End-stage kidney disease: towards shared decision-making and patient-reported outcomes

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'We should place the highest value not on living, but on living well'

Socrates

Voor Steven, Bram, Koen
en mijn ouders

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Chapter 1

Introduction and outline

Introduction

The kidneys, two bean-shaped organs located behind the lower ribs on the dorsal side, play a crucial role in the regulation of body water volume and removal of waste products. When the kidney structure or function is impaired for more than three months with health consequences, this is defined as chronic kidney disease (CKD) [1, 2]. Examples of abnormalities in kidney structure or function are a glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2, albuminuria, and abnormalities detected by histology or imaging [1, 2]. In the Netherlands, more than 12% of the population (2 million people) have CKD [3].

If CKD worsens, patients should receive education on the different treatment options for end-stage kidney disease (ESKD; defined as an estimated GFR < 15 ml/min/1.73 m^2), namely kidney transplantation, dialysis (i.e. hemodialysis (HD) and peritoneal dialysis (PD)), and conservative care [1, 4]. In the last decade, more attention has been paid to the fact that this education should be a shared decision-making process to address *'the ethical need to fully inform patients about the risks and benefits of treatments, as well as the need to ensure that patients' values and preferences play a prominent role'* [4].

The model for shared decision-making was first described in 1972 [5] and has since been further developed. Elwyn *et al.* transformed the components of the shared decision-making process into 3 sequential conversations: choice talk, option talk, and decision talk [6]. In the choice talk, the healthcare professional tells the patient that there are treatment options. In the option talk(s), all treatment options with advantages and disadvantages and any contraindications are discussed. It is also indicated that it is important that the chosen treatment option is feasible and fits into daily life. Finally, a decision talk is held in which a joint decision is made. The goal of these 3 sequential conversations is to transform a patient's (possible) initial preferences into informed preferences (Figure 1) [6].

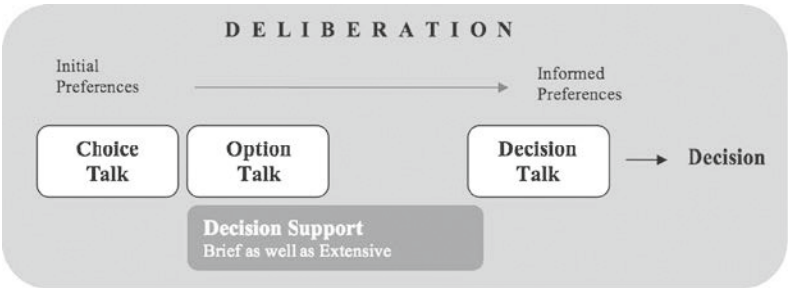

Figure 1. Conversations during shared decision-making process (source: Elwyn G, et al., *Shared decision making: a model for clinical practice.* J Gen Intern Med, 2012)

Tools can support the shared decision-making process during the ESKD education. In 2017, three Dutch tools, also called patient decision aids, became available: the Option Grids, the Dutch Kidney Guide, and the 3 Good Questions. The Option Grids are tables that describe the answers to frequently asked patient questions regarding certain treatment options. Two Dutch Option Grids are available: (1) Permanent damage to your kidneys: kidney replacement therapy or conservative treatment, (2) Permanent damage to your kidneys: options for kidney replacement therapy [7]. The Dutch Kidney Guide is a website that contains film clips of over 40 patients who are treated with kidney transplantation, various forms of HD and PD, and conservative care. In these film clips, patients explain the impact of the treatments on 19 domains of their daily lives (e.g. work, vacation, pets) [8]. The 3 Good Questions are: (1) What are my options? (2) What are the possible benefits and risks of those options? (3) What does that mean in my situation? [9, 10] While the 2 Option Grids and Dutch Kidney Guide were specifically designed for ESKD patients, the 3 Good Questions are applicable to conversations about treatment decisions between any patient and healthcare professional.

The 3 Good Questions are also featured in a national campaign on shared decision-making, initiated by patient organizations (i.e. Patiëntenfederatie Nederland) and organizations from medical-specialists (i.e. Federatie Medisch Specialisten), general practitioners (i.e. Landelijke Huisartsen Vereniging and Nederlands Huisartsen Genootschap), nursing and paramedical care (i.e. Verpleegkundigen & Verzorgenden Nederland), which started in the Netherlands in September 2021 [11]. The goal of this campaign is to promote shared decision-making by getting patients and caregivers to ask questions, listen better, and prepare conversations. Prior to the campaign, a survey among Dutch patients and healthcare professionals showed that 46% of healthcare professionals say they make shared decisions with the patient, while only 37% of patients say they make decisions together with their healthcare professional [12]. The campaign provides tips and tools to make better and more frequent shared decisions, since shared decision-making leads to an increase in satisfaction, therapy adherence, involvement, and being informed on the one hand, and a decrease in doubt, regret, and costs on the other hand [11, 13-15].

Each year in the Netherlands, approximately 2,000 patients reach ESKD [16]. In 2021, 18,107 Dutch ESKD patients were treated with a form of kidney replacement therapy (KRT), either kidney transplantation or dialysis [17]. Unfortunately, it is unknown how many Dutch patients are currently treated with conservative care. About one-third of patients treated with KRT are treated with a form of dialysis either HD or PD [17].

In HD, a connection is made between a patient's vascular access (i.e. central venous catheter, arteriovenous fistula or graft) and the dialysis machine. The patient's blood flows into the dialysis machine where it passes through a dialyzer. The dialyzer contains 2 compartments, one for the patient's blood and one for the dialysate fluid, which are separated by a semi-permeable

membrane. Through processes such as diffusion and convection, waste products and excess body water from the blood pass through the membrane into the dialysate fluid and are removed. HD can be performed in a hospital/dialysis center (in-center HD) or at home (home HD), with in-center HD often done by a nurse while at home it can be done by a nurse, family caregiver or the patient him/herself. In addition, it can be performed during the day or at night. Different HD schedules are used, such as 3 sessions of 4 hours per week during the day, 6 sessions of 2 hours per week during the day or every other night for 8 hours. The schedule with 3 sessions of 4 hours per week is most commonly used and therefore called 'conventional HD'. HD has advantages, such as professional care and socialization with other patients when performed in-center [18, 19]. However, conventional HD is intermittent, thus unphysiological, and has disadvantages, such as fluid restrictions, dialysis hangover, access complications, higher mortality compared to PD, and the need to travel to and from the hospital/dialysis center [18-20].

In PD, the peritoneal membrane in the patient's abdomen acts as a dialysis membrane. Dialysate fluid is instilled into the abdomen through an abdominal catheter called the PD catheter. Waste products and excess body water from the blood compartment flow through the peritoneal membrane into the dialysate fluid through diffusion and ultrafiltration, the latter due to the presence of a transmembrane osmotic gradient. Diffusion and ultrafiltration occur day and night when PD patients have dialysate fluid in their abdomen. PD is performed at home most often by the patient, and sometimes by a partner, family caregiver or medical homecare nurse. When a patient receives help to perform PD, it is referred to as assisted PD [21]. PD has advantages, such as patient autonomy, less hospital visits, and preservation of residual kidney function [18, 19]. However, PD also has potential complications, such as peritonitis and risk of membrane failure [18, 19, 22].

In the last decades, many studies have been conducted on the mortality and morbidity of dialysis patients. The mortality rate of dialysis patients is high, more than 50% of patients die within 5 years after starting dialysis [20, 23]. The morbidity of dialysis patients is also high, specifically by cardiovascular diseases such as coronary artery disease and atrial fibrillation [24], and stroke [25], often leading to hospitalizations [26-29]. Notwithstanding the fact that research on the mortality and morbidity of dialysis patients is important, there is an increasing call for studies on patient reported outcomes, such as quality of life [29-32]. Health-related quality of life (HRQoL) can be determined with patient reported outcome measures (PROMs), questionnaires that, in addition to HRQoL, focus on patients' symptoms and functional status [33]. Initially, PROMs were developed for use in research, but in recent years they have also been used increasingly in clinical care [33-35].

Dialysis patients have a poor quality of life [36, 37]. Performing a home dialysis therapy, i.e. PD or home HD, has potential advantages such as self-care, fewer hospital visits, and the ability to engage in professional or social activities, which could contribute to a better quality of life [38-

44]. However, recent data regarding the effects of dialysis at home on HRQoL, clinical outcomes, and costs compared with in-center HD are lacking. Therefore, we initiated the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO), to shed more light on this important topic. DOMESTICO started in 2017 and consists of a retrospective and a prospective cohort, and an implementation project called 'Good Practices and Shared Decision-Making' (Figure 2).

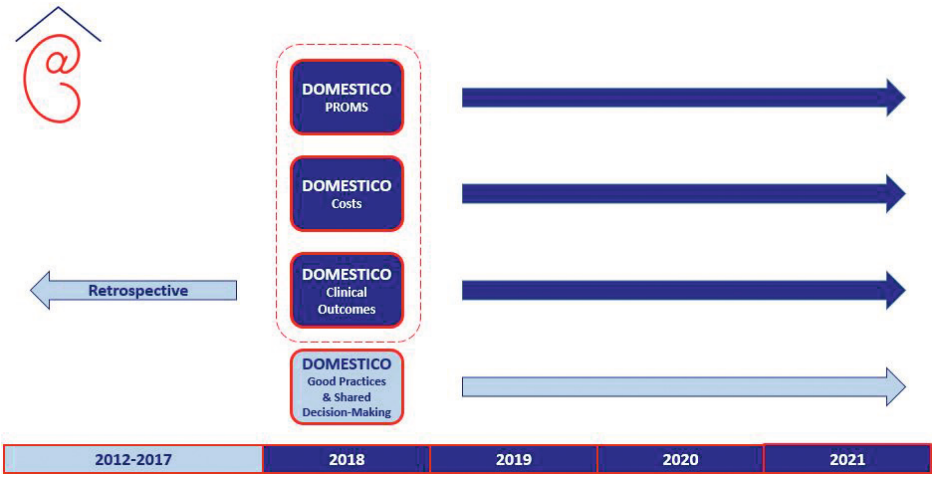

Figure 2. Overview of the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO)

For the retrospective part of DOMESTICO, data are collected from adult patients (≥ 18 years) from 41 Dutch hospitals who started dialysis treatment (i.e. PD or HD) between January 1, 2012 and January 1, 2017. In this cohort, the causes and modifiable factors of technique failure in home and nocturnal dialysis will be investigated. In addition, clinical outcomes (including hospitalization, blood pressure and metabolic regulation, mortality) of home and nocturnal dialysis patients will be compared with those of in-center HD patients.

For the prospective part of DOMESTICO which started on December 22, 2017, patients starting dialysis in 59 dialysis centers across the Netherlands and Belgium are included. The primary objective is to determine the effects of home dialysis on HRQoL compared to in-center HD, measured with PROMs. Secondary objectives are; 1) to perform a cost-effectiveness analysis of home dialysis compared to in-center HD; 2) to determine the clinical outcomes of home dialysis, particularly hospitalization and mortality, compared to in-center HD and to identify modifiable factors [45].

The implementation project 'Good Practices and Shared Decision-Making' was conducted from January 2018 to May 2019 and aimed to improve the education process regarding different ESKD

treatment options (i.e. conservative care and KRT) through the application of Good Practices and Shared Decision-Making. The project was conducted in 12 Dutch hospitals and several products were developed, such as a workshop "Shared decision-making: from information to dialogue" in which shared decision-making and the three Dutch patient decision aids were discussed, a care pathway for kidney failure, and various protocols with Good Practices for ESKD education and KRT.

Thesis outline

The overall aim of this thesis is to gain further insights in (1) patient education and shared decision-making, (2) traditional clinical outcomes of dialysis such as bleeding, hospitalization, technique failure and PD peritonitis, and (3) an important patient reported outcome; HRQoL. This thesis contains articles with the first results from DOMESTICO retrospective and the implementation project.

Patients who progress to ESKD face a very intensive education process about the different treatment options, which many find very stressful, confronting, and burdensome. Therefore, it is important to provide proper education and make a final treatment decision based on SDM, so that the medical knowledge of the healthcare professional is combined with the values and preferences of the individual patient [4]. In addition, the traditional clinical outcomes of dialysis also remain relevant, as they can have a major impact on the burden experienced by patients. However, given the high burden and mortality of dialysis, it is also incredibly important to focus on what really matters to patients, namely HRQoL.

The first part of this thesis focuses on patient education and shared decision-making. In **chapter 2** we describe the use of the 3, previously mentioned, Dutch patient decision aids (i.e. 3 Good Questions, Option Grids, and Dutch Kidney Guide) by healthcare professionals and the degree of shared decision-making as experienced by advanced chronic kidney disease patients. In addition, we describe a workshop we developed with the Dutch Kidney Patients Association to train healthcare professionals how to implement the patient decision aids.

Shared decision-making is addressed in various (inter)national guidelines which provide recommendations regarding education and dialysis treatment [1, 2, 21, 46-48]. One would expect that this would result in similar proportions of patients being treated with home dialysis in various centers. However, there seems to be practice variation which could be explained by so-called 'good practices', practices that are developed locally and with which healthcare professionals have good experience, but that are not evidence-based and therefore not added to (inter)national guidelines [49, 50]. **Chapter 3** describes a scoping review we performed to identify and summarize

the available literature describing good practices for dialysis education, treatment, and electronic health (eHealth).

As mentioned, PD can be performed by a patient autonomously or in the context of assisted PD [21]. Assisted PD programs are available in most European countries, but the percentage of patients receiving assisted PD varies considerably [51-55]. **Chapter 4** describes the results of an online survey among healthcare professionals of European nephrology units. This survey was used to investigate the factors associated with the availability of an assisted PD program at a center level and whether the availability of this program is associated with the proportion of home dialysis patients.

The second part of this thesis focuses on the traditional clinical outcomes of dialysis. The specific dialysis modality with which a patient is treated (i.e. HD or PD) may affect their morbidity. In **chapter 5 and 6** the risks of bleeding and hospitalization in patients on HD are compared with patients on PD.

Chapters 7 and 8 focus on patients performing PD. **Chapter 7** describes our study regarding the modifiable causes and risk factors of technique failure (i.e. transfer to in-center HD for ≥ 30 days or death) in PD, which is highly relevant to address in order to improve technique survival. Peritonitis is one of those modifiable causes [56]. **Chapter 8** describes the results of treating Candida peritonitis, which normally requires catheter removal resulting in high technique failure rates, with an amphotericin B catheter lock combined with oral flucytosine and intraperitoneal fluconazole in order to preserve the catheter and improve technique failure.

The third part of this thesis focuses on HRQoL. For dialysis patients, quality of life is an important outcome parameter [30, 57-61]. However, little is known about differences in quality of life between home dialysis (i.e. PD and home HD) and in-center HD patients across the world. We conducted a systematic review and meta-analysis describing randomized controlled trials and observational studies that compared HRQoL in home dialysis patients versus in-center HD patients (**chapter 9**). This systematic review and meta-analysis prompted the design of the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO). The rationale and design of this nationwide, prospective, observational cohort study investigating the effect of home dialysis therapies on HRQoL, clinical outcomes and costs, in comparison with in-center HD is described in **chapter 10**.

Finally, the last part of this thesis summarizes and discusses the results described in the previous chapters, emphasizing the relevance of this thesis (**chapter 11**).

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Part I

Patient education and shared decision-making

Chapter 2

Value of patient decision aids for shared decision-making in end-stage kidney disease

Anita van Eck van der Sluijs, Sanne Vonk, Anna A. Bonenkamp, Karen Prantl, Aase T. Riemann, Brigit C. van Jaarsveld and Alferso C. Abrahams on behalf of the DOMESTICO study group

Submitted

Abstract

Background Ideally, shared decision-making forms the basis of education on end-stage kidney disease therapies. Patient decision aids, specifically developed for this, have implementation barriers. We evaluated the use of 3 decision aids (3 Good Questions, Option Grids, Dutch Kidney Guide) by healthcare professionals in relation to patient-experienced shared decision-making. Also, we developed a workshop for professionals on decision aid implementation.

Methods Questionnaires regarding education/use of decision aids were distributed to healthcare professionals. Patients with eGFR<30 ml/min/1.73m^2 completed SDM-Q-9/collaboRATE questionnaires. Shared decision-making differences between hospitals were analyzed with one-way ANOVA and logistic regression.

Results In 12 Dutch hospitals, 7 educational conversations were conducted per patient, but only 25–67% used one of the decision aids. Of 117 healthcare professionals, 56% applied shared decision-making by using 3 Good Questions (28%), Option Grids (31–33%) and Kidney Guide (51%). Of 182 patients, 61–85% were satisfied with their education. Of worst scoring hospitals, only 50% used Option Grids/Kidney Guide, compared to 100% of best scoring hospitals which also had a lower number of conversations (p=0.05), but provided information about all treatment options and more often provided information at home. After the workshop, patients' shared decision-making scores did not change.

Conclusions Patients and healthcare professionals are reasonably satisfied with shared decision-making although the use of decision aids is limited. Hospitals that use decision aids had higher shared decision-making scores and required fewer conversations. Future research should identify barriers in order to implement decision aids in daily practice to achieve a *shared decision*.

Introduction

The global incidence of end-stage kidney disease (ESKD) is rapidly increasing [1-4]. While ESKD poses a significant global burden, it also has a tremendous impact on the daily life of the individual patient. Patients not only have to deal with complications of ESKD, but also face an intensive education process regarding the different treatment options, i.e. conservative care and kidney replacement therapies (KRT). To choose a specific treatment, a healthcare professional's medical knowledge must be combined with an individual patient's values and preferences [5]. This process of shared decision-making aims not only to ensure that a decision is medically sound, but also that the patient is satisfied, both in terms of the process and the final decision.

The model for sharing in medical decision-making was first described in 1972 [6], but it was not until 1997 that an article was published which provided more clarity regarding the actual shared decision-making (SDM) model and its key characteristics: (1) two participants: physician and patient; (2) both participate in the process; (3) both share information; (4) both agree to the decision [7]. Since then, numerous articles regarding SDM for patients with kidney disease have been published [8-15] and the use of SDM is incorporated in national and international renal guidelines [5, 16-18].

Although many guidelines advocate the use of SDM in the care for patients with kidney disease, studies have shown that a large proportion of patients with ESKD do not experience the decision as a shared one [14, 19-21]. To improve this situation, patient decision aids (PDAs) have been developed. PDAs are tools, developed in various forms such as written materials or web-based formats, that provide support during the SDM process and serve to supplement the information provided by healthcare professionals [22, 23]. In 2017, three PDAs became available in the Netherlands, namely the 3 Good Questions, 2 Option Grids and the Dutch Kidney Guide. The 3 Good Questions are: (1) What are my options? (2) What are the possible benefits and risks of those options? (3) What does that mean in my situation? They were developed in Australia in 2011, translated into Dutch and tested in 2015 [24, 25]. These 3 Good Questions can improve shared decision-making between the patient and the healthcare professional, and improve quality and safety of the education process [24]. Option Grids form the second PDA which are based on those developed by The Option Grid Collaborative [26, 27]. Option Grids are tables that describe the answers to frequently asked patient questions regarding certain treatment options. Two Dutch Option Grids are available: (1) Permanent damage to your kidneys: kidney replacement therapy or conservative treatment, (2) Permanent damage to your kidneys: options for kidney replacement therapy [28]. Finally, the Dutch Kidney Guide is a website that contains film clips of more than 40 patients who are treated with 9 different treatment modalities, from conservative care to various forms of hemodialysis, peritoneal dialysis, and kidney transplantation. In these film clips, patients explain the impact of these treatments on 19 domains of their daily lives. For example, patients tell

about the consequences of their treatment on eating/drinking, going on vacation, self-sufficiency regarding treatment, pets at home, sleep quality, work and school, etcetera [29].

Despite the fact that much attention has been paid to the development of PDAs, studies have also shown that there are barriers to the implementation of PDAs in daily practice [30]. For the Dutch PDAs, it is unknown whether they are sufficiently implemented in daily practice. Therefore, we evaluated the use of these PDAs by healthcare professionals and the degree of SDM as experienced by patients with advanced chronic kidney disease (CKD). Subsequently, we developed a workshop to train healthcare professionals how to implement these PDAs.

Methods

Study design

A survey was conducted in which questionnaires were distributed to healthcare professionals and patients with advanced CKD in 12 Dutch hospitals who participated in the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO), a multi-center cohort study among patients treated with dialysis in the Netherlands [31]. In addition, a SDM workshop was provided to the healthcare professionals with the aim of promoting the implementation of the Dutch PDAs.

Healthcare professionals' questionnaire

During the period April 2018 to September 2018, a questionnaire was distributed to all healthcare professionals (i.e. nephrologists (in training), nurses, social workers, dieticians) involved in the education process about ESKD treatment options in 12 Dutch hospitals (Supplemental figure 1). In the Netherlands, education is usually given to patients with CKD when the estimated glomerular filtration rate (eGFR) falls below 20 ml/min/1.73m^2. Education is provided by a team of healthcare professionals consisting of nephrologists (in training), nurses, social workers and dietitians, and in some hospitals physician assistants or nurse practitioners are also involved [32]. The education process includes several conversations with these healthcare professionals about the treatment options available for ESKD.

The healthcare professionals' questionnaire consisted of 6 general questions about the provided education in their center regarding ESKD treatment options, 4 questions about whether respondents were familiar with the 3 Dutch PDAs (i.e. 3 Good Questions, Option Grids, and Dutch Kidney Guide) and used them, 2 questions about what should be added or removed in the education process, and 4 questions focusing on SDM (Supplemental table 1). Participation was voluntary and anonymous.

Patients' questionnaire

To assess the degree of SDM experienced by patients, a questionnaire was distributed to all patients who had completed the education process regarding ESKD treatment options in 12 Dutch hospitals. The questionnaire consisted of the nine-item Shared Decision-Making Questionnaire (SDM-Q-9) and the collaboRATE, to which we added 7 general questions about the provided education regarding ESKD treatment options and 2 questions about perceived barriers against home hemodialysis and peritoneal dialysis (Supplemental table 2). The SDM-Q-9 contains 9 statements regarding SDM which are rated on a 6-point Likert scale (from 0 'completely disagree' to 5 'completely agree') [33, 34], while the collaboRATE contains 3 questions regarding SDM which are rated on a 10-point Likert scale (from 0 'no effort was made' to 9 'every effort was made') [35]. Participation was again voluntary and anonymous.

The patients' questionnaires were distributed during two different periods; from April to November 2018 and from December 2018 to April 2020 (Supplemental figure 1). This was done to assess whether there was a difference in the degree of SDM experienced by patients in the period before an SDM workshop was given in a hospital compared to the period after the workshop was conducted.

SDM workshop

In collaboration with the Dutch Kidney Patients Association, we developed a 2-hour SDM workshop. During the period October 2018 to March 2019, the workshop was given in 10 of the 12 participating Dutch hospitals (Supplemental figure 1). The goal of the workshop was to provide healthcare professionals with information regarding SDM and the 3 Dutch PDAs and to encourage them to start applying them in daily practice.

First, the results from the healthcare professionals' questionnaire and research on SDM was presented. Second, information was provided on Glyn Elwyn's SDM model in which the patient is guided to make a treatment choice according to 3 consecutive conversation types: choice talk, option talk, and decision talk [36]. Third, the background and content of the 3 Dutch PDAs (i.e. the 3 Good Questions, Option Grids, and Dutch Kidney Guide) were discussed and their application was also practiced. Finally, it was discussed how the PDAs could be integrated into the education process about ESKD treatment options that already existed in that specific hospital.

Statistical analysis

Descriptive statistics were used to evaluate all questions of the healthcare professionals' questionnaire and the general questions of the patients' questionnaire. From the patient questionnaire, the Likert scales of the SDM-Q-9 and collaboRATE were both converted into a score from 0 to 100, with a higher score indicating better SDM [34]. A one-way ANOVA was performed to evaluate the difference in both scores between participating hospitals. Subsequently, logistic

regression was used to explore differences between the best scoring hospitals and the worst scoring hospitals. Finally, descriptive statistics were again used to explore the relation between the use of the PDAs and the degree of SDM.

All statistical analyses were performed with SPSS Statistics version 26 (SPPS, Chicago, Illinois, USA).

Results

Education process in participating hospitals

A total of 12 hospitals across the Netherlands participated, of which 2 were academic hospitals and the remaining non-academic teaching hospitals. Twenty-five percent of the hospitals initiated the education process regarding ESKD treatment options for patients with advanced CKD at an eGFR between 25 and 30 ml/min/1.73m^2, 33% between 20 and 25 ml/min/1.73m^2, and 42% between 15 and 20 ml/min/1.73m^2. Sixty-seven percent of the hospitals had a set format for the education process, which included a home visit in 75% of the hospitals. A median of 7 [interquartile range 6 – 9] conversations were conducted with the patient during the education process. Only 25% of the hospitals reported using the 3 Good Questions during the education process, this was 42% and 67% for the Option Grids and Dutch Kidney Guide, respectively.

Use of Patient Decision Aids by healthcare professionals

A total of 117 healthcare professionals (27% physicians, 8% physician assistants, 38% nurses, 14% social workers, 13% other) completed the questionnaire: 81% found the general impression of their own education process (very) good, 80% found the total number of consults good, and 56% found the amount of information they provided good, while 28% found it too much. SDM was applied according to 56% of professionals, however only 28% reported to use the 3 Good Questions, 31–33% the Option Grids, and 51% the Kidney Guide.

Patients perspectives on Shared Decision-Making during the first period

Between April and November 2018, 182 patients from the 12 hospitals completed the questionnaires: 71% found the education overall (very) good and 61% found the educational materials (very) good. Regarding the amount of information, 85% found the received amount of information and 82% the total number of conversations about right (Figure 1a).

Figure 2a and b show the SDM-Q-9 and collaboRATE scores of the participating hospitals. The mean SDM-Q-9 score was 75±22 and the mean collaboRATE score 86±14. The hospital that scored the worst on both questionnaires had a mean SDM-Q-9 score of 66 and a collaboRATE score of 77. The best scores on the questionnaires were encountered in two different hospitals: the highest mean SDM-Q-9 score was 87 and the highest collaboRATE score was 90.

Overall, no significant difference was found between hospitals in either score (SDM-Q-9 p=0.70; collaboRATE p=0.58). However, when the hospital that scored best on the SDM-Q-9 was compared with the other individual hospitals, a significant difference was found with the hospital that scored worst on the SDM-Q-9 (p=0.03).

Relation between use of Patient Decision Aids and degree of Shared Decision-Making

When hospitals with the worst SDM-Q-9 score (<70) were compared to those with the best score (>77), only 50% of the worst scoring hospitals used the Option Grids and Kidney Guide, compared to 100% of the best scoring hospitals. The majority of the worst scoring hospitals started education for patients with advanced CKD at an eGFR between 20–30 ml/min/1.73 m^2, while the best scoring hospitals all started between 15–20 ml/min/1.73 m^2. The mean number of individual conversations between healthcare professionals and the patient was higher in the worst scoring hospitals than in the best scoring hospitals (8±1 vs. 7±1, p=0.054). Although the number of conversations was lower, best scoring hospitals provided information about all treatment options, including nocturnal hemodialysis and conservative care, and more often provided information during a home visit.

Shared Decision-Making workshop

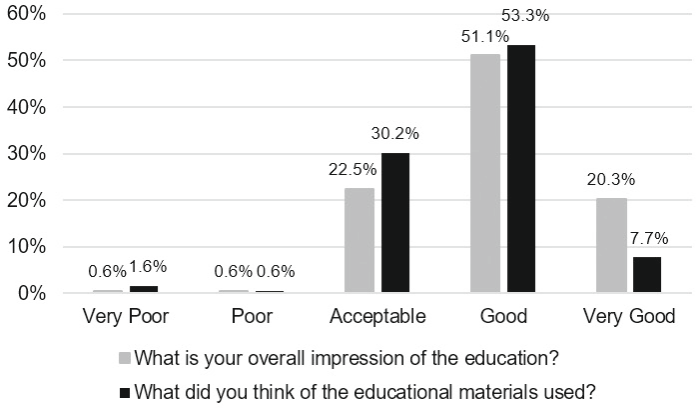
During the period October 2018 to March 2019, 10 hospitals participated in the SDM workshop. A total of 114 healthcare professionals joined the workshop: 29 nephrologists (in training), 5 physician assistants/nurse practitioners, 40 nurses, 14 social workers, 13 dietitians, and 13 other professionals (e.g. research nurses). At 9 of the 10 workshops also a patient with CKD was present, highlighting the patient perspective regarding the education process about ESKD treatment options. The presence of a patient who could explain the patient perspective was considered a great additional value to the workshop by the healthcare professionals. The workshop was appreciated with a 7.5±0.4 on a range from 0 (worst) to 10 (perfect).

Patients perspectives on Shared Decision-Making during the second period

Between December 2018 and April 2020, 117 patients in 8 hospitals completed the questionnaires: 82% found the education overall (very) good and 56% found the educational materials (very) good. Regarding the amount of information, 82% found the received amount of information and 91% the total number of conversations about right (Figure 1b).

The mean SDM-Q-9 score was 73±24 and the mean collaboRATE score 89±13. The worst scores on the questionnaires were encountered in two different hospitals: the lowest mean SDM-Q-9 score was 55±20 and the lowest collaboRATE score was 86±13. The hospital that scored the best on both questionnaires had a mean SDM-Q-9 score of 77±19 and a collaboRATE score of 94±8. Figure 3a shows all SDM-Q-9 scores of the hospitals and figure 3b shows all collaboRATE scores. Compared to the results of the first period (figures 2a and 2b), there is no difference in SDM-Q-9 and collaboRATE scores.

Figure 1a. Impression regarding education process during first period



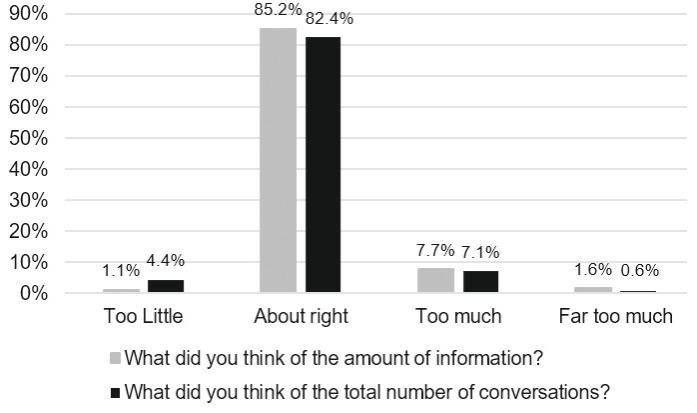
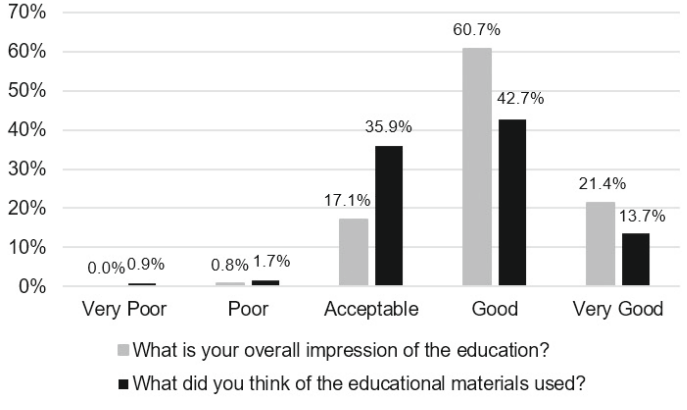


Figure 1b. Impression regarding education process during second period



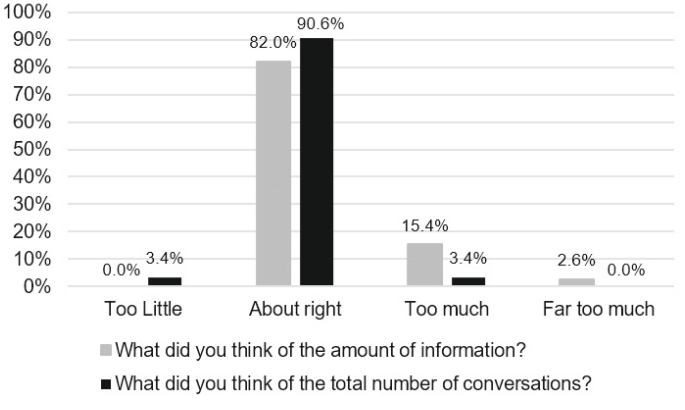
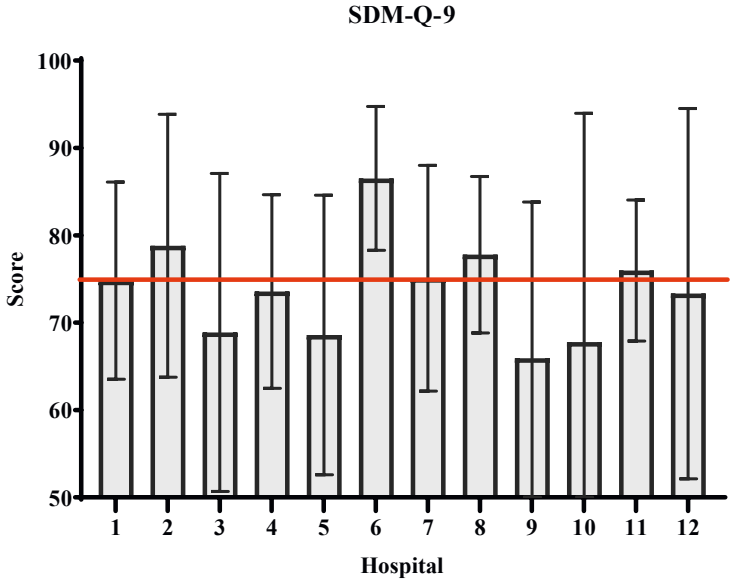
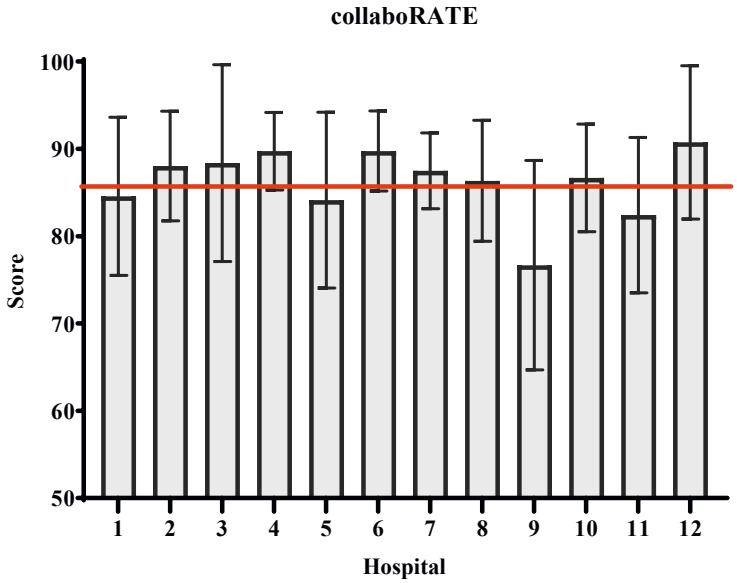


Figure 2a. SDM-Q-9 score of participating hospitals during first period



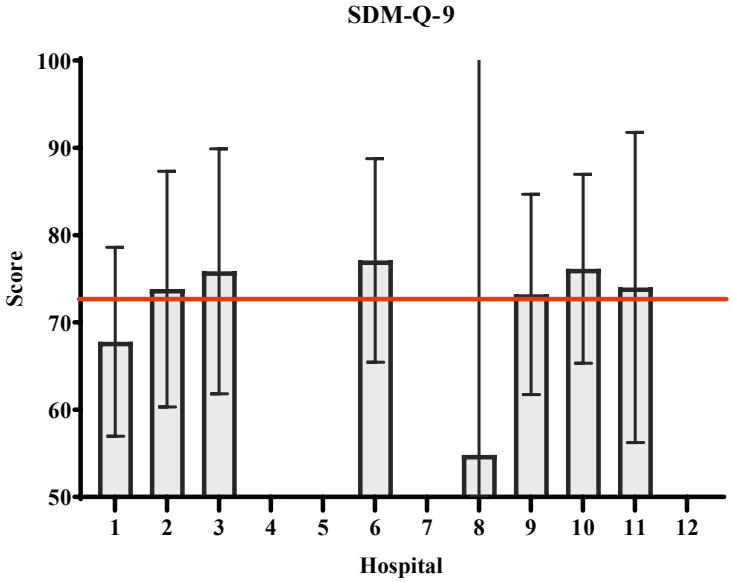
The red line indicates the mean SDM-Q-9 score of 75.

Figure 2b. CollaboRATE score of participating hospitals during first period



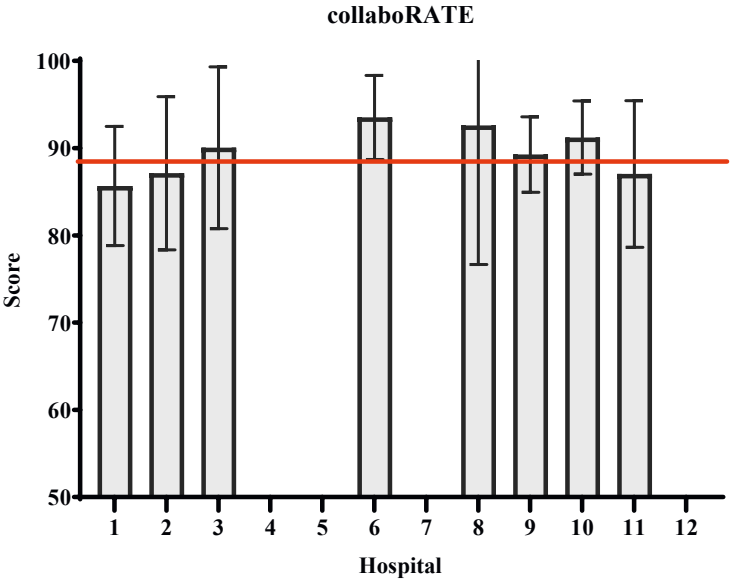
The red line indicates the mean collaboRATE score of 86.

Figure 3a. SDM-Q-9 score of participating hospitals during second period



The red line indicates the mean SDM-Q-9 score of 73.
During the second period only 8 of the 12 hospitals participated.

Figure 3b. CollaboRATE score of participating hospitals during second period



The red line indicates the mean collaboRATE score of 89.
During the second period only 8 of the 12 hospitals participated.

Overall, no significant difference was found between hospitals in either score (SDM-Q-9 p=0.86; collaboRATE p=0.81), not even if we compared the hospital with the best or the worst score to the other hospitals.

Discussion

Our survey shows that in the Netherlands the education process regarding ESKD treatment mostly starts at an eGFR between 15 and 20 ml/min/1.73m^2 with a median of 7 conversations between the patient and healthcare professionals. Patients with CKD and healthcare professionals are reasonably satisfied with the education process regarding ESKD treatment options and the degree of SDM in the Netherlands. However, healthcare professionals use the Dutch PDAs (i.e. the 3 Good Questions, Option Grids, and the Dutch Kidney Guide), tools specifically designed to support SDM, only to a limited extent. Compared to hospitals with the worst SDM-Q-9 score, the number of conversations in hospitals with the best SDM-Q-9 score is lower but all treatment options are discussed, often during a home visit. After a workshop introducing SDM and the PDAs, the extent to which patients with CKD experienced SDM during the education process remained the same.

To make a decision regarding a treatment option for ESKD is a very complicated process for patients with CKD: several factors play a role in making the decision, such as previous personal experience, burden of treatment, family, and culture and religion [37]. In addition, gut instinct and emotions also play an essential role in making a decision [37]. For healthcare professionals, it is difficult to explain and foresee the disease course in a given patient, which is critical for patients who must make a decision, as CKD is often asymptomatic and the disease course can be unpredictable [38]. This is why it is so important to apply SDM, which combines the professional's medical knowledge with the patient's personal preferences to make this important decision together.

Healthcare professionals often think they already practice SDM, as our survey also shows, but patients rarely feel that the decision about a treatment option for ESKD has really been made together [14, 19-21]. A major barrier to SDM that seems to play a role is implicit persuasion [39]. A recent study by van Dulmen *et al*. showed that nephrologists applied implicit persuasion during the ESKD treatment decision talk, for example by selectively presenting treatment options or naming pros and cons of treatment options unequally [39]. An older study also showed that nephrologists apply implicit persuasion, for example by informing younger patients less frequently about the option of conservative care [8]. This practice hinders a patient with CKD from making an informed choice together with their healthcare professional.

Important tools that can promote the process of SDM is adopted are PDAs. PDAs are "interventions that support patients by making their decisions explicit, providing information about options

and associated benefits/harms, and helping clarify congruence between decisions and personal values" [22]. PDAs exist to support the SDM process and serve to supplement the information provided by healthcare professionals [22, 23]. In 2017, a review of Davis *et al.* described 10 new PDAs for decisions regarding KRT and 3 new PDAs for decisions regarding conservative care developed in Australia, Canada, the United States, and the United Kingdom [23]. One of the 13 PDAs bears some resemblance to the Dutch PDAs the Option Grids. This is a website, hosted by Healthwise in the United States, called 'Kidney Failure: What Type of Dialysis Should I Have?' [Kidney Failure: What Type of Dialysis Should I Have? (healthwise.net)]. It contains six sections: providing facts about kidney disease and the decision to be made; comparing options; asking patients about their feelings regarding dialysis options; asking patients for a decision; a 'quiz'; and providing a summary of the preceding. The similarities to the Option Grids are the design with information relevant to patients and the comparison of different dialysis treatments. The main differences with the Option Grids is that the website does not focus on kidney transplantation or conservative care and is only an online PDA, making it less suitable for patients with lower eHealth literacy.

Multiple studies have demonstrated the beneficial effects of PDAs, for example, in terms of patient knowledge of risks and benefits [22, 23]. However, the implementation of PDAs depends on aspects such as the notion of healthcare professionals that they can improve their SDM skills, the willingness to use the PDAs and effective systems in which they are used [22]. Scalia *et al.* reported in their systematic review that healthcare professionals indicate time constraints, lack of training in the use of PDAs, and disagreement about the content and format of PDAs, as the most important barriers to the integration of PDAs [30].

Despite the fact that barriers to the integration of PDAs are well known, there is a lack of studies on the actual use of PDAs within the education process regarding ESKD treatment options. Our study showed that one year after the publication of the 3 Dutch PDAs, only 28% of the healthcare professionals surveyed used the 3 Good Questions, 31–33% used the Option Grids, and only 51% used the Kidney Guide. Although we did not investigate the reason for the limited use of the PDAs, discussions with the hospitals we contacted revealed that the previously mentioned barriers will certainly play a role in this. Future research should therefore focus on finding solutions to overcome these barriers, as PDAs are valuable tools for the SDM process [22, 23].

To our knowledge, this is the first survey providing detailed insight in the use of 3 PDAs by healthcare professionals and the degree of SDM as experienced by patients with CKD. In addition, a large number of healthcare professionals from multiple centers participated in our SDM workshop. Our survey has some limitations. First, the SDM-Q-9 and collaboRATE, used by patients to examine the perceived level of SDM, were not developed specifically for patients with CKD. However, both the SDM-Q-9 and collaboRATE have been tested in patients with chronic diseases making them

very likely to be useful in patients with CKD as well [33-35]. Second, the way patients completed the questionnaire may have been influenced by recall and response bias and the patients who completed the questionnaire during the two periods were different, since patients of the first period had already chosen an ESKD treatment option and were not going through the education process again. However, this does reflect daily practice. Third, the SDM scores were already quite high in the first period which may have led to a ceiling effect. However, our survey provides an important insight into the current education process regarding ESKD treatment options and opportunities for improvement of the education process.

In conclusion, although patients with advanced CKD and healthcare professionals are reasonably satisfied with the extent of SDM during the education process regarding ESKD treatment options, the use of specifically developed PDAs is limited. Hospitals that did use PDAs had higher SDM scores and required fewer conversations during the education process. After a workshop introducing SDM and the PDAs, the extent to which patients with CKD experienced SDM during the education process remained the same. Future research should identify the barriers to the use of PDAs in order to implement them in daily practice to achieve an optimal *shared decision*.

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Supplemental material

Supplemental table 1. Healthcare professional questionnaire

Questions	Answer options
What is your profession?	Physician – physician assistant/nurse practitioner – dialysis nurse – dietitian – social worker
What is your overall impression of ESKD education?	5-point Likert scale ranging from 'bad' to 'very good'
What do you think about the organization of ESKD education?	5-point Likert scale ranging from 'bad' to 'very good'
What do you think about the total number of conversations a patient has during ESKD education?	5-point Likert scale ranging from 'far too little' to 'far too much'
What do you think about the quality of information given during the conversations?	5-point Likert scale ranging from 'bad' to 'very good'
What do you think about the amount of information given during the conversations?	5-point Likert scale ranging from 'far too little' to 'far too much'
What do you think of the educational materials used?	5-point Likert scale ranging from 'bad' to 'very good'
To what extent are you familiar with the decision aids listed below? • Option Grid 'Permanent damage to your kidneys: renal replacement therapy or conservative treatment' • Option Grid 'Permanent damage to your kidneys: options for renal replacement therapy' • Dutch Kidney Guide • 3 Good Questions	never heard of – heard of, never used – heard of, used – no opinion
What should be added to ESKD education?	Open question
What should be removed from ESKD education?	Open question
Do you think patients are completely informed based on current ESKD education?	5-point Likert scale ranging from 'completely disagree' to 'completely agree'
Do you think patients are objectively informed based on current ESKD education?	5-point Likert scale ranging from 'completely disagree' to 'completely agree'
Do you think patients can make a good decision based on current ESKD education?	5-point Likert scale ranging from 'completely disagree' to 'completely agree'
Do you think patients make their decision together with their physician (shared decision-making)?	5-point Likert scale ranging from 'completely disagree' to 'completely agree'

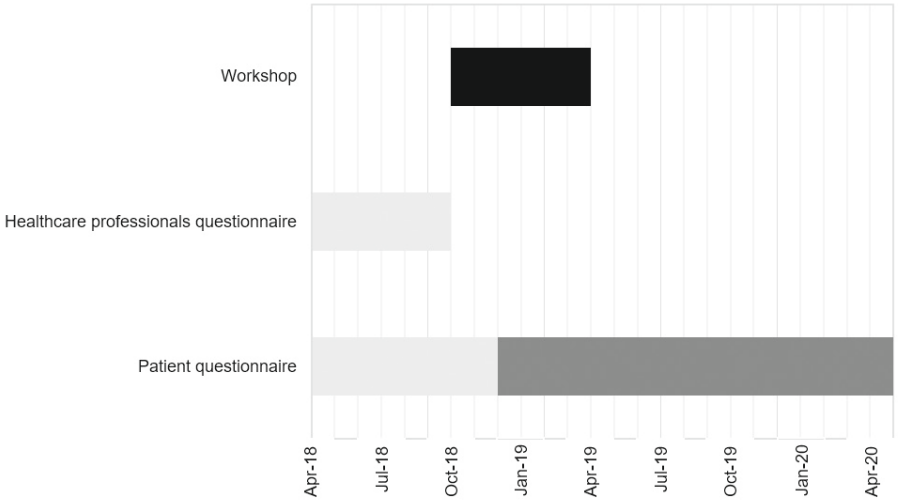
Supplemental table 2. Patient questionnaire

SDM-Q-9	Answer options
My doctor made clear that a decision needs to be made	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor wanted to know exactly how I want to be involved in making the decision	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor told me that there are different options for treating my medical condition	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor precisely explained the advantages and disadvantages of the treatment options	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor helped me understand all the information	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor asked me which treatment option I prefer	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor and I thoroughly weighed the different treatment options	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor and I selected a treatment option together	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
My doctor and I reached an agreement on how to proceed	6-point Likert scale ranging from 'completely disagree' to 'completely agree'
collaboRATE	
How much effort was made to help you understand your health issues?	10-point Likert scale ranging from 'No effort was made' to 'Every effort was made'
How much effort was made to listen to the things that matter most to you about your health issues?	10-point Likert scale ranging from 'No effort was made' to 'Every effort was made'
How much effort was made to include what matters most to you in choosing what to do next?	10-point Likert scale ranging from 'No effort was made' to 'Every effort was made'
General questions	
What treatment options have you had conversations about?	Conservative care – Kidney transplantation – Peritoneal dialysis – Home hemodialysis – In-center hemodialysis (multiple answers possible)
What is your overall impression of the conversations?	5-point Likert scale ranging from 'bad' to 'very good'
What do you think about the amount of information given during the conversations?	5-point Likert scale ranging from 'far too little' to 'far too much'
Was the information given during the conversations clear?	Yes – No – Other (with explanation)
What do you think of the educational materials used?	5-point Likert scale ranging from 'bad' to 'very good'
What do you think of the total number of conversations?	5-point Likert scale ranging from 'far too little' to 'far too much'
What treatment did you choose?	Conservative care – Kidney transplantation – Peritoneal dialysis – Home hemodialysis – In-center hemodialysis (one answer)

Supplemental table 2. Patient questionnaire (continued)

Question regarding perceived barriers	
What did you find to be barriers/obstacles to home hemodialysis?	Lack of space – costs – fear – unfamiliarity – burden for myself – burden for my family – 'hospital at home' – I had no choice – I received no information - other (with explanation) (multiple answers possible)
What did you find to be barriers/obstacles to peritoneal dialysis?	Lack of space – costs – fear – unfamiliarity – burden for myself – burden for my family – 'hospital at home' – abdominal catheter – Infections – I had no choice – I received no information - other (with explanation) (multiple answers possible)

Supplemental figure 1. Timeline



Chapter 3

Good practices for dialysis education, treatment, and eHealth: A scoping review

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Abstract

Background Recommendations regarding dialysis education and treatment are provided in various (inter)national guidelines, which should ensure that these are applied uniformly in nephrology and dialysis centers. However, there is much practice variation which could be explained by good practices: practices developed by local health care professionals, which are not evidence-based. Because an overview of good practices is lacking, we performed a scoping review to identify and summarize the available good practices for dialysis education, treatment, and eHealth.

Methods EMBASE, Pubmed, the Cochrane Library, CINAHL databases and Web of Science were searched for relevant articles using all synonyms for the words 'kidney failure', 'dialysis', and 'good practice'. Relevant articles were structured according to the categories dialysis education, dialysis treatment or eHealth, and assessed for content and results.

Results Nineteen articles (12 for dialysis education, 3 for dialysis treatment, 4 for eHealth) are identified. The good practices for education endorse the importance of providing complete and objective predialysis education, assisting peritoneal dialysis (PD) patients in adequately performing PD, educating hemodialysis (HD) patients on self-management, and talking with dialysis patients about their prognosis. The good practices for dialysis treatment focus mainly on dialysis access devices and general quality improvement of dialysis care. Finally, eHealth is useful for HD and PD and affects both quality of care and health-related quality of life.

Conclusion Our scoping review identifies 19 articles describing good practices and their results for dialysis education, dialysis treatment, and eHealth. These good practices could be valuable in addition to guidelines for increasing shared decision-making in predialysis education, using patients' contribution in the implementation of their dialysis treatment, and advanced care planning.

Introduction

According to the latest estimates, more than 320 million patients are treated with dialysis worldwide [1]. In most developed countries, patients start dialysis after having received education on different treatment options (i.e. dialysis, transplantation, and conservative care) [2-4]. Recommendations regarding education and dialysis treatment are given in various (inter)national guidelines [5-10]. These, preferably evidence-based, recommendations assist health care professionals in the guidance and treatment of chronic kidney disease (CKD) patients in order to provide the best possible care.

Guidelines should ensure that complete and objective education is provided to CKD patients about all treatment options [5]. In addition, guidelines should assure that practical execution of a specific dialysis treatment (i.e. hemodialysis (HD) or peritoneal dialysis (PD)) is more or less the same in all centers. However, this does not always seem to be the case. In 2010, it was shown that variation in center-specific factors (e.g. number of patients, in-center HD treatment capacity, and availability of a late dialysis shift) in the United States influenced the utilization of home dialysis (i.e. home HD and PD) [11]. This also appears to be true for many other countries when looking at the variation in PD utilization [12]. In addition, practice variation *within* a country seems to associate with a broad range in the percentage of dialysis patients treated with home dialysis [13]. Probably part of this variation can be explained by so-called 'good practices' which are developed locally.

The term 'good practice', also referred to as 'best practice', denotes '*…a practice that has been proven to work well and produce good results, and is therefore recommended as a model.'* [14, 15]. Good practices are practices that are developed locally and with which health care professionals have good experience, but are not evidence-based and therefore not added to (inter)national guidelines [14, 15]. As a result, these practices are not distributed and applied nationally, such as the recommendations from (inter)national guidelines. Although not evidence-based, good practices can have additional advantages and are therefore worthwhile exploring. Moreover, local good practices for dialysis education and treatment could potentially explain the previously mentioned practice variation.

An overview regarding these good practices is lacking in current published literature. Thus, we performed a scoping review to identify and summarize the available literature describing good practices for dialysis education, treatment, and electronic health (eHealth).

Methods

Search strategy and selection criteria

EMBASE, Pubmed, the Cochrane Library, CINAHL databases and Web of Science were searched for relevant articles using all synonyms for the words 'kidney failure', 'dialysis', and 'good practice' (Table 1).

Table 1. Search strings

Database	Search
EMBASE	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 OR 'peritoneal dialys*':ab,ti OR 'peritoneum near/3 dialys*':ab,ti OR 'end stage renal*':ab,ti OR 'kidney disease':ab,ti OR 'kidney failure':ab,ti OR 'peritoneal dialysis'/exp OR 'hemodialysis'/exp OR 'kidney disease'/exp AND 'good practice*':ab,ti OR 'best practice*':ab,ti
Pubmed	(hemodialys*[Title/Abstract] OR haemodialys*[Title/Abstract] OR hemo-dialys*[Title/Abstract] OR haemo-dialys*[Title/Abstract] OR "renal dialys*"[Title/Abstract] OR "dialys modalit*"[Title/Abstract] OR "artificial kidney*"[Title/Abstract] OR "peritoneal dialys*"[Title/Abstract] OR "peritoneum dialys*"[Title/Abstract] OR "End-Stage Kidney*"[Title/Abstract] OR "End Stage Kidney*"[Title/Abstract] OR "End-Stage Renal*"[Title/Abstract] OR "End Stage Renal*"[Title/Abstract] OR "Kidney failure"[Title/Abstract] OR "Renal Failure"[Title/Abstract] OR ESRD[Title/Abstract]) OR (renal dialysis[MeSH Terms] OR artificial kidneys[MeSH Terms] OR chronic kidney failure[MeSH Terms] OR dialysis, peritoneal[MeSH Terms] OR hemodialysis, home[MeSH Terms] OR kidney failure[MeSH Terms]) AND (("Good practice*"[Title/Abstract] OR "Best practice*"[Title/Abstract]) OR best practices[MeSH Terms])
Cochrane	((hemodialys* OR haemodialys* OR hemo-dialys* OR haemo-dialys* OR 'renal dialys*' OR 'dialys modalit*' OR 'artificial kidney*' OR 'peritoneal dialys*' OR 'peritoneum dialys*' OR 'end-stage renal*' OR 'end stage renal*' OR 'chronic kidney failure' OR 'end-stage kidney*' OR 'end stage kidney*' OR ESRD OR 'renal failure'):ti,ab,kw) OR (MeSH descriptor: [Renal Dialysis] Explode all trees) OR (MeSH descriptor: [Kidneys, Artificial] Explode all trees) OR (MeSH descriptor: [Renal Insufficiency, Chronic] Explode all trees) AND (("good practice*" OR 'best practice*'):ti,ab,kw) OR (MeSH descriptor: [Practice Guidelines as Topic] Explode all trees)

Table 1. Search strings (continued)

Database	Search
CINAHL	(TI "hemodialys*") OR (TI "haemodialys*") OR (TI "hemo-dialys*") OR (TI "haemo-dialys*") OR (TI "renal dialys*") OR (TI "dialys modalit*") OR (TI "artificial kidney*") OR (TI "peritoneal dialys*") OR (TI "peritoneum dialys*") OR (TI "End-Stage Kidney*") OR (TI "End Stage Kidney*") OR (TI "End-Stage Renal*") OR (TI "End Stage Renal*") OR (TI "Kidney Failure") OR (TI "Renal Failure") OR (TI "ESRD") OR (AB "hemodialys*") OR (AB "haemodialys*") OR (AB "hemo-dialys*") OR (AB "haemo-dialys*") OR (AB "renal dialys*") OR (AB "dialys modalit*") OR (AB "artificial kidney*") OR (AB "peritoneal dialys*") OR (AB "peritoneum dialys*") OR (AB "End-Stage Kidney*") OR (AB "End Stage Kidney*") OR (AB "End-Stage Renal*") OR (AB "End Stage Renal*") OR (AB "Kidney Failure") OR (AB "Renal Failure") OR (AB "ESRD") OR (MH "Renal Replacement Therapy+") OR (MH "Dialysis+") OR (MH "Renal Insufficiency+") OR (MH "Kidney, Artificial") AND (AB "good practice*") OR (AB "best practice*") OR (TI "good practice*") OR (TI "best practice*") OR (MH "Professional Practice, Theory-Based+") OR (MH "Professional Practice, Research-Based+") OR (MH "Practice Guidelines")
Web of Science	TS=(hemodialys* OR haemodialys* OR hemo-dialys* OR haemo-dialys* OR "renal dialys*" OR "dialys modalit*" OR "artificial kidney*" OR "peritoneal dialys*" OR "peritoneum dialys*" OR "End-Stage Kidney*" OR "End Stage Kidney*" OR "End-Stage Renal*" OR "End Stage Renal*" OR "Kidney Failure" OR "Renal Failure" OR ESRD) AND TS=("good practice*" OR "best practice*")

After removal of duplicates, two authors (AES and SV) independently screened titles and abstracts. Articles were eligible for inclusion if they provided a thorough description of the content of a good practice regarding dialysis education, treatment or eHealth for adult patients. Articles of all study types were included, however articles that described a guideline, review or meta-analysis were subsequently excluded after being screened for additional references.

Articles were excluded if they referred to a practice already covered in (inter)national guidelines, or if they reported on implementation projects, diabetes mellitus care or exercise programs for dialysis patients. In addition, articles were excluded if no full text or only a published abstract was available or if they were written in a language other than English.

The remaining articles were read full text by two authors (AES and SV) and screened for additional references. Final inclusion was based on consensus between the two authors (AES and SV) based on the previously mentioned in- and exclusion-criteria. In case of disagreement, the opinion of a third author (ACA) was decisive.

Data extraction

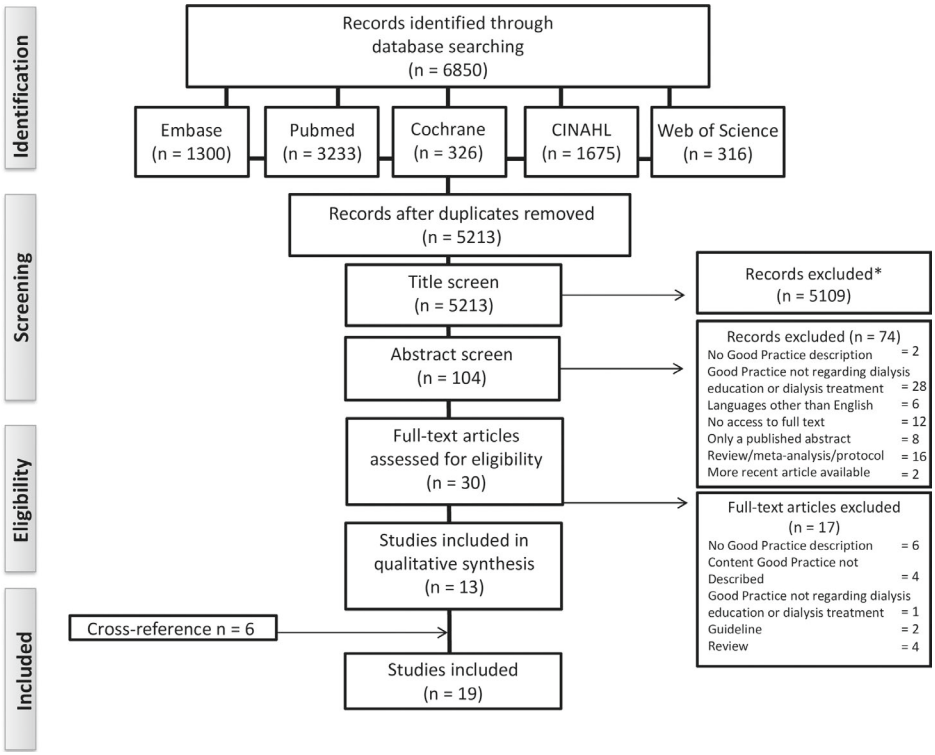
Data extraction was executed and checked by two authors (AES and SV). The included studies were structured according to the category to which the good practice was related. The following categories were used: dialysis education, dialysis treatment, and eHealth. After classifying the articles in the aforementioned categories, the following data were extracted: study design, number of participants investigated, good practice description, results, and study conclusion.

Results

Study selection

The initial literature search was performed on May 2, 2019, and last updated on January 12, 2021. Figure 1 provides an overview of the search.

Figure 1. Selection flow diagram



* Exclusion criteria for title screen: No good practice regarding dialysis modality education/treatment or eHealth, implementation project, diabetes mellitus care or exercise program for dialysis patients, guideline, meta-analysis, protocol, review, and language other than English.

After removal of duplicates, the search provided 5,213 articles. Subsequently 5,109 articles were excluded based on the title and another 74 were excluded based on the abstract. The full-text of the remaining 30 articles was assessed for eligibility. In total, 17 articles were excluded for the following reasons: no good practice described [5, 16-20], content of the good practice not described [21-24], good practice not regarding dialysis education or dialysis treatment [25], articles describing a guideline [26, 27] or review [23, 28-30]. The remaining 13 articles were screened for additional references, resulting in 6 cross-references (Figure 1) [31-36]. No additional cross-references were found in the articles describing guidelines, reviews or meta-analyzes. So, in total 19 articles were included [31-49].

Study characteristics

Characteristics of the 19 included articles are presented in Tables 2-4. Twelve articles described good practices for dialysis education (Table 2), three for dialysis treatment (Table 3), and four for eHealth (Table 4). All articles were published during the past 20 years and 47% of them came from the United States of America (USA). Most studies (58%) had a qualitative design, while the others were cohort studies (21%), case-control studies (11%), and randomized controlled trials (11%).

Dialysis education

Four of the twelve articles that described good practices for dialysis education, focused on providing objective predialysis education for CKD patients (Table 2) [31, 32, 40, 45]. Fortnum *et al.* [40] presented the 'My Kidneys, My Choice' decision aid, a patient-centered tool to support the education of CKD patients and promote shared decision-making. Health care professionals found the decision aid to be helpful for understanding treatment options and patients' priorities, and for supporting decision making.

Lacson Jr. *et al.* [31] initiated a standardized predialysis treatment options education program that consisted of education provided during a single group class session, followed by contacts after 30, 90, and 180 days during which treatment options were repeatedly discussed. Compared to controls, patients who followed the standardized education program were significantly more likely to choose PD (odds ratio (OR) 5.13) or to start in-center HD with a fistula or graft (OR 2.06), and had a lower mortality (OR 0.61) during the first 90 days of dialysis treatment [31].

Manns *et al.* [32] developed a two-phase patient-centered educational intervention, showing manuals and a video for self-care dialysis (i.e. PD, home HD, and self-care HD) in phase 1 and conducting a small group session in phase 2. The intervention significantly increased the proportion of patients who intended to initiate self-care dialysis (intervention group 82.1% vs. standard care group 50%).

Wu *et al.* [45] presented a multidisciplinary predialysis education program consisting of quarterly individual nurse-led lectures for CKD patients stage 3 and 4, while this was intensified to monthly lectures for CKD patients stage 5. Compared to controls, patients who followed the multidisciplinary education program had a significant lower risk of requiring dialysis (hazard ratio (HR) 0.117) and lower mortality (HR 0.103) after a mean follow-up of 11.7 months.

Five of the twelve articles that described good practices for dialysis education, focused on PD patients [33, 37-39, 41]. Luongo *et al.* [41] described a five-step approach (i.e. preparation, environment, special considerations, interview, and special concerns) for nurses to interview CKD patients who may choose PD as dialysis treatment. The goal of the interview was to reduce stress and anxiety in the patient and to promote shared decision-making. Although this approach has not been tested, the authors concluded that it guides PD nurses in providing correct information to future PD patients without overwhelming them.

The qualitative studies of Figueiredo *et al.* [38] and Firanek *et al.* [39] focused on PD training. Figueiredo *et al.* [38] provided a detailed description of a 5-day PD training course, with an introduction on day 1, supervised procedure practice sessions on days 2 to 4, and a review of the provided information and check of the patient's competence on day 5. The authors concluded that with this training course PD nurses ensure that the patient can perform PD safely and effectively. Firanek *et al.* [39] visited six centers to identify successful components of the PD training programs. Subsequently, they provided an overview of these successful components focused on setting and staff, training methods, educational documents, training structure, automated peritoneal dialysis (APD) training content, and delivery of APD training.

Successful home visit programs were described by Farina *et al.* [37] and Martino *et al.* [33]. The main similarities between the two programs were: assessment of the home where PD was performed, assessment of the PD procedure performed by the patient, and the patient's compliance to pharmacological and dialysis therapy. While Farina *et al.* did not examine the effect of the intervention, Martino *et al.* reported that PD patients who received a home visit had a significantly longer PD duration (52 weeks) and a lower technique failure rate (11.5%) compared with controls (PD duration 48.8 weeks, technique failure rate 23.3%) [33].

The last three articles focused on an educational program for HD patients [44] and conversations with dialysis patients [42, 43]. Wingard *et al.* [44] described a 3-month educational program for HD patients that focused on health self-management, rehabilitation, nutritional counselling, and interventions for achieving goals such as anemia management, adequate dialysis dose, logistical, and psychosocial support. Compared to controls, patients who completed the program had significantly fewer hospitalization days per patient year (7.2 vs. 10.5) and a lower mortality

(HR 0.59) after a maximum follow-up duration of 12 months. The authors concluded that the program not only reduced morbidity and mortality, but also increased job satisfaction for nurses.

Mandel *et al.* [42] described a 6-step guide for serious illness conversations with dialysis patients to discuss their prognosis. The guide consisted of the following steps: set up the conversation, assess the patient's illness understanding, share the patient's prognosis, explore key topics, close the conversation, and document the conversation. The article by Michel *et al.* [43] also described an approach for talking with dialysis patients about their prognosis based on four aspects: who to tell, when to tell, what to tell, and how to tell. The authors concluded that this approach can help discussing prognosis with dialysis patients, taking into account the patient's preferences.

Table 2. Characteristics of studies on dialysis education

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Farina [37] USA 2001	Qualitative N=n.a.	Home visit for PD patients Goals: • Visit prior to training: assess home environment, social and family dynamics. • Visit after training: assess application of PD procedures. Components • Before visit: establish home visit policy, explain reason for visit to patient, secure directions to patient's home, verify visit, review violence prevention, notify supervisor of planned visit. • During visit: review reason for visit, asses home (clean work area, adequate lighting, running water/soap, draft free room, free of pets, storage of supplies), survey equipment, compliance issues, family dynamics/adaptation skills, assessment of procedures/technique, medicines, provision of patient education, review of findings/ recommendations. • After visit: review results with health care team and brainstorm to resolve problems, follow up on any issues that need to be resolved, track results of home visits over period of time, identify trends and opportunities for improvement.	n.a.	A home visit is a valuable tool and gives PD staff opportunity to monitor the environment where dialysis is performed.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Figueiredo [38] 10 countries[a] 2016	Qualitative N=n.a.	PD training course syllabus[b] • Day 1: Establish a report, describe goals and plan of the course, demonstrate steps of different procedures, assess patient learning styles/barriers, explain how learning will occur, introduce concepts of PD. • Day 2: Review goals, provide repeated supervised practice sessions of PD exchange and exit-site care with feedback from previous day, review concepts of asepsis, peritonitis, residual renal function, fluid balance, documentation, move from simple to more complex learning. • Day 3: Continue supervised procedure practice with feedback, review concepts through discussion and questions, introduce problem solving. • Day 4: Continue supervised procedure practice with feedback, including acknowledgment of skills mastered, review concepts through discussion and questions, continue to problem solve through "what if" scenarios. • Day 5: Review all previously presented concepts and practice all procedures until proficiency demonstrated.	n.a.	After completion of the PD training syllabus, the PD nurse will have provided education to a patient and/or caregiver such that the patient/ caregiver has the required knowledge, skills and abilities to perform PD at home safely and effectively.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Firanek [39] USA 2013	Qualitative N=n.a.	Features of successful nurse-led APD training • Setting and staff: dedicated staff members, training patients in clinic (home-like atmosphere, all necessary materials), home visit soon after training, then annually. • Training methods: five-step method; 1) overview (understand why learning procedure is necessary), 2) silent demonstration, 3) talking demonstration, 4) patient verbalizes each step procedure to demonstrate understanding/recall, 5) patient demonstrates procedure. • Educational documents: "less is more" in initial stages of patient training, 2 categories of educational documents (cycler, monitoring/ troubleshooting). • Training structure: first CAPD training (2.5–7 days for 3–7.5 h/day), then APD training (1–4 days for 3–7.5 h/day). • APD training content: minimal educational materials, more complex topics at slower pace with simplified language and practical examples. • Delivery of APD training: verbal explanation of APD cycler, return demonstration by patient, instructions for washing hands/setting up supplies/starting cycler/preparing solution bags/loading set/connecting bags/priming and connecting patient/disconnecting patient/emergency disconnection/shut down cycler/clean and care for cycler, monthly education through verbal/written quizzes.	n.a.	Patient training programs should focus on basic and essential information patients need to master in order to dialyze successfully and safely at home. Clinics reinforced learning by several methods, including written quizzes to asses and document patient learning, and reviewing the quiz to reinforce learning and disseminate more information.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion

Fortnum [40] Australia and New Zealand 2015	Qualitative N=25	'My Kidneys, My Choice' decision aid for CKD patients focusing on SDM
		1. 'My Kidneys' (Deliberation talk): create awareness of need to make a decision for patient.
		2. 'My Lifestyle' (Deliberation/Choice talk): let patient acknowledge lifestyle impacts on options, educate about choices.
		3. 'My Options' (Choice/Option talk): start discussions/recap about treatment options.
		4. 'My Choice' (Decision talk): ask patient for readiness to make a decision, recentralize them in the SDM process, clarify they have understood options.
		5. 'My Questions': open page for patient to note questions, bring it back to subsequent appointments.
			25 health professionals:
			• use aid: 11 times (±7.7)
			• mean score (1 'no help' to 4 'very helpful')
			  • support understanding of options: 3.24±0.72
			  • assist understanding of patients' priorities: 3.04±0.83
			  • support decision making: 3.17±0.72
				The decision aid has the potential to improve decision making practice for CKD patients. Early acceptance is high.

Lacson Jr [31] USA 2011	Cohort N=5600	Standardized predialysis treatment options education (TOP) for CKD patients Goal: provide objective treatment options education to CKD patients and their families about renal transplant, ICHD, HHD, PD, conservative therapy. Content: • Single group class session. • 30, 90, 180 days follow-up contact: 1) review treatment options, 2) inquire about each patient's kidney function and dialysis access planning, 3) provide feedback to referring physician.	Adjusted OR for TOPs attendees vs. controls: • Select PD: 5.13 (95%CI 3.58-7.35) • Start ICHD with fistula/graft: 2.06 (95%CI 1.88-2.26) • Mortality: 0.61 (95%CI 0.50-0.74)	Attending TOP was associated with more frequent selection of PD, fewer tunneled HD catheters and lower mortality risk during the first 90 days of dialysis treatment.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Luongo [41] USA 2004	Qualitative N=n.a.	Interview CKD patients for PD (Five-Step Approach) 1. Preparation: nurse explores questions regarding interview goals and competencies needed for interview, patient's medical history/health care experience/culture/ background. 2. Environment: private room. 3. Special considerations: PD nurse must identify and manage variety of patient situations (geriatric patients, patients who do not speak or understand English, hearing or visually impaired, anxious or illiterate patients). 4. Interview: social history, home environment, language/education, physical limitations, general questions (e.g. previous experience, family member with CKD/RRT), financial issues, CKD/RRT education and information (e.g. review kidney function, PD), self-care issues. 5. Special concerns: pay attention to signs/situations that may predict future problems.	n.a.	The PD nurse has an important role in the patient's health care experience and must use previous experience, clinical knowledge, and careful judgement to offer the future patient the correct information and support.
Mandel [42] USA 2017	Qualitative N=n.a.	Serious Illness Conversation Guide for dialysis patients 1. Set up conversation: introduce idea/benefits, ask permission. 2. Assess illness understanding/information preferences. 3. Share prognosis: tailor information to patient preference, allow silence, explore emotion. 4. Explore key topics: goals, fears/worries, sources of strength, critical abilities, tradeoffs, family engagement/involvement. 5. Close the conversation: summarize what you've heard, make recommendation, affirm commitment to patient. 6. Document conversation.	n.a.	The Guide provides a tested, scalable structure for conducting serious illness conversations and assists in developing/adapting the care plan to ensure goal-consistent care.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Manns [32] Canada 2005	RCT N=62	Educational intervention for CKD patients to promote self-care dialysis Phase 1: • 4 written patient manuals; 1 manual "Choosing the type of dialysis best suited to you", 3 manuals on self-care dialysis (PD, HHD, self-care in-center HD). • 15-minute video "Choosing the type of dialysis best suited to you". Phase 2: 90-minute small group interactive session involving 3–6 patients, nephrologist, predialysis nurse.	Intervention group vs. standard care group: • Intention to start self-care dialysis: 82.1% vs. 50%, p=0.015	A two-phase educational intervention can increase the proportion of patients who intend to initiate self-care dialysis.

Martino [33] Italy 2014	Case-control N=188	Home visit program for PD patients
		• Home visits every 3 months between 2 visits PD center by skilled PD nurses.
		• Additional home visit in case of medical suggestions.
		• During home visit:
		  • Nurse supervises environment of PD exchange, storage place of material, possible mistakes during procedures, compliance to pharmacological and dialysis therapy.
		  • Nurse supports patients by suggesting possible solutions, reinforcing patient knowledge, and/or anticipating a medical visit to the PD center.
			Home visit group vs. standard care group:
			• Treatment duration: 52 weeks vs. 48.8 weeks, p=0.018
			• Technique failure: 11.5% vs. 23.3%, p=0.004
			No difference for peritonitis and hospitalization rate.
				The home visit program reduces technique failure and extends PD treatment.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Michel [43] USA 2005	Qualitative N=n.a.	Conversations about prognosis with ESKD patients 1. Who to Tell; assess decision-making capacity of the patient, ask patient if he/she wants to hear prognosis and wants to participate in decision-making process. 2. When to Tell: early in course of progressive disease. 3. What to Tell: estimate of prognosis, life expectancy, likely QOL. 4. How to Tell: Method of Buckman and Kayson[c] for breaking bad news.	n.a.	The approach should help discuss prog-nosis in a way that is sensitive to patients' preferences in accor-dance with guideline recommendations.
Wingard [44] USA 2009	Case-control N=1938	RightStart program for HD patients 3-month educational program coordinated by case manager (meeting 1–2 times/week during 1st month, every 1–2 weeks for next months). • Intensive education focused on health self-management and rehabilitation. • Intensive nutritional counselling by dietitian, reinforced by case manager. • Interventions for achieving goals for anemia management, adequate dialysis dose, nutrition, reduction of catheter use, medication review, logistical and psychosocial support. • Collaboration with facility staff/medical director to ensure prompt and overall care.	RightStart vs. standard care patients: • Hospital days per patient year at 12 months: 7.2 vs. 10.5, p<0.001 • Mortality per 100 patient years at 12 months: 17 vs. 30, HR 0.59, p<0.001	The RightStart program decreases the number of hospital days and mortality for HD patients.

Table 2. Characteristics of studies on dialysis education (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion

Wu [45] Taiwan 2009	Cohort N=573	Multidisciplinary predialysis education (MPE) for CKD patients
		• Individual lectures CKD patients by nurse:
		  • Stage 3 CKD (lecture every 3 months): healthy renal function, uremia presentation, risk factors and complications of renal progression, introduction to various RRTs (HD, PD, renal transplant).
		  • Stage 4 CKD (lecture every 3 months): discussions on management CKD complications, indications of RRT, evaluation vascular/peritoneal access.
		  • Stage 5 CKD (lecture every month): monitor timely RRT initiation, care of vas-cular/peritoneal access, dialysis-associated complications, registration for renal transplant waiting list.
		• All patients: dietary counselling (every 6 months).
			MPE vs. standard care group (mean follow–up 11.7±0.9 months):
			• Requiring dialysis: 13.9% vs. 43.0%, adjusted HR 0.117 (95%CI 0.075-0.183)
			• All-cause mortality: 1.7% vs. 10.1%, adjusted HR 0.103 (95%CI 0.040-0.265)
				MPE may decrease the incidence of dialysis and reduce mortality in late-stage CKD patients.

APD=automated peritoneal dialysis; CAPD=continuous ambulatory peritoneal dialysis; CI=confidence interval; CKD=chronic kidney disease; ESKD=end-stage kidney disease; GP=good practice; HD=hemodialysis; HHD=home hemodialysis; HR=hazard ratio; ICHD=in-center HD; MPE=Multidisciplinary predialysis education; N=number of people investigated; n.a.=not applicable; OR=odds ratio; PD=peritoneal dialysis; QOL=quality of life; RCT=randomized controlled trial; RRT=renal replacement therapy; SDM=shared decision-making; TOP=treatment options education; USA=United States of America.

a. Australia, Brazil, Canada, China, Guatemala, Japan, Mexico, New Zealand, United Kingdom, and the United States.

b. Based on Knowles's principles for adult education: 1) adults are internally motivated and self-directed; 2) adults bring life experiences and knowledge to learning experiences; 3) adults are goal-oriented; 4) adults are relevancy oriented; 5) adults are practical; 6) adult learners like to be respected [50].

c. 6-step approach of Buckman and Kayson for breaking bad news: 1) give news in person, in private, with sufficient time, without interruption; 2) find out what the patient's preexistent knowledge is; 3) find out what the patient wants to know; 4) give a warning first, then provide a small amount of information in simple language at an appropriate pace for the patient; 5) respond to the patient's feelings and concerns; 6) determine the next steps, identify sources of support, and make an early follow-up appointment [51].

Dialysis treatment

The three articles that described good practices for dialysis treatment were all qualitative studies (Table 3) [46-48]. Abdel-Aal *et al.* [46] provided a detailed description of the procedure for insertion of a PD catheter by interventional radiologists. Various aspects of pre-procedure preparation, such as bowel preparation and fasting, were discussed followed by a detailed explanation of the PD catheter insertion with explanatory photos. The procedure was described as a cost-effective and minimally invasive alternative to traditional surgical placement of a PD catheter.

Craswell *et al.* [47] described practices for insertion, maintenance, and removal of central venous catheters (CVCs) for HD. The practices for insertion consisted of patient education for insertion, anatomical site selection and decision-making, and training. The practices for maintenance consisted of education, dressing practices, and assessment and monitoring for infection. The practices for removal consisted of the decision for removal and complications of removal. The authors concluded that an interdisciplinary team is very important for patient education and catheter care.

Desai *et al.* [48] reported 155 good practices that could potentially improve outcomes of dialysis centers, such as dialysis dose and anemia management, and overall survival in dialysis patients. The 155 good practices were divided into the following domains: facility characteristics and amenities, facility-based health maintenance, staff working climate, general dialysis care practices, physician practices, nursing practices, technician practices, and miscellaneous practices. Through a survey among 342 respondents, a top 30 of good practices that had the most impact on overall outcomes in dialysis was compiled. The majority of the top 30 good practices focused on conducting a successful multidisciplinary team meeting, performing audits, training nurses, reviewing the performance of health care professionals, and enhancing communication and teamwork.

Table 3. Characteristics of studies on dialysis treatment

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Abdel-Aal [46] USA 2014	Qualitative N=n.a.	PD catheter placement by interventional radiologists • Pre-procedure preparation: history/physical examination, stop anticoagulants 5 days before procedure, bowel preparation, fasting for 6h before procedure, pre-procedure antibiotics i.v., empty bladder, mark entry and exit site catheter. • Catheter placement procedure: patient in supine position, ultrasonography to determine safest entry and exit site, shave hair of abdomen and prep with antiseptic scrub, mild/moderate sedation, local anesthesia, ultrasound guided needle placement, fluoroscopic guided wire placement, placement catheter over wire, create exit site and catheter tunnel, fluoroscopic visualization to exclude kink in catheter and confirm proper location, testing of inflow and drainage catheter with 1L normal saline, incision closure and dressing.	n.a.	Placement of the PD catheter by IR is a cost-effective, minimally invasive alternative to traditional surgical placement.
Craswell [47] Australia 2020	Qualitative N=n.a.	Practices for CVCs insertion / maintenance / removal Insertion: • Patient education prior to insertion: instructional, didactic approach. • Anatomical site selection and decision-making: preference for tunneled catheter, renal team responsible for decision-making regarding site/device. • Extent of training and de-skilling: lower skill level professional/insertion in different settings/after hours related to higher infection rates. • Patient cohort challenges: specific patient cohorts (e.g. ethnic background) affect infection rates. Maintenance: • Assessment and monitoring for infection: nurses responsible. • Dressing practices and procedures to promote maintenance: nurses responsible. • Education about maintenance: patients and staff. Removal: • Decision for removal: clinical decision, prompt in case of infection suspicion. • Catheter type dictates removal. • Complications of removal: uncommon (prolonged/difficult removal secondary to CVC being stuck, bleeding).	n.a.	This study demonstrates the perceived importance of the interdisciplinary team in the insertion, and management of dialysis CVCs and education of patients.

Table 3. Characteristics of studies on dialysis treatment (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Desai [48] USA 2008	Qualitative N=342[a]	Good Practices to improve outcomes of dialysis centers (e.g. dialysis dose, anemia management) and survival in dialysis patients 155 candidate practices, categorized in 8 major domains: 1. Facility characteristics and amenities 2. Facility-based health maintenance 3. Staff working climate 4. General dialysis care practices 5. Physician practices 6. Nursing practices 7. Technician practices 8. Miscellaneous practices	Outcomes related to: a. characteristics of multidisciplinary care conferences b. technician proficiency in protecting vascular access c. nurses training to provide education in fluid manage-ment, vascular access d. random/blinded audits of staff performance e. communication and teamwork among staff Disagreement about: 1. importance of facility-based health maintenance practices 2. optimal staffing ratios 3. frequency of dialysis-based physician visits 4. optimal frequency of multidisciplinary care	This study provides a "conceptual map" of candidate practices and highlights areas of general agreement and disagreement. These findings can help to provide targets for future research in quality improvement.

CVC=central venous catheter; GP=good practice; IR=interventional radiologists; i.v.=intravenous; N=number of people investigated; n.a.=not applicable; PD=peritoneal dialysis; USA=United States of America

a. 342 respondents (nephrologists and nurses) for questionnaires regarding candidate good practices.

Table 4. Characteristics of studies on eHealth

Study, Country, Year	Study design, N	GP description	Results	Study conclusion
Kaldoudi [34] Greece 2007	Qualitative N=n.a.	Telehomecare for PD patients The PERKA[a] service supports data collection and transmission from a patient's home via phone or data networks to the PD clinic for monitoring and archiving: • PD data: PD method, PD prescription, actual PD daily treatment schema conducted (number of fluid exchanges, duration, solute type/volume, UF volume). • General biometric data and biosignals: body weight, blood pressure, heart rate, oxygen saturation, temperature (if required, ECG and glucose levels). • Free text or sound report and/or response to a structured questionnaire. The system contains a patient unit, a data collection unit, a web-based portal application, a database for patient data and a database for administrative data.	n.a.	The PERKA system enables telehome-care services for all PD patients.
Li [35] China 2014	RCT N=135	Post-discharge nurse-led telephone support for PD patients[b] Pre-discharge planning protocol (by nurse case manager): • Assessing patient's physical, social, cognitive, emotional needs. • Conducting an individualized education program to strengthen and consolidate past learning experiences, clarify misconceptions and optimize health outcomes. Standardized 6-week post-discharge nurse-led telephone support: • Weekly telephone call for 6 consecutive weeks: first call within 72h after discharge to assess the patient's status and to give advice. • Content of each telephone call is guided by the pre-discharge planning protocol and specific problems identified in pre-discharge assessment.	Effect of intervention: • QOL: better for symptom/problem (p=0.01), work status (p=0.02), staff encouragement (p=0.01), patient satisfaction (p=0.01), energy/fatigue (p=0.02) • Less clinic visits (p=0.039) • Blood chemistry and complication control: no effect.	Post-discharge nurse-led telephone support is helpful for some aspects of quality of life and reducing clinic visits of PD patients.

Table 4. Characteristics of studies on eHealth (continued)

Study, Country, Year	Study design, N	GP description	Results	Study conclusion

Sicotte [49] Canada 2011	Cohort N=19	Telehemodialysis
		• Remote team of nephrologists and nurses provides specialized clinical supervision by tele-communicating with local care teams and patients.
		• Electronical health record that allowed the remote team to view laboratory results, vital signs and medication taken by the patient, and observe variables recorded by the dialysis machine in real-time as the treatments were administered.
		• Two organizational models: virtual patient rounds or telecase reviews with multidisciplinary teams.
			Medication changes per month (follow-up 2 years):
			• Chibougamau community
			  • Pre teleHD: 2.2±1.3
			  • Post teleHD: 1.8±1.5
			• Chisasibi community
			  • Pre teleHD: 8.1±5.4
			  • Post teleHD: 3.1±1.1
			Intracommunity p=0.01, intercommunity p=0.002.
			No difference in number of HD sessions/month and transfers to hospital.
				TeleHD can maintain the quality of care and can provide distant supervision while maintaining the level of care utilization. Different organizational models did not lead to differences in health condition or care utilization.

Viglino [36] Italy 2020	Cohort N=107	Videodialysis (VD) for assisted PD patients Components: • Remote Station (patient's home): video camera, monitor, microphone, technological box. • Control Station (center): webcam, computer, phone. • System connecting the 2 stations: real-time, high-quality audio-video transmission. Method of use: nursing staff can follow patients/caregivers during the phases: multi-user connection, acquisition and recording of dialysis parameters, performance of CAPD/APD procedure, filling dialysis sheets. VD sessions are also used for exit site care, assessing dialysis/clinical issues, checking adherence to pharmacological/ dietary therapy.	Peritonitis episodes: • VD patients: 1/84.2 months • Caregiver patients: 1/62.6 months. • Self-care patients: 1/45.2 months. Time to first peritonitis not different between groups. VD: 17.6% reduction in transfer from PD to HD due to reduced compliance/lack of caregiver availability.	VD-assisted PD is a reliable, safe system which requires no technological know-how and is easy to use when self-care is not possible due to physical, cognitive or psychological barriers.

APD=automated peritoneal dialysis; CAPD=continuous ambulatory peritoneal dialysis; ECG=electrocardiogram; GP=good practice; HD=hemodialysis; N=number of people investigated; n.a.=not applicable; PD=peritoneal dialysis; QOL=quality of life; RCT=randomized controlled trial; UF=ultrafiltration; VD=videodialysis

a. The PERKA consortium consists of the School of Medicine in Democritus University of Thrace and two software companies (ALPHA Information Technology SA and VIDAVO Information Systems Inc.).

b. Unplanned admission to the Nephrology department and the PD catheter had to be in situ for at least 3 months.

eHealth

Four articles described good practices for eHealth, one of which focused on HD [49] and three on PD (Table 4) [34-36]. The qualitative article on PD by Kaldoudi *et al.* [34] described the components of an eHealth system by which data could be collected such as PD method, prescription, body weight and hearth rate. Viglino *et al.* [36] described an eHealth system which led to a reduction in peritonitis episodes and a 17.6% reduction in the number of transfers from PD to HD because reduced compliance or lack of availability of a caregiver was no longer an issue. The authors concluded that this system can be a valuable tool for increasing the number of PD patients.

While Kaldoudi *et al.* [34] and Viglino *et al.* [36] focused more on the technical aspects of eHealth systems for PD patients, Li *et al.* [35] conducted a randomized controlled trial to investigate the effect of post-discharge telephone support for PD patients. Patients were included if they performed PD for a minimum of 3 months and were admitted to a nephrology department. The control group received routine care, while patients in the intervention group were visited by a nurse who assessed their needs and provided individualized education. After discharge from the hospital, the nurse called the patients from the intervention group every week during a period of 6 weeks to assess their status and to give advice. This approach led to a significant improvement of several health-related quality of life domains (e.g. symptoms, energy, work status) and a reduction in the number of hospital visits.

Finally, Sicotte *et al.* [49] reported two eHealth models for in-center HD patients: virtual patients rounds and telecase reviews with a multidisciplinary team. During the virtual patient rounds, a remote nephrologist and nurse had contact with a patient and his/her nurse at the dialysis center. During the telecase review, a remote nephrologist and nurse had contact with the general practitioners and nurses at the dialysis center via videoconference, without the patient being present. Both models led to a significant reduction in the number of medication changes per month during a follow-up of 2 years. The authors concluded that eHealth can provide distant supervision which improves the level of care utilization.

Discussion

This scoping review identifies 19 articles with good practices that could be used in addition to guidelines. The twelve articles with good practices for dialysis education endorse the importance of providing complete and objective predialysis education to CKD patients, assisting PD patients in performing PD adequately, educating HD patients on self-management, and talking with dialysis patients in general about their prognosis. The three articles with good practices for dialysis

treatment provide practices regarding dialysis access devices and numerous candidate good practices for dialysis centers. Finally, eHealth is useful for HD and PD and affects both quality of care and health-related quality of life.

Good practices are locally implemented practices with which health care professionals have good experience, but which are not necessarily evidence-based [14, 15]. Therefore, they are generally not added to (inter)national guidelines. For dialysis treatment, there are many guidelines with proven treatment methods, while guidelines for dialysis education are scarce [10, 52]. This probably explains why we have found many good practices for dialysis education and only a few for dialysis treatment.

Six of the 12 articles regarding dialysis education report a positive effect of the described good practice(s) [31-33, 40, 44, 45]. Complete and objective education to CKD patients by a multidisciplinary team decreases the dialysis incidence and mortality [45]. Moreover, it increases the use of home dialysis [31, 32]. The European Renal Best Practice (ERBP) Advisory Board also underscores complete and objective education to enable CKD patients to choose a dialysis modality that is most suitable for them [5]. Another useful good practice is a decision aid for CKD patients, which supports the shared decision-making process according to health care professionals [40]. A Cochrane review, describing 105 decision aids for patients facing various treatment or screening decisions, also states that decision aids increase participants' knowledge, decrease decisional conflicts, and facilitate active participation in decision making [53]. However, the review includes no decision aids specifically for nephrological care. A randomized study among 133 CKD patients concludes that an online decision aid can improve knowledge and decrease decisional conflict and uncertainty about choice of dialysis treatment [54]. So, decision aids are important for use during dialysis education.

A home visit also seems to be a very relevant tool for PD education, since Martino *et al.* [33] report that their home visit reduces technique failure and extends PD treatment. The positive effect of a home visit is also found in a French study of 359 patients on assisted PD, which found that it increases the probability of patients remaining peritonitis free from 33.9% to 50.8% at 3 years ($p=0.028$) [55]. Home visits conducted in two other studies, with the aim of providing dialysis education for CKD patients, result in a higher probability for patients to receive home dialysis [56, 57]. So, home visits seem to be important not only for PD patients, but also for CKD patients who have yet to make a treatment choice.

The articles regarding dialysis treatment provide guidance on PD catheter placement by interventional radiologists and the insertion, maintenance, and removal of CVCs [46, 47]. The International Society for Peritoneal Dialysis (ISPD) guideline on peritoneal dialysis access only briefly mentions image-guided percutaneous PD catheter placement [58], so the procedure

described by Abdel-Aal *et al.* can be a relevant addition [46]. The (inter)national guidelines for CVCs also describe insertion, maintenance, and removal practices [59-61], however only the most recent guideline [62] underscores the importance of patient education as Craswell *et al.* did [47]. Finally, the 155 candidate good practices reported by Desai *et al.* could lead to general quality improvement of dialysis care [48].

The articles regarding eHealth show that this good practice improves quality of care for HD patients [49], quality of life for PD patients [35], and reduces the number of peritonitis episodes [36]. In 2017, Rosner *et al.* [63] conducted a review on the use of eHealth in the care for dialysis patients. They found 19 articles describing mostly small, single-center studies published between 1999 and 2017, 13 articles for PD and 6 articles for HD. Most of the articles used video conferencing, remote monitoring, or monthly visits with physical examination (e.g. electronic stethoscopes) using eHealth as technology. All articles report positive results of their eHealth system on various outcomes such as patient independence, quality of life, and hospitalization. Rosner *et al.* conclude that there still is a lack of evidence regarding the use of eHealth, however they mention possible benefits for example increased uptake and acceptance of home dialysis, treatment monitoring in the home environment, improved patient satisfaction, and potential for cost savings [63]. In the current time with the coronavirus disease 2019 (COVID-19) pandemic, eHealth may play an important role through, for example, video conferences and remote patient monitoring [64-66].

Our review has several limitations. First, there is a probability that we have not identified all articles describing good practices. This is partly because many articles do not label their practice as 'good practice', making them less likely to appear in the search. However, by also using 'best practice' and 'practice guidelines' as a search topic, we believe that we have attenuated this problem. Second, most of the studies are qualitative in nature and describe no results, making it impossible to determine an effect of the described good practices. Finally, most of the studies that described results investigate a small number of patients and report on different outcomes, making mutual comparison impossible.

In conclusion, our scoping review identifies 19 articles describing good practices and their results for dialysis education, dialysis treatment, and eHealth. These good practices could be valuable in addition to guidelines for increasing shared decision-making in predialysis education, using patients' contribution in the implementation of their dialysis treatment, and advanced care planning. Good practices can inspire and support health care professionals to change their practices and this could possibly help to improve outcomes and quality of life for CKD and dialysis patients. Additional research on good practices could be useful to identify more good practices and determine the impact of these practices on CKD and dialysis patients.

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Chapter 4

Assisted peritoneal dialysis across Europe: Practice variation and factors associated with availability

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Abstract

Background In Europe, the number of elderly end-stage kidney disease patients is increasing. Few of those patients receive peritoneal dialysis (PD), as many cannot perform PD autonomously. Assisted PD programmes are available in most European countries, but the percentage of patients receiving assisted PD varies considerably. Hence, we assessed which factors are associated with the availability of an assisted PD programme at a center level and whether the availability of this programme is associated with proportion of home dialysis patients.

Methods An online survey was sent to healthcare professionals of European nephrology units. After selecting one respondent per center, the associations were explored by χ^2 tests and (ordinal) logistic regression.

Results In total, 609 respondents completed the survey. Subsequently, 288 respondents from individual centers were identified; 58% worked in a center with an assisted PD programme. Factors associated with availability of an assisted PD programme were Western European and Scandinavian countries (OR: 5.73; 95%CI: 3.07 – 10.68), non-academic centers (OR: 2.01; 95% CI: 1.09 – 3.72) and centers with a dedicated team for education (OR: 2.87; 95% CI: 1.35 – 6.11). Most Eastern & Central European respondents reported that the proportion of *incident* and *prevalent* home dialysis patients was <10% (72% and 63%), while 27% of Scandinavian respondents reported a proportion of >30% for both *incident* and *prevalent* home dialysis patients. Availability of an assisted PD programme was associated with a higher incidence (cumulative OR: 1.91; 95%CI: 1.21 – 3.01) and prevalence (cumulative OR: 2.81; 95%CI: 1.76 – 4.47) of patients on home dialysis.

Conclusions Assisted PD was more commonly offered among non-academic centers with a dedicated team for education across Europe, especially among Western European and Scandinavian countries where higher incidence and prevalence of home dialysis patients was reported.

Introduction

Since 2001, the number of end-stage kidney disease (ESKD) patients worldwide treated with dialysis has increased from 1 to 2 million and is expected to double again by 2030 [1-3]. The majority of these patients are treated with in-center haemodialysis (ICHD) [4, 5], although treatment with peritoneal dialysis (PD) has many advantages: it can be performed at home, there is no need for a vascular access and patients' residual kidney function is better preserved [6, 7]. These advantages are especially relevant for the increasing number of elderly patients, who form the bulk of ESKD patients [8, 9]. However, the percentage of elderly ESKD patients receiving PD is low and varies between 4% and 21% depending on the country [4, 5, 8, 10, 11].

If given a choice, many more elderly would like to receive PD, but comorbidity and frailty often limit the possibility to perform self-care PD [9, 12, 13]. Important conditions that limit self-care PD include decreased strength to lift PD bags, decreased dexterity, decreased vision, anxiety and cognitive impairment [12, 14]. Due to these conditions, up to 80% of elderly patients need some degree of assistance while performing PD [15-18].

The definition of assisted PD varies in literature [19]. In the most liberal way, it is defined as '*a PD modality performed at the patient's home with the help of a healthcare technician, a community nurse, a family member, or a partner*' [20]. Patients on assisted PD have similar rates of all-cause hospitalisation compared to ICHD patients, and similar or even better rates of peritonitis and technique survival compared to self-care PD patients [15, 21-23]. Assisted PD patients have higher mortality rates compared to self-care PD patients, which can be attributed to a higher comorbidity and frailty [15, 22]. However, health-related quality of life is comparable [24-27] and assisted PD is less expensive than ICHD in most countries depending on reimbursement strategy [28, 29]. Furthermore, introduction of assisted PD has been shown to have a positive effect on maintaining the size of a PD programme [30], which can be important to ensure experience and quality of care.

Assisted PD programmes are available in many countries, but the percentage of patients actually receiving assisted PD varies considerably [6, 11, 19, 31, 32]. This variation may be due to differences in clinical background and experience of healthcare professionals, center characteristics, organisational and financial factors, as shown in studies regarding PD in general [6, 33-37]. However, this has not been specifically investigated for assisted PD so far.

Therefore, we first assessed the factors that are associated with the availability of an assisted PD programme at a center level, to get insight into the causes of practice variation. Secondly, we investigated the association between the availability of an assisted PD programme and the proportion of incident and prevalent patients on home dialysis (i.e. PD and home haemodialysis (HHD)) at a center level, to get insight into the influence of availability of assisted PD on the uptake of home dialysis.

Methods

Study design

An online survey was sent to nephrologists (in training), dialysis nurses and administrative heads of nephrology units in Europe. The survey was developed by members of the EuroPD Future Leadership Initiative after two conference meetings in May-June 2019. The members discussed how the care for ESKD patients could be improved by helping nephrology departments with their home dialysis programmes. The following topics were discussed: PD training, urgent start PD, age-related differences in use of PD, remote patient monitoring, organisation of nephrology units, center size effect, and regional collaboration between centers. Subsequently, four topics (impact of urgent start PD, impact of assisted care programmes, impact of access placement policy and impact of center size) were selected through a three-step Delphi round [38]. During a final meeting in October 2019, questions were formulated for each topic after conducting a narrative literature review. The final survey consisted of 56 questions (Appendix 1).

The open survey was developed in SurveyMonkey and mailed to all EuroPD members for distribution across Europe via their colleagues and their national and regional nephrology societies. Participation was voluntary and anonymous. Respondents could submit the survey between 11 December 2019 and 15 January 2020. The survey was approved by the Ethical Committee of the Ghent University Hospital (EC 2019/1972).

Statistical analysis

Descriptive statistics were used for the professional background, center type and country of employment of all respondents. The countries were classified into European regions: Eastern & Central Europe, Western Europe, Scandinavia and the Mediterranean [39]. Ukraine and the Russian Federation were added to the Eastern & Central European region.

Generally, the policy regarding the availability of an assisted PD programme is determined at a center level. To perform analyses at a center level, one respondent per center was selected by comparing respondents based on the following characteristics: country, region, center type and size, and the proportion of incident and prevalent ESKD patients on a home based therapy. If there were several respondents per center, the respondent with the largest experience was chosen for the analyses.

For the analysis of the availability of an assisted PD programme at a center level, the answers to the question ‘Does your unit provide a structured programme for assisted PD?’ were converted from a 5-point Likert scale into a dichotomous variable (scores 1 to 3: no, scores 4 and 5: yes). In addition, answers regarding the following variables were grouped into categories: center type (non-academic vs academic), likelihood that chronic kidney disease (CKD) patients would receive

education on kidney function/kidney failure/PD/HHD/ICHD (6-point Likert scale converted into a dichotomous variable), reimbursement of PD as compared to ICHD (8 categories converted into 4) and the proportion of incident and prevalent home dialysis patients (< 10%, 10-20%, 20-30%, > 30%).

The univariable association between employment regions, center characteristics and organisational factors (independent variables) on the one hand and the availability of an assisted PD programme at a center level (dependent variable) on the other hand was explored by logistic regression. For categorical variables, the first category was used as a reference. In addition, a multivariable analysis was done to explore which variables were truly independent.

Subsequently, descriptive statistics were used to present an overview of financial factors: the profitability of PD (i.e. difference between reimbursement and disposable costs) and the impact of the distribution between kidney replacement (KRT) modalities (i.e. PD, HHD, ICHD, kidney transplantation) on the income of nephrologists for centers with and without an assisted PD programme. The univariable association between profitability of PD and the impact of the distribution between KRT modalities on nephrologists' income (independent variables) on the one hand and the availability of an assisted PD programme at a center level (dependent variable) on the other hand was also explored by logistic regression.

Finally, the univariable association between the availability of an assisted PD programme (independent variable) and the proportion of incident and prevalent home dialysis patients (defined as both PD and HHD) at a center level (dependent variable) was analysed with a χ^2 test. In addition, ordinal logistic regression (logistic regression with proportion of incident and prevalent home dialysis patients as outcome) was performed to adjust for center type, center size (i.e. total number of dialysis patients), the presence of a dedicated team for education and European region (multivariable association). The five categories of the variable 'presence of a dedicated team for education' were transformed into a dichotomous variable. Answers 'no' and 'do not know' were indicated as 'no', while 'yes, less than 1 fulltime equivalent', 'yes, 1 fulltime equivalent' and 'yes, 2 or more full time equivalents' were indicated as 'yes'. Ordinal logistic regression gives a cumulative odds ratio (OR) that indicates the probability of being in a higher category compared to the previous category.

All statistical analyses were performed with SPSS Statistics version 25 (SPPS, Chicago, Illinois, USA).

Results

Characteristics of respondents

In total, 609 respondents completed the online survey. Fifty-three percent of the respondents were nephrologists with more than 10 years of experience (Supplemental Table 1). Forty-nine percent of the respondents worked in a non-academic center and half of the respondents worked in Western Europe (Supplemental Tables 1 and 2).

After completing the aforementioned selection procedure, 295 respondents from individual centers were identified (Supplemental table 1 and 2). Data on the availability of an assisted PD programme were missing in 7 respondents, thus the following analyses were conducted with 288 respondents.

Center characteristics and organisational factors associated with the availability of an assisted PD programme

Of the 288 respondents, 167 (58%) worked in a center with an assisted PD programme. The association between employment regions, center characteristics and organisational factors on the one hand and the availability of an assisted PD programme on the other hand is presented in Table 1. Compared to the Eastern & Central European region, respondents from Western Europe and Scandinavia indicated significantly more often that an assisted PD programme was available (Table 1). Compared to the Eastern & Central European and Mediterranean regions combined, respondents from Western European and Scandinavian regions combined also indicated significantly more often that an assisted PD programme was available (crude OR: 7.11; 95% CI: 4.91 – 10.29).

Regarding center characteristics, non-academic centers and centers with 100—200 dialysis patients significantly more often had an assisted PD programme (Table 1). Compared to centers with <100 patients (i.e. centers with <50 and 50—100 patients combined), centers with >100 dialysis patients (i.e. centers with 100—200 and >200 patients combined) also significantly more often had an assisted PD programme (crude OR: 2.13; 95% CI: 1.32 – 3.43).

Regarding organisational factors, centers that provided education to CKD patients on kidney function, kidney failure, PD and HHD significantly more often had an assisted PD programme (Table 1). Education to CKD patients on PD had the strongest association with an OR of 19.77 (95% CI: 2.53 – 154.72). Also, centers with a dedicated team for education significantly more often had an assisted PD programme, with an increasing OR if more fulltime-equivalent was available.

Table 1. Association between employment regions, center characteristics and organisational factors with the availability of an assisted PD programme[a]

	Assisted PD programme		
	Yes (n=167)	No (n=121)	Crude OR (95% CI)
Employment regions			
Eastern & Central Europe	14 (8)	27 (22)	Reference
Mediterranean	34 (20)	59 (49)	1.11 (0.51 – 2.40)
Western Europe	101 (61)	31 (26)	6.28 (2.94 – 13.45)
Scandinavia	18 (11)	4 (3)	8.68 (2.46 – 30.63)
Center characteristics			
Non-academic center	107 (64)	60 (50)	1.81 (1.13 – 2.92)
Center size[b]			
< 50 patients	13 (8)	19 (16)	Reference
50 –100 patients	46 (27)	46 (38)	1.46 (0.65 – 3.30)
100 – 200 patients	73 (44)	29 (24)	3.68 (1.61 – 8.41)
> 200 patients	35 (21)	27 (22)	1.90 (0.80 – 4.50)
Organisational factors			
Likely for CKD patient to receive education on			
Kidney function[c]	134 (80)	83 (69)	3.23 (1.25 – 8.33)
Kidney failure[c]	138 (83)	86 (71)	5.88 (1.60 – 21.69)
PD[c]	140 (84)	85 (70)	19.77 (2.53 – 154.72)
HHD[d]	112 (67)	47 (39)	4.40 (2.45 – 7.91)
ICHD[c]	138 (83)	92 (76)	2.50 (0.58 – 10.72)
Dedicated team for education			
No	24 (14)	39 (32)	Reference
Yes, <1 FTE	46 (27)	40 (33)	1.87 (0.96 – 3.62)
Yes, 1 FTE	41 (25)	18 (15)	3.70 (1.75 – 7.85)
Yes, ≥2 FTE	55 (33)	21 (17)	4.26 (2.08 – 8.70)
Unknown	1 (1)	3 (3)	-

PD=peritoneal dialysis; OR=odds ratio; CI=confidence interval; CKD=chronic kidney disease; HHD=home haemodialysis; ICHD=in-center haemodialysis; FTE=fulltime-equivalent

a. Data are presented as number (n) with percentage (%). Percentages are displayed as percentage of the number of respondents in the vertical column.
b. Indicated by the total number of dialysis patients taken care of by the respondent's nephrology team.
c. Missing: 26 in group with and 24 in group without structured programme.
d. Missing: 29 in group with and 26 in group without structured programme.

In the multivariable analysis, only center size was no longer an independent predictor for the presence of an assisted PD programme (OR: 1.44; 95% CI: 0.78 – 2.67), while Western European and Scandinavian regions (OR: 5.73; 95% CI: 3.07 – 10.68), non-academic centers (OR: 2.01; 95% CI: 1.09 – 3.72), education on PD (OR: 9.04; 95% CI: 1.07 – 76.18) and a dedicated team for education (OR 2.87; 95% CI 1.35 – 6.11) remained independent predictors.

Financial factors associated with the availability of an assisted PD programme

The association between profitability of PD and the impact of the distribution between KRT modalities on nephrologists' income on the one hand and the availability of an assisted PD programme on the other hand is presented in Table 2. Thirty percent of all respondents indicated that they did not know what the profitability of PD was in their center. In addition, there was no association between profitability of PD and the availability of an assisted PD programme.

Regarding the distribution between KRT modalities, 82% of all respondents indicated that it did not affect the income of nephrologists. Respondents from centers with an assisted PD programme reported this slightly more often than respondents from centers without such a programme, 85% versus 79%, respectively. In centers where ICHD is more profitable, an assisted PD programme was less often available compared to centers where the distribution between KRT modalities has no impact on income (OR: 0.41; 95%CI: 0.20 – 0.84).

Table 2. Association between financial factors and the availability of an assisted PD programme[a]

	Assisted PD programme		Crude OR (95% CI)
	Yes (n=167)	No (n=121)	
Profitability of PD			
Equal to ICHD	56 (34)	37 (31)	Reference
Better than ICHD	7 (4)	4 (3)	1.16 (0.32 – 4.23)
Worse than ICHD	51 (30)	46 (38)	0.73 (0.41 – 1.30)
Unknown	53 (32)	34 (28)	1.03 (0.57 – 1.87)
Impact of KRT distribution on income nephrologists			
No impact	141 (85)	95 (79)	Reference
PD more profitable	12 (7)	3 (2)	2.70 (0.74 – 9.81)
ICHD more profitable	14 (8)	23 (19)	0.41 (0.20 – 0.84)

PD=peritoneal dialysis; ICHD=in-center haemodialysis; KRT=kidney replacement therapy

a. Data are presented as number (n) with percentage (%). Percentages are displayed as percentage of the number of respondents in the vertical column.

Proportion of ESKD patients on a home dialysis modality

The proportion of *incident* ESKD patients on a home dialysis modality is depicted in Figure 1. Of all respondents, 39% indicated that the incidence in their center was <10%, while only 11% indicated that the incidence was >30%. When focusing on the incidence according to region, a much higher percentage (72%) of respondents from Eastern & Central Europe indicated that the incidence in their center was <10%, while only 9% indicated that the incidence was >30%. For Scandinavia, an incidence >30% was indicated by 27% of respondents.

Figure 1. Proportion of incident ESKD patients on home dialysis according to region

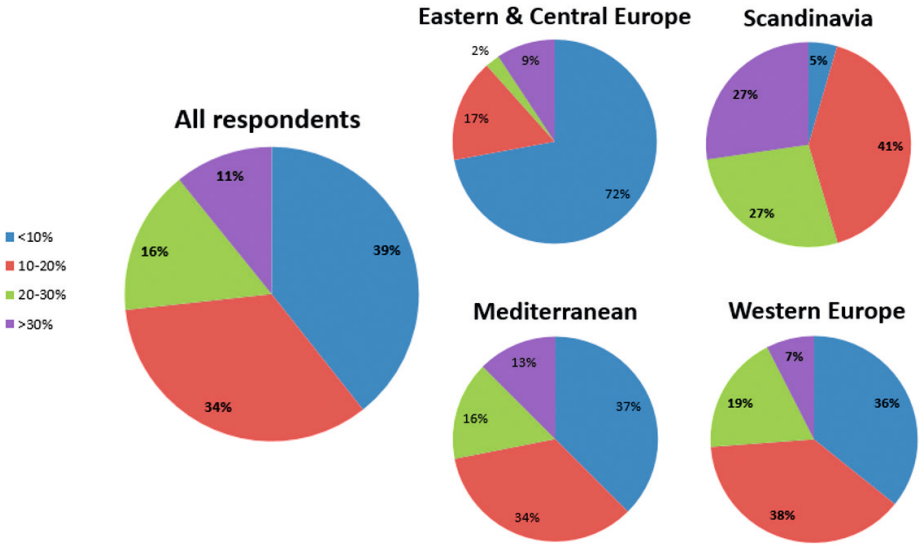
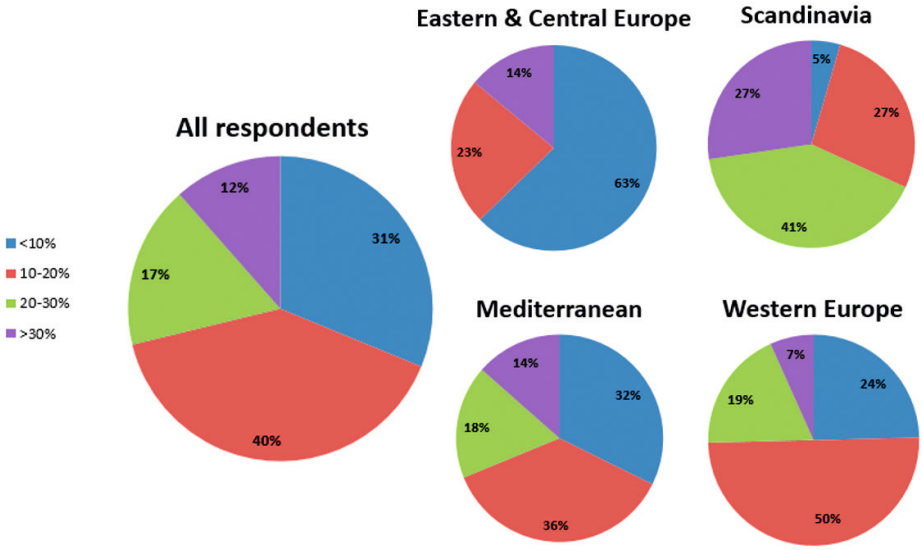


Figure 2. Proportion of prevalent ESKD patients on home dialysis according to region

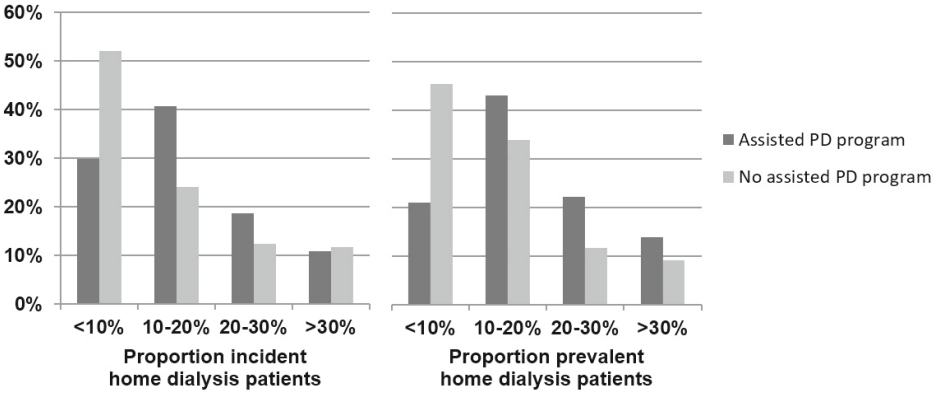


The proportion of *prevalent* ESKD patients on a home dialysis modality is depicted in Figure 2. Of all respondents, 31% indicated that the prevalence was <10% and 12% indicated that the prevalence was >30%. When focusing on the regions, a much higher percentage (63%) of respondents from Eastern & Central Europe indicated that the prevalence was <10%, while only 14% indicated that the prevalence was >30%. Again, Scandinavia had the highest percentage (27%) of respondents indicating that the prevalence was >30%.

Association between the availability of an assisted PD programme and proportion of home dialysis

The proportions of incident and prevalent patients on a home dialysis modality, according to the availability of an assisted PD programme, are depicted in Figure 3. A χ^2 test of independence showed a significant association between the availability of an assisted PD programme and an increasing proportion of incident as well as prevalent ESKD patients on a home dialysis modality ($p \leq 0.001$). This association persisted in an ordinal logistic regression analysis, taking into account center type, size, presence of a dedicated team for education and European region. With this analysis, the cumulative OR for the association between the availability of an assisted PD programme and proportion of *incident* ESKD patients on a home dialysis modality was 2.22 (95% CI: 1.38 – 3.57). The cumulative OR for the association between the availability of an assisted PD programme and proportion of *prevalent* ESKD patients was 3.29 (95% CI: 2.03 – 5.33).

Figure 3. Availability of an assisted PD programme and proportion of patients on a home dialysis modality



On the left, the proportion of *incident* patients on home dialysis is shown for centers with an assisted PD programme (dark grey bars) and centers without an assisted PD programme (light grey bars). Just over 40% of centers with an assisted PD programme have 10 – 20% of their *incident* patients on a home dialysis modality, while 52% of centers without an assisted PD programme have <10% of their *incident* patients on home dialysis.
On the right, the proportion of *prevalent* patients on home dialysis is shown for centers with an assisted PD programme (dark grey bars) and centers without an assisted PD programme (light grey bars): 43% of centers with an assisted PD programme have 10 – 20% of their *prevalent* patients on a home dialysis modality, while almost 46% of centers without an assisted PD programme have <10% of their *prevalent* patients on home dialysis.

Discussion

Our study among healthcare professionals from European nephrological units shows that assisted PD programmes are significantly more often available in Western Europe and Scandinavia. In addition, we show that assisted PD programmes are more often available in non-academic centers

and centers with a dedicated team for education. Also, there seems to be a relationship with reimbursement strategy and impact on the nephrologist's income since a larger proportion of respondents without an assisted PD programme indicated that ICHD is more profitable. Finally, having an assisted PD programme is associated with a higher incidence and prevalence of patients on a home dialysis modality.

This is the first study to investigate variations in center characteristics, organisational and financial factors, and their effect on the availability of an assisted PD programme across Europe. Only one previous study has investigated the effect of variations in some of the abovementioned factors, but this was a study on home dialysis in general (i.e. PD and haemodialysis combined) conducted in a single country. This study consisted of a survey among 286 German nephrologists and concluded that centers with assisted home dialysis had more experienced physicians and more prevalent dialysis patients [40].

Although we cannot prove causal relationships, our study can provide guidance on what is needed to treat more patients with assisted PD. While a factor such as center type cannot be influenced, the positive effect of organisational factors, as a reflection of dedication, seems to be relevant. Indeed, lack of staff, expertise, motivation and patient education are reported barriers that play a role in the uptake of PD [36, 40-43]. A Chinese-German study stated that '*a timely pre-dialysis education, implementation of a structured model for care, education and training of helping staff, and constantly monitoring of quality parameters is necessary*'" to promote assisted PD [44]. So, to treat more patients with assisted PD in Europe, it seems appropriate to invest in a dedicated team of healthcare professionals who provide adequate education and support patients on assisted PD.

Our study also suggests that reimbursement might play a role in the uptake of assisted PD programmes. Numerous European studies have indicated that low reimbursement for PD is an important barrier for PD utilisation [36, 40, 41], although assisted PD has shown to be a cost-effective treatment for frail elderly patients [31]. The fact that appropriate reimbursement, besides experience with PD, influences the number of patients on assisted PD is illustrated by a study comparing the assisted PD experiences of Canada and the United States [11]. In Canada, physicians have sufficient experience with PD, reimbursement is equal for PD and ICHD and assisted PD programs are available, while in the United States, experience with PD is limited, reimbursement for PD is less than for ICHD and assisted PD programmes are not available. As a result, the percentage of incident patients older than 65 years who receive PD is 21% in Canada, while this is only 7% in the United States [11]. Also, two French studies showed that the implementation of assisted PD at a single center increased the use of PD in incident patients from 21% to more than 40% [45] and that availability of assisted PD was associated with an 1.78 times increased rate of PD initiation, with elderly patients benefitting most [30].

Our study has some limitations. First, there may have been self-selection bias, as healthcare professionals with an assisted PD programme could have been more likely to respond to the survey. However, still centers without an assisted PD programme were relatively well represented in our study. Second, there may have been a recall bias, for example regarding PD profitability. Thirty percent of the respondents in our study did not know what the profitability of PD was in their center, while 32% indicated that the profitability of PD was equal to ICHD, which probably obscures underappreciated differences; indeed, health economics are complex and likely to be poorly understood. Third, the dichotomisation and categorisation of the response options may also have led to bias. Finally, no analysis could be performed regarding the individuals who facilitated assisted PD, caregivers or family members for example, which could have influenced reimbursement. In addition, reimbursement may also be influenced by geographic location; however, we were unable to perform that analysis due to a limited number of respondents per country. However, this is the first study providing valuable information on practice variation and factors associated with the availability of an assisted PD programme across Europe.

In conclusion, assisted PD programmes are significantly more often available in Western Europe and Scandinavia, in non-academic centers and centers with a dedicated team for education. Importantly, assisted PD programmes are associated with a higher incidence and prevalence of patients on home dialysis. Further research should focus more on (the differences in) reimbursement policies for assisted PD per country.

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Supplemental material

Supplemental table 1. Professional background, employment regions, and center type

	All respondents (n=609) [a]	Selected respondents (n=295)
Professional background		
Nephrologist in training	55 (9)	11 (4)
Nephrologist with <5 yrs. Experience	96 (16)	34 (12)
Nephrologist with 5 – 10 yrs. Experience	102 (16.5)	40 (14)
Nephrologist with 10 – 20 yrs. Experience	167 (27)	92 (31)
Nephrologist with >20 yrs. Experience	159 (26)	107 (36)
Dialysis nurse with 5 – 10 yrs. Experience	2 (0.5)	0
Dialysis nurse with 10 – 20 yrs. Experience	22 (4)	7 (2)
Administrative head of unit	6 (1)	4 (1)
Employment regions		
Eastern & Central Europe	67 (11)	43 (15)
Mediterranean	166 (27)	96 (32)
Western Europe	318 (52)	134 (45)
Scandinavia	57 (9)	22 (8)
Center type		
Non-academic center	299 (49)	171 (58)

Data are presented as number (n) with percentage (%)
a. For employment regions: 1 missing.

Supplemental table 2. Country of employment of respondents according to region

Eastern & Central Europe	All respondents[a]	Selected respondents	Western Europe	All respondents[a]	Selected respondents
Albania	1 (0.2)	1 (0.3)	Austria	1 (0.2)	1 (0.3)
Bosnia-Herzegovina	1 (0.2)	1 (0.3)	Belgium	32 (5.3)	10 (3.4)
Bulgaria	1 (0.2)	1 (0.3)	France	86 (14.1)	46 (15.6)
Croatia	33 (5.4)	15 (5.1)	Germany	8 (1.3)	5 (1.7)
Cyprus	1 (0.2)	1 (0.3)	Ireland	5 (0.8)	5 (1.7)
Czech Republic	1 (0.2)	1 (0.3)	The Netherlands	147 (24.1)	43 (14.6)
Hungary	2 (0.3)	2 (0.7)	Switzerland	22 (3.6)	15 (5.1)
Lithuania	1 (0.2)	1 (0.3)	United Kingdom	17 (2.8)	9 (3.1)
Montenegro	1 (0.2)	1 (0.3)			
Romania	3 (0.5)	3 (1)			
Russian Federation	3 (0.5)	3 (1)			
Serbia	3 (0.5)	3 (1)			
Slovakia	2 (0.3)	2 (0.7)			
Slovenia	9 (1.5)	4 (1.4)			
Turkey	4 (0.7)	3 (1)			
Ukraine	1 (0.2)	1 (0.3)			
Mediterranean			**Scandinavia**		
Andorra	1 (0.2)	1 (0.3)	Denmark	2 (0.3)	2 (0.7)
Greece	9 (1.5)	9 (3.1)	Norway	34 (5.6)	9 (3.1)
Israel	3 (0.5)	3 (1)	Sweden	21 (3.4)	11 (3.7)
Italy	38 (6.2)	24 (8.1)			
Portugal	11 (1.8)	10 (3.4)			
Spain	104 (17.1)	49 (16.6)			

Data are presented as number (n) with percentage (%)

a. The country of employment is missing for 1 respondent.

Appendix

1. What is your professional background?

- Nephrologist in training
- Nephrologist with <5 years of experience
- Nephrologist with 5 to 10 years of experience
- Nephrologist with 10 to 20 years of experience
- Nephrologist with >20 years of experience
- Nurse with <5 years of experience
- Nurse with 5 to 10 years of experience
- Nurse with 10 to 20 years of experience
- Administrative head of unit

2. What is the size of your dialysis center? (please consider all patients taken care of by your nephrology team on either PD or HD, be it at home or in center)

- <50 patients
- 50-100 patients
- 100-200 patients
- >200 patients

3. What type of center are you working in?

- Academic tertiary center
- Non-academic tertiary center
- Non-academic regional hospital based center, not private
- Non-academic regional hospital based center, private
- Private center out of hospital

4. In what country do you work?

5. In which region do you work?

6. What is (estimated) the proportion of <u>incident</u> ESKD patients on home based therapy in your unit? (so patients starting their renal replacement therapy at home within the first 3 months after start)

- <10%
- 10-15%
- 15-20%
- 20-25%
- 25-30%
- 30-40%
- >40%

7. What is (estimated) the proportion of <u>prevalent</u> ESKD patients on home based therapy in your unit?

- <10%
- 10-15%
- 15-20%
- 20-25%
- 25-30%
- 30-40%
- >40%

8. What is the average waiting time for a cadaveric transplantation in your unit?

- Less than 1 year
- 1-2 years
- 2-3 years
- more than 3 years

9. What is (estimated) the proportion of <u>incident</u> ESKD patients having a <u>pre-emptive (living or cadaveric)</u> transplantation in your unit?

- <10%
- 10-15%
- 15-20%
- 20-25%
- 25-30%
- 30-40%
- >40%
- Do not know

10. In general terms, in your country/region, how is the reimbursement of PD as compared to center HD?

- The reimbursement for PD and center HD is equal
- The reimbursement for center HD is higher, so it is more profitable than PD
- The reimbursement for center HD is higher, but costs are also higher, so it is equally profitable as PD
- The reimbursement for PD is higher than for center HD, but due to costs for disposables (dialysate bags, lines, cycler, connectology…) it is less profitable
- The reimbursement for PD is equal as for center HD, but due to disposable costs it is less profitable
- The reimbursement for PD is higher than for center HD and it is more profitable than center HD
- The reimbursement for PD is lower than for center HD, but, and due to disposable costs, it is less profitable
- I do not know

11. In your unit:

- The partition between the different renal replacement therapies (center HD, PD, Home HD, Transplantation) does not really impact the income of the nephrologists
- The partition between the different renal replacement therapies (center HD, PD, Home HD, Transplantation) has a substantial impact on the income of the nephrologists, and center HD is more profitable
- The partition between the different renal replacement therapies (center HD, PD, Home HD, Transplantation) has a substantial impact on the income of the nephrologists, and PD is more profitable

12. In your region, transport of patients to and from the dialysis unit for hemodialysis (more than one can apply):

- Is fully reimbursed
- Is well organized centrally (by the center or some organization)
- Organization of transport is seen as a major problem by many patients
- Is partially reimbursed; patients pay only a small contribution
- Is partially reimbursed; but patients pay a substantial contribution
- Has to be organized and paid by the patient himself
- Is problematic in view of the distances and traffic conditions
- I do not know

13. Does your unit provide:

	1- not at all	2	3	4	5-very organised
A structured pre-dialysis training program for patients	o	o	o	o	o
A structured PD program	o	o	o	o	o
A structured home HD program	o	o	o	o	o
A structured transplant program for cadaveric donation	o	o	o	o	o
A structured transplant program for living donation	o	o	o	o	o
A structured program for assisted PD	o	o	o	o	o

14. Do you have in your center a dedicated team for an advanced CKD/pre-dialysis/low clearance education program?

- No
- Yes, less than 1 full time equivalent
- Yes, 1 full time equivalent
- Yes, 2 or more full time equivalents
- Do not know

15. If no, or unknown, how is this low clearance program organized?

16. How does the lack of availability of a structured low clearance clinic influence the prevalence of ESKD patients in your home based therapy program according to your opinion?

- Not at all
- Slightly
- Modestly
- Substantially
- I have never thought about this
- Not applicable

17. Is it possible in your unit to get a PD catheter placed in a new patient within 48 hours?

- Yes
- Yes, most of the time
- Sometimes
- Mostly not
- No
- We have to refer the patient to another unit to place a PD catheter

18. What are to your opinion underlying reasons why this is not possible?

19. How long would it take to get a planned PD catheter placement on average?

- less than a week
- one to two weeks
- two to three weeks
- a month or more

20. In your unit, is there a nephrologist that can place PD catheters at the bedside under local anesthesia?

- Yes
- No

21. What are to your opinion, the advantages of being able to use such a bedside technique?

22. What are, to your opinion, barriers to allow being able to use such a bedside technique?

23. Who does place the PD catheters in your center? (more than one can fit)

- Senior surgeon
- Junior surgeon
- Dedicated surgeon
- Interventional radiologist
- Nephrologist
- Other

24. How do you appreciate the commitment of these operators to the issue of placement of PD catheters?

0-very low	1	2	3	4	5-very high
o	o	o	o	o	o

25. Is it possible in your unit to replace a non-functioning catheter within 48-72 hours in a patient already on PD?

- Yes
- Yes, most of the time
- Sometimes
- Mostly not
- No

26. Can you describe the impact on the management of the patient of such a mechanical related issue?

27. Do you or a colleague place the permanent HD catheters yourself?

- Yes
- No

28. Who does place the permanent HD catheters? (more than one can fit)

- Senior surgeon
- Junior surgeon
- Dedicated surgeon
- Interventional surgeon
- Other

29. Is it possible in your unit to place a permanent HD catheter within 48 hours?

- Yes
- Yes, most of the time
- Sometimes
- Mostly not
- No

30. Do you have a structured follow up of outcome results of PD catheter function in your unit?

- Yes
- No
- I do not know

31. Who is getting the results of this structured follow up?

32. What is the likelihood that in your center, a patient suffering from chronic kidney disease with long term nephrology follow-up at your unit, will receive education on:

	0 (no patient)	1	2	3	4	5 (all patients)
What is the function of the kidney?	o	o	o	o	o	o
What is kidney failure?	o	o	o	o	o	o
Conservative medical care for end stage kidney disease	o	o	o	o	o	o
Peritoneal dialysis	o	o	o	o	o	o
Home hemodialysis	o	o	o	o	o	o
In Center hemodialysis	o	o	o	o	o	o
Kidney transplantation	o	o	o	o	o	o

33. What is the likelihood that in your center, a patient suffering from chronic kidney disease who present as a crash lander (unplanned start, emergency start dialysis), will at some stage during the first 3 months receive education on:

	0 (no patient)	1	2	3	4	5 (all patients)
What is the function of the kidney?	o	o	o	o	o	o
What is kidney failure?	o	o	o	o	o	o
Conservative medical care for end stage kidney disease	o	o	o	o	o	o
Peritoneal dialysis	o	o	o	o	o	o
Home hemodialysis	o	o	o	o	o	o
In Center hemodialysis	o	o	o	o	o	o
Kidney transplantation	o	o	o	o	o	o

34. A 48 year-old woman not previously known to your unit presents at your emergency department. Diagnosis of established end stage renal disease is made. Rank the following in order of <u>probability</u>. (4= most probable, 1= least probable)

≡

The patient will start on HD by a central venous line

≡

The patient will start on HD by a central venous line and AV access will be planned

≡

The patient will start on HD by a central venous line and different RRT modalities, including PD, will be discussed for follow up treatment

≡

The patient will receive a PD catheter and PD will be started within 48 hours

35. Score the following (0= completely not, 5= I would seriously be concerned):

	0 (completely not)	1	2	3	4	5 (I would seriously be concerned)
Would you be concerned to have an elderly patient on PD at home?	o	o	o	o	o	o
Would you be concerned to have a frail patient on PD at home?	o	o	o	o	o	o

36. Do you have facilities/procedures to provide assistance to enable frail patients to perform dialysis at their place of residence?

- Yes
- No

37. For which modalities? (more than one can apply)

- APD
- CAPD
- Home HD

38. What degree of assistance do you offer? (more than one can apply)

- Practical/logistical support (eg carry boxes, prepare machine etc)
- Patient connection to the device/bag
- Patient disconnection from the device/bag
- Measurement of patients parameters
- Medication administration: EPO, iron IV, …
- Other (please specify)

39. Who performs the assistance? (more than one can apply)

- Family/non-professional relatives
- Qualified renal nurse from your unit
- Nurse assistant from your unit
- Qualified district nurse
- Qualified private nurse
- Nurse assistant or technician or Healthcare assistant from community service
- Personnel from a dialysis company
- Other (please specify)

40. Is there a specific reimbursement for this assistance for PD patients?

- No
- Yes, to the patient
- Yes, directly to the renal unit
- Yes, directly to the person who provides the assistance
- I do not know

41. Is this reimbursement sufficient to? (more than one can apply)

- cover the additional costs of assisted PD
- be profitable to the renal unit
- be profitable to the person providing the assisted care
- act as an incentive for assisted PD
- I do not know

42. A 80 year old person with poor mobility, ESKD, has decided to start RRT; she has mild cognitive impairment, but is still living alone.
What modality(ies) of renal substitution would you offer her?
(conservative management included)

43. Why would you offer these modality(ies) of renal substitution?

44. Would you consider assisted PD in this patient?

- Yes, certainly
- Yes, maybe
- Probably not
- Most likely not
- Certainly not

45. What advantages do you see for assisted PD in this patient?

46. What disadvantages do you see for assisted PD in this patient?

47. A 80 year old person with poor mobility on APD for one year, is being assisted for her APD treatment by her daughter. However, the daughter is no longer able to provide this assistance. What alternative therapy would you offer her?

48. Would you consider assisted PD in this patient?

- Yes, certainly
- Yes, maybe
- Probably not
- Most likely not
- Certainly not

49. Why would you or would you not consider assisted PD in this patient?

50. A 55 year old patient 2 months on PD and on waiting list for transplantation, presents for the 3th time with a slow outflow problems, resistant to laxatives. The abdominal X-Ray demonstrates a translocation of the PD catheter in the upper abdomen.

List in order of likelihood what is most likely (5: most likely; 1 least likely) which approach you would prefer in this patient:

≡

Ask surgeon for surgical intervention to solve the technical catheter issue

≡

Transfer to other specialized PD center to solve the technical catheter issue

≡

Transfer to in center HD on permanent central venous catheter

≡

Place a central venous catheter and plan AV fistula

≡

Plan AV fistula and continue PD as a bridge to HD

51. Do you have established collaboration agreements with other units for management of the following? (more than one can apply)

- Catheter related issues
- Presumed EPS
- Infectious complications
- Assisted PD
- Training and education
- Challenging clinical case discussions
- For none of these
- I do not really know this

52. Do you have an established quality assessment program for the following? (more than one can apply)

- Catheter related issues
- Presumed EPS
- Infectious complications
- Assisted PD
- Training and education
- Survival
- Technique success
- For none of these
- I do not really know this

53. Has your unit ever done special initiatives to increase the prevalence of homebased therapies?

- Yes
- No

54. Can you describe what type of initiative?

55. Was the result as expected?

56. if you wish to participate in the lottery to receive free registration tickets for the joined ISPD/EUroPD meeting - May 2-5, 2020 in Glasgow, please enter your email address below:

Part II

Traditional clinical outcomes of dialysis

Chapter 5

Bleeding risk of hemodialysis and peritoneal dialysis patients

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Abstract

Background Dialysis patients have an increased bleeding risk as compared with the general population. However, there is limited information whether bleeding risks are different for patients treated with hemodialysis or peritoneal dialysis. From a clinical point of view, this information could influence therapy choice. Therefore, the aim of this study was to investigate the association between dialysis modality and bleeding risk.

Methods Incident dialysis patients from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) were prospectively followed for major bleeding events over three years. Hazard ratios with 95% confidence intervals (CI) were calculated for hemodialysis compared with peritoneal dialysis using a time-dependent cox regression analysis, with updates on dialysis modality.

Results In total, 1745 patients started dialysis, of whom 1211 (69.4%) received hemodialysis and 534 (30.6%) peritoneal dialysis. The bleeding rate was 60.8/1000 person-years for hemodialysis patients and 34.6/1000 person-years for peritoneal dialysis patients. The time-dependent Cox regression analysis showed that after adjustment for age, sex, primary kidney disease, prior bleeding, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use, erythropoietin use, arterial hypertension, residual GFR, hemoglobin and albumin levels, bleeding risk for hemodialysis patients compared with peritoneal dialysis was 1.5-fold (95% CI 1.0 – 2.2) increased.

Conclusions In this large prospective cohort of incident dialysis patients, hemodialysis patients had an increased bleeding risk compared with peritoneal dialysis patients. Especially, hemodialysis patients with a history of prior bleeding had an increased bleeding risk.

Introduction

For over 30 years, end-stage kidney disease patients have been known to have an increased bleeding risk. Bleeding event rates for end-stage kidney disease patients treated with hemodialysis or peritoneal dialysis range between 42 and 89/1000 person-years [1-5] compared with 0.5 – 0.9/1000 person-years in the general population [6-8]. The increased bleeding risk could be explained by anemia (especially in the era before introduction of erythropoietin), platelet dysfunction and impaired interaction between platelets and the vessel wall [9-11]. Furthermore, the high prevalence of antiplatelet and anticoagulant drug use could also play an important role [9, 11, 12].

There are limited data about differences in bleeding risk of hemodialysis patients compared with peritoneal dialysis patients. Most studies that investigated bleeding risk in dialysis patients have focused on hemodialysis patients with atrial fibrillation. These studies showed a high bleeding risk in hemodialysis patients using vitamin K antagonists [13, 14]. Therefore, there is doubt whether the benefit of vitamin K antagonists in preventing stroke outweighs the high bleeding risk in dialysis patients. Only four studies compared the bleeding risk of patients on different dialysis modalities and showed that hemodialysis patients have a higher risk than peritoneal dialysis patients for subdural hematomas and gastrointestinal bleeding [15-18]. Three of these studies were retrospective cohort studies conducted in Taiwan [15, 17, 18]. They showed that, compared with peritoneal dialysis patients, hemodialysis patients have a 1.6-fold increased risk for subdural hematomas [15] and a 1.1- to 3.2-fold increased risk for gastrointestinal bleeding [17, 18]. However, prospective data regarding the difference in total bleeding risk between hemodialysis and peritoneal dialysis patients are lacking.

From a clinical perspective, it is important to know whether hemodialysis compared with peritoneal dialysis increases bleeding risk. There may be a preferred dialysis modality for specific subgroups of patients regarding bleeding risk. Therefore, we investigated the association between dialysis modality and bleeding risk.

Methods

Study population

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), conducted in 38 dialysis centers, prospectively included end-stage kidney disease patients who started dialysis treatment from 1997. Patients were ≥18 years and had no previous renal replacement therapy. Follow-up of patients was conducted until bleeding event within three years of follow-up, death or censored in case of kidney transplantation, loss to follow-up or until December 2013. All patients provided written informed consent and local medical ethics committees approved the study.

Demographic and clinical data

Data on age, sex, dialysis modality and primary kidney disease were collected at start of dialysis treatment. Primary kidney disease was classified according to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) codes [19]. We grouped patients into four classes of primary kidney disease: diabetes mellitus, glomerulonephritis, renal vascular disease and other kidney diseases. Data on prior bleeding, cardiovascular disease, erythropoietin use and use of antithrombotic drugs (i.e. antiplatelet drugs or vitamin K antagonists) were also collected at start of dialysis treatment. Prior bleeding was defined as a bleeding event leading to hospitalization and cardiovascular disease as ischemic heart disease (hospitalization for acute coronary syndrome or bypass surgery/percutaneous angioplasty), congestive heart failure or peripheral vascular disease. Blood pressure, hemoglobin, albumin, urea and creatinine were routinely measured in the dialysis centers at three months after the start of dialysis treatment. Blood pressure was measured before and after dialysis treatment over a 2-week period. The systolic and diastolic blood pressure values were both the average of up to six measurements. Arterial hypertension was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. Residual glomerular filtration rate (GFR) was calculated as the mean of creatinine and urea clearance, using creatinine and urea measurements in blood and 24 hours urine collections, corrected for body surface area (ml/min/1.73m^2).

Bleeding

Bleeding was defined as an event leading to hospitalization or death within three years of follow-up. The following causes of death were classified as a result of bleeding: hemorrhagic pericarditis, gastrointestinal hemorrhage, hemorrhage from a peptic ulcer, hemorrhage from vascular access or dialysis circuit, hemorrhage from ruptured vascular aneurysm, hemorrhage from surgery and other hemorrhage (including cerebral and subdural hemorrhage) (ERA-EDTA codes 13, 23, 25 – 28, 71) [19].

Statistical analysis

Baseline characteristics were presented as percentages or medians with interquartile range (IQR). Kaplan-Meier bleeding curves were generated for both dialysis modalities over three years of follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for hemodialysis in comparison with peritoneal dialysis using Cox proportional hazard analyses. Adjustment of HRs was first performed for baseline variables age, sex, primary kidney disease, prior bleeding, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use and erythropoietin use. In addition, a second adjustment of HRs was performed in which arterial hypertension, residual GFR, hemoglobin and albumin levels were added to the other variables. Furthermore, a time-dependent Cox regression analysis, with updates on dialysis modality, was performed to account for potential influence of changes in dialysis modality over time.

Multiple imputation was performed to account for missing data, using the fully conditional specification [20-23]. The imputation model contained all baseline characteristics including dialysis modality, bleeding outcome and mortality [21].

Interaction analyses were performed to identify patients with an increased bleeding risk. For these analyses, adjusted HRs of bleeding were calculated for hemodialysis patients with and without antithrombotic drug use, cardiovascular disease and prior bleeding in comparison with peritoneal dialysis patients without antithrombotic drug use, cardiovascular disease and prior bleeding (reference group). The same reference group of peritoneal dialysis patients was also used for calculation of the number needed to treat (NNT).

Statistical analyses were conducted with IBM SPSS Statistics version 25.

Results

Baseline characteristics

A total of 1745 patients were included, of whom 1211 patients (69.4%) started with hemodialysis and 534 patients (30.6%) with peritoneal dialysis. Baseline characteristics are described in Table 1. Hemodialysis patients, compared with peritoneal dialysis, were older (66 versus 54 years), more often female (40% versus 35%), used more often antiplatelet drugs (26% versus 15%) and vitamin K antagonists (16% versus 5%), and had a slightly lower residual GFR (3 versus 4 ml/min/1.73m^2). A small percentage of both hemodialysis and peritoneal dialysis patients had a history of prior bleeding (7 and 4%, respectively).

Table 1. Baseline characteristics

	Hemodialysis* (N = 1211)		Peritoneal dialysis** (N = 534)	
Age, median (IQR), [years]	66	(54-73)	54	(44-65)
Female sex, N (%)	488	(40%)	187	(35%)
Primary Kidney Disease, N (%)				
Diabetes mellitus	188	(16%)	93	(17%)
Glomerulonephritis	142	(12%)	96	(18%)
Renal vascular disease	260	(21%)	69	(13%)
Other	621	(51%)	276	(52%)
Prior bleeding, N (%)	83	(7%)	19	(4%)
Cardiovascular disease, N (%)	490	(40%)	134	(25%)
Antiplatelet drug use, N (%)	316	(26%)	80	(15%)
Vitamin K antagonist use, N (%)	195	(16%)	26	(5%)
Erythropoietin use, N (%)	896	(74%)	348	(65%)
Arterial hypertension, N (%)	750	(63%)	234	(45%)
Residual GFR, median (IQR), [ml/ min/1.73m^2]	3	(1-5)	4	(2-6)
Hemoglobin, median (IQR), [mmol/L]	6.7	(6.1-7.4)	7.3	(6.7-8.0)
Albumin, median (IQR), [g/ L]	37	(33-40)	36	(33-40)

N= number; IQR= interquartile range; GFR= glomerular filtration rate

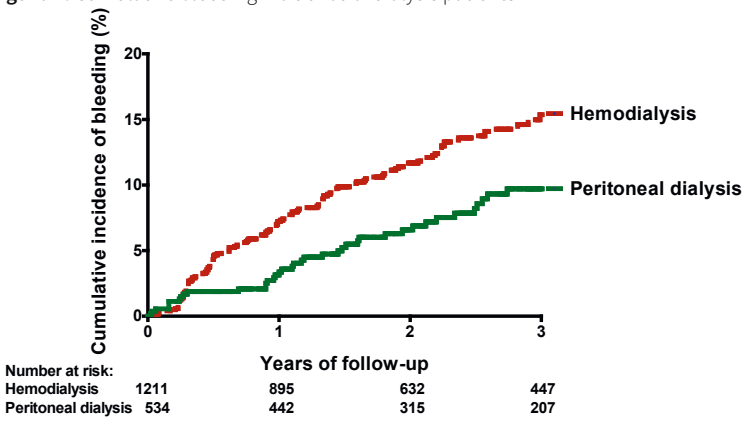
* Missings in hemodialysis patients: Prior bleeding 12 (1.0%), arterial hypertension 23 (1.9%), residual GFR 269 (22.2%), hemoglobin 20 (1.7%) and albumin 50 (4.1%).

** Missings in peritoneal dialysis patients: Prior bleeding 4 (0.7%), arterial hypertension 11 (2.1%), residual GFR 48 (9.0%), hemoglobin 10 (1.9%) and albumin 18 (3.4%).

Bleeding events

Within three years of follow-up, 183 patients had a first bleeding event on dialysis after a median follow-up of 2.2 years (IQR 1.0 – 3.0). The bleeding rate was 52.3/1000 person-years. Of the 183 patients with bleeding events, 144 patients were treated with hemodialysis and 39 patients with peritoneal dialysis at baseline. After three years, the cumulative bleeding incidence was 15.5% for hemodialysis patients and 9.7% for peritoneal dialysis patients (Figure 1).

Figure 1. Cumulative bleeding incidence of dialysis patients



Hemodialysis patients had a bleeding rate of 60.8/1000 person-years and peritoneal dialysis patients had a bleeding rate of 34.6/1000 person-years. The crude HR of bleeding was 1.7 (95% CI 1.2 – 2.5) in hemodialysis patients compared with peritoneal dialysis patients. Hemodialysis patients had a 1.5-fold (95% CI 1.0 – 2.1) increased bleeding risk after adjustment for age, sex, primary kidney disease, prior bleeding, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use and erythropoietin use. Additional adjustment for arterial hypertension, residual GFR, hemoglobin and albumin levels resulted in a 1.4-fold (95% CI 1.0 – 2.1) increased bleeding risk (Table 2). The time-dependent Cox regression analysis showed a HR of 1.5 (95% CI 1.0 – 2.2) after adjustment for age, sex, primary kidney disease, prior bleeding, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use, erythropoietin use, arterial hypertension, residual GFR, hemoglobin and albumin levels (Table 2).

Table 2. Hazard ratios of bleeding for hemodialysis versus peritoneal dialysis

	N	Incidence rate per 1000 person-years	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted** HR (95% CI)	Time-dependent Adjusted** HR (95% CI)
Peritoneal dialysis	534	34.6	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Hemodialysis	1211	60.8	1.7 (1.2-2.5)	1.5 (1.0-2.1)	1.4 (1.0-2.1)	1.5 (1.0-2.2)

N= number; HR= Hazard ratio; CI=confidence interval

* Adjusted for age, sex, primary kidney disease, prior bleeding, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use, and erythropoietin use.

** Adjusted for age, sex, primary kidney disease, prior bleeding, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use, erythropoietin use, arterial hypertension, residual GFR, hemoglobin and albumin levels.

During the study, 13 patients died as a result of bleeding of whom 12 were treated with hemodialysis and one with peritoneal dialysis. Of the 12 fatal bleeding events in hemodialysis patients, four were due to hemorrhage from a ruptured vascular aneurysm, three due to gastrointestinal hemorrhage, two due to hemorrhage from surgery, one due to hemorrhage from vascular access or dialysis circuit and two due to other hemorrhage. The fatal bleeding event in the peritoneal dialysis patient was due to gastrointestinal hemorrhage. The fatal bleeding rate for hemodialysis patients was 5.1/1000 person-years and for peritoneal dialysis patients 0.9/1000 person-years.

Interaction analyses

First, stratification for antithrombotic drug use (i.e. antiplatelet drugs or vitamin K antagonists) was performed for which peritoneal dialysis patients without antithrombotic drugs served as the reference group. The three groups for this analysis were: hemodialysis patients without antithrombotic drugs, peritoneal dialysis patients with antithrombotic drugs and hemodialysis patients with antithrombotic drugs. For hemodialysis patients without antithrombotic drugs, the time-dependent adjusted HR for bleeding was 1.7 (95% CI 1.1 – 2.7) compared with peritoneal dialysis patients without antithrombotic drugs. For peritoneal dialysis patients with antithrombotic

drugs, the time-dependent adjusted HR was also 1.7 (95% CI 0.8 – 3.4). For hemodialysis patients with antithrombotic drugs, the time-dependent adjusted HR was 1.9 (95% CI 1.1 – 3.1) compared with the reference group. The NNT was 27 for hemodialysis patients with antithrombotic drugs (Table 3).

In addition, we analysed the two antithrombotic drugs separately. Vitamin K antagonists use led to a 1.8-fold (95% CI 1.1 – 3.1) increased (time-dependent adjusted) bleeding risk for hemodialysis patients compared with peritoneal dialysis patients without vitamin K antagonists use. Antiplatelet drug use resulted in a time-dependent adjusted HR of 1.7 (95% CI 1.0 – 2.9) for bleeding in hemodialysis patients as compared with peritoneal dialysis patients without antiplatelet drug use.

Secondly, stratification for cardiovascular disease was performed for which peritoneal dialysis patients without cardiovascular disease served as the reference group. The three groups for this analysis were: hemodialysis patients without cardiovascular disease, peritoneal dialysis patients with cardiovascular disease and hemodialysis patients with cardiovascular disease. For hemodialysis patients without cardiovascular disease, the time-dependent adjusted HR for bleeding was 1.8 (95% CI 1.1 – 2.9) compared with peritoneal dialysis patients without cardiovascular disease. For peritoneal dialysis patients with cardiovascular disease, the time-dependent adjusted HR was 1.5 (95% CI 0.8 – 2.9). For hemodialysis patients with cardiovascular disease, the time-dependent adjusted HR was 1.4 (95% CI 0.8 – 2.5) compared with the reference group. The NNT was 29 for hemodialysis patients with cardiovascular disease (Table 3).

Thirdly, stratification for prior bleeding was performed for which peritoneal dialysis patients without prior bleeding served as the reference group. The three groups for this analysis were: hemodialysis patients without prior bleeding, peritoneal dialysis patients with prior bleeding and hemodialysis patients with prior bleeding. For hemodialysis patients without prior bleeding, the time-dependent adjusted HR for bleeding was 1.4 (95% CI 1.0 – 2.1) compared with peritoneal dialysis patients without prior bleeding. For peritoneal dialysis patients with prior bleeding, the time-dependent adjusted HR was 0.7 (95% CI 0.1 – 5.3). For hemodialysis patients with prior bleeding, the time-dependent adjusted HR was 3.0 (95% CI 1.7 – 5.3) compared with the reference group. The NNT was 10 for hemodialysis patients with prior bleeding (Table 3).

Table 3. Hazard ratios of bleeding for hemodialysis versus peritoneal dialysis stratified for antithrombotic drug use, cardiovascular disease and prior bleeding

		N	Incidence rate per 1000 person-years	NNT	Crude HR (95% CI)		Adjusted HR (95% CI)		Time-dependent Adjusted HR (95% CI)	
Dialysis modality	**Antithrombotic drug use**									
Peritoneal dialysis	No	430	30.0	reference	1	(reference)	1	(reference)	1	(reference)
Hemodialysis	No	712	56.6	38	1.9	(1.2-2.9)	1.6*	(1.0-2.6)	1.7*	(1.1-2.7)
Peritoneal dialysis	Yes	104	56.4	38	1.8	(0.9-3.7)	1.7*	(0.8-3.5)	1.7*	(0.8-3.4)
Hemodialysis	Yes	499	67.3	27	2.2	(1.4-3.4)	1.8*	(1.1-3.0)	1.9*	(1.1-3.1)
Dialysis modality	**Cardiovascular disease**									
Peritoneal dialysis	No	400	30.9	reference	1	(reference)	1	(reference)	1	(reference)
Hemodialysis	No	721	58.2	37	1.9	(1.2-2.9)	1.6**	(1.0-2.6)	1.8**	(1.1-2.9)
Peritoneal dialysis	Yes	134	47.4	61	1.5	(0.8-3.0)	1.3**	(0.6-2.6)	1.5**	(0.8-2.9)
Hemodialysis	Yes	490	65.0	29	2.1	(1.3-3.2)	1.4**	(0.8-2.3)	1.4**	(0.8-2.5)
Dialysis modality	**Prior bleeding**									
Peritoneal dialysis	No	511	34.4	reference	1	(reference)	1	(reference)	1	(reference)
Hemodialysis	No	1116	56.5	45	1.6	(1.1-2.4)	1.4***	(0.9-2.1)	1.4***	(1.0-2.1)
Peritoneal dialysis	Yes	19	50.0	64	1.4	(0.3-6.0)	1.3***	(0.3-5.5)	0.7***	(0.1-5.3)
Hemodialysis	Yes	83	133.1	10	3.8	(2.2-6.6)	2.8***	(1.6-5.1)	3.0***	(1.7-5.3)

N= number; NNT= number needed to treat; HR= Hazard ratio; CI=confidence interval

*Adjusted for age, sex, primary kidney disease, prior bleeding, cardiovascular disease, erythropoietin use, arterial hypertension, residual GFR, hemoglobin and albumin levels.

**Adjusted for age, sex, primary kidney disease, prior bleeding, antiplatelet drug use, vitamin K antagonist use, erythropoietin use, arterial hypertension, residual GFR, hemoglobin and albumin levels.

***Adjusted for age, sex, primary kidney disease, cardiovascular disease, antiplatelet drug use, vitamin K antagonist use, erythropoietin use, arterial hypertension, residual GFR, hemoglobin and albumin levels.

Discussion

In this large prospective cohort of incident dialysis patients, both hemodialysis (60.8/1000 person-years) and peritoneal dialysis patients (34.6/1000 person-years) had increased bleeding risks compared with the general population (0.5 – 0.9/1000 person-years).[6-8] It is important to realize that the prevalence of antithrombotic drug use is higher in dialysis patients than in the general population [9, 11, 12]. The main finding of our study was that hemodialysis patients had a 1.5-fold increased bleeding risk compared with peritoneal dialysis patients after adjustment for confounders. In addition, hemodialysis patients had highly increased bleeding risks when they used antithrombotic drugs or had a history of bleeding, which resulted in low numbers needed to treat (27 and 10, respectively). The importance of previous bleeding in increasing the risk of new bleeding events is consistent with previous studies, which showed that this was the most important risk factor [3, 24].

This is the first prospective study comparing the bleeding risk of hemodialysis and peritoneal dialysis patients taking into account all bleeding events. So far the bleeding risk has only been investigated in an American and Taiwanese cohort, which also showed an increased bleeding risk for hemodialysis patients compared with peritoneal dialysis patients [15-18]. However, unlike our study, the studies in these cohorts all focused on a single bleeding source, namely gastrointestinal or subdural. In the American cohort described by Wasse *et al.*, 698 upper gastrointestinal bleeding cases among dialysis patients were investigated. The adjusted relative risk (RR) for a first upper gastrointestinal bleeding was non-significantly lower for peritoneal dialysis patients compared with hemodialysis patients (RR 0.88, 95% CI 0.72 – 1.07) [16]. In the Taiwanese cohort, three retrospective studies were conducted [15, 17, 18]. First, the study of *Wang et al.* described subdural hematomas among 10136 hemodialysis and 10136 peritoneal dialysis patients [15]. The adjusted HR of a subdural hematoma was significantly higher for hemodialysis patients compared with peritoneal dialysis patients (HR 1.62, 95% CI 1.17 – 2.33). Secondly, the study of Lee *et al.* described gastrointestinal bleeding events combined with diverticula among 8955 hemodialysis and 1791 peritoneal dialysis patients [17]. With 1417 events (1274 in hemodialysis, 143 in peritoneal dialysis patients), the risk was significantly lower in peritoneal dialysis patients compared with hemodialysis patients (HR 0.78, 95% CI 0.64 – 0.96). Finally, the study of Huang *et al.* described peptic ulcer bleeding events among 2328 hemodialysis and 2239 peritoneal dialysis patients [18]. The adjusted risk for peptic ulcer bleeding, compared with a control group of patients without kidney disease, was lower for peritoneal dialysis patients (HR 3.71, 95% CI 2.00 – 6.87) than for hemodialysis patients (HR 11.96, 95% CI 7.04 – 20.31) [18].

A possible explanation for the increased bleeding risk of hemodialysis patients could be the use of low molecular weight heparin during hemodialysis sessions, which is necessary to prevent clotting in the extracorporeal system [25, 26]. Especially, the combination of high heparin dosages

during hemodialysis sessions and vitamin K antagonist use could have led to an increased bleeding risk. There is a recent debate whether the benefit (i.e. stroke reduction) of vitamin K antagonists in hemodialysis patients outweighs the bleeding risk [27]. In peritoneal dialysis patients, the stroke and bleeding risks associated with vitamin K antagonists could be different. A previous study showed that warfarin reduced the incidence of stroke without increasing the risk of intracranial hemorrhage in peritoneal dialysis patients [28]. Also, the increased bleeding risk in hemodialysis patients could result from intermittent puncture with needles of the vascular access. Unfortunately, data regarding the bleeding risk specifically related to the vascular access were lacking in our study. Another explanation for the increased bleeding risk of hemodialysis patients could be that those patients are less vital than peritoneal dialysis patients. Although we have adjusted for many confounders, residual confounding could not be excluded.

To our knowledge, this is the first large prospective cohort study comparing overall bleeding risk of hemodialysis and peritoneal dialysis patients. While prior studies primarily focused on gastrointestinal bleeding sources, our study also incorporated non-gastrointestinal bleeding sources in all dialysis patients. Furthermore, the accuracy of the recorded data is high, since nurses and nephrologists who treated these dialysis patients have recorded the bleeding events. Our study has several limitations. First, data were collected between 1997 and 2013, a period when strategies regarding the use of antithrombotic drugs differed from current practice. However, we believe that the results are still relevant for dialysis patients nowadays. Secondly, bleeding was defined as death due to bleeding or bleeding requiring hospitalization, but was not validated or defined by the bleeding criteria of the International Society on Thrombosis and Hemostasis [29]. However, we think that our definition of bleeding incorporates important clinical endpoints. Thirdly, data about the presence of atrial fibrillation or the use of heparin was missing. Another limitation of our study is the possibility of detection bias. Bleeding could be more often detected in hemodialysis patients than in peritoneal dialysis patients, since most hemodialysis patients visit a dialysis center three times a week and therefore have more contact with healthcare professionals. However, we think that the detection bias is limited, since we used bleeding requiring hospitalization as outcome. In case of such a major bleeding, we believe that peritoneal dialysis patients will also seek contact with healthcare professionals. Finally, it could theoretically be possible that confounding by indication occurred, since patients were not randomized between hemodialysis or peritoneal dialysis. Although the bleeding risk is usually not taken into account when choosing a dialysis modality, we have corrected for multiple confounders in our analysis. Since randomized controlled trials comparing bleeding rates of hemodialysis and peritoneal dialysis patients will probably never be conducted, clinicians should make decisions together with their patients based on observational studies.

In conclusion, hemodialysis patients have a 1.5-fold increased bleeding risk compared with peritoneal dialysis patients. An important subgroup is patients with previous bleeding problems. These patients may have an even higher bleeding risk with hemodialysis. End-stage kidney disease patients should receive information about all treatments and subsequently make shared decisions with their nephrologist [30]. Ideally, the bleeding risk for a patient with a specific (bleeding) history could be incorporated in this decision since bleeding can potentially lead to hospitalization or death.

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Chapter 6

Differences in hospitalization between peritoneal dialysis and hemodialysis 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 analyse 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 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, analysed with a multi-state model that attributed each hospitalization to the current dialysis modality.

Results In total, 695 patients (252 PD, 443 HD) 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 with HD. The risk for first hospitalization was 1.3 times (95%CI 1.1-1.6) higher for PD compared with 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%).

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

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 hemodialysis (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 hospitalised [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-center 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 1 January 2012 and 1 January 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 1 January 2017. The study was approved by local medical ethics committees of the participating dialysis centers. Reporting of the study conforms to broad EQUATOR guidelines [22].

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 categorised into: glomerulonephritis/pyelonephritis, cystic kidney disease, renovascular kidney disease, diabetes mellitus, and other/unknown [23]. Comorbidities were classified according to both the Charlson Comorbidity Index (CCI) and the Davies score [24, 25]. 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 h 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 h. The start and end dates of each hospitalization were recorded along with the reason using ICD-10 codes [26]. 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 ischaemia or infarction, cardiac arrest or arrhythmia, cardiac failure and haemorrhagic pericarditis), vascular disease (including pulmonary embolus, stroke, cerebrovascular haemorrhage, 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<.001). Only 4% of the PD patients had an acute start of dialysis, whereas 20% of HD patients did (p<.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
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= hemodialysis; SD=standard deviation; CCI= Charlson comorbidity index; KRT= kidney replacement therapy; IQR=interquartile range; GFR= glomerular filtration rate.

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=.001). Patients transitioned more often from PD to HD (33%) than from HD to PD (11%) (p<.001).

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

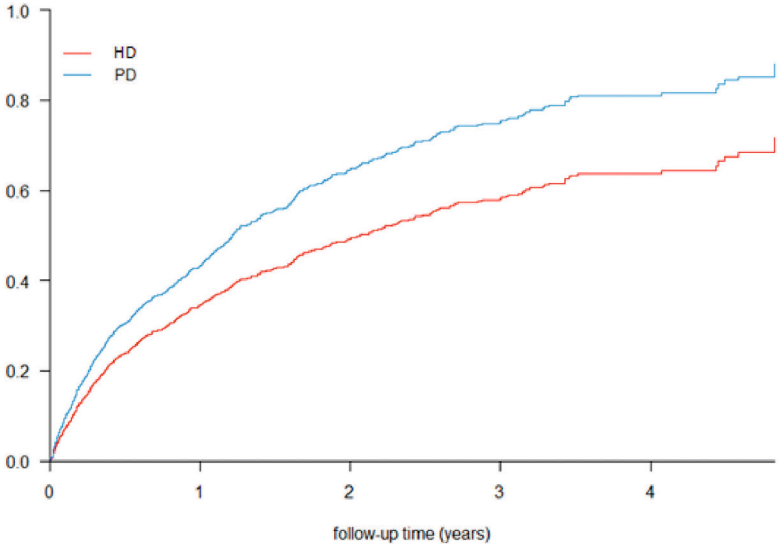
Dialysis modality	Crude HR (95% CI)		Adjusted* HR (95% CI)		Adjusted** HR (95% CI)	
Hospitalizations per patient-year						
PD vs HD	1.1	(1.03-1.3)	1.1	(1.02-1.3)	1.1	(1.02-1.3)
Risk for first hospitalization during first year after dialysis initiation						
PD vs HD	1.3	(1.1-1.6)	1.3	(1.1-1.6)	1.3	(1.1-1.6)
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= hemodialysis.
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.

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).

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



PD= peritoneal dialysis; HD= hemodialysis.
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.

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.

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 / 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 / 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= hemodialysis.
* 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= hemodialysis; N/A= not applicable.
a. Access-related includes vascular access infection, fistula operation and PD catheter leakage/exchange/removal.
b. Cardiac disease includes myocardial ischaemia/infarction, cardiac arrest/arrhythmia, cardiac failure, haemorrhagic pericarditis.
c. Vascular disease includes pulmonary embolus, stroke, cerebrovascular haemorrhage, ruptured vascular aneurysm, mesenteric infarction and peripheral arterial disease.
d. 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 with (in-center) 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, 27]. 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 in-center HD hospitalizations [20]. Several other studies have identified infections and specifically peritonitis as an important cause for PD hospitalizations [16, 18, 21, 28].

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. In-center 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 contrary, 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 with 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 [29, 30]. However, our study has some limitations. First, all types of admissions with a minimum duration of 24 h were analysed, 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 HD patients were treated with home HD (*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 hospitalization. Thus, we do not think that accounting for competing risks would 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 with 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 7

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.

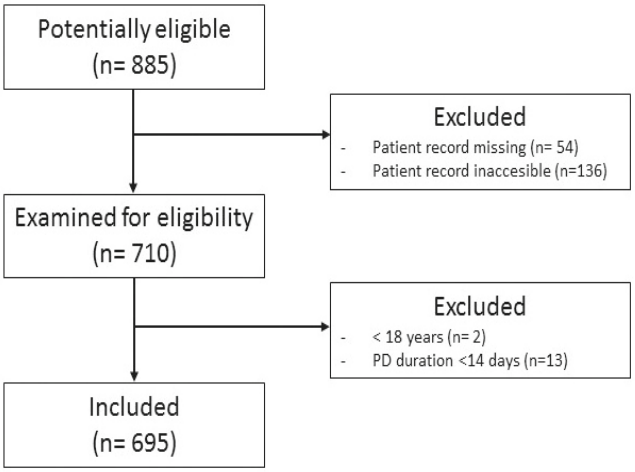
Finally, a funnel plot was constructed to evaluate the early technique failure rate of the participating centers, adjusted for age and sex. This is a graphical method to evaluate center performance with a reference standard, i.e. the overall early technique failure rate, and an indication of precision 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)	
Black	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
Charlson comorbidity index, n (%)				0.001
2 (low)*	168 (32)	58 (25)	110 (38)	
3-4 (intermediate)	212 (41)	95 (41)	117 (40)	
≥5 (severe)	139 (27)	77 (33)	62 (21)	
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/m^2	239 (46)	98 (42)	141 (49)	
25 – 30 kg/m^2	177 (34)	85 (36)	92 (32)	
≥ 30 kg/m^2	107 (20)	51 (22)	56 (19)	
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

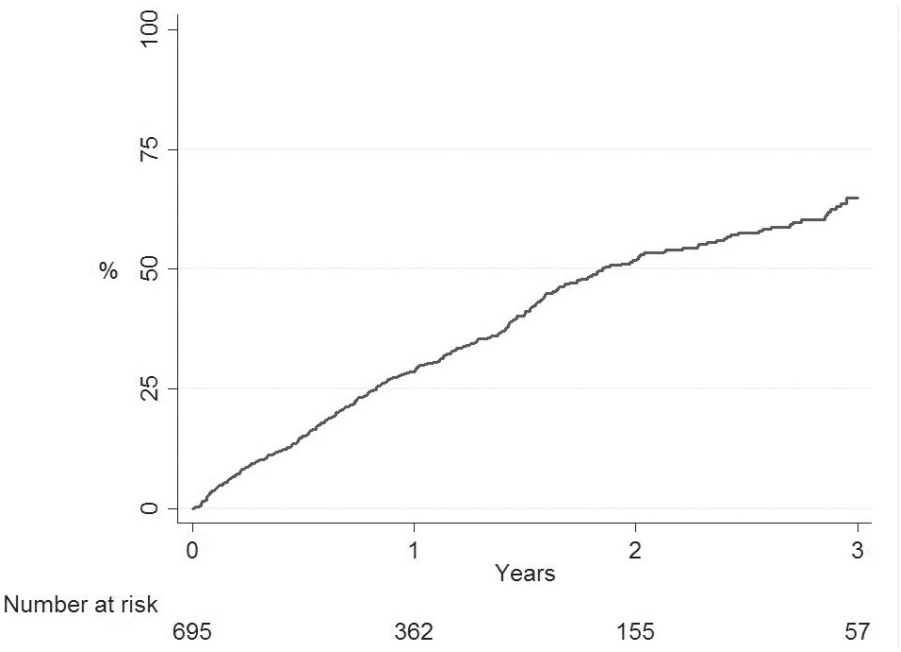
BMI, body mass index; APD, automated peritoneal dialysis; SD, standard deviation; IQR, interquartile range. Groups are defined according to the 30-day definition of technique failure.
* kidney failure alone represents a Charlson Comorbidity Index of 2 points.

Incidence of technique failure

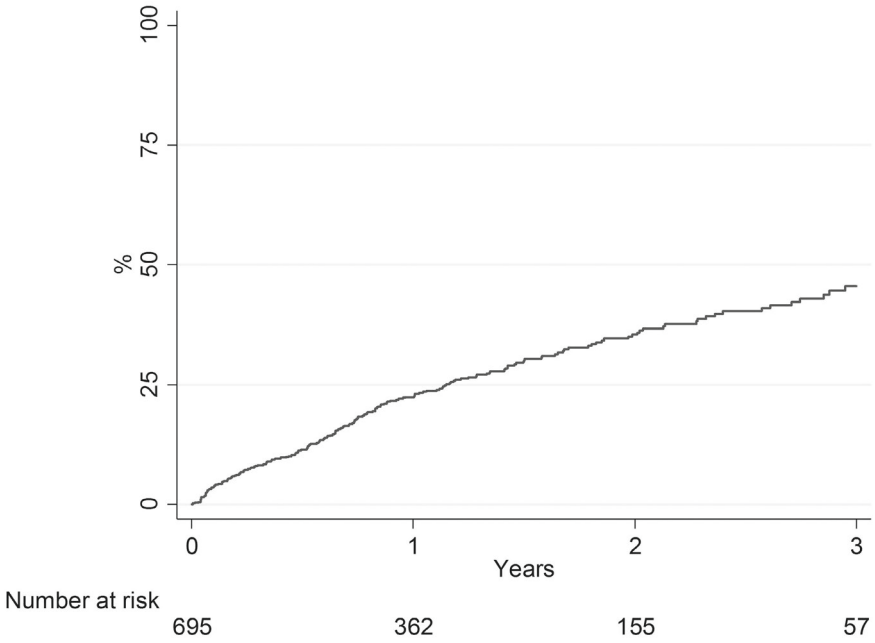
A total of 318 patients developed technique failure during the study, of whom 22 patients experienced a recurrent episode of technique failure. The PD patients experienced a mean of 0.36 episodes of technique failure per person–year of follow-up. The 1- and 2-year technique failure rates were 29% and 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)

A



B

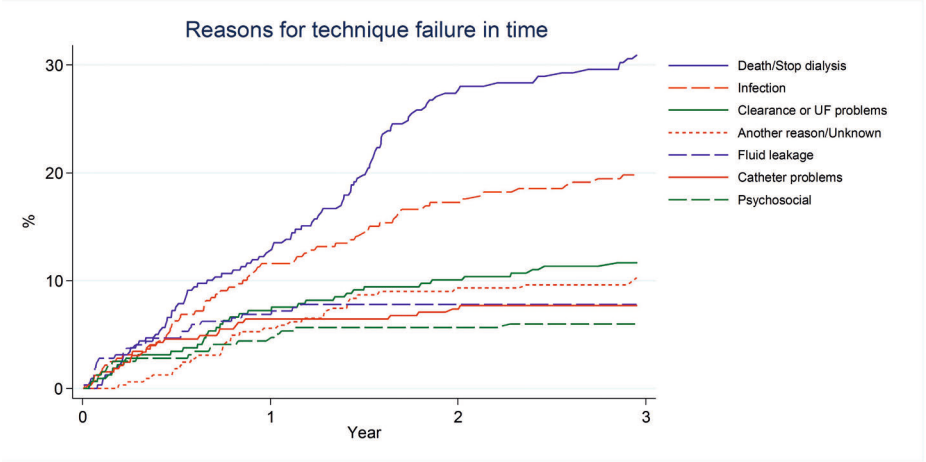


Technique failure was defined as a transfer to CHD for ≥ 30 days, death on PD or death within 30 days after transfer to CHD. First day of receiving CHD was the date assigned as technique failure.

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.

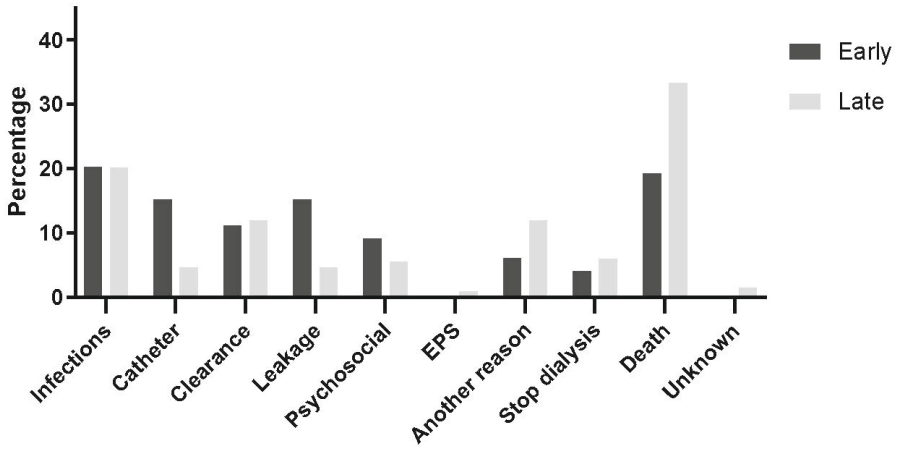
Figure 3. Cumulative incidence of different causes for technique failure



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 (Supplemental 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 (Supplemental Table S2).

Table 2. 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

Model 1 is adjusted for sex and age.
Model 2 is adjusted for sex, age, 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 (Supplemental 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 (Supplemental 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.

The center variation in technique failure rate is shown in Supplemental Figure S1. 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 (Supplemental Figure S2). 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 (Supplemental Figure S3 and Supplemental 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.[7],* 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%. In an older study by Descoeudres *et al.[23]*, 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%. 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

Supplemental 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 sex and age.
Model 2 is adjusted for sex, age, 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. In this competing risk analysis both kidney transplantation and death were competing events.

Supplemental 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 sex and age.
Model 2 is adjusted for sex, age, 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.

Supplemental 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 sex and age.
Model 2 is adjusted for sex, age, 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. In this competing risk analysis kidney transplantation was a competing event.

Supplemental 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)

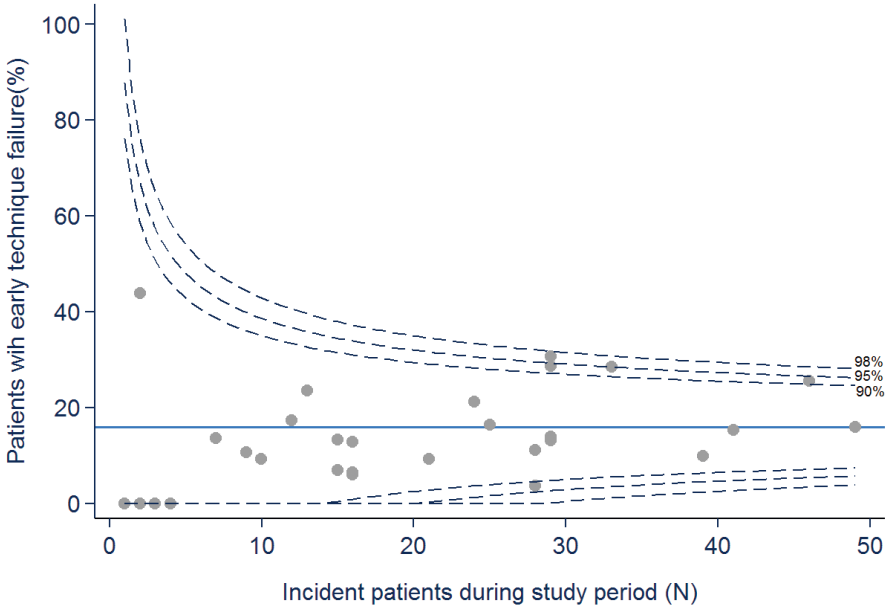
PD, peritoneal dialysis; GDP, glucose degradation products; HHD, home hemodialysis.

Supplemental 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%)

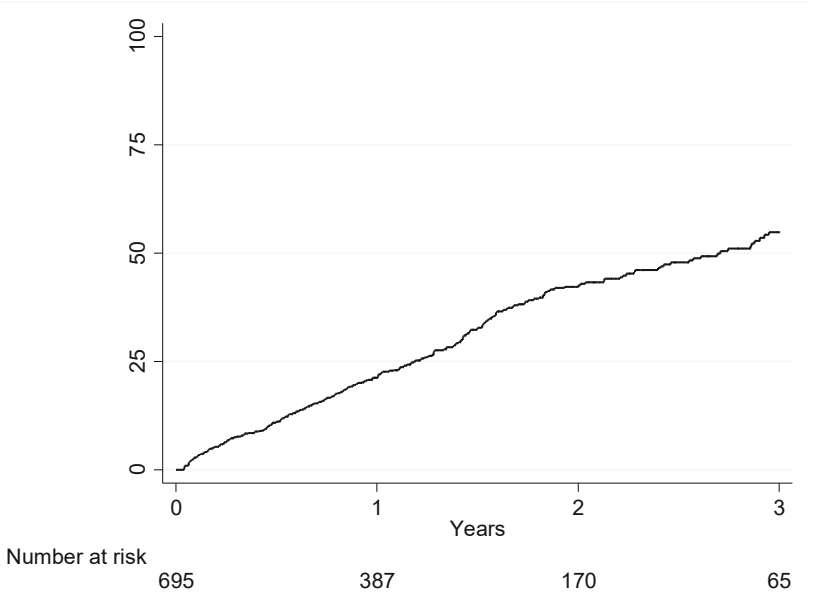
Technique failure according to the 30-day definition was defined as a transfer to CHD for ≥ 30 days, death on PD or death within 30 days after transfer to CHD.
Permanent technique failure according to the 180-day definition was defined as a transfer to CHD for ≥ 180 days, death on PD or death within 180 days after transfer to CHD.
All were in accordance with the standardized definition as proposed by Lan *et al. [Perit Dial Int. 2016;36(6):623-30]*.

Supplemental Figure S1. Funnel plot of early technique failure in incident study patients



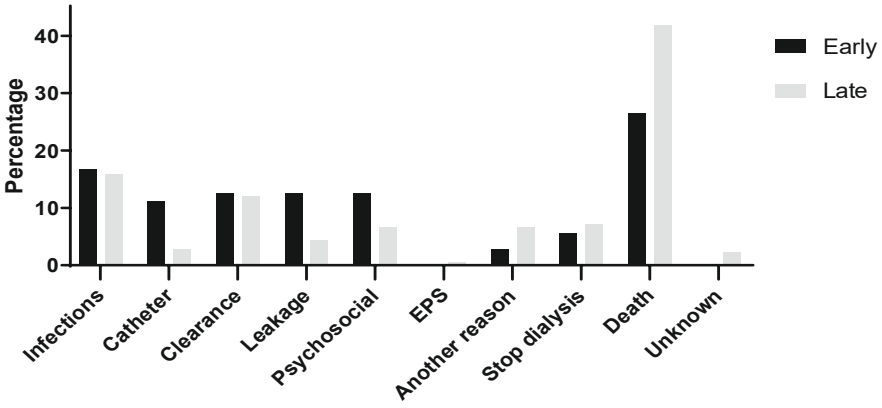
Each circle represents the early technique failure rate for a participating center (n=31). Rates are adjusted for age and sex. The overall early technique failure rate is used as a reference (blue). The 90%, 95%, and 98% control limits are provided as dotted lines. Using the 95% control limit, one center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

Supplemental Figure S2. 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.

Supplemental Figure S3. 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).

Chapter 8

Salvage of the peritoneal dialysis catheter in *Candida* peritonitis using amphotericin B catheter lock

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Abstract

Candida species form biofilms, that facilitates adherence to peritoneal dialysis (PD) catheters and making them less susceptible to antifungal therapy. Therefore, the International Society for Peritoneal Dialysis recommends immediate PD catheter removal in case of *Candida* peritonitis. However, in 2007, our institution showed that *Candida* peritonitis could be successfully treated without catheter removal with a treatment strategy including amphotericin B as catheter lock. To confirm the efficacy and safety of this lock-based protocol, we evaluated the outcome of *Candida* peritonitis episodes since then. A retrospective, single-center study was conducted in which we analysed all *Candida* peritonitis episodes in PD patients, treated with the lock-based protocol between July 2006 and March 2018. Eleven non-relapse *Candida* peritonitis episodes in 10 patients were treated with the lock-based protocol. Seven of the 11 episodes (64%) were cured without PD catheter removal (5 episodes cured immediately, 1 episode cured after an early relapse and 1 episode cured after a late relapse), in 2 episodes (18%) the catheter had to be removed, and 2 patients died (18%). This study confirms our previous findings that an amphotericin B lock-based protocol has potential to cure *Candida* peritonitis without PD catheter removal. However, further research is needed given the limitations of this study. Until that time, the lock-based *Candida* protocol could be used in patients who are not severely ill and in whom PD catheter removal is not desirable.

Introduction

Candida species cause 3 – 16% of peritonitis episodes in peritoneal dialysis (PD) patients [1-4]. They form biofilms, facilitating adherence to foreign bodies such as PD catheters and making them less susceptible to antifungal therapy [5]. Because of this, the International Society for Peritoneal Dialysis recommends immediate removal of the catheter in case of *Candida* peritonitis [6]. Although catheter removal is largely performed, mortality rate varies (0 – 61%) and PD catheter replacement is often unsuccessful, resulting in high technique failure rates (30 – 100%) [1, 3, 7, 8].

In 2007, Boer et al. reported eight cases of *Candida* peritonitis that were treated successfully without catheter removal between 2000 and 2006 in the University Medical Center Utrecht by using an amphotericin B catheter lock combined with oral flucytosine and intraperitoneal (IP) fluconazole [9]. To confirm the efficacy and safety of the lock-based protocol, we evaluated the outcome of *Candida* peritonitis episodes treated with this protocol since then.

Methods

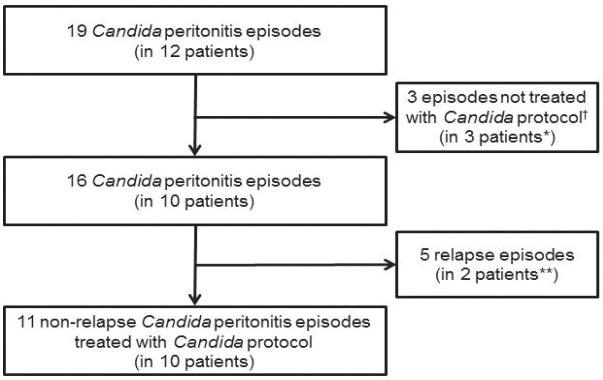
In a retrospective, single-center study, all *Candida* peritonitis episodes in PD patients, treated with the lock-based protocol between July 2006 and March 2018, were analysed. Patients who performed automated PD were switched to continuous ambulatory PD when effluent cultures revealed *Candida* species. *Candida* peritonitis was treated with oral flucytosine (500mg BID) and IP fluconazole (150mg every 48 hours in the night exchange). Additionally, after each instillation of PD fluid (usually four times daily), the PD catheter and connecting tube were filled with 5-10 mL of a solution containing 0.1 mg/mL amphotericin B. The catheter lock was removed when draining the dialysate between exchanges. Treatment duration was 4 weeks.

Possible outcomes were cure without PD catheter removal, early relapse, initial cure with late relapse, PD catheter removal or death. Early relapse was defined as *Candida* peritonitis occurring within 4 weeks after completion of antifungal treatment [6], while initial cure with late relapse was defined as a peritonitis with the same *Candida* species more than 4 weeks after completion of treatment. The outcome of both types of relapses was allocated to the initial peritonitis episode. Death was ascribed to peritonitis if it occurred within 30 days after presentation or was assigned directly to peritonitis.

Results

During the study period, 165 patients were treated with PD for 276 patient-years. The overall *Candida* peritonitis rate in these patients was 0.05 episodes per patient-year and they had no episodes with non-*Candida* fungi. Nineteen *Candida* peritonitis episodes occurred of which 11 episodes were analysed (Figure 1).

Figure 1. Flow chart of *Candida* peritonitis episodes



† In these episodes, *Candida* was cultured in the presence of abdominal sepsis due to a bowel perforation. In two of them, no antifungal therapy was initiated at all and treatment was stopped, while the third episode was treated with caspofungin. Eventually, all three patients died within a few days after presenting with peritonitis.
* Two patients had one *Candida* peritonitis episode, while one patient had multiple *Candida* peritonitis episodes. Therefore the number of patients incorporated in the analysis decreased from 12 to 10.
** These patients had multiple *Candida* peritonitis episodes, therefore the number of patients incorporated in the analysis remained the same.

Three episodes were excluded since they were not treated according to the lock-based protocol (see Figure 1, for a detailed explanation), and five episodes were excluded because they were relapses.

Eleven non-relapse *Candida* peritonitis episodes that occurred in 10 patients are presented in Table 1. Overall peritonitis rate in these patients was 1.46 episodes per patient-year. The first *Candida* peritonitis occurred at 57.2 ± 11.8 years with a median PD duration of 20.8 months (interquartile range (IQR) 11.2 – 29.8). *Candida albicans* and *Candida parapsilosis* were cultured in six and five episodes, respectively, and both strains were flucytosine, fluconazole, and amphotericin B susceptible. The lock-based protocol started a median of 2 days (IQR 1.5 – 3.0) after presentation with peritonitis.

Seven of the 11 *Candida* peritonitis episodes (64%) were cured without PD catheter removal (Table 1). Of those seven episodes, five episodes (46%) were immediately cured, one episode

(9%) was cured after an early relapse, and one episode (9%) was cured after a late relapse. In two episodes (18%), the catheter had to be removed; for the first patient (#4) due to refractory *Candida* peritonitis in combination with clinical detoriation and for the second patient (#7) due to refractory *Stenotrophomonas* peritonitis. In the second patient, both *Stenotrophomonas* and *Candida* were cultured at presentation with peritonitis. *Candida* was successfully eradicated with the lock-based protocol, while *Stenotrophomonas* persisted despite treatment. Eventually, a new catheter was inserted in this patient and PD was restarted.

Two patients (18%) died due to sepsis. The first patient (#5) developed three late relapses, 1, 4 and 6 months after initial presentation. In this patient, haemodialysis was not possible. She died 26 days after the last episode due to a sepsis for which she refused treatment, but notably with negative *Candida* cultures. The second patient (#8) died two days after developing a *Candida* peritonitis. The peritonitis occurred subsequent to a *Candida* bloodstream infection related to a central venous catheter (CVC) located in the femoral vein.

Table 1. Characteristics of 10 patients with 11 *Candida* peritonitis episodes

Patient	Sex	Renal disease	Comorbidity[a]	Months on PD	Episode date	Antibiotics <3 months	Fungal prophylaxis[b]	PD modality	Effluent culture	Outcome
1	M	ADPKD	Hypertension	49	08-2006	+	Fluconazole	CAPD	*C. parapsilosis*	Cure
2	F	Chronic pyelonephritis	Hypertension	33	02-2008	+	Nystatin	APD	*C. parapsilosis*	Cure
3	F	TMA	Hypertension	14	05-2012	Unknown	Unknown	CAPD	*C. parapsilosis*	Initial cure, late relapse; eventually cure[c]
					03-2013	Unknown	Unknown	APD	*C. albicans*	Early relapse; eventually cure[d]
4	F	Nephro-sclerosis	Hypertension, CVA, vascular dementia	72	09-2012	Unknown	Unknown	APD	*C. albicans*	Catheter removal[e]
5	F	Lithium nephropathy	CVA, bipolar disorder	23	08-2013	+	Nystatin	CAPD	*C. albicans*	Initial cure, late relapses; eventually death[f]
6	M	Anti-GBM nephritis	PAF	92	09-2013	+	Unknown	APD	*C. albicans*	Cure
7	M	Fanconi syndrome	Hypertension, DVT	54	07-2014	+	Unknown	CAPD	*C. parapsilosis* *S. maltophilia*	Catheter removal[g]
8	M	Primary FSGS	Hypertension, DM	7	07-2015	+	Nystatin	CAPD	*C. albicans*	Death[h]
9	F	Lithium nephropathy	Bipolar disorder	6	12-2015	+	Nystatin	CAPD	*C. parapsilosis,* CNS, *Brevibacterium casei, Roseomonas* species	Cure
10	M	TMA	Hypertension, sarcoidosis, UCTD, NSIP	26	01-2018	+	None (allergy)	APD	*C. albicans*	Cure

M: male; F: female; ADPKD: autosomal dominant polycystic kidney disease; TMA: thrombotic microangiopathy; GBM: glomerular basement membrane; FSGS: focal segmental glomerulosclerosis; CVA: cerebrovascular accident; PAF: paroxysmal atrial fibrillation; DVT: deep venous thrombosis; DM: diabetes mellitus; UCTD: undifferentiated connective tissue disease; NSIP: nonspecific interstitial pneumonia; PD: peritoneal dialysis; CAPD: continuous ambulatory PD; APD: automated PD; CNS: coagulase negative staphylococci; CVC: central venous catheter.

a. Only the most relevant co-morbidities are displayed.
b. Fungal prophylaxis that was provided when antibiotics were started in the previous 3 months.
c. This relapse occurred in August 2012 and was cured.
d. This relapse occurred 20 days after completion of antifungal therapy and was cured.
e. The catheter was removed because of refractory *Candida* peritonitis and clinical detoriation.
f. The relapses occurred 1, 4 and 6 months after the first episode. The patient was treated with the lock-based protocol but subsequently developed a sepsis for which she refused treatment. She died 26 days after the last episode, but at that time the effluent cultures had already become negative for *Candida*.
g. The catheter was removed because of refractory *Stenotrophomonas* peritonitis but with effluent cultures that had already become negative for *Candida*.
h. The patient died two days after developing a *Candida* peritonitis. The *Candida* peritonitis occurred subsequent to a *Candida* bloodstream infection related to a CVC located in the femoral vein.

Discussion

In this study, *Candida* peritonitis was cured without removing the PD catheter in 64% of the episodes by applying amphotericin B intra-catheter in addition to oral flucytosine and IP fluconazole. When these results are combined with our previous study [9], the cure rate was 79% (15 out of 19 episodes in 16 patients were cured), the patient survival rate was 88%, the catheter removal rate was 11% and the technique survival rate was 81%. These results are better than those reported in literature since 2007, with a cure rate of only 0 – 22% [3, 10] and mortality rates up to 61% [7], despite catheter removal rates of 58 – 100% [7].

The unique feature of our protocol is the intra-catheter instillation of amphotericin B aimed at eradicating the *Candida*-induced biofilm. With intra-catheter instillation, the lumen is exposed to a high concentration of amphotericin B, while direct toxicity to the peritoneum is prevented because the drug is flushed out of the catheter during drainage of the peritoneal cavity. Amphotericin B intra-catheter can suppress fungal metabolic activity, inhibit biofilm formation and sterilise foreign bodies such as CVCs [11]. A review of in vivo studies with amphotericin B intra-catheter concluded that it is useful as lock therapy in addition to systemic therapy in patients with CVC related infections [5]. Since CVCs are made of the same material as PD catheters, these findings support our results in PD patients.

Our study has some limitations. First, it is retrospective and conducted in a single center without a control group. Second, the amphotericin B catheter lock was added to oral flucytosine and IP fluconazole, but it is unknown whether the amphotericin B catheter lock is also effective when combined with other systemic or IP antifungal therapy. Third, several aspects of the protocol such as the concentration of amphotericin B, the frequency of application and the total duration of therapy are based on expert opinion. Fourth, we cannot exclude spill of the amphotericin B catheter lock into the peritoneal cavity [12]. IP amphotericin B is associated with persistent leucocytosis and abdominal pain due to local chemical irritation attributed to the sodium desoxycholate solvent [13, 14]. However, concentrations of IP amphotericin B used in previous studies are higher than the concentration in case of spill of amphotericin B using our protocol [14]. Moreover, our patients have not experienced the aforementioned side effects. Finally, three patients with abdominal sepsis due to a bowel perforation were not treated with the lock-based protocol, which influenced peritonitis outcomes.

In conclusion, an amphotericin B lock-based protocol has potential to cure *Candida* peritonitis without PD catheter removal. The protocol is simple to use, safe, and could prevent transfer to haemodialysis which often necessitates CVC insertion. However, given the limitations of this study, it is important to conduct further research in prospective, well-controlled, multicenter studies. Until that time, the lock-based *Candida* protocol could be used in patients who are not severely ill and in whom PD catheter removal is not desirable.

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Part III

Focus on Health-Related Quality of Life

Chapter 9

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 worldwide.

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 HD.

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 were pooled using a random-effects model and results were expressed as standardized mean difference (SMD) with 95% confidence intervals (CIs). 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 peritoneal dialysis patients (95%), and used the 12-item or 36-item Short-Form Health survey questionnaires (83%). More than half 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), while home dialysis patients from Latin America had a lower physical score (SMD -0.20, 95%CI -0.28 to -0.12). 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 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.

Trial registration PROSPERO 95985.

Introduction

End-stage renal disease (ESRD) is associated with poor survival. Patients starting on dialysis therapy 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 (HD) 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 (QoL) far more important than survival [5-10]. Many patients experience dialysis as a heavy burden; they even have poorer health-related QoL (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 during the last 10 years.

Reducing the impact of ESRD and its treatment on daily life could potentially improve HRQoL. Performing dialysis at home, instead of being treated with in-center HD, 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 engage in daily social activities [18, 21-23]. Home HD (HHD) enables an intensified dialysis regimen, allowing a reduction in medication burden [24]. All these factors could contribute to an improvement in 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 in-center HD patients. Interpretation of these studies is hampered by a large variety in type of questionnaire used and applied study design [25-27]. In addition, because these studies are conducted in different countries, disparity exists in study populations since the percentage of patients receiving home dialysis varies across the world. This difference in practice patterns, together with a difference in local cultures, is suggested to influence HRQoL [28]. Investigators of 'the Dialysis Outcomes and Practice Patterns Study' found different HRQoL scores between in-center HD patients across Japan, Europe, and the United States after adjustment for several confounders, including comorbid conditions [28]. Due to inequalities among studies, it is difficult to determine whether home dialysis patients have better HRQoL. Differences in HRQoL of home dialysis patients and in-center HD 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 of home dialysis and in-center HD 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 because the perception of QoL in patients treated with dialysis has 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 inclusion and exclusion criteria. All articles comparing the HRQoL of adult (i.e. ≥ 18 years) home dialysis patients with the HRQoL of in-center HD patients were included. Articles other than randomized controlled trials and observational studies were excluded, such as validation and reliability studies on QoL 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 (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 in-center HD patients, the authors were e-mailed. 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 dialysis modality, country and subcontinent of conductance, number of participants with characteristics (age, dialysis vintage, and sex), and type of HRQoL questionnaire used. From all studies, HRQoL scores were extracted and evaluated. If no standard deviation 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 summary scores of the 12-item or 36-item Short Form Health Survey (SF) were not available, the physical functioning score or the mental health score was used, respectively. If the abbreviated 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 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 $I^2 > 75\%$ [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, the 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 with in-center HD. Additional analyses were conducted for the following subgroups: type of questionnaire used, different age categories (<45, 45 – 60 and >60 years), and dialysis vintage (<36 vs ≥ 36 months). Finally, a sensitivity analysis was conducted that excluded articles for which the standard deviation was calculated or substituted. All analyses were performed with Stata/SE, version 14.1, for Windows (StataCorp LP).

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 registration number 95985.

Results

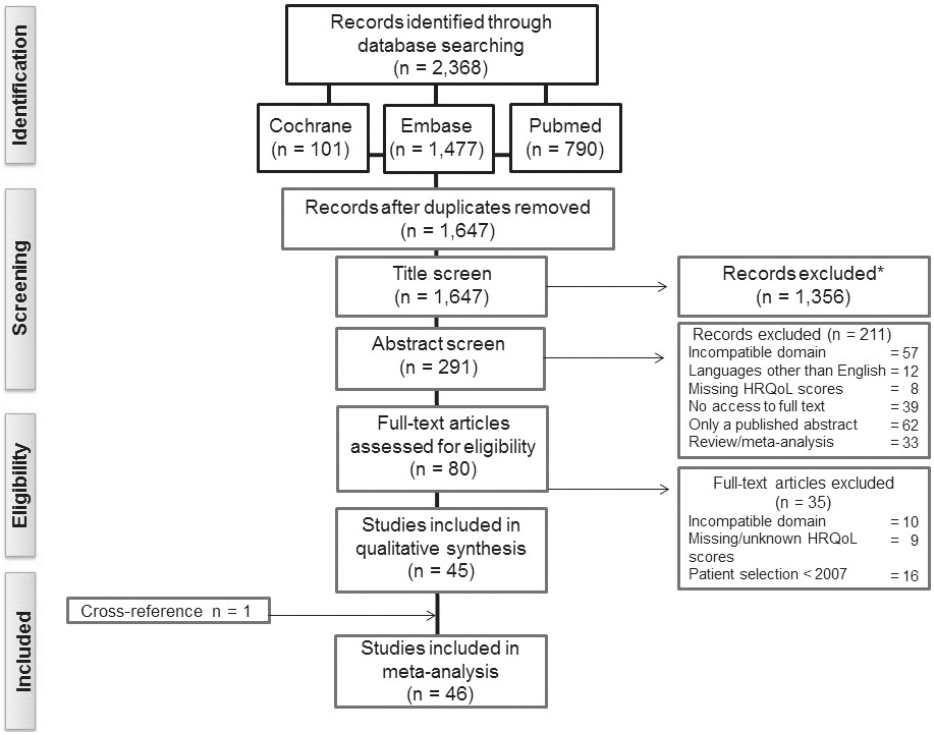
Study selection

The initial literature search was performed on November 21, 2017, and 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 inclusion 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 it was excluded [47].

The full texts of the remaining 80 articles were retrieved and assessed for eligibility. A total of 35 articles were excluded for the following reasons: comparison group other than in-center HD [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 *et al*. [17] (Frequent Hemodialysis Network trials) and Jardine *et al*. [81] (ACTIVE dialysis trial) were excluded because they focused on frequent HD 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].

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 *et al.* and Liu *et al.* [91, 92], Chkhotua *et al.* and Maglakelidze *et al.* [94, 95], Griva *et al.* and Yang *et al.* [103, 104], 2 articles by Kontodimopoulos [111, 112], and 2 articles by Theofilou [120, 121], leaving 41 studies for analysis.

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, and validation and reliability studies on quality of life questionnaires.

Study characteristics

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

Table 1. Study characteristics of 41 studies

Study	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ICHD)	Age, y (SD) (home/ICHD)	Dialysis vintage, mo (SD) (home/ICHD)	HRQoL question-naire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclusion
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	NA	NA	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)	NA	SF	43.2 (9.8) / 47.4 (10.2)	44.5 (10.9) / 50.2 (12.6)	NA
Baykan, 2012	PD	Turkey, Eastern Europe	41 / 42	40.6 (11.9) / 49.1 (12.0)	NA	SF	53.2 (7.6) / 47.0 (9.2)	45.2 (6.7) / 42.2 (6.7)	NA
Borowiak, 2009	PD	Poland, Eastern Europe	50 / 50	58.9 (13.2) / 59.6 (13.4)	NA	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)	NA	KDQOL	40.3 (12.0) / 37.4 (12.6)	50.3 (10.0) / 51.0 (10.3)	Favors PD
Chkhotua, 2011 and **Maglakelidze** 2011	PD	Georgia, Eastern Europe	43 / 120	NA	NA	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	NA	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)	NA	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

Table 1. Study characteristics of 41 studies (continued)

Study	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ICHD)	Age, y (SD) (home/ICHD)	Dialysis vintage, mo (SD) (home/ICHD)	HRQoL question-naire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclusion
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)	NA	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
Ibrahim, 2011	PD	Malaysia, Asia	91 / 183	NA	NA	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)	NA	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	NA	NA	KDQOL	38.7 (9.0) / 39.3 (9.7)	44.8 (6.4) / 44.6 (7.0)	Favors PD
Kontodimopoulos, 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)	NA	SF	25.4 (25.3) / 32.1 (20.6)	45.6 (12.1) / 46.1 (10.5)	NA

Table 1. Study characteristics of 41 studies (continued)

Study	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ICHD)	Age, y (SD) (home/ICHD)	Dialysis vintage, mo (SD) (home/ICHD)	HRQoL question-naire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclusion
Neumann, 2018	PD	Germany, Western Europe	153 / 200	59.0 (15.4) / 59.8 (16.0)	NA	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
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)	NA	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)	NA	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)	NA

Table 1. Study characteristics of 41 studies (continued)

Study	Home dialysis modality	Country, Subcontinent*	No. of patients (home/ICHD)	Age, y (SD) (home/ICHD)	Dialysis vintage, mo (SD) (home/ICHD)	HRQoL question-naire	Physical score, mean (SD) (home/ICHD)	Mental score, mean (SD) (home/ICHD)	Study conclusion
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
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	NA	NA	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	NA	NA	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	NA	NA	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)	NA	WHOQOL-BREF	3.0 (0.9) / 2.9 (0.8)	3.7 (0.7) / 3.7 (0.6)	Equal
TOTAL	NA	NA	4,158 7,854	55.9 (13.8) 54.8 (14.1)	34.1[#] (22.8-43.4) 56.9[#] (31.0-77.2)	NA	NA	NA	NA

EQ-5D VAS, EuroQol-5D Visual Analogue Scale; HHD, home hemodialysis; HRQoL, Health-Related Quality of Life; ICHD, in-center hemodialysis; KDQOL, Kidney Disease Quality Of Life instrument; NA, not applicable or not available; PD, peritoneal dialysis; SD, standard deviation; SF, Short Form Health Survey (12-item or 36-item); UK, United Kingdom; USA, United States of America; WHOQOL-BREF, abbreviated World Health Organization Quality of Life questionnaire.

[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.

Mean age of the home dialysis population was 55.9 ± 13.8 years, while in-center HD 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 months) and 56.9 months for in-center HD patients (IQR 31.0-77.2 months). Most (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 in-center HD population (range 44%-85%). In the included studies, there were no randomized controlled trials of in-center HD versus home dialysis. Furthermore, most studies had a cross-sectional design, comparing prevalent patients receiving in-center HD 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 in-center HD patients. However, after a median follow-up period of 14.7 months, HRQoL between dialysis modalities was equal. Because follow-up results of PD and in-center HD patients were not shown in the article, in the following meta-analysis, only baseline data of this study could be used.

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 in-center HD 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 in-center HD 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 in-center HD were obtained from the author. These unpublished data showed improvement in MCS scores for in-center HD patients, but PCS scores 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

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 in-center HD patients. The study by Wright *et al.* compared two home dialysis populations (HHD and PD) with in-center HD 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 with in-center HD patients, with an SMD of 0.14 (95% CI 0.04 to 0.24). HRQoL on the mental domain was equal between the two groups (SMD 0.06, 95% CI -0.03 to 0.15).

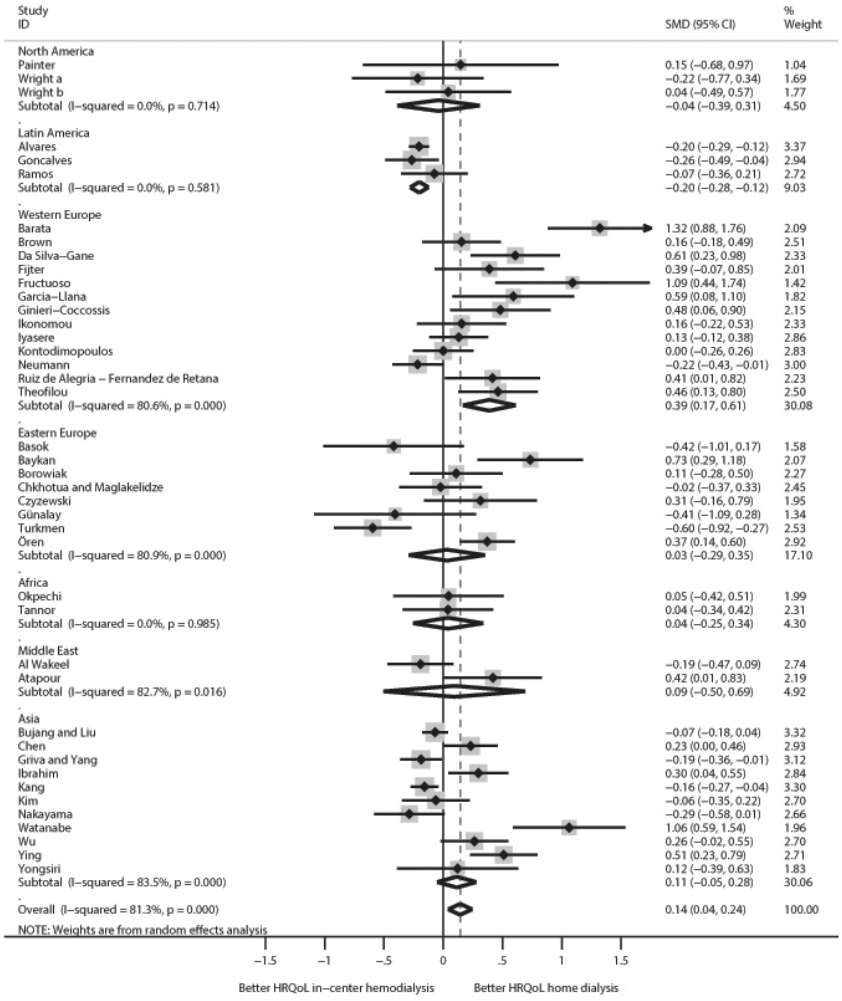
A comparison among subcontinents showed that patients receiving home dialysis in Western Europe had higher physical HRQoL scores compared with in-center HD patients (SMD 0.39, 95% CI 0.17 to 0.61), whereas patients receiving home dialysis from Latin America had lower physical HRQoL scores (SMD -0.20,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

If studies were divided according to overall level of bias, 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 or influence heterogeneity (Figures S1A and B, and S2A and B).

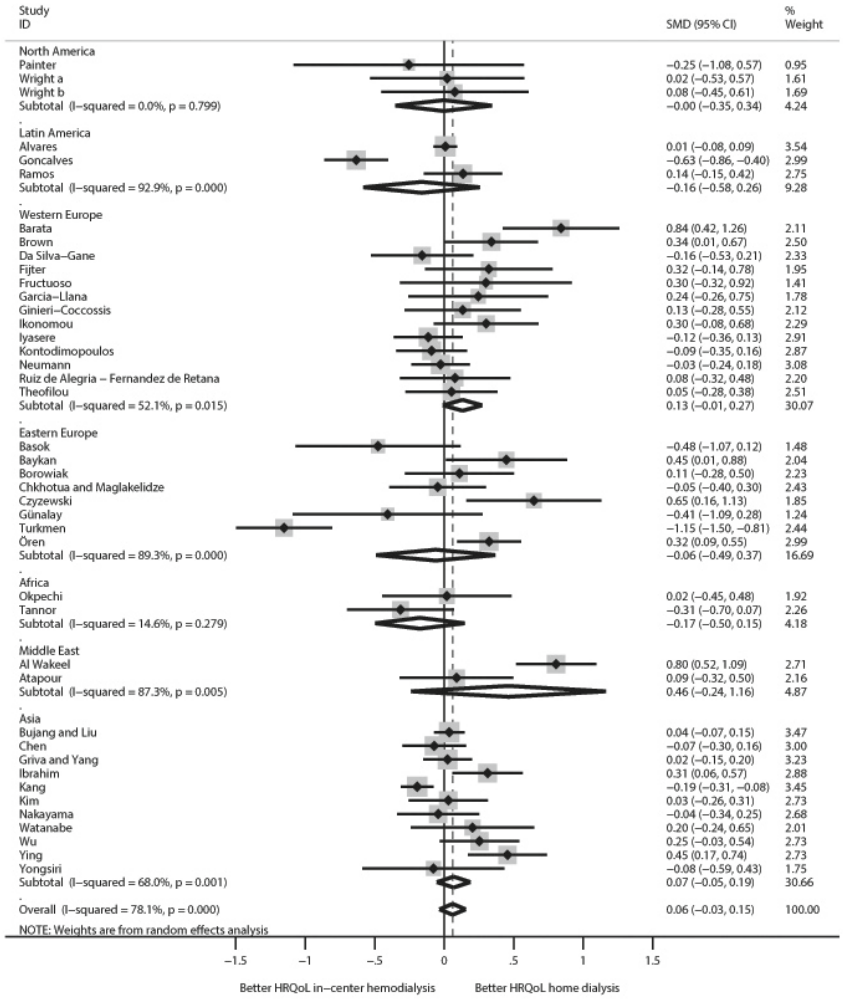
The standard deviation for the HRQoL scores in 5 studies had to be calculated, if sufficient data were available [95, 98, 108], or substituted [102, 106]. Also, WHOQOL-BREF scores in two studies were transformed into a 100-scale [101, 121]. To further explore the robustness of data, sensitivity analysis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

Figure 2. Meta-analysis of Health-Related Quality of Life (HRQoL) among subcontinents

A.



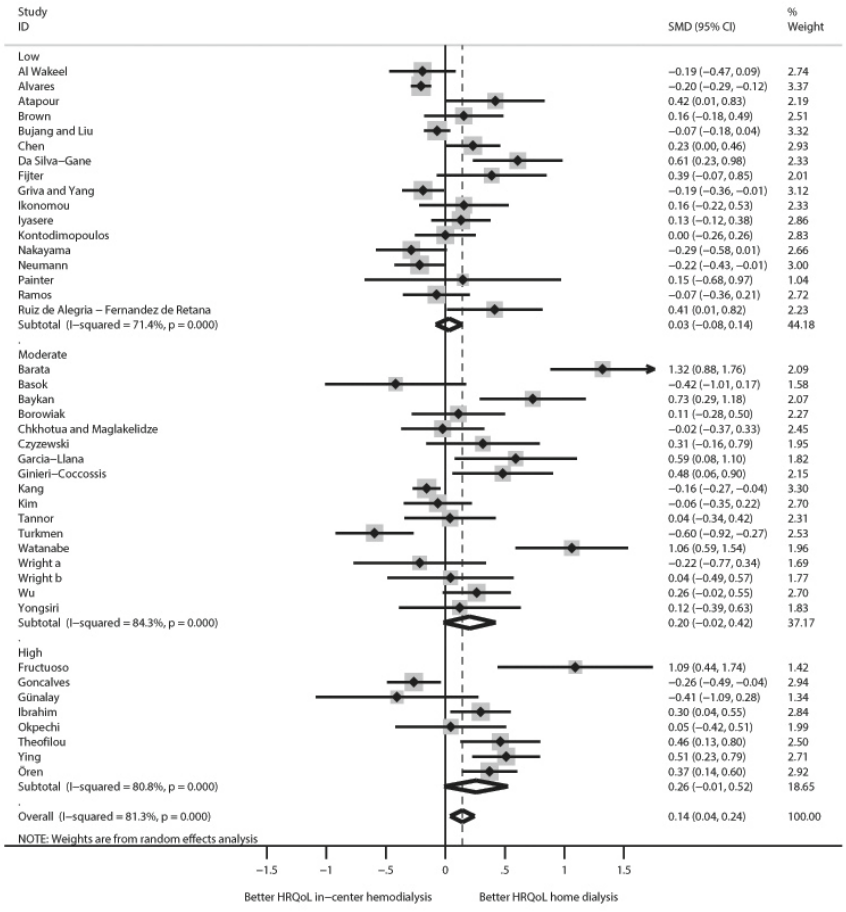
B.



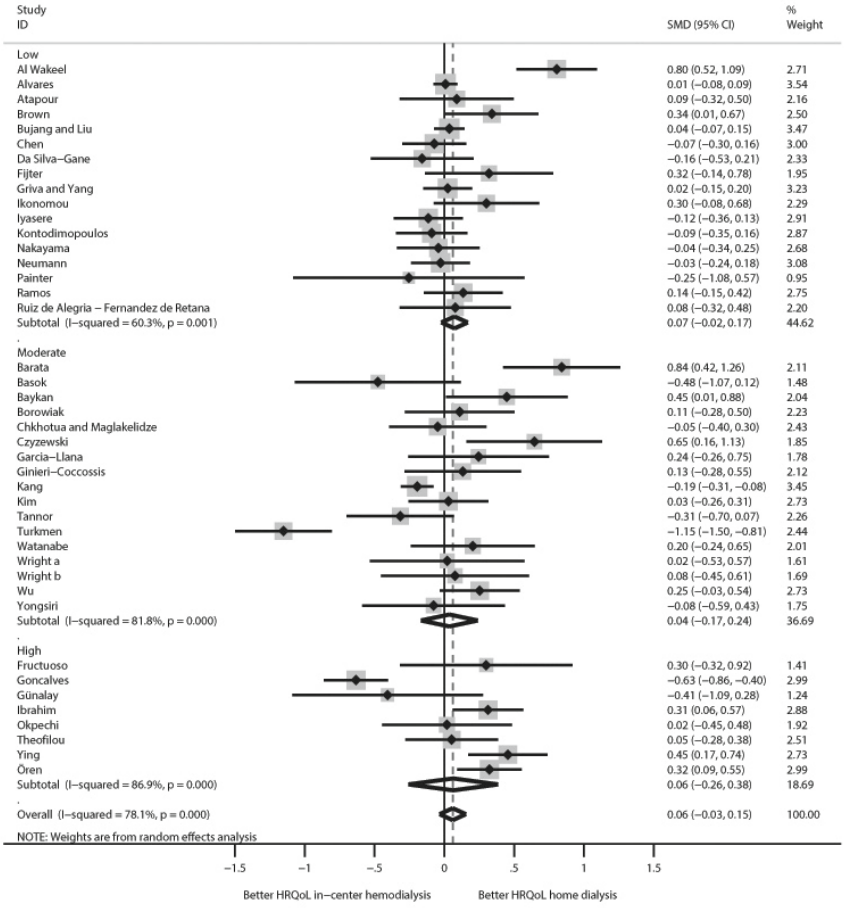
CI, confidence interval; SMD, standardized mean difference.
(A) Physical and (B) mental HRQoL among subcontinents.

Figure 3. Meta-analysis of Health-Related Quality of Life (HRQoL) among level of bias

A.



B.



CI, confidence interval; SMD, standardized mean difference.
(A) Physical and (B) mental HRQoL among level of bias.

Discussion

This meta-analysis shows better physical HRQoL for patients treated with home dialysis compared with patients receiving in-center HD, while mental HRQoL is comparable between these two patient groups. However, higher physical HRQoL scores in home dialysis patients were found only in Western Europe. Home dialysis patients from Latin America were found to have poorer physical HRQoL compared with in-center HD 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 with in-center HD patients lacks the necessary robustness.

The finding that home dialysis patients from Western Europe had better physical HRQoL compared with in-center HD patients could be explained because 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 poorer physical HRQoL. However, these results could also be subject to confounding by indication because in Brazil, the country in which these studies were conducted, it is common practice to perform PD only if patients are not eligible for in-center HD [84]. Brazilian in-center HD patients may be healthier and therefore physically in better condition than PD patients in general [84, 102]. This was emphasized by Ramos *et al.* because in this study, PD and in-center HD 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) [129]. In Latin America, up to 52% of patients with ESRD 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 the patients in need of 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 rarely 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 in-center HD 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, 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 with 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 Health Survey, it is stated that the questionnaire should be completed by the patient alone before any contact with the clinician to avoid influencing the patient and reduce the 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 randomized controlled trials with randomization between home and in-center dialysis were found in the literature search, presumably because previous experiences have shown that a patient's choice between home dialysis and in-center HD 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 in-center HD 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 in-center HD patients even in adjusted analysis [138], while Manns *et al.* reported that *choosing* home dialysis improved HRQoL even before 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 symptoms 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. However, 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 show 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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Supplemental material

Supplemental 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*

Supplemental table S2. HRQoL questionnaires

Questionnaire	Content
Short Form Health Survey (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].

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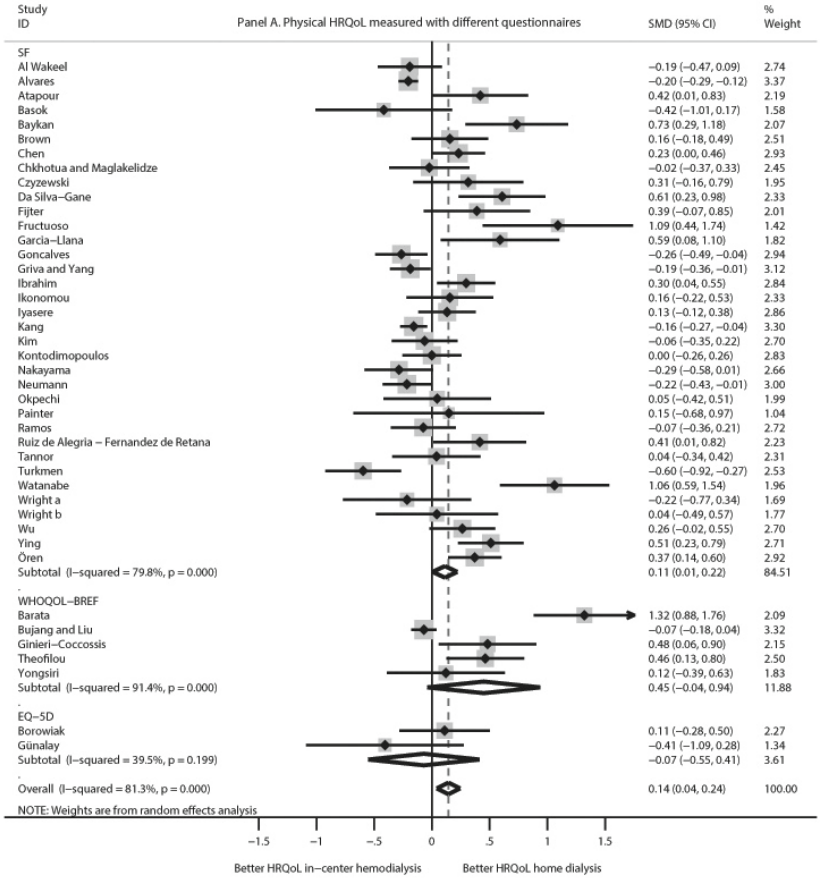
Supplemental table S3. Criteria used in Risk of Bias assessment

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	NA 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

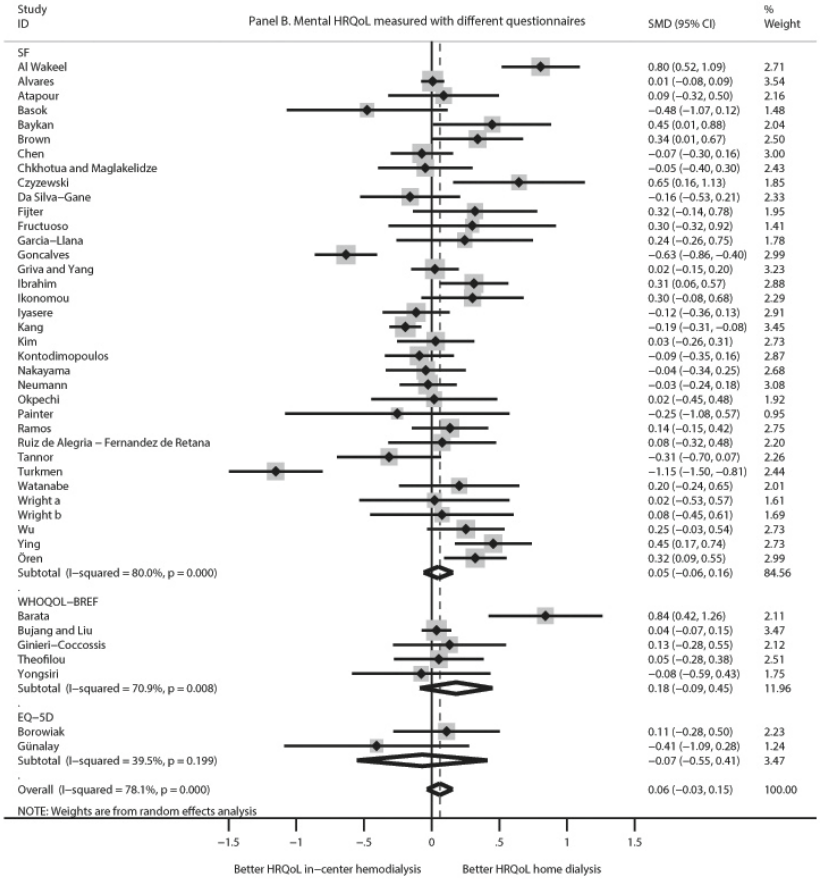
Supplemental table S4. Critical appraisal of 41 studies

Study	Design	Patient selection	Comparability	Outcome	Confounding	Follow-up	Selective reporting	Overall Risk of Bias	Conflict of interest
Al Wakeel, 2012	-	+	?	+	+	NA	+	Low	?
Alvares, 2012	-	+	-	+	+	NA	+	Low	+
Atapour, 2016	-	+	+	?	+	NA	+	Low	?
Barata, 2015	-	?	?	?	-	NA	?	Moderate	?
Basok, 2009	-	?	?	+	-	NA	+	Moderate	?
Baykan, 2012	-	?	?	?	-	NA	+	Moderate	+
Borowiak, 2009	-	?	?	-	?	NA	+	Moderate	?
Brown, 2010	-	+	+	+	+	NA	+	Low	-
Bujang, 2015 and **Liu**, 2014	-	+	+	+	-	NA	+	Low	+
Chen, 2017	-	+	?	+	+	NA	+	Low	+
Chkhotua, 2011 and **Maglakelidze**, 2011	-	?	?	+	-	NA	-	Moderate	?
Czyzewski, 2014	-	?	?	+	-	NA	-	Moderate	?
Da Silva-Gane, 2012	+	+	-	+	+	+	-	Low	+
De Fijter, 2018	-	+	-	+	+	NA	+	Low	+
Fructuoso, 2011	-	?	-	-	+	NA	+	High	?
Garcia-Llana, 2013	-	+	-	+	?	NA	+	Moderate	-
Ginieri-Coccossis, 2008	-	?	+	+	-	NA	+	Moderate	+
Goncalves, 2015	-	?	?	-	-	NA	-	High	?
Griva, 2014 and **Yang**, 2015	-	+	-	+	+	NA	+	Low	+
Günalay, 2018	-	?	-	?	-	NA	+	High	?
Ibrahim, 2011	-	+	?	-	-	NA	?	High	?
Ikonomou, 2015	-	+	?	+	+	NA	+	Low	+
Iyasere, 2016	-	+	+	+	+	NA	+	Low	-
Kang, 2017	-	?	+	?	+	NA	+	Moderate	+
Kim, 2013	-	+	?	+	?	NA	-	Moderate	?
Kontodimopoulos, 2008 and 2009	-	+	+	+	+	NA	+	Low	?
Nakayama, 2015	-	+	+	+	-	NA	+	Low	-
Neumann, 2018	+	?	+	+	+	+	+	Low	+
Okpechi, 2013	-	-	-	-	-	NA	+	High	?
Ören, 2013	-	+	-	-	+	NA	-	High	?
Painter, 2012	+	+	+	+	-	+	+	Low	+
Ramos, 2015	-	+	+	+	+	NA	+	Low	?
Ruiz de Alegria - Fernandez de Retana, 2013	+	+	+	+	+	+	-	Low	+
Tannor, 2017	-	+	-	+	-	NA	+	Moderate	+
Theofilou, 2011 and 2013	-	+	?	-	-	NA	?	High	?
Turkmen, 2012	-	+	+	?	-	NA	-	Moderate	+
Watanabe, 2014	-	?	+	+	-	NA	+	Moderate	+
Wright, 2015	-	+	?	+	-	NA	+	Moderate	+
Wu, 2013	-	?	+	+	-	NA	+	Moderate	+
Ying, 2014	-	+	?	-	-	NA	-	High	?
Yongsiri, 2014	-	?	+	?	-	NA	+	Moderate	+

Supplemental figure S1. Meta-analysis of Health-Related Quality of Life in different questionnaires

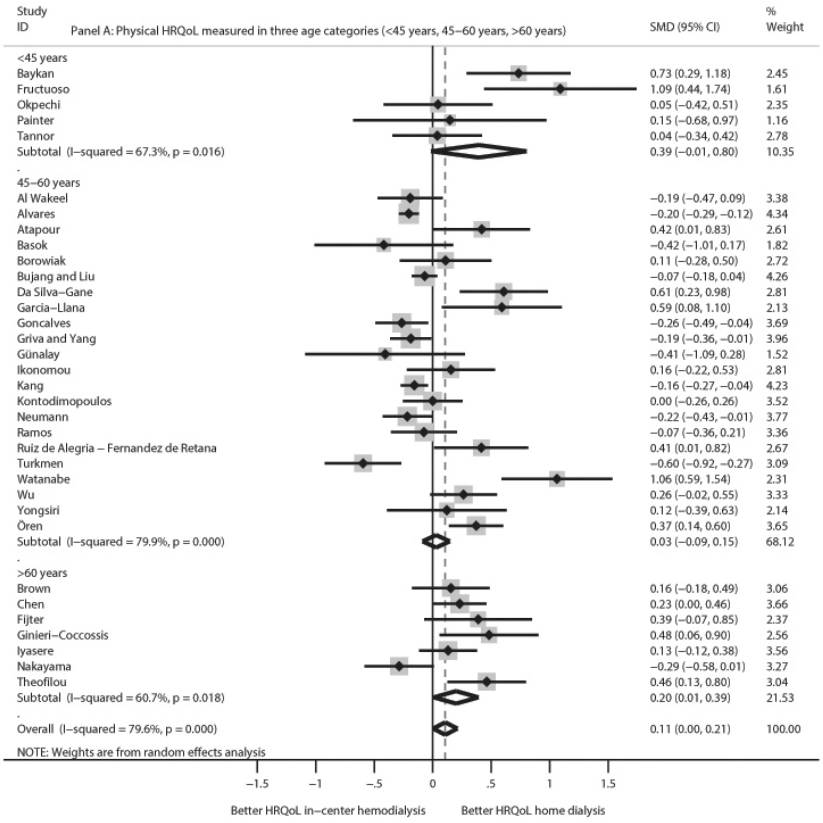


Legend: SMD, standardized mean difference; 95% CI, 95% confidence interval; SF, Short Form (including KDQOL); WHOQOL–BREF, World Health Organization Quality of Life–BREF; EQ–5D, EuroQol–5D; HRQoL, Health–Related Quality of Life.

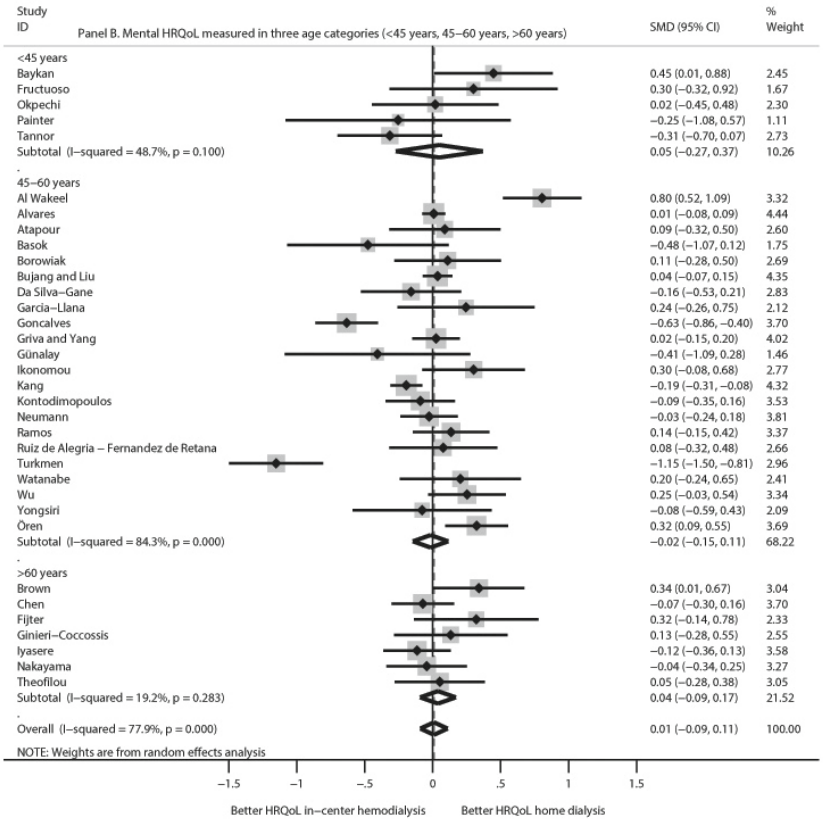


Legend: SMD, standardized mean difference; 95% CI, 95% confidence interval; SF, Short Form (including KDQOL); WHOQOL−BREF, World Health Organization Quality of Life−BREF; EQ−5D, EuroQol−5D; HRQoL, Health−Related Quality of Life.

Supplemental figure S2. 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.



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

Chapter 10

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

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* These authors contributed equally to this article

Abstract

Background More than 6200 End-Stage Renal Disease patients in the Netherlands are dependent on dialysis, either performed at home or in a dialysis center. Visiting a dialysis center 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-center hemodialysis 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-center hemodialysis patients. During a 3-year period 800 home dialysis patients (600 peritoneal dialysis and 200 home hemodialysis patients) and a comparison group of 800 in-center hemodialysis patients will be included from 53 Dutch dialysis centers (covering 96% of Dutch centers) and 1 Belgian dialysis center (covering 4% of Flemish centers).

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-center hemodialysis. 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).

Introduction

In the Netherlands, over 6200 patients with End-Stage Renal Disease (ESRD) 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%, optimizing 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-center hemodialysis (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 1519 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 hospitalization 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 centers (covering 96% of Dutch centers) and 1 Belgian dialysis center 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).

Figure 1. Participating centers

The red dots indicate the participating centers: 53 Dutch dialysis centers (covering 96% of Dutch centers) and 1 Belgian dialysis center.

Study population

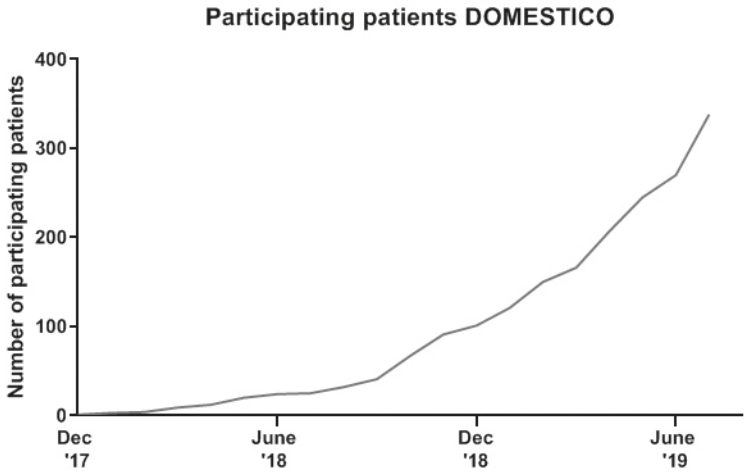
All patients, aged 18 years and older, with ESRD that start with a form of dialysis in the participating centers, between December 2017 and December 2020, are eligible for this study. These patients are allowed to have a history of renal replacement therapy (RRT), however they have to (re)start dialysis 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.

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 hemodialysis session performed in a center (excluding continuous RRT).

The first patient was included in December 2017 and the study has currently started in 45 centers 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 and the Dialysis Symptom Index (DSI) [39, 40]. These questionnaires were carefully selected as 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 ESRD 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 hospitalization, mortality, other clinical parameters, costs, and technique failure.

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

- Cardiac (including myocardial ischemia/infarction, cardiac arrest/arrhythmia, cardiac failure, fluid overload/pulmonary edema, hemorrhagic pericarditis);
- Vascular disease (including pulmonary embolus, stroke, cerebrovascular hemorrhage, ruptured vascular aneurysm, mesenteric infarction, peripheral arterial disease);
- Infection, non-dialysis related (including bacteremia/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 categorized into the following categories (using ERA-EDTA codes) [48]:

- Sudden death 'with unknown cause';
- Cardiac (including myocardial ischemia/infarction, cardiac arrest/arrhythmia, cardiac failure, fluid overload/pulmonary edema, hemorrhagic pericarditis);
- Vascular (including pulmonary embolus, stroke, cerebrovascular hemorrhage, ruptured vascular aneurysm, mesenteric infarction, peripheral arterial disease);
- Infectious, dialysis related (including dialysis access infection, peritonitis);
- Infectious, non-dialysis related (including bacteremia/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 hospitalization and mortality, several clinical parameters will be recorded including blood pressure and use of antihypertensive drugs, hemoglobin 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 healthcare 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.

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

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].

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 generalized 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 hospitalization, 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 analyze both outcomes. Since the ratio between PD patients and home hemodialysis (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 ESRD 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 randomized 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 ESRD 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.

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Additional file 1. Local ethics committees/IRBs DOMESTICO

Admiraal de Ruyter Hospital (ADRZ2018-016 DOMESTICOpro)
Alrijne Hospital (19.172yw.tk)
Amphia Hospital (1620)
Bernhoven (T2018-03-02)
Bravis Hospital (PAC-2018-25-DOMESTICO studie)
Canisius-Wilhelmina Hospital (113-2018)
Catharina Hospital (CZE-2018.25)
Clinical Trial Center Maastricht (Maastricht UMC+) (181041)
Deventer Hospital (ME 18-30)
Dianet (Amsterdam and Utrecht)
Diapriva Dialysis Center
Elisabeth-TweeSteden Hospital
Elyse Clinics
Erasmus Medical Center (MEC-2018-1419)
Flevohospital (F18/24)
Franciscus Gasthuis & Vlietland (2018-073/T110)
Gelre Hospitals (18.22)
Haaglanden Medical Center (2018-023)
HagaHospital (T18-114)
Hospital Gelderse Vallei (1901-002)
Isala (190101)
Jeroen Bosch Hospital (2018.17.01)
Laurentius Hospital (C09064-MW/LH)
Maasstad Academie (L2018072)
Martini Hospital (2018-020)
Máxima Medical Center (L18.140)
Meander Medical Center (Niercentrum Midden Nederland) (TWO 18-63)
Medical Center Leeuwarden (COV 305)
Northwest Clinics (L018-034)
OLVG Amsterdam (WO 18.041)
Radboudumc Technology Center Clinical studies
Reinier de Graaf Gasthuis (18-418)
Rode Kruis Hospital (Dialysiscenter Beverwijk) (18.006/dw)
Slingeland Hospital (OND.2018.019 DOMESTICO)
Spaarne Gasthuis (2018.97)
St. Antonius Hospital (L18.035)
Treant Zorggroep (19119)

University Medical Center Groningen (local approval for University Medical Center Groningen and Dialysis Center Groningen) (2018/693)
University Medical Center Utrecht (18-096/R)
Viecuri Medical Center (394)
VU University Medical Center (2017.491)
Zaans Medical Center
Zuyderland (Z2018097)

This list contains the 44 (out of 53) local ethics committees from which approval for DOMESTICO is obtained. For any future centers which will be included in our study, additional ethical approval will be sought.

Part IV

Summary and discussion

Chapter 11

Summary and General discussion

Globally, 1 in 10 people have chronic kidney disease (CKD), which is currently the 10th leading cause of death with 1.3 million deaths in 2019 [1, 2]. In the Netherlands, 2 million patients have CKD of which more than 18,000 are end-stage kidney disease (ESKD) patients treated with kidney replacement therapy [3, 4]. CKD patients face an intensive education process before choosing an ESKD treatment option (i.e. kidney transplantation, dialysis, conservative care), with the final choice ideally being a shared decision with their healthcare professional [5, 6]. When ESKD patients start with a form of dialysis (i.e. hemodialysis (HD) or peritoneal dialysis (PD)), their morbidity and mortality is high [7-14]. However, in both research and clinical practice, the focus is increasingly shifting from traditional clinical outcomes (e.g. mortality) to patient reported outcomes (PROs), such as health-related quality of life (HRQoL) [14-16]. These topics were addressed in this thesis.

In **part I** of this thesis, we focused on patient education and shared decision-making (SDM). **Part II** looked at traditional clinical outcomes of dialysis, namely bleeding, hospitalization, PD technique failure and peritonitis. Finally, in **part III**, we looked at an important PRO, namely HRQoL. The next chapter will place the results from the chapters in this thesis in a broader perspective and make recommendations for future research.

Part I: Patient education and shared decision-making

Ideally, SDM, which combines the medical knowledge of a healthcare professional with the values and preferences of an individual patient, forms the basis of the education process about ESKD treatment options [5, 17-19]. Although SDM is recommended in many nephrology guidelines, a large proportion of ESKD patients do not experience their decision as a shared one [20-23]. For example, the use of implicit persuasion, which according to a recent study was often used during the decision talk when the patient and healthcare professional choose the ESKD treatment option, may affect SDM [24].

Patient decision aids (PDAs) have been developed to support the SDM process during ESKD education. In the Netherlands, three PDAs are available, namely the 3 Good Questions, Option Grids, and Dutch Kidney Guide [25-28]. However, it is unknown whether the Dutch PDAs have been implemented to a sufficient extent in daily practice, since research on other PDAs has shown that there are barriers to the implementation in daily practice [29].

In **chapter 2**, we conducted a survey on the use of the Dutch PDAs among 117 healthcare professionals involved in ESKD education in 12 Dutch hospitals participating in the 'Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes' (DOMESTICO), a multi-center cohort study among incident dialysis patients in the Netherlands [30]. SDM was applied according to 56% of professionals, but only 28% reported using the 3 Good Questions, 32% the Option Grids, and 51% the Kidney Guide. In addition, 182 CKD patients with an eGFR < 30 ml/min/1.73m^2

completed an SDM-Q-9 and collaboRATE questionnaire to assess the perceived degree of SDM in their hospital [31-33]. On a scale of 0 – 100, the mean SDM-Q-9 score was 75±22 and the mean collaboRATE score 86±14. A workshop, held at participating hospitals to provide healthcare professionals with information regarding SDM and the 3 Dutch PDAs, did not change the SDM scores of CKD patients. Hospitals with a high SDM score used the Option Grids and Kidney Guide twice as often as hospitals with a low SDM score. In addition, hospitals with a high SDM score also required fewer conversations during ESKD education, while they focused on all treatment options and conducted home visits more often.

This survey showed that Dutch CKD patients and healthcare professionals are reasonably satisfied with the extent of SDM during the education process regarding ESKD treatment options. However, the use of specifically developed PDAs is limited. Future research should identify barriers to the use of the 3 Dutch PDAs in order to implement them in daily practice to achieve an optimal *shared decision*.

Stacey *et al.* argued that the implementation of PDAs depends on aspects such as the notion of healthcare professionals that PDAs can improve their SDM skills, the willingness to use the PDAs, and effective systems in which they are used [34]. Often, the implementation of a so-called 'good practice', '*…a practice that has been proven to work well and produce good results, and is therefore recommended as a model.',* poses no problem [35, 36]. Good practices have the advantage that healthcare professionals are often eager to use them because these good practices are already integrated in daily clinical care with positive experience. **Chapter 3** presented the results of a scoping review that identified and summarized 19 articles describing good practices for dialysis education, treatment, and electronic health (eHealth).

The 12 articles with good practices for education endorsed the importance of providing complete and objective predialysis education, assisting PD patients in adequately performing PD, educating HD patients on self-management, and talking with dialysis patients about their prognosis. The three articles with good practices for dialysis treatment focused mainly on dialysis access devices and general quality improvement of dialysis care. Finally, four articles described good practices regarding eHealth, which was useful for both HD and PD and affected quality of care and HRQoL.

As described in chapter 3, assisting patients with adequately performing PD is considered to be a good practice. As the number of, particularly elderly, end-stage kidney disease patients increases, this good practice appears to be becoming increasingly important since elderly often cannot perform PD autonomously [37-40]. Studies indicate that up to 80% of elderly patients need some degree of assistance while performing PD [41-44]. Assisted PD programs are available in many European countries, but the percentage of patients actually receiving assisted PD varies considerably [45-48]. Our survey among 288 healthcare professionals of European nephrology

units, presented in **chapter 4**, showed that Western European and Scandinavian countries (OR 5.73; 95% confidence interval (CI) 3.07 – 10.68), non-academic centers (OR 2.01; 95% CI 1.09 – 3.72) and centers with a dedicated team for education (OR 2.87; 95% CI 1.35 – 6.11) were associated with the availability of an assisted PD program at a center level. In addition, availability of an assisted PD program was associated with a higher incidence (cumulative OR 1.91; 95% CI 1.21 – 3.01) and prevalence (cumulative OR 2.81; 95% CI 1.76 – 4.47) of patients receiving dialysis at home (i.e. PD and home HD). Especially among Western European and Scandinavian countries a higher incidence and prevalence of home dialysis patients was reported.

Recently, a survey among nephrologists from 13 European countries also showed that education is the most important factor in improving the availability of assisted PD, not only patient education, but also education of healthcare professionals regarding the advantages of PD [49].

In conclusion, **part I** of this thesis has shown that the commitment of healthcare professionals and availability of effective systems that incorporate good practices, such as an assisted PD program, are vital for optimal patient education and shared decision-making.

Part II: Traditional clinical outcomes of dialysis

When patients start dialysis, they often face the 'traditional' clinical outcomes, such as bleeding and hospitalization, sometime during their treatment. Since HD and PD are completely different treatments (see **chapter 1** for an explanation of both treatments), it is important to investigate the differences in these traditional clinical outcomes between the two dialysis treatments.

Our prospective study in **chapter 5** showed that, in a group of 1,211 HD and 534 PD patients from the 'Netherlands Cooperative Study on the Adequacy of Dialysis' (NECOSAD), bleeding risk for HD patients compared with PD patients was 1.5-fold (95% CI 1.0 – 2.2) increased. In addition, a history of bleeding or the use of antiplatelet drugs or vitamin K antagonists led to highly increased bleeding risks for hemodialysis patients with hazard ratios (HR) ranging from 1.7 – 3.0. From a clinical perspective, these bleeding risks could be incorporated in the patient education and may influence the choice for a specific dialysis modality.

Another traditional clinical outcome that could be incorporated in patient education and play a role in choosing a particular dialysis modality is hospitalization. In addition to being an indirect measure of morbidity and a risk factor for mortality, hospitalization also negatively affects HRQoL [50-52]. Previous research on hospitalization of HD and PD patients was hampered by the fact that most studies only analyzed data from patients who remained on their initial dialysis modality or did not account for transitions between dialysis modalities [13, 53-58]. However, a transition from one dialysis modality to another, for example from PD to HD, occurs frequently in daily practice.

Our retrospective study in **chapter 6**, among 695 patients (252 PD, 443 HD) from the previously mentioned DOMESTICO, accounted for changes in dialysis modality by examining hospitalization rate with a multi-state model that attributed each hospitalization to the current dialysis modality. Out of a total of 1.480 hospitalizations, the adjusted HR for hospitalization rate was 1.1 (95% CI 1.02 – 1.3) for PD compared with HD. The risk for first hospitalization was 1.3 times (95% CI 1.1 – 1.6) higher for PD compared with HD during the first year after dialysis initiation, and 1.9 times (95% CI 1.4 – 2.5) higher for the period thereafter. The number of hospitalizations and number of hospital days per patient-year were significantly higher for PD. The most common cause of PD hospitalizations was peritonitis (23%). Beside the fact that, from a clinical perspective, the hospitalization risks could be included in patient education and influence the choice of a specific dialysis modality, this study underscores the importance of adequate infection prevention to reduce the number of hospitalizations for PD patients.

As shown by our study in **chapter 7**, infections are also an important cause of PD technique failure, which is defined as a transfer to HD for ≥ 30 days, death on PD or death within 30 days after transfer to HD [59]. In the retrospective DOMESTICO cohort, the 1- and 2-year technique failure rates among 695 PD patients were 29% and 52%, respectively. The median time to technique failure was 1.85 years. The 1- and 2-year death-censored technique failure rates were 23% and 35%, respectively. In addition to death, PD-related infections were the most common cause of technique failure (20%). Thus, infection prevention is of utmost importance to reduce the rate of technique failure.

Candida peritonitis is an example of a PD-related infection that results in a high technique failure rate, as the International Society for Peritoneal Dialysis recommends immediate removal of the PD catheter in case of *Candida* peritonitis and PD catheter replacement is often unsuccessful [60-64]. In **chapter 8**, we described the results of a retrospective, single-center study in which a treatment protocol consisting of an amphotericin B catheter lock combined with oral flucytosine and intraperitoneal fluconazole was used. With the lock-based protocol, 7 of 11 non-relapse *Candida* peritonitis episodes (64%) in 10 patients were cured without PD catheter removal, two episodes (18%) required catheter removal, and two patients died (18%). This study demonstrated that an amphotericin B lock-based protocol has the potential to cure *Candida* peritonitis without PD catheter removal and thus prevent technique failure. However, this needs to be confirmed by new studies with a control group, since previous studies have only investigated the use of amphotericin B as a lock therapy in central venous catheters rather than PD catheters, and our study has several limitations, such as being a retrospective study without control group in a single center [65]. Until then, the lock-based *Candida* protocol could be used in patients who are not severely ill and in whom removal of the PD catheter is not desirable.

In conclusion, **part II** of this thesis has shown that the occurrence of certain 'traditional' clinical outcomes differs between HD and PD, with a higher bleeding risk for HD patients but a higher

hospitalization risk for PD patients, mainly related to infections. Moreover, PD-related infections lead to a high PD technique failure rate, which calls for more attention to infection prevention or a different approach to the treatment of specific PD-related infections, such as for *Candida* peritonitis.

Part III: Focus on Health-Related Quality of Life

During the last decade, both research and clinical practice have increasingly focused on PROs, such as HRQoL [14-16, 66]. Since dialysis is a burdensome treatment, it seems highly relevant to include the impact of a specific dialysis modality on HRQoL when choosing a particular dialysis treatment. Many studies have examined the HRQoL of home dialysis (i.e. PD and home HD) patients compared to in-center HD patients [67-69]. However, it was suggested that differences in the countries where the studies were conducted and differences in practice patterns and local cultures would influence HRQoL [70]. In **chapter 9**, we conducted a systematic review and meta-analysis of the difference in HRQoL between home dialysis and in-center HD patients, with a special focus on differences across the world.

Our meta-analysis of 4,158 home dialysis patients and 7,854 in-center HD patients showed a marginally better physical HRQoL score in home dialysis patients compared to in-center HD patients (standardized mean difference (SMD) 0.14; 95% CI 0.04 – 0.24), although heterogeneity between studies was high (I^2>80%). The HRQoL on the mental domain was not significantly different between the two groups (SMD 0.06; 95% CI -0.03 – 0.15). A comparison among subcontinents showed that patients on home dialysis in Western Europe had higher physical HRQoL scores compared to in-center HD patients (SMD 0.39; 95% CI 0.17 – 0.61), whereas patients on home dialysis from Latin America had lower physical HRQoL scores (SMD -0.20; 95% CI -0.28 – -0.12). This could be explained by differences in patient populations, as home dialysis patients from Western Europe were younger [71-73], while home dialysis patients from Latin America were unhealthier and in poorer condition than in-center HD patients [74, 75]. The HRQoL on the mental domain showed no difference between subcontinents.

The high heterogeneity among studies was the most important limitation of our meta-analysis, despite several subgroup analyzes. Therefore, large prospective studies with adequate adjustments for confounders are necessary to establish whether home dialysis results in better HRQoL. Such a study is the prospective part of DOMESTICO.

Chapter 10 described the rationale and design of this nationwide, prospective, observational cohort study that will compare the HRQoL of adult patients on home dialysis with a control group consisting of in-center HD patients. Secondary outcomes are clinical outcomes and costs. During a 3-year period 800 home dialysis patients (600 PD and 200 home HD patients) and a comparison

group of 800 in-center HD patients will be included from 56 Dutch dialysis centers (covering 96% of Dutch centers) and 3 Belgian dialysis center (covering 4% of Flemish centers). The findings of this study are expected to give more guidance to healthcare professionals, in particular to assess which type of patients may benefit most from home dialysis. This will ameliorate the shared decision-making process.

In conclusion, **part III** of this thesis has shown that HRQoL is a relevant PRO. However, the effect of different dialysis modalities on HRQoL is not yet clear, despite previous studies. The ongoing DOMESTICO study will provide information on the effect of home dialysis therapies on HRQoL, clinical outcomes and costs, compared to in-center HD.

Future research

Recently, results on HRQoL from the 'Dialysis Outcomes and Practice Patterns Study' (DOPPS) and the 'Peritoneal Dialysis Outcomes and Practice Patterns Study' (PDOPPS) were published [76]. The HRQoL scores of 1,626 HD patients and 909 PD patients from 6 countries, namely Australia, New Zealand, Canada, Japan, the United Kingdom, and the United States of America, were compared. What was remarkable was that significant intercountry differences were observed in the HRQoL scores, making generalizability of the results beyond the studied countries impossible. Therefore, the expected results of the prospective part of the DOMESTICO study will certainly be of interest to the Dutch CKD population [30].

Since the initiation of DOMESTICO, two articles have already been published with some of the results of the prospective study. Colombijn *et al.* showed in a cross-sectional analysis among a subset of 162 patients participating in DOMESTICO that, three months after dialysis initiation, the mean number of simultaneously prescribed types of medication was 12 [77]. After adjusting for possible confounders, both physical and mental HRQoL scores were lower when patients had a higher number of medications. Upon completion, DOMESTICO will provide longitudinal data to assess whether these results can be confirmed, so that potential interventions aimed at reducing the medication burden can be developed, taking into account the long-term outcomes of dialysis patients.

The DOMESTICO study started in 2017 and is currently ongoing, so part of it ran during the peak of the coronavirus disease 2019 (COVID-19) pandemic. To investigate what the impact of the COVID-19 pandemic was on the mental HRQoL of dialysis patients Bonenkamp *et al.* analyzed it among 177 patients [78]. Compared to 3-6 months before the start of the COVID-19 pandemic, mental HRQoL scores remained the same during the first wave of the pandemic (February – July 2020). This could indicate better coping of dialysis patients with the COVID-19 pandemic due to things like higher resilience or the fact that the majority of the patients performed in-center HD (75%) so they were

less socially isolated and could get more support from healthcare professionals. However, since the first wave, the COVID-19 pandemic is still present. The prospective DOMESTICO study will provide further insight into the long term impact of the COVID-19 pandemic on mental HRQoL.

The results of the prospective part of the DOMESTICO study are expected to affect the Dutch CKD population, but attention should also be paid to informal caregivers of these patients. Dialysis initiation more often leads to the occurrence of informal caregiver burden and informal caregivers of dialysis patients experience a poorer quality of life than the general population [79, 80]. However, in the effort to provide patients with a form of home dialysis, informal caregivers are very important in this regard [81, 82]. The DOMESTICO 'Informal caregivers' project will investigate the effect of starting (home) dialysis on informal caregivers of dialysis patients [83]. The project will look at both positive and negative experiences and quality of life, in particular focusing on possible differences between informal caregivers of home dialysis patients and those of in-center HD patients. With this information, informal caregivers of dialysis patients can be better supported.

As the age of dialysis patients in the Netherlands increases, it becomes more relevant to pay attention to the special needs of elderly CKD and dialysis patients [84]. In recent years, the 'Geriatric assessment in OLder patients starting Dialysis' (GOLD) study showed that geriatric impairments, such as impaired functional performance, immobility and frailty, were common in a Dutch group of 196 dialysis and 89 conservative care patients aged 65 years and older [85]. Moreover, dialysis patients were hospitalized more frequently, while survival in dialysis patients above 80 years was similar compared to conservative care patients [86]. For dialysis patients, HRQoL did not seem to change during the first 6 months after dialysis initiation. De Rooij *et al.* confirmed this result with data from the 'European Quality' (EQUAL) study [87]. These results could play a role in the education process regarding ESKD treatment options for elderly, however current evidence is limited.

Therefore, the 'DIALysis or not: Outcomes in older kidney patients with GerIatriC Assessment' (DIALOGICA) study was initiated in February 2020 [88]. This prospective, observational cohort started will include patients aged ≥ 65 years with an estimated glomerular filtration rate (eGFR) of 15–20 mL/min/1.73m^2 in the first stage of the study. Patients enter the second stage of the study when dialysis is initiated or eGFR declines ≤ 10 mL/min/1.73m^2. In both stages nephrogeriatric assessments will be performed annually. The study aims to compare HRQoL, clinical outcomes, and costs between dialysis and conservative care patients.

Another study that will provide relevant information for the elderly patient is the 'Optimising Access Surgery in Senior Haemodialysis Patients' (OASIS) study [89]. This multicenter randomized controlled trial aims to determine the best vascular access for HD patients aged ≥ 70 years, as current data on vascular access is based only on observational studies. Patients will be

randomized between receiving an autologous arteriovenous fistula, an arteriovenous graft, or a central venous catheter. The number of access-related interventions per patient year between the three treatment arms will be compared.

When ESKD patients in the Netherlands start dialysis, they are asked for permission to participate in RENINE, a nationwide registry of patients receiving kidney replacement therapy [90]. In 2016, RENINE incorporated a registry of patient reported outcome measures (PROMs), which are questionnaires that investigate patients' symptoms, functional status, and HRQoL [91]. Recently, van der Willik *et al.* published an article containing data of 2978 dialysis patients from the RENINE/PROMs registry. They showed that 50% of the patients suffer from pruritus and pruritus was associated with worse HRQoL [92].

This thesis and all the ongoing studies show a shift towards PROs, which are incredibly important outcomes. Therefore, more research with PROMs is needed in the future.

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Appendices

Summary in Dutch (Nederlandse samenvatting)

Questionnaires

DOMESTICO Study Group members

Acknowledgements (Dankwoord)

List of publications

Curriculum Vitae

Nederlandse samenvatting

De nieren, twee boonvormige organen die zich achter de onderste ribben aan de rugzijde bevinden, spelen een cruciale rol bij de regulatie van de hoeveelheid lichaamswater en de afvoer van afvalstoffen uit het lichaam. Wanneer de nierfunctie gedurende meer dan drie maanden verstoord is én dit gevolgen heeft voor de gezondheid, spreekt men van chronische nierschade (CNS) [1, 2]. In Nederland heeft meer dan 12% van de bevolking CNS (2 miljoen mensen) [3].

Als CNS verergert richting eindstadium nierfalen, krijgen patiënten voorlichting over de verschillende behandelopties, namelijk niertransplantatie, dialyse en conservatieve behandeling [1, 4]. De laatste jaren is er tijdens de voorlichting meer aandacht voor gedeelde besluitvorming, oftewel Samen beslissen, zodat patiënten alle voor- en nadelen van de behandelingen kunnen afwegen, maar dat ook hun voorkeur en waarden en normen worden meegenomen in de uiteindelijke beslissing. Het model voor Samen beslissen is in 1972 voor het eerst beschreven en sindsdien verder ontwikkeld waarbij het de volgende gesprekken omvat: keuzegesprek, optiegesprek en besluitvormingsgesprek (**Figuur 1**) [5].

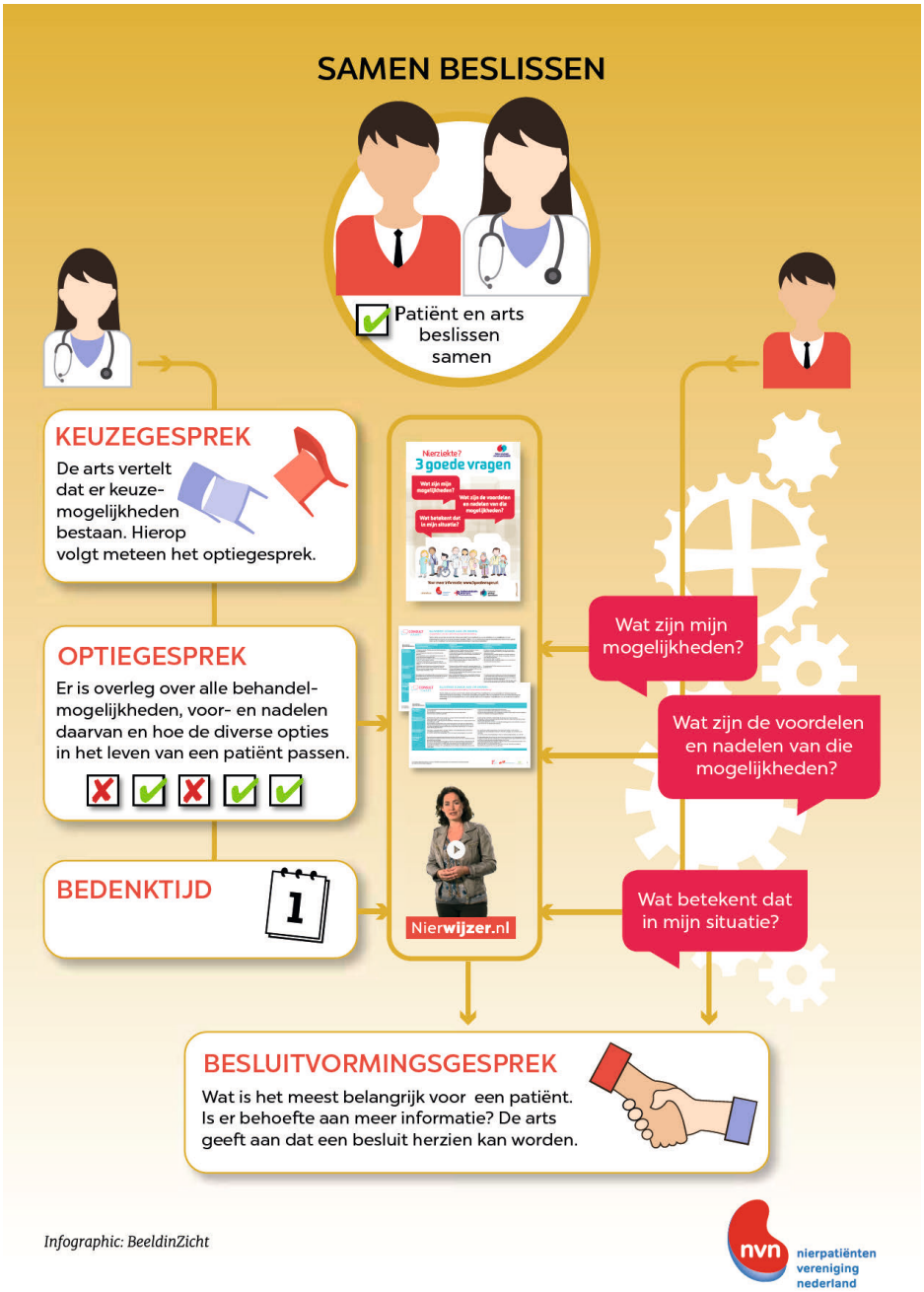
Zoals weergegeven in **figuur 1** zijn er ook 3 keuzehulpen om het Samen beslissen-proces te ondersteunen: de 3 Goede Vragen, de consultkaarten en de Nierwijzer.

De 3 Goede Vragen zijn: (1) ‘Wat zijn mijn mogelijkheden?’, (2) ‘Wat zijn de voordelen en nadelen van die mogelijkheden?’ en (3) ‘Wat betekent dat in mijn situatie?’ [6].

De consultkaarten bevatten antwoorden op veel gestelde vragen van patiënten over bepaalde behandelopties. Er zijn twee consultkaarten beschikbaar: (1) ‘Blijvende schade aan uw nieren: nierfunctievervangende behandeling of conservatieve behandeling’ en (2) ‘Blijvende schade aan uw nieren: mogelijkheden voor een nierfunctievervangende behandeling’ [7].

De Nierwijzer is een website met filmpjes van ruim 40 patiënten die behandeld worden met niertransplantatie, dialyse of conservatieve behandeling. In deze filmpjes vertellen patiënten over de impact van de behandelingen op hun dagelijks leven (bijv. werk, vakantie) [8].

Figuur 1. Gesprekken tijdens proces van Samen beslissen (bron: Nierpatiënten Vereniging Nederland).



Sinds september 2021 is er een Nederlandse campagne over Samen beslissen, waarbij het doel is om Samen beslissen te stimuleren door patiënten en verzorgers gesprekken te laten voorbereiden, vragen te laten stellen en beter te laten luisteren.

Elk jaar ontwikkelen in Nederland ongeveer 2.000 patiënten eindstadium nierfalen [9]. In 2021 werden 6.248 Nederlanders behandeld met een vorm van dialyse, namelijk hemodialyse (dialyse via de bloedbaan) of peritoneale dialyse (buikdialyse) [10].

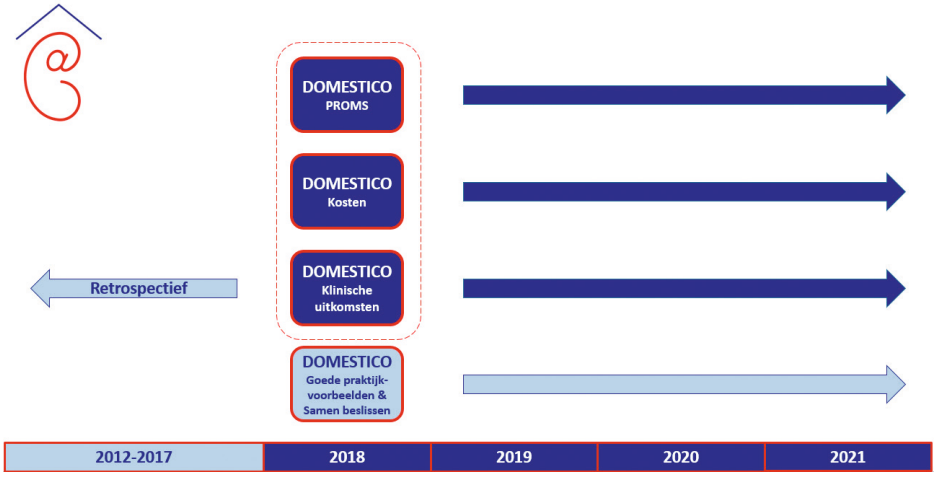
Bij hemodialyse (afgekort tot HD) wordt een verbinding gemaakt tussen de bloedvaten van de patiënt en een dialysemachine. Het bloed van de patiënt stroomt door de kunstnier en daar worden de afvalstoffen en overtollig lichaamswater uit het bloed verwijderd. HD kan worden uitgevoerd in een ziekenhuis of dialysecentrum (centrumdialyse), maar kan ook thuis worden gedaan. Centrumdialyse wordt door een verpleegkundige gedaan, terwijl thuisHD wordt gedaan door de patiënt zelf, een mantelzorger of een verpleegkundige. HD vindt meestal 3x per week gedurende 4 uur plaats, maar kan ook 's nachts worden uitgevoerd (nachtdialyse). CentrumHD heeft voordelen, zoals professionele zorg en sociaal contact met andere patiënten tijdens de dialyse. CentrumHD heeft echter ook nadelen, omdat patiënten hun vochtinname moeten beperken, ze een 'dialyse kater' kunnen krijgen en ze reistijd hebben van én naar het ziekenhuis.

Bij peritoneale dialyse (afgekort tot PD) worden afvalstoffen en overtollig lichaamswater uit het bloed verwijderd via het buikvlies van de patiënt. Hiervoor laat men dialysevloeistof in de buikholte lopen via een buikkatheter, de PD-katheter. PD wordt meestal thuis uitgevoerd door de patiënt zelf, en soms door een partner, mantelzorger of verpleegkundige van de thuiszorg. Wanneer een patiënt hulp krijgt bij het uitvoeren van PD, wordt dit 'geassisteerde PD' genoemd. PD heeft voordelen, zoals zelfstandigheid van de patiënt en minder ziekenhuisbezoeken. PD kent echter ook complicaties, zoals kans op een buikvliesontsteking (PD peritonitis) of de mogelijkheid dat het buikvlies niet goed meer werkt waardoor PD gestaakt moet worden (PD membraanfalen).

Tijdens de laatste decennia zijn er veel studies gedaan naar het risico op ziekte of overlijden van dialysepatiënten. Dialysepatiënten hebben een hoog risico op ziekte zoals hart- en vaatziekten, tevens overlijdt meer dan 50% van de patiënten binnen 5 jaar na start van dialyse [11-14]. De laatste jaren is er echter een toenemende vraag naar studies die patiëntgerapporteerde uitkomsten onderzoeken, zoals gezondheidsgerelateerde kwaliteit van leven [15, 16]. Dialysepatiënten hebben namelijk een slechte kwaliteit van leven. Het uitvoeren van thuisdialyse, d.w.z. PD of thuis HD, heeft potentiële voordelen zoals behoud van autonomie en flexibiliteit, minder ziekenhuisbezoeken en de mogelijkheid om professionele of sociale activiteiten uit te voeren, wat zou kunnen bijdragen aan een betere kwaliteit van leven. Recente gegevens over de effecten van thuisdialyse op gezondheidsgerelateerde kwaliteit van leven, klinische uitkomsten en kosten in vergelijking met

centrumdialyse ontbreken echter. Daarom startten wij in 2017 met de 'Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO)' (**Figuur 2**).

Figuur 2. Overzicht van de 'Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes (DOMESTICO)'.



PROMs: patient reported outcome measures; vragenlijsten betreffende kwaliteit van leven.

DOMESTICO bestaat uit 3 deelprojecten. Ten eerste, DOMESTICO retrospectief waarbij gegevens worden verzameld van volwassen patiënten (≥ 18 jaar) die tussen 1 januari 2012 en 1 januari 2017 zijn gestart met een dialysebehandeling (d.w.z. PD of HD) in 41 Nederlandse ziekenhuizen. In deze deelstudie worden de oorzaken en beïnvloedbare factoren van techniek falen van thuis- en nachtdialyse onderzocht. Daarnaast worden de klinische uitkomsten (waaronder ziekenhuisopname en overlijden) van thuis- en nacht-dialysepatiënten vergeleken met die van centrumdialyse-patiënten.

Ten tweede, DOMESTICO prospectief, dat op 22 december 2017 van start is gegaan, waarbij patiënten worden geïncludeerd die starten met dialyse in 59 centra verspreid over Nederland en België. Het belangrijkste doel is om het effect van thuisdialyse op de gezondheidsgerelateerde kwaliteit van leven te bepalen in vergelijking met centrumdialyse. Andere doelen zijn; 1) het uitvoeren van een kosten-effectiviteitsanalyse van thuisdialyse in vergelijking met centrumdialyse; 2) het bepalen van de klinische uitkomsten van thuisdialyse, met name ziekenhuisopname en overlijden, in vergelijking met centrumdialyse en het identificeren van beïnvloedbare factoren.

Ten derde, het implementatieproject 'Goede praktijkvoorbeelden en Samen beslissen' dat heeft plaatsgevonden tussen januari 2018 en mei 2019. Dit project had als doel om het

voorlichtingstraject over de behandelopties bij eindstadium nierfalen te verbeteren door het toepassen van goede praktijkvoorbeelden en Samen beslissen. Het project werd uitgevoerd in 12 Nederlandse ziekenhuizen. Er werden verschillende producten ontwikkeld, zoals een workshop “Samen beslissen: van voorlichting naar dialoog” waarin Samen beslissen en de 3 eerder beschreven keuzehulpen werden besproken, een nierfalen-zorgpad en verschillende protocollen met goede praktijkvoorbeelden.

Het doel van dit proefschrift is om verder inzicht te verschaffen in **(1)** patiëntenvoorlichting en Samen beslissen, **(2)** traditionele klinische uitkomsten van dialyse zoals bloedingen, ziekenhuisopnames, techniek falen en PD peritonitis, en **(3)** een belangrijke patiëntgerelateerde uitkomst; gezondheidsgerelateerde kwaliteit van leven. Dit proefschrift bevat artikelen met de eerste resultaten van DOMESTICO retrospectief en het implementatieproject.

Deel I: Patiëntenvoorlichting en Samen beslissen

Idealiter vormt Samen beslissen, waarbij de medische kennis van de zorgverlener wordt gecombineerd met de waarden en voorkeuren van de individuele patiënt, de basis van het voorlichtingsproces over de behandelopties bij eindstadium nierfalen [4, 17, 18]. Hoewel Samen beslissen in veel Nefrologische richtlijnen wordt aanbevolen, heeft een groot deel van de patiënten niet het idee dat dit daadwerkelijk wordt toegepast [19, 20]. Zoals reeds eerder beschreven, zijn er in Nederland 3 keuzehulpen om het Samen beslissen-proces te ondersteunen: de 3 Goede Vragen, de consultkaarten en de Nierwijzer [6-8]. Het is echter onbekend of deze keuzehulpen daadwerkelijk worden gebruikt, aangezien uit onderzoek naar andere keuzehulpen is gebleken dat er barrières zijn voor toepassing van keuzehulpen in de dagelijkse praktijk [21].

In **hoofdstuk 2** beschreven we een enquête over het gebruik van de Nederlandse keuzehulpen onder 117 zorgverleners uit 12 Nederlandse ziekenhuizen. Samen beslissen werd volgens 56% van de zorgverleners toegepast, maar slechts 28% gaf aan de 3 Goede Vragen te gebruiken, 32% de consultkaarten en 51% de Nierwijzer. Daarnaast vulden 182 CNS-patiënten vragenlijsten in over de mate waarin zij Samen beslissen hadden ervaren. Op een schaal van 0 – 100 (hoe hoger de score hoe beter het Samen beslissen wordt ervaren) was de ene gemiddelde Samen beslissen-score 75 en de andere score 86. Een workshop over Samen beslissen en de 3 Nederlandse keuzehulpen, gegeven aan zorgverleners in de deelnemende ziekenhuizen, gaf geen verandering van de Samen beslissen-scores van de CNS-patiënten. Ziekenhuizen met een hoge Samen beslissen-score gebruikten de consultkaarten en de Nierwijzer twee keer zo vaak als ziekenhuizen met een lage Samen beslissen-score. Daarnaast hadden ziekenhuizen met een hoge Samen beslissen-score ook minder gesprekken tijdens de nierfalen voorlichting, terwijl zij zich wel richtten op alle behandelopties en er vaker een huisbezoek werd gedaan.

Deze enquête toonde dat Nederlandse CNS-patiënten en zorgverleners redelijk tevreden zijn over de mate van Samen beslissen tijdens de nierfalen voorlichting, maar dat het gebruik van speciaal ontwikkelde keuzehulpen beperkt is. Toekomstig onderzoek moet zich richten op de barrières voor het gebruik van de Nederlandse keuzehulpen.

Eerder onderzoek naar andere keuzehulpen toonde dat het belangrijk is dat zorgverleners bereid zijn óm ze te gebruiken én dat er effectieve zorgsystemen zijn waarin ze worden gebruikt [22]. In tegenstelling tot keuzehulpen, hebben 'goede praktijkvoorbeelden' ('…*a practice that has been proven to work well and produce good results, and is therefore recommended as a model.*') het voordeel dat zorgverleners ze graag gebruiken omdat ze al met positieve ervaringen in de dagelijkse praktijk zijn ingevoerd [23, 24]. **Hoofdstuk 3** presenteerde de resultaten van een literatuuronderzoek waarin 19 artikelen werden gevonden die goede praktijkvoorbeelden beschrijven voor dialyse voorlichting (b.v. PD-patiënten helpen bij het adequaat uitvoeren van PD, HD-patiënten informeren over zelfmanagement), dialyse behandeling (artikelen over algemene kwaliteitsverbetering van de dialysezorg) en eHealth (artikelen over nut van eHealth en invloed op gezondheidsgerelateerde kwaliteit van leven/zorg).

In hoofdstuk 3 werd 'het assisteren van patiënten bij het adequaat uitvoeren van PD' beschreven als een goed praktijkvoorbeeld. Naarmate het aantal, vooral oudere patiënten met eindstadium nierfalen toeneemt, lijkt dit goede praktijkvoorbeeld steeds belangrijker te worden, aangezien tot 80% van de oudere patiënten hulp nodig heeft bij het uitvoeren van PD [25]. In veel Europese landen zijn programma's voor geassisteerde PD beschikbaar, maar het percentage patiënten dat dit daadwerkelijk krijgt varieert behoorlijk. In **hoofdstuk 4** werden de resultaten gepresenteerd van een enquête onder 288 nefrologische zorgverleners in Europa. Uit de enquête bleek dat een programma voor geassisteerde PD bijna 6 keer vaker aanwezig was in West-Europese en Scandinavische landen ten opzichte van andere Europese landen, ruim 2 keer vaker aanwezig was in niet-academische ziekenhuizen en bijna 3 keer vaker aanwezig was in ziekenhuizen met een speciaal team voor de nierfalen voorlichting. Ook was de aanwezigheid van een programma voor geassisteerde PD geassocieerd met meer thuisdialyse.

Concluderend laat **deel I** van dit proefschrift zien dat betrokkenheid van zorgverleners en beschikbaarheid van effectieve zorgsystemen waarin goede praktijkvoorbeelden zijn opgenomen, zoals een geassisteerd PD-programma, van groot belang zijn voor optimale patiëntenvoorlichting en Samen beslissen.

Deel II: Traditionele klinische uitkomsten van dialyse

Wanneer patiënten met dialyse starten, kunnen zij geconfronteerd worden met complicaties. Dit worden ook wel 'traditionele' klinische uitkomsten genoemd en deze kunnen verschillend zijn voor HD en PD patiënten. In dit proefschrift hebben we 2 traditionele klinische uitkomsten onderzocht, namelijk bloedingen en ziekenhuisopnames.

Hoofdstuk 5 toonde dat het bloedingsrisico voor HD patiënten 1.5 keer hoger is dan voor PD patiënten. Bovendien zorgde een voorgeschiedenis van bloedingen of het gebruik van bloedverdunnende medicatie voor een sterk verhoogd bloedingsrisico bij HD patiënten. Dit bloedingsrisico zou meegenomen moeten worden in de patiëntenvoorlichting en de keuze voor een specifieke dialysemodaliteit kunnen beïnvloeden.

Een andere 'traditionele' klinische uitkomst is ziekenhuisopname. Een ziekenhuisopname is niet alleen een risicofactor voor overlijden, maar het heeft ook een negatieve invloed op gezondheidsgerelateerde kwaliteit van leven. In **hoofdstuk 6** beschreven we de ziekenhuisopnames bij 252 PD patiënten en 443 HD patiënten die behandeld werden in 31 Nederlandse ziekenhuizen uit DOMESTICO retrospectief. Na correctie voor beïnvloedende factoren, bleek het aantal ziekenhuisopnames van PD patiënten 1,1 keer hoger dan voor HD patiënten. Gedurende het eerste jaar na start van dialyse, was het risico op een eerste ziekenhuisopname 1,3 keer hoger voor PD patiënten in vergelijking met HD patiënten, en in de jaren daarna 1,9 keer hoger. De belangrijkste oorzaak van ziekenhuisopname bij PD patiënten was een PD peritonitis. Deze studie geeft het belang weer van preventie van infecties om het aantal ziekenhuisopnames voor PD patiënten te verminderen.

Uit onze studie in **hoofdstuk 7** bleek ook dat infecties een belangrijke oorzaak zijn van PD techniek falen, waarbij een PD patiënt noodgedwongen over moet naar HD óf overlijdt. In DOMESTICO retrospectief, was de kans op PD techniek falen het eerste jaar 29% en het tweede jaar 52%. PD gerelateerde infecties en overlijden waren de belangrijkste oorzaken voor techniek falen. Een PD gerelateerde infectie met *Candida,* een schimmel, is ook geassocieerd met een grote kans op techniek falen, omdat de richtlijn aangeeft dat in zo'n geval de PD-katheter direct verwijderd moet worden [26]. In **hoofdstuk 8** werd een behandelprotocol beschreven waarmee een *Candida* peritonitis potentieel kan worden genezen zonder dat de PD-katheter verwijderd hoeft te worden. Het is echter een kleine studie bij 10 patiënten, dus het behandelprotocol moet worden onderzocht in nieuwe studies en tot die tijd is het toepassen van het behandelprotocol alleen geadviseerd voor patiënten met een *Candida* peritonitis die niet erg ziek zijn en waarbij verwijderen van de PD-katheter niet wenselijk is.

Concluderend laat **deel II** van dit proefschrift zien dat 'traditionele' klinische uitkomsten verschillen tussen HD en PD patiënten, met een hoger risico op bloedingen bij HD patiënten, maar een hoger risico op ziekenhuisopname voor PD patiënten, vooral door infecties. Bovendien leiden infecties tot een hoger risico op PD techniek falen. Dus meer aandacht voor het voorkomen van infecties of een andere aanpak van specifieke PD-gerelateerde infecties, zoals *Candida* peritonitis, is belangrijk.

Deel III: Gezondheidsgerelateerde kwaliteit van leven

De afgelopen 10 jaar is er zowel in de wetenschap als de dagelijkse klinische praktijk steeds meer aandacht gekomen voor gezondheidsgerelateerde kwaliteit van leven. Aangezien dialyse een belastende behandeling is, is het belangrijk om de invloed van een specifieke dialysevorm op de gezondheidsgerelateerde kwaliteit van leven mee te nemen in de behandelkeuze. Veel studies hebben gekeken naar het verschil in gezondheidsgerelateerde kwaliteit van leven tussen thuisdialyse en centrumdialyse patiënten en mogelijke verschillen tussen landen. Daarom voerden wij een literatuuronderzoek uit dat beschreven staat in **hoofdstuk 9**. Onze analyse van 4158 thuisdialyse patiënten en 7854 centrumdialyse patiënten toonde een betere fysieke gezondheidsgerelateerde kwaliteit van leven, maar een gelijke mentale gezondheidsgerelateerde kwaliteit van leven bij thuisdialyse patiënten in vergelijking met centrumdialyse patiënten. Dit was vooral het geval bij patiënten uit West-Europa, terwijl thuisdialyse patiënten uit Latijns-Amerika juist een lagere fysieke gezondheidsgerelateerde kwaliteit van leven hadden. Dit kon verklaard worden door het feit dat thuisdialyse patiënten in Latijns-Amerika ongezonder waren en een slechtere conditie hadden dan centrumdialyse patiënten. Een beperking van ons literatuuronderzoek was echter dat de studies onderling zeer verschillend waren. Daarom zijn grote studies met aandacht voor beïnvloedbare factoren belangrijk om vast te stellen of thuisdialyse leidt tot betere gezondheidsgerelateerde kwaliteit van leven. Zo'n studie is DOMESTICO-prospectief. In **hoofdstuk 10** beschreven we de achtergrond en opzet van deze studie waarin de gezondheidsgerelateerde kwaliteit van leven van thuisdialyse patiënten vergeleken zal worden met die van centrumdialyse patiënten. Daarnaast zal ook gekeken worden naar 'traditionele' klinische uitkomsten en kosten.

Concluderend laat **deel III** van dit proefschrift zien dat gezondheidsgerelateerde kwaliteit van leven een belangrijke patiëntgerapporteerde uitkomst is, maar dat het effect van de verschillende dialysevormen op gezondheidsgerelateerde kwaliteit van leven nog onbekend is. Hier zal DOMESTICO-prospectief hopelijk verandering in brengen.

Samenvattend, laat dit proefschrift, samen met andere in Nederland lopende studies, een duidelijke verschuiving zien richting Samen beslissen en het belang van patiëntgerapporteerde uitkomsten voor patiënten met eindstadium nierfalen.

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Questionnaires

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

	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 <u>past 4 weeks</u>, how much <u>did pain interfere</u> 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 <u>past 4 weeks</u>. 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 <u>past 4 weeks</u>…

	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 <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> 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)

Below 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 circling '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	◻	◻	◻	◻	◻
Shortness of breath	No/Yes	◻	◻	◻	◻	◻
Lightheadedness or dizziness	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	◻	◻	◻	◻	◻
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	◻	◻	◻	◻	◻
Decreased 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.

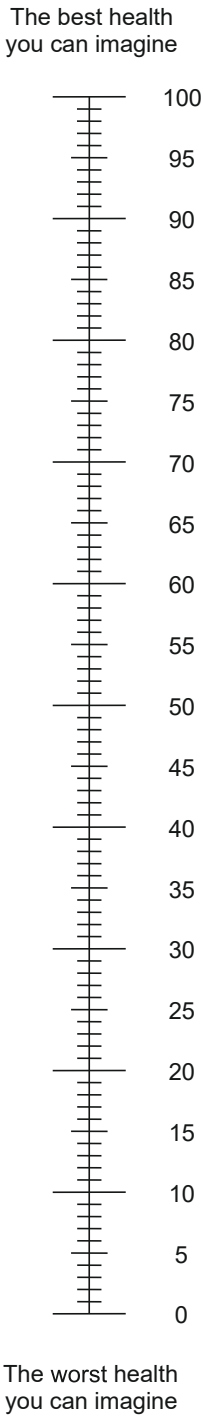
This scale is numbered from 0 to 100.

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

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

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

YOUR HEALTH TODAY = ☐



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Curriculum vitae

Anita van Eck van der Sluijs was born on September 18, 1985 in Utrecht and raised in Ede. In 2003, she graduated from secondary school at the Marnix College in Ede and started her study Medicine at Utrecht University.

During her study, Anita did two internships abroad where she got to know Suriname and Australia better.

In 2009, she obtained her medical degree and started working at the department of Internal Medicine at Ziekenhuis Gelderse Vallei in Ede. In January 2011, she was able to continue her residency in Internal Medicine there (under the supervision of dr. R. Heijligenberg). In September 2013, her residency continued at the University Medical Center Utrecht (under supervision of prof. dr. M.M.E. Schneider and prof. dr. H.A.H. Kaasjager), where she started her Nephrology specialization in February 2015 (under supervision of dr. P.J. Blankestijn and dr. M.B. Rookmaaker).

In June 2017, Anita interrupted her residency for a PhD research project at the department of Nephrology and Hypertension of the University Medical Center Utrecht. She conducted research for the Dutch nOcturnal and home dialysis Study To Improve Clinical Outcomes (DOMESTICO) which formed the basis for this thesis (under supervision of dr. A.C. Abrahams, dr. B.C. van Jaarsveld and prof. dr. M.C. Verhaar). In October 2020, Anita resumed her residency partly at the University Medical Center Utrecht and partly at Rijnstate in Arnhem (under supervision of dr. L.J.M. Reichert).

Since January 2021, Anita is working as an internist-nephrologist at Deventer Ziekenhuis, where she became a member of the Vrijgevestigde Specialisten Deventer in August 2022.