. Productivity losses of these informal caregivers might result in overall higher costs. Overall, including all medical and non-medical costs would yield the ultimate answer to the cost-effectiveness of home dialysis.

As mentioned earlier in this chapter, more patients might be eligible for home dialysis treatment. Important barriers that were presented in this discussion are insufficient education of patients and operational barriers: patients can receive home dialysis only if the treatment option is offered and if the treatment is available. This requires a robust healthcare organization and infrastructure, such as sufficient access to home care support, and policies that promote home dialysis. After all, providing home dialysis to incident patients is more challenging than starting patients on CHD: home dialysis requires infrastructure and a dedicated team. An increase in the number of patients receiving home dialysis would enable health-care resources for home dialysis to be used more efficiently. Combined with potentially lower costs, home dialysis might be a sustainable option for the growing population of patients with ESKD. We, as physicians, are responsible not only for the health of our individual patients, but also for future patients with ESKD.

This thesis aimed to identify opportunities to offer home dialysis to a larger patient population and to improve the technique survival of peritoneal dialysis. The prevention of PD infections and catheter problems might contribute to a long-term treatment with PD. Furthermore, the presented results might help to improve treatment decision making and overall HRQoL of all dialysis patients. Access to home dialysis should be improved, to provide more patients an opportunity to choose home dialysis as treatment modality.

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Appendices

Nederlandse samenvatting

Wereldwijd neemt het aantal patiënten met chronische nierinsufficiëntie en eindstadium nierfalen toe.[1, 2] Het groeiend aantal patiënten vormt een groot economisch probleem, omdat dialyse een relatief dure therapie is. Dialyse bestaat grofweg uit centrumhemodialyse (CHD) en thuisdialyse, waaronder zowel peritoneale dialyse (PD) als thuis hemodialyse (THD) vallen. In veruit de meeste landen is het aantal patiënten dat met thuisdialyse behandeld wordt veel lager dan het aantal patiënten dat behandeld wordt in een dialysecentrum.[2, 3] Dit is opvallend, omdat thuisdialyse geassocieerd is met gelijke overleving als CHD maar ook met meer vrijheid en flexibiliteit dan CHD.[4] Bovendien is thuisdialyse mogelijk goedkoper.[5-9] Met een wereldwijd groeiend aantal patiënten met eindstadium nierfalen, is het dus interessant om uitkomsten van thuisdialyse in de huidige populatie verder te onderzoeken.

In Nederland hebben we te maken met een uitgesproken groei in het aantal oudere patiënten met nierfalen en dus met een verandering van de dialysepopulatie.[10] Deze ontwikkeling vraagt om meer individualisering van de zorg en om meer aandacht voor kwaliteit van leven dan voor overleving. Het uiteindelijke doel in de spreekkamer is de therapie te vinden die het beste bij de patiënt past.

In dit proefschrift wordt in de huidige populatie gekeken naar de geschiktheid voor thuisdialyse, naar manieren om de techniekoverleving op thuisdialyse te verbeteren en naar kwaliteit van leven, als belangrijke patiënt-gerapporteerde uitkomst.

Deel I – geschiktheid voor thuisdialyse in de huidige populatie
Er zijn waarschijnlijk meer patiënten geschikt voor thuisdialyse dan er op dit moment behandeld worden met thuisdialyse. In Nederland wordt 20% van de dialysepatiënten behandeld met PD of THD, terwijl in studies geschat wordt dat meer dan 80 % van de patiënten medisch gezien in aanmerking komt voor thuisdialyse.[11-13] Uit eerdere studies bleek ook dat wanneer patiënten uitgebreide voorlichting krijgen, meer dan 60% voor thuisdialyse kiest.[13, 14] In **hoofdstuk 2** laten we zien dat de Nederlandse thuisdialyse populatie de afgelopen jaren ouder wordt, door zowel de vergrijzing als doordat jongere patiënten vaker getransplanteerd worden. Hoewel het absolute aantal oudere thuisdialysepatiënten dus toenam, zagen we dat de relatieve incidentie op thuisdialyse over de jaren min of meer gelijk bleef. In patiënten in de leeftijd van 65-74, veranderde de incidentie thuisdialyse van 29 tot 25% in 20 jaar tijd, en bij patiënten boven de 75

jaar veranderde de incidentie tussen de 17 en 19%. In vergelijking tot andere landen waar het percentage oudere patiënten op thuisdialyse hoger ligt (Australië 24%, Nieuw Zeeland 47%)[15], suggereren deze resultaten dat er mogelijk meer oudere patiënten in Nederland kunnen starten met thuisdialyse.

Naast leeftijd, wordt ook het hebben van veel comorbiditeiten vaak gezien als barrière voor het starten van thuisdialyse.[16] In de retrospectieve DOMESTICO studie vonden wij echter geen relatie tussen het hebben van veel comorbiditeit en thuisdialyse, als er gecorrigeerd werd voor onder andere BMI en leeftijd (**hoofdstuk 3**). Patiënten met veel comorbiditeiten hadden een even grote kans te starten met CHD als thuisdialyse. Alleen patiënten met ernstig overgewicht én veel comorbiditeiten hadden een kleinere kans te starten met thuisdialyse. In dit hoofdstuk suggereren we dat er andere factoren, zoals BMI en leeftijd, allicht een grote rol spelen in de selectie van thuisdialyse dan comorbiditeit. De gemiddelde waardes van BMI en leeftijd verschilde tussen de centra onderling echter nauwelijks, terwijl er wel grote verschillen zijn tussen centra in het aantal patiënten dat thuis dialyseert. Juist daarom is het goed mogelijk dat centrum factoren, zoals verpleegkundige tekorten, een belangrijke rol spelen. Ook in studies uit het buitenland wordt geopperd dat de variatie in het aantal thuisdialyse patiënten tussen centra mogelijk deels verklaard kan worden door factoren als kleine centrumgrootte en het aanbieden van weinig opties voor meer flexibele dialyse (langere dialysesessies, dialyse gedurende de nacht etc).[17, 18] Ook in andere landen om ons heen wordt eenzelfde variatie gezien in het percentage patiënten op thuisdialyse tussen verschillende centra. Vaak is het echter niet haalbaar om alle mogelijke keuzeopties (nachtdialyse, intensieve dialyse, thuisdialyse met een dialyse assistent etc.) aan te bieden. Derhalve is regionale samenwerkingen nodig om alle keuzeopties aan de patiënt te kunnen aanbieden.

Het is vanuit de spreekkamer lastig te beoordelen welke patiënt baat zal hebben van thuisdialyse. In **hoofdstuk 4** van dit proefschrift, beschrijven we de resultaten van een implementatieproject over voorlichting. Dit project bestond uit vragenlijsten over de geschiktheid voor thuisdialyse (voor zowel patiënt, maatschappelijk werker als nefroloog) en een huisbezoek. We vonden dat een maatschappelijk werker (tijdens een huisbezoek) de geschiktheid van een patiënt voor thuisdialyse goed kan beoordelen. Met name de specificiteit van het oordeel van de maatschappelijk werker was hoog, aangevende dat zij goed in staat was te onderscheiden welke patiënt waarschijnlijk minder geschikt was voor thuisdialyse. Belangrijke vragen die een hoge associatie met

thuisdialysebehandeling bleken te hebben waren onder andere, 'is het huis geschikt voor thuisdialyse', 'is er een goede verhouding tussen draagkracht en draaglast' en 'heeft de patiënt een goed steunsysteem'. Het missen van steun vanuit de omgeving, is in eerder onderzoek genoemd als een belangrijke barrière voor het starten van thuisdialyse.[19] Het betrekken van de familie bij de behandelkeuze, draagt waarschijnlijk bij aan de steun die later gegeven wordt. Gedurende het huisbezoek bestaat er ook de mogelijkheid de familie te betrekken bij de diagnose van eindstadium nierfalen. Daarom raden wij in dit hoofdstuk aan een huisbezoek op te nemen in het pre-dialyse programma.

Deel II – verbeteren van techniek overleving op peritoneale dialyse

Dialysepatiënten worden gemiddeld 1-2 keer per jaar opgenomen in het ziekenhuis.[20] Gebruikmakend van data uit de retrospectieve DOMESTICO studie, toonden wij in **hoofdstuk 5** dat PD patiënten twee keer vaker dan CHD patiënten opgenomen worden in het ziekenhuis. Het is goed mogelijk dat patiënten vaker opgenomen worden door de aard van de therapie, maar het kan ook het resultaat zijn van de locatie van de therapie. Men kan zich goed voorstellen dat patiënten die een thuisbehandeling krijgen laagdrempeliger opgenomen worden in het ziekenhuis, dan patiënten die driemaal per week gezien worden op de dialysezaal. PD patiënten werden het vaakste opgenomen voor een peritonitis. Daarom benadrukken wij in dit hoofdstuk dat het belangrijk is om infecties vanuit de PD catheter te voorkomen, om zo mogelijk het risico op ziekenhuisopnames te verlagen.

PD catheter gerelateerde infecties en peritonitiden waren ook een zeer belangrijke oorzaak van techniekfalen (**hoodstuk 6**). In dit hoofdstuk presenteren we de primaire uitkomstmaat van de retrospectieve DOMESTICO studie: techniekfalen. Het eerste jaar na start van PD had het hoogste risico op techniekfalen, zoals ook uit eerder onderzoek gebleken is.[21] Weinig onderzoeken hebben echter gekeken naar de redenen van techniekfalen, met name de onderzoeken naar laat techniekfalen zijn zeer gering.[22-24] Infecties waren een belangrijke oorzaak voor zowel laat als vroeg techniekfalen, catheter problemen en lekkages waren belangrijke oorzaken voor het vroeg falen van de techniek. Dit zijn allen oorzaken die in essentie te voorkomen zijn en dus een potentiele positieve invloed kunnen hebben op langdurige techniekoverleving op PD. Wij vonden bovendien dat ultrafiltratie-falen maar een oorzaak was voor 10% van de gevallen van techniekfalen (vroeg en laat gecombineerd), passend bij de hypothese die hierboven geschetst wordt. Langdurige therapie met PD is afhankelijk

van het voorkomen van techniekfalen, en dus de preventie van PD infecties en catheter problemen.

Deel III – meer aandacht voor kwaliteit van leven

Kwaliteit van leven is een belangrijk onderwerp in studies geworden, sinds patiënten kwaliteit van leven zien als een belangrijke uitkomstenmaat.[25-28] Kwaliteit van leven past beter bij een individualistische aanpak van zorg, dan een traditionele uitkomstmaat als overleving. Het doel moet zijn om de therapie te kiezen die het beste bij de patiënt past, en dat is niet per definitie de therapie met de beste uitkomstmaten. Bovendien zit er weinig verschil in uitkomstmaten tussen de verschillende dialysemodaliteiten, zodat kwaliteit van leven extra belangrijk kan zijn voor patiënten met nierfalen. In **hoofdstuk 7** presenteren we de resultaten van een systematische review en meta-analyse naar kwaliteit van leven van thuisdialyse en CHD patiënten. Op basis van 46 studies uit verschillende landen, vonden wij dat thuisdialysepatiënten gemiddeld hogere kwaliteit van leven scores hadden. Echter, de kwaliteit van deze studies was laag en bovendien waren er maar weinig studies die over de tijd (longitudinaal) kwaliteit van leven gemeten hebben. Bovendien waren in de studies met name prevalente patiënten geïncludeerd. Algemeen neemt kwaliteit van leven van dialysepatiënten in de loop van de tijd af[29], terwijl in sommige studies een switch naar bijvoorbeeld thuishemodialyse gepaard lijkt te gaan met een verbetering van kwaliteit van leven.[30] Daarom moeten de resultaten van deze meta-analyse met de nodige voorzichtigheid worden geïnterpreteerd en concluderen wij dat longitudinaal vervolgonderzoek noodzakelijk is.

Ten tijde van dit promotietraject raakte de wereld in de ban van het SARS-CoV-2 virus. In **hoofdstuk 8** onderzoeken we daarom het effect van de COVID-19 pandemie op de mentale gezondheid van dialysepatiënten. Hiervoor werden kwaliteit van leven metingen voor en tijdens de pandemie gebruikt van dialysepatiënten uit de prospectieve DOMESTICO studie. We vonden dat de pandemie geen invloed had op de algehele score van mentale kwaliteit van leven, noch op verschillende psychische symptomen zoals angst en somberheid. Wij suggereren dat dialysepatiënten gemiddeld veerkrachtig zijn, omdat zij in het dagelijks leven al geconfronteerd worden met vele uitdagingen. Een andere verklaring kan zijn dat dialysepatiënten, met name CHD patiënten, minder last hebben van de door het kabinet opgestelde maatregelen. Immers komen zij gemiddeld 3 keer per week naar het ziekenhuis.

De NOCTx studie was een Nederlandse studie naar kransslagaderverkalking in patiënten met een niertransplantatie in vergelijking tot patiënten die behandeld werden met nachtelijke hemodialyse. Als secundaire uitkomstmaat werd ook kwaliteit van leven meegenomen. De algemene kwaliteit van leven was niet statistisch verschillend tussen de twee therapieën (**hoofdstuk 9**). Alleen het domein 'effecten van nierziekte' was geassocieerd met een significante lagere score in nachtelijke hemodialyse patiënten. In een aantal andere onderdelen van kwaliteit van leven werden wel nog klinisch relevante verschillen gevonden: namelijk de algehele score van fysieke kwaliteit van leven en een aantal nierziekte specifieke domeinen waren beter in patiënten met een niertransplantatie. Niertransplantatie gaat gepaard met de beste overleving en met vermoedelijk ook een betere kwaliteit van leven, zoals onze studie toonde. Daarom heeft een niertransplantatie ook altijd de eerste voorkeur, maar voor patiënten die niet geschikt zijn voor niertransplantatie, kan nachtelijke hemodialyse overwogen worden.

Deel IV – toekomstperspectief en conclusie
De kwaliteit van leven van thuisdialyse patiënten alsmede de kosteneffectiviteit van deze therapieën zullen onderzocht gaan worden in de prospectieve DOMESTICO studie. In **hoofdstuk 10** staat het doel en de opzet van deze studie beschreven. Veel artikelen in dit proefschrift hebben gediend als een aanzet of een onderbouwing voor dit multicenter onderzoek. Resultaten uit de prospectieve studie en dit proefschrift zouden kunnen helpen bij de besluitvorming rondom therapiekeuze voor patiënten met nierfalen, met als doel de therapie te vinden die het beste bij de patiënt en diens omgeving past.

Concluderend vond dit proefschrift redenen om aan te nemen dat in de huidige populatie mogelijk meer patiënten geschikt zijn voor thuisdialyse. Daarnaast zouden preventieve interventies op het gebied van PD infecties en catheters de levensduur op PD kunnen verlengen. De gepresenteerde resultaten over kwaliteit van leven kunnen helpen in de besluitvorming rondom therapiekeuze voor alle dialysepatiënten. Wij zijn als onderzoeksgroep van mening dat er meer aandacht mag zijn voor thuisdialyse, zodat thuisdialyse vaker als behandelmogelijkheid overwogen wordt.

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Appendix A

Treatment distribution in percentage of incident patients (treatment modality at day 91)

	ERA-EDTA 2003 HD/HDF	ERA-EDTA 2012 HD/HDF	ERA-EDTA 2018 HD/HDF	ERA-EDTA 2003 PD	ERA-EDTA 2012 PD	ERA-EDTA 2018 PD
Austria	88	83	83	10	12	11
Belgium, Dutch-speaking	86	88	87	14	10	11
Denmark	64	65	60	32	28	30
Finland	69	72	71	29	27	25
Greece	89	92	93	10	7	7
Iceland	81	47	48	14	32	33
Norway	68	64	59	19	20	29
Spain, Catalonia	90	73	77	6	17	14
Spain, Valencian region	85	79	75	15	18	20
Sweden	65	60	59	31	32	33
The Netherlands	67	71	68	28	16	17
United Kingdom, England/Wales	66	70	72	30	21	20
United Kingdom, Scotland	75	78	72	22	14	19

Adapted from ERA-EDTA annual report: 2003, Table A.3.9(1); 2012, Table A.3.9 (2); 2018, Table B.3.10 (3)

Treatment distribution in percentage prevalent patients (including kidney transplants)

	ERA-EDTA 2003 HD/HDF	ERA-EDTA 2012 HD/HDF	ERA-EDTA 2018 HD/HDF	ERA-EDTA 2003 PD	ERA-EDTA 2012 PD	ERA-EDTA 2018 PD
Austria	47	45	45	4	5	4
Belgium, Dutch-speaking	52	53	52	6	5	4
Denmark	45	42	38	16	10	10
Finland	32	33	33	9	7	7
Greece	74	74	77	8	5	5
Iceland	34	26	22	16	10	7
Norway	22	24	25	4	4	7
Spain, Catalonia	51	41	38	3	4	4
Spain, Valencian region	57	54	50	5	5	6
Sweden	36	34	33	11	9	8
The Netherlands	34	35	31	13	6	5
United Kingdom, England/Wales	39	42	39	15	7	6
United Kingdom, Scotland	40	42	37	11	5	4

Adapted from ERA-EDTA annual report: 2003, Table A.4.9 (1); 2012, Table A.4.9 (2); 2018, Table B.4.10 (3)

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Appendix B

Short-Form 12 (generic)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer each question by choosing just one answer. If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is

O Excellent

O Very good

O Good

O Fair

O Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	O	O	O
3. Climbing several flights of stairs.	O	O	O

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	Yes	No
4. Accomplished less than you would like.	O	O
5. Were limited in the kind of work or other activities.	O	O

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
6. Accomplished less than you would like.	O	O
7. Did work or activities less carefully than usual.	O	O

8. During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?

O Not at all

O A little bit

O Moderately

O Quite a bit

O Extremely

These questions are about how you have been feeling during the past 4 weeks<. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bite of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	O	O	O	O	O	O
10. Did you have a lot of energy?	O	O	O	O	O	O
11. Have you felt down-hearted and blue?	O	O	O	O	O	O

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

O All of the time

O Most of the time

O Some of the time

O A little of the time

O None of the time

Dialysis Symptom Index (kidney disease specific HRQoL questionnaire)

Following is a list of physical and emotional symptoms that people on dialysis may have. For each symptom, please indicate if you had the symptom during the past week by clicking 'yes' or 'no'. If 'yes', please indicate how much that symptom bothered you.

During the past week: Did you experience this symptom?		**If yes, how much did it bother you?**				
		Not at all	A little bit	Some-what	Quite a bit	Very much
Constipation	No/Yes	☐	☐	☐	☐	☐
Nausea	No/Yes	☐	☐	☐	☐	☐
Vomiting	No/Yes	☐	☐	☐	☐	☐
Diarrhea	No/Yes	☐	☐	☐	☐	☐
Decreased appetite	No/Yes	☐	☐	☐	☐	☐
Muscle cramps	No/Yes	☐	☐	☐	☐	☐
Swelling in legs	No/Yes	☐	☐	☐	☐	☐
Lightheadedness or dizziness	No/Yes	☐	☐	☐	☐	☐
Shortness of breath	No/Yes	☐	☐	☐	☐	☐
Restless legs or difficulty keeping legs still	No/Yes	☐	☐	☐	☐	☐
Numbness or tingling in feet	No/Yes	☐	☐	☐	☐	☐
Feeling tired or lack of energy	No/Yes	☐	☐	☐	☐	☐
Cough	No/Yes	☐	☐	☐	☐	☐
Dry mouth	No/Yes	☐	☐	☐	☐	☐
Bone or joint pain	No/Yes	☐	☐	☐	☐	☐
Chest pain	No/Yes	☐	☐	☐	☐	☐

During the past week: Did you experience this symptom?		If yes, how much did it bother you?				
		Not at all	A little bit	Some-what	Quite a bit	Very much
Headache	No/Yes	☐	☐	☐	☐	☐
Muscle soreness	No/Yes	☐	☐	☐	☐	☐
Difficulty concentrating	No/Yes	☐	☐	☐	☐	☐
Dry skin	No/Yes	☐	☐	☐	☐	☐
Itching	No/Yes	☐	☐	☐	☐	☐
Worrying	No/Yes	☐	☐	☐	☐	☐
Feeling nervous	No/Yes	☐	☐	☐	☐	☐
Trouble falling asleep	No/Yes	☐	☐	☐	☐	☐
Trouble staying asleep	No/Yes	☐	☐	☐	☐	☐
Feeling irritable	No/Yes	☐	☐	☐	☐	☐
Feeling sad	No/Yes	☐	☐	☐	☐	☐
Feeling anxious	No/Yes	☐	☐	☐	☐	☐
Decreased interest in sex	No/Yes	☐	☐	☐	☐	☐
Difficulty becoming sexually aroused	No/Yes	☐	☐	☐	☐	☐

EQ-5D-5L (generic HRQoL questionnaire for economic evaluation)

Under each heading, please tick the ONE box that best describes your health TODAY.	
MOBILITY	
I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑
SELF-CARE	
I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	
I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑
PAIN / DISCOMFORT	
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑
ANXIETY / DEPRESSION	
I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

We would like to know how good or bad your health is TODAY.

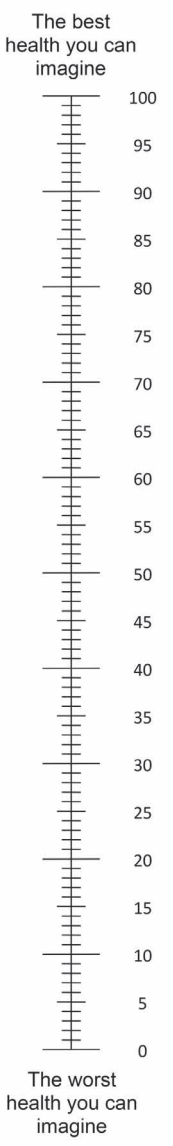
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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List of publications

This thesis

- **Bonenkamp AA,** Hoekstra T, Hemmelder MH, van Eck van der Sluijs A, Abrahams AC, van Ittersum FJ, van Jaarsveld BC. Trends in home dialysis use differ among age categories in past two decades: a Dutch registry study. *European Journal of Clinical Investigation. 2021 Jul 22:e13656. Epub ahead of print.*
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- van Eck van der Sluijs A, Vonk S, van Jaarsveld BC, **Bonenkamp AA**, Abrahams AC. Good practices for dialysis education, treatment, and eHealth: A scoping review. *PLoS One. 2021 Aug 11;16(8):e0255734.*
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